AUGMENTIN DUO 457 mg/5 mL – Mixed fruit flavour

Amoxicillin trihydrate – Potassium clavulanate

1. NAME OF THE MEDICINAL PRODUCT

Augmentin Duo

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, each 5 mL contains 400 mg amoxicillin (as amoxicillin trihydrate) and 57 mg clavulanic acid (as potassium clavulanate).

3. PHARMACEUTICAL FORM

A white to off-white dry powder for reconstitution in water to form a white to tan mixed-fruit flavoured suspension.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AUGMENTIN should be used in accordance with local official antibiotic-prescribing guidelines and local susceptibility data.

AUGMENTIN suspension (457 mg/5 mL), for twice daily oral dosing, is indicated for short term treatment of bacterial infections at the following sites when amoxicillin resistant beta-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered.

Upper respiratory tract infections (including ENT) e.g. recurrent tonsillitis, sinusitis, otitis media.

Lower respiratory tract infections e.g. acute exacerbations of chronic bronchitis, lobar and bronchopneumonia.

Urinary tract infections e.g. cystitis, urethritis, pyelonephritis

Skin and soft tissue infections e.g. cellulitis, animal bites.

Dental infections e.g. severe dental abscess with spreading cellulitis.

Susceptibility to AUGMENTIN will vary with geography and time (see Pharmacological Properties, Pharmacodynamics for further information). Local susceptibility data should be consulted where available, and microbiological sampling and susceptibility testing performed where necessary.

Mixed infections caused by amoxicillin-susceptible organisms in conjunction with AUGMENTIN susceptible beta-lactamase-producing organisms may be treated with

AUGMENTIN suspension 457 mg/5 mL. These infections should not require the addition of another antibiotic resistant to beta-lactamases.

4.2 Posology and method of administration

Dosage depends on the age, weight and renal function of the patient and the severity of the infection.

Dosages are expressed throughout in terms of amoxicillin/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of AUGMENTIN is optimised when taken at the start of a meal.

Treatment should not exceed 14 days without review.

Therapy can be started parenterally and continued with an oral preparation.

AUGMENTIN bottle presentations for suspension may be supplied with a plastic dosing device. For preparation of the suspensions see Special Precautions for disposal and other handling.

The usual recommended daily dosage is:

- Lower dose: 25/3.6 to 45/6.4 mg/kg/day in two divided doses for mild to moderate infections (upper respiratory tract infections e.g. recurrent tonsillitis, lower respiratory infections and skin and soft tissue infections).

- Higher dose: 45/6.4 to 70/10 mg/kg/day in two divided doses for the treatment of more serious infections (upper respiratory tract infections e.g. otitis media and sinusitis, lower respiratory tract infections e.g. bronchopneumonia and urinary tract infections).

No clinical data are available on doses above 45/6.4 mg/kg/day in children under 2 years.

There are no clinical data for AUGMENTIN 457 mg/5 mL to make dosage recommendations for children under 2 months old.

The tables below give dosage guidance for children.

Children 2 years and over

AUGMENTIN suspension 457 mg/5 mL		
Body weight (kg)	For lower dose range (mL every 12 hours)	For higher dose range (mL every 12 hours)
12 to 16	2.5	5
17 to 26	5	7.5
27 to 35	7.5	10
36 to < 40	10	12.5

Children aged 2 months to under 2 years

AUGMENTIN suspension 457 mg/5 mL		
Body Weight (kg)	Lower dose at 25/3.6 mg/kg/day (mL every 12 hours)	Higher dose at 45/6.4 mg/kg/day (mL every 12 hours)
2	0.3	0.6
3	0.5	0.8
4	0.6	1.1
5	0.8	1.4
6	0.9	1.7
7	1.1	2.0
8	1.3	2.3
9	1.4	2.5
10	1.6	2.8
11	1.7	3.1
12	1.9	3.4
13	2.0	3.7
14	2.2	3.9
15	2.3	4.2

Renal Impairment

No adjustment in dose is required in patients with creatinine clearance greater than 30 mL/min.

AUGMENTIN suspension 457 mg/5 mL is not recommended in patients with a creatinine clearance of less than 30 mL/min.

Hepatic Impairment

Administer with caution; monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation.

4.3 Contraindications

AUGMENTIN is contraindicated

- in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins.

- in patients with a previous history of AUGMENTIN-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Before initiating therapy with AUGMENTIN, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity (see Contraindications). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to AUGMENTIN (see Undesirable Reactions). Drug-induced enterocolitis syndrome has been reported mainly in children receiving AUGMENTIN (see Undesirable Reactions). Drug-induced enterocolitis syndrome is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicinal product administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, lethargy, diarrhoea, hypotension or leucocytosis with neutrophilia. In severe cases, drug-induced enterocolitis syndrome can progress to shock. If an allergic reaction occurs, AUGMENTIN therapy must be discontinued and appropriate alternative therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous (i.v.) steroids and airway management (including intubation) may also be required.

AUGMENTIN should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or

significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving AUGMENTIN and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Changes in liver function tests have been observed in some patients receiving AUGMENTIN. The clinical significance of these changes is uncertain but AUGMENTIN should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for up to six weeks after treatment has ceased.

In patients with renal impairment AUGMENTIN suspension 457 mg/5 mL is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria (see Overdose).

AUGMENTIN 457 mg/5 mL suspension contain aspartame, which is a source of phenylalanine and so should be used with caution in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with AUGMENTIN may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of AUGMENTIN and allopurinol.

In common with other antibiotics, AUGMENTIN may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

In the literature, there are rare cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of AUGMENTIN.

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered AUGMENTIN have shown no teratogenic effects. In a single study in women with pre-term, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with AUGMENTIN may be associated with an increased risk of necrotising enterocolitis in neonates. As with all medicines, use should be avoided in pregnancy, unless considered essential by the physician.

Lactation

AUGMENTIN may be administered during the period of lactation. With the exception of the risk of sensitisation, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on Ability to Drive and Use Machines

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable Effects

Data from large clinical trials were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at < 1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency.

The following convention has been used for the classification of frequency:

very common ≥ 1/10

common ≥ 1/100 to < 1/10

uncommon ≥ 1/1000 to < 1/100

rare ≥ 1/10,000 to < 1/1000

very rare < 1/10,000.

Infections and infestations

Common Mucocutaneous candidiasis

Blood and lymphatic system disorders

Rare	Reversible leucopenia (including neutropenia) and thrombocytopenia
Very rare	Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time.

Immune system disorders

Very rare	Angioneurotic oedema, anaphylaxis (see Special warnings and precautions for use), serum sickness-like syndrome, hypersensitivity vasculitis (see also Skin and subcutaneous tissue disorders).

Nervous system disorders

Uncommon	Dizziness, headache
Very rare	Reversible hyperactivity, aseptic meningitis, convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Cardiac disorders

Very rare	Kounis syndrome (see Special warnings and precautions for use).

Gastrointestinal disorders

Adults

Very common	Diarrhoea
Common	Nausea, vomiting

Children

Common	Diarrhoea, nausea, vomiting

All populations

Nausea is more often associated with higher oral dosages. If gastrointestinal reactions are evident, they may be reduced by taking AUGMENTIN at the start of a meal.

Uncommon	Indigestion
Very rare	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis, drug-induced enterocolitis syndrome (see Special warnings and precautions for use).
	Black hairy tongue
	Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.

Hepatobiliary disorders

Uncommon	A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
Very Rare	Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children.

Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Skin and subcutaneous tissue disorders

Uncommon	Skin rash, pruritus, urticaria
Rare	Erythema multiforme
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) (see also Immune system disorders).
	If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Linear IgA disease.

Renal and urinary disorders

Very rare Interstitial nephritis, crystalluria (see Overdose)

To Report any side effect(s):

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via gulf.safety@gsk.com.

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Gastrointestinal symptoms may be treated symptomatically with attention to the water electrolyte balance.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Special warnings and precautions for use).

AUGMENTIN can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

ATC Code

Anatomical Therapeutic Chemical (ATC) code: J01CR02.
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

Resistance to many antibiotics is caused by bacterial enzymes which destroy the antibiotic before it can act on the pathogen. The clavulanate in AUGMENTIN suspension anticipates this defence mechanism by blocking the beta-lactamase enzymes, thus rendering the organisms sensitive to amoxicillin's rapid bactericidal effect at concentrations readily attainable in the body.

Clavulanate by itself has little antibacterial activity; however, in association with amoxicillin as AUGMENTIN it produces an antibiotic agent of broad-spectrum with wide application in hospital and general practice.

Pharmacodynamic Effects

In the list below, organisms are categorised according to their in vitro susceptibility to AUGMENTIN.

In vitro susceptibility of micro-organisms to AUGMENTIN
Where clinical efficacy of Augmentin has been demonstrated in clinical trials this is indicated with an asterisk (*). Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to amoxicillin, it can be considered susceptible to AUGMENTIN.
Commonly susceptible species
<u>Gram-positive aerobes:</u> Bacillius anthracis Enterococcus faecalis Listeria monocytogenes Nocardia asteroides Streptococcus pyogenes*† Streptococcus agalactiae*† Streptococcus spp. (other beta-hemolytic)*† Staphylococcus aureus (methicillin susceptible)* Staphylococcus saprophyticus (methicillin susceptible) Coagulase negative staphylococcus (methicillin susceptible)
<u>Gram-negative aerobes:</u> Bordetella pertussis Haemophilus influenzae* Haemophilus parainfluenzae Helicobacter pylori Moraxella catarrhalis* Neisseria gonorrhoeae Pasteurella multocida Vibrio cholerae
<u>Other:</u> Borrelia burgdorferi Leptospira ictterohaemorrhagiae Treponema pallidum

Gram positive anaerobes:
Clostridium spp.
Peptococcus niger
Peptostreptococcus magnus
Peptostreptococcus micros
Peptostreptococcus spp.
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides spp.
Capnocytophaga spp.
Eikenella corrodens
Fusobacterium nucleatum
Fusobacterium spp.
Porphyromonas spp.
Prevotella spp.
Species for which acquired resistance may be a problem
Gram-negative aerobes:
Escherichia coli*
Klebsiella oxytoca
Klebsiella pneumoniae*
Klebsiella spp.
Proteus mirabilis
Proteus vulgaris
Proteus spp.
Salmonella spp.
Shigella spp.
Gram-positive aerobes:
Corynebacterium spp.
Enterococcus faecium
Streptococcus pneumoniae*†
Viridans group streptococcus

Inherently resistant organisms
Gram-negative aerobes:
Acinetobacter spp.
Citrobacter freundii
Enterobacter spp.
Hafnia alvei
Legionella pneumophila
Morganella morganii
Providencia spp.
Pseudomonas spp.
Serratia spp.
Stenotrophomas maltophilia
Yersinia enterolitica
Others:
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia spp.
Coxiella burnetti
Mycoplasma spp.

Infections caused by amoxicillin-susceptible organisms are amenable to AUGMENTIN treatment due to its amoxicillin content. Mixed infections caused by amoxicillin-susceptible organisms in conjunction with AUGMENTIN-susceptible beta-lactamase producing organisms may therefore be treated with AUGMENTIN.

5.2 Pharmacokinetics

Absorption

The two components of AUGMENTIN suspension 457 mg/5 mL, amoxicillin and clavulanate, are each fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of AUGMENTIN is optimised when taken at the start of a meal.

The mean AUC values for amoxicillin are essentially the same following twice a day dosing with the AUGMENTIN 875/125 mg tablet or three times a day dosing with the AUGMENTIN 500/125 mg tablet, in adults. No differences between the 875 mg twice daily and 500 mg three times daily dosing regimes are seen when comparing the amoxicillin $T_{1/2}$, or C_{max} after normalisation for the different doses of amoxicillin

administered. Similarly, no differences are seen for the clavulanate $T_{1/2}$, C_{max} or AUC values after appropriate dose normalisation.

The time of dosing of AUGMENTIN relative to the start of a meal has no marked effects on the pharmacokinetics of amoxicillin in adults. In a study of the AUGMENTIN 875/125 mg tablet, the time of dosing relative to ingestion of a meal had a marked effect on the pharmacokinetics of clavulanate. For clavulanate AUC and C_{max}, the highest mean values and smallest inter-subject variabilities were achieved by administering AUGMENTIN at the start of a meal, compared to the fasting state or 30 or 150 minutes after the start of a meal.

The mean Cmax, Tmax, T1/2 and AUC values for amoxicillin and clavulanate are given below for an 875 mg/125 mg dose of amoxicillin /clavulanic acid administered at the start of a meal.

Mean Pharmacokinetic Parameters

Drug Administration	Dose (mg)	Cmax (mg/L)	Tmax* (hours)	AUC (mg.h/L)	T1/2 (hours)
AUGMENTIN 1 g					
Amoxicillin	875	12.4	1.5	29.9	1.36
Clavulanate	125	3.3	1.3	6.88	0.92

*Median values

Amoxicillin serum concentrations achieved with AUGMENTIN are similar to those produced by the oral administration of equivalent doses of amoxicillin alone.

Distribution

The pharmacokinetics of the two components of AUGMENTIN are closely matched. Both clavulanate and amoxicillin have low levels of serum binding; about 70% remains free in the serum.

Doubling the dosage of AUGMENTIN approximately doubles the serum levels achieved.

5.3 Preclinical safety data

No further information of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

AUGMENTIN dry powder for suspension contains xanthan gum, hydroxypropyl methylcellulose, colloidal silica, succinic acid, silicon dioxide, aspartame and dry flavours (raspberry, orange “1”, orange “2” and golden syrup).

For important information about some of these excipients see Special warnings and precautions for use.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

Do not take after the expiry date shown on the pack.

The dry powder should be stored in unopened containers in a dry place at or below 30°C.

Once reconstituted, the suspension must be stored in a refrigerator (2°C to 8°C) and used within 7 days. Do not freeze. (See also Special Precautions for disposal and other handling).

6.5 Nature and Contents of Container

Clear glass bottles containing powder for reconstitution. Bottles may be supplied with either an aluminium screw cap with a ring seal or a plastic child-resistant cap with a removable foil-backed seal on the bottle. Fill-lines are indicated on the bottle label. Bottles may be supplied with a plastic dosing device.

6.6 Special Precautions for disposal and other handling

For bottles with aluminium screw caps, check the cap ring seal is intact before using. Alternatively, for bottles with a plastic child-resistant cap, check the foil-backed bottle seal is intact before using.

At time of use, the dry powder should be reconstituted to form an oral suspension, as detailed below:

- Invert and shake bottle to loosen powder.
- Add volume of water (indicated below). Invert and shake well.
- Alternatively, fill the bottle with water to just below the mark on bottle label. Invert and shake well, then top up with water to the mark. Invert and shake again.
- Allow to stand for 5 minutes to ensure full dispersion.
- Shake well before taking each dose.

AUGMENTIN suspension 457 mg/5 mL		
Fill Weight (g)	Volume of water to be added to reconstitute (mL)	Final volume of reconstituted oral suspension (mL)

6.3	31	35
12.6	62	70
25.2	124	140

A plastic dosing device may be supplied with the pack which can be used to measure the dose accurately.

Discard any unused suspension after 7 days.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

7. Marketing Authorisation Holder

GSK LIFE SCIENCES FZE REP. OFFICE Dubai, United Arab Emirates

P.O. Box 50199

8. Marketing Authorisation Number

Registration number: 3617-4605-3

9. Date of first Authorisation/renewal of the authorisation

Date of first authorisation: 19 June 2000

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10. Date of revision of the text

Version number: GDS29/IPI18

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swissmedic
Text approved
Text approve
May 29, 2024
Taking into account the corrections

Augmentin

Suspension

Composition

Active ingredients

Amoxicillin anhydrous and Amoxicillin trihydrate

clavulanic acid and potassium clavulanate.

Auxiliary materials

Suspension 457 mg/5 ml (400/57): Aromatics: Vanillin and other aromatics, Aspartame; Excipients in powder form

Dosage form and amount of active substance per unit

Galenische Form	Amoxicillin anhydrous and Amoxicillin trihydrate	clavulanic acid and potassium clavulanate	Ratio Amoxicillin: clavulanic acid
5 mL suspension 457 mg (400/57)	400 mg	57 mg	7 : 1

Indications/possible applications

Augmentin should be used in accordance with the official local recommendations for the use of antibiotics and taking into account local sensitivity data.

Augmentin is indicated for Gram-positive and Gram-negative bacterial infections with Augmentin-susceptible pathogens (especially germs that are resistant to amoxicillin due to their β-lactamase production, see "Properties/effects").

Tonsillitis

Infections of the lower airways

Otitis media

The sensitivity of pathogens to Augmentin may vary geographically and may change over time. Local susceptibility data should therefore be taken into account and, if necessary, susceptibility tests should be carried out.

Dosage / Application

The dose depends on the patient's age, body weight and kidney function as well as the severity of the infection

Usual dosage

Adults and children over 40 kg

For the treatment of infections in adults and children over 40 kg, see the Information for healthcare professionals for Augmentin film-coated tablets.

Children up to 40 kg

a) General dosage guidelines

The general dosage guidelines per kg and day (see below) must be observed!

The daily dose should be divided into 2 single doses.

Augmentin should only be used for the infections listed here.

Age	**Daily dose**
Under 2 years	***Acute otitis media:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
Over 2 years	***Tonsillitis and mild to moderate lower respiratory tract infections:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
	Otitis media: **51 - 80 mg/kg/day (44.6 mg AMX/6.4 mg CLV to 70 mg/10 mg)**

b) Dosage recommendations

Augmentin 457 mg (400/57) Suspension is used for certain infections in children from 2 months of age (see "General dosing guidelines ”).

The 35 mL suspension pack contains a dosing pipette graduated in 0.2 mL increments up to 5 mL. The 70 mL and 140 mL packs contain a dosing cup with the following graduations: 2.5; 5; 7.5 and 10 mL.

Tonsillitis and mild to moderate lower respiratory tract infections:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
13 – 15 kg	2 - 3 years	2x daily 2,5 mL
16 – 18 kg	3 - 5 years	2x daily 3 mL
19 – 21 kg	5 - 6 years	2x daily 3,5 mL
22 – 30 kg	6 - 10 years	2x daily 5 mL
31 - 40 kg	10 - 12 years	2x daily 7,5 mL

Acute otitis media:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
4 - 6 kg	2 - 6 months	2x daily 1 mL
7 - 9 kg	6 - 12 months	2x daily 1,6 mL
10 - 12 kg	1 - 2 years	2x daily 2 mL
13 – 17 kg	2 - 4 years	2x daily 5 mL
18 – 26 kg	4 - 8 years	2x daily 7,5 mL
27 – 35 kg	8 - 10 years	2x daily 10 mL
36 – 40 kg	10 - 12 years	2x daily 12,5 mL

Special dosing instructions

Patients with renal dysfunction

Augmentin should not be administered to patients with a creatinine clearance of less than 30 mL/min.

If creatinine clearance is above 30 mL/min, no dose adjustment is required.

Type of application

Augmentin should preferably be taken at the beginning of a meal to optimize absorption and gastrointestinal tolerance.

The dose depends on the patient's age, body weight and kidney function, as well as the severity of the infection. Parenteral therapies can be continued orally.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins or to any ingredient of Augmentin, as well as in patients who developed jaundice or hepatic dysfunction during previous Augmentin therapy.

Infectious mononucleosis, lymphocytic leukemia: Patients suffering from these diseases are particularly predisposed to exanthema formation during amoxicillin therapy.

Warnings and precautions

- Augmentin should not be administered to patients with impaired renal function (creatinine clearance of less than 30 mL/min) (see "Special dosing instructions ").
- Before starting treatment with Augmentin, it should be ascertained whether hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens have already been detected.
    - Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction. Symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin clavulanate (see "Adverse reactions"). If an allergic reaction occurs, Augmentin should be discontinued and appropriate alternative therapy initiated.
- Emergency measures should be prepared in the event of anaphylactic or anaphylactoid reactions. These reactions require the immediate injection of adrenaline (caution: cardiac arrhythmia). Adrenaline administration can be repeated if necessary. Then intravenous administration of glucocorticoids (e.g. 250 - 1000 mg prednisolone). The glucocorticoid administration can be repeated if necessary. Oxygen, intravenous steroids and ventilation, including intubation, may also be required. In children, the dosage of the preparations should be adjusted according to body weight or age. Further therapeutic measures such as intravenous administration of antihistamines and volume substitution should be considered. Careful monitoring of the patient is necessary as the symptoms may recur.
  Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalized exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Adverse reactions"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered
- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Adverse reactions"). DIES is an allergic reaction with the main symptom of persistent vomiting (1-4 hours after ingestion of the drug) in the absence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy,

diarrhea, hypotension or leukocytosis with neutrophilia. Severe cases including progression to shock have occurred.

- If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and suitable alternative therapy initiated.
- If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
- Long-term use can lead to the proliferation of non-susceptible germs. In such a case, appropriate clarification and therapy must be initiated.
- The occurrence of diarrhea during or after treatment with Augmentin, especially if it is severe, persistent and/or bloody, may be a symptom of Clostridium difficile infection. The most severe form is pseudomembranous colitis. If such a complication is suspected, treatment with Augmentin should be discontinued immediately and the patient should be examined in detail so that specific antibiotic therapy (e.g. metronidazole, vancomycin) can be used if necessary. The use of peristaltic inhibitors is contraindicated in this clinical situation.
- During long-term therapy, periodic monitoring of renal, hepatic and hematopoietic functions is recommended.
- In patients taking amoxicillin-clavulanate and oral anticoagulants, an abnormal prolongation of the prothrombin time (increased INR) has rarely been reported. If anticoagulants are prescribed at the same time, appropriate monitoring should therefore be carried out. In order to maintain the desired level of anticoagulation, the dose of oral anticoagulants may need to be adjusted.
- Augmentin should only be used with caution in cases of liver dysfunction.
- The suspensions contain aspartame and should therefore be used with caution in patients with phenylketonuria.
- In the case of severe gastrointestinal disorders with vomiting and diarrhea, adequate absorption of Augmentin is no longer guaranteed. Parenteral application should then be considered.
- Crystalluria has been observed very rarely in patients with reduced urine output, especially with parenteral treatment. Acute renal failure may occur as a possible consequence of crystal formation. When administering high doses of amoxicillin, ensure sufficient fluid intake and appropriate urine excretion to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate in the bladder catheter at room temperature. Therefore, the normal urine flow in the catheter should be checked regularly.

Interactions

Probenecid inhibits the renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.

Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives can be reduced or completely eliminated due to the impairment of the intestinal flora. This reduces the effectiveness of the contraceptives.

Because amoxicillin only acts on bacteria in the growth phase, there is an interaction with bacteriostatic antibiotics.

There is a possibility of interaction with glycosides (e.g. digoxin) because antibiotics can cause damage to the intestinal flora, leading to increased absorption of glycosides in some patients.

The concomitant use of allopurinol during treatment with amoxicillin may increase the likelihood of allergic skin reactions. No data are available on the combination of Augmentin with allopurinol.

The literature describes rare cases of an increased International Normalized Ratio (INR) in patients taking acenocoumarol or warfarin who are prescribed amoxicillin therapy. If concomitant administration is necessary, the prothrombin time or International Normalized Ratio should be carefully monitored when adding or discontinuing amoxicillin.

In patients taking mycophenolate mofetil, a decrease of approximately 50% in the concentration of the active metabolite mycophenolic acid prior to administration was reported after initiation of treatment with an oral amoxicillin-clavulanic acid combination. The change in pre-administration concentration may not accurately reflect changes in total MPA exposure.

Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy, breastfeeding

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times higher than in humans) with orally and parenterally administered Augmentin showed no teratogenic effects.

In a study in women with premature rupture of the fetal membrane, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in newborns (incidence of proven necrotizing enterocolitis in newborns of 1.5% with Augmentin treatment versus 0.5% without Augmentin treatment).

Augmentin should therefore not be used during pregnancy unless clearly necessary.

Breastfeeding

Since traces of Augmentin pass into breast milk, there is a possibility of a hypersensitivity reaction in sensitive newborns. An impairment of the intestinal flora of infants is theoretically conceivable, but has not yet been observed at the recommended dosages. Breastfeeding should therefore be avoided during treatment with Augmentin.

Effect on the ability to drive and operate machinery

Certain drug reactions which vary from individual to individual (see "Undesirable effects") may impair the patient's concentration and reaction to such an extent that the ability to drive or operate machinery may be impaired.

Undesirable effects

The frequencies of the very common to rare adverse effects were taken from the data material of large clinical studies. The frequencies of the remaining adverse reactions (i.e. with an incidence <1/10,000) are mainly derived from the data of the post-marketing reports and therefore refer to the frequency of reporting and not to the actual frequency of occurrence.

The following definitions were used to classify the frequency of adverse effects:

Very common (≥1/10)

Common (<1/10, ≥1/100)

Uncommon (<1/100, ≥1/1000)

rare (<1/1000, ≥1/10’000)

very rare (<1/10‘000)

Not known (cannot be estimated from the available data)

Infections and parasitic diseases

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding time and prothrombin time (Quick value). (see "Warnings and precautions" and "Interactions).

Testimonials (Post-Marketing Data)

Rare: Thrombocytosis.

Diseases of the immune system

Very rare: Angioneurotic edema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see Diseases of the skin and subcutaneous tissue).

Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions “).

Data from clinical studies

Common: reversible eosinophilia (hypersensitivity reaction).

Testimonials (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, itchy erythema, angioneurotic oedema; abdominal pain, vomiting and other abdominal signs; dyspnoea with bronchospasm or laryngeal oedema; circulatory symptoms such as drop in blood pressure up to anaphylactic shock). A Herxheimer reaction is possible during the treatment of typhoid fever, lues or leptospirosis. If a hypersensitivity reaction occurs, treatment must be discontinued immediately (see also "Diseases of the skin and subcutaneous cell tissue").

Diseases of the nervous system

Uncommon: Dizziness, headaches.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired renal function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Testimonials (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioral changes, drowsiness, dysesthesia.

Heart diseases

Testimonials (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Diseases of the gastrointestinal tract

Very common: Diarrhea.

Common: Nausea, vomiting.

Nausea occurs more frequently with higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the beginning of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare:

- Antibiotic-induced colitis (including pseudomembranous colitis and hemorrhagic colitis) (see "Warnings and precautions “).
- There are reports of superficial tooth discoloration in children after use of the suspension. Good oral hygiene could prevent the occurrence of tooth discoloration, as this can generally be removed by brushing your teeth.
- Black hair tongue (only after use of the oral forms).
- A cohort study of 576 nine-year-old children showed that the administration of amoxicillin at the age of 0 - 9 months significantly increased the risk of fluorosis of the definitive maxillary incisors. Fluorosis can manifest itself as white streaks, cosmetically unpleasant discoloration, enamel indentations and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions")

Drug-induced enterocolitis syndrome (DIES)

(Testimonials (Post-Marketing Data).

Data from clinical studies

Very common: loose stool.

Common: Abdominal pain.

Liver and biliary diseases

Uncommon:

- A moderate increase in AST and/or ALT levels was observed in patients receiving Augmentin.
- Temporary increase in lactate dehydrogenases and alkaline phosphatases.

Rare: Hepatitis and cholestatic jaundice.

The risk appears to be slightly increased with longer treatment duration, age ≥ 65 years and in men. Such side effects have been reported extremely rarely in children. The incidence of these side effects with Augmentin is approx. 5 times higher than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, but in some cases may not be noticed until several weeks after the end of treatment and are usually reversible. Liver events can be serious and, in extremely rare circumstances, can even lead to death. However, these cases occurred almost exclusively in patients with a serious underlying disease or who were also taking medication with a known potential for side effects in the liver.

Diseases of the skin and subcutaneous tissue

Uncommon: Skin rash (in the form of maculopapular or morbiliform exanthema) and Drug Reaction, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and Drug Reaction exanthema with eosinophilia and systemic symptoms (DRESS). (see Diseases of the immune system).

If dermatitis occurs as a hypersensitivity reaction, treatment should be discontinued (see also "Warnings and precautions “).

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome).

Frequency unknown: Linear IgA disease.

Diseases of the kidneys and urinary tract

Very rare: Interstitial nephritis.

Renal dysfunction with increased urea nitrogen and creatinine concentrations in serum.

Frequency unknown: Crystalluria (including acute kidney injury)

The reporting of suspected adverse reactions after authorization is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

In the event of an overdose, gastrointestinal symptoms and a disturbance of the fluid and electrolyte balance may occur. It can be treated symptomatically with activated charcoal and fluid intake.

Augmentin can be removed from the body by hemodialysis.

Severe overdoses of amoxicillin result in very high urine levels, especially after parenteral administration.

Amoxicillin crystalluria and concomitant acute renal failure have been reported (see "Warnings and precautions ”).

Properties/effects

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semi-synthetic aminopenicillin from the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative germs. The bactericidal effect of amoxicillin is based on the inhibition of bacterial cell wall synthesis by blocking the transpeptidases. Amoxicillin is acid-stable, but sensitive to penicillinases.

Clavulanic acid is a β-lactam that has a mild antibacterial effect against some strains of bacteria. The main effect of clavulanic acid lies in its enzyme-inhibiting activity against many types of β-lactamases.

Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases, which are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.

This inhibition protects amoxicillin from destruction by β-lactamases and thus allows amoxicillin to fully develop its antibiotic effect.

The combination of amoxicillin and clavulanic acid makes many germs sensitive that would be resistant to amoxicillin due to their β-lactamase formation. This synergistic effect is seen at clavulanic acid concentrations reached in the body after parenteral or oral administration.

Pharmacodynamics

Spectrum of action

In vitro susceptibility of the pathogens

In the following list, the germs are categorized according to their in vitro sensitivity to Augmentin.

* Clinical efficacy against Augmentin has been proven in clinical studies.

+ Germs that do not produce β-lactamases. If an isolate is sensitive to amoxicillin, it can be considered sensitive to Augmentin.

Usually sensitive germs:

Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides

- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+
- Streptococcus agalactiae*+
- Streptococcus viridans +
- Streptococcus spp. (other β-hemolytic streptococci)*+
- Staphylococcus aureus (methicillin-sensitive) *
- Staphylococcus saprophyticus (methicillin-sensitive)
- Coagulase-negative staphylococci (methicillin-sensitive))

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp..

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Germs for which acquired resistance can be a problem:

Gram-negative aerobes:

- Escherichia coli *
    - Klebsiella oxytoca

- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant germs:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

Not specified.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are well absorbed in the intestine. For optimal absorption, it is recommended to take them at the beginning of a meal. The absorption curves of the two components are similar; the maximum serum levels of amoxicillin and clavulanic acid are reached approx. 1 to 1½ hours after oral administration. After ingestion of a 375 mg tablet (250/125), they are around 5 mg/L (amoxicillin) and 3 mg/L (clavulanic acid).

The total absorbed amounts are usually 80% for amoxicillin and 70% for clavulanic acid.

Distribution

Amoxicillin is bound to plasma proteins to approx. 18%, clavulanic acid to approx. 25%. The distribution volumes are 22 liters for amoxicillin and 16 liters for clavulanic acid.

Since high serum concentrations of amoxicillin and clavulanic acid are achieved after oral administration of Augmentin, good penetration into body fluids can be expected.

Therapeutic concentrations of both active substances were found in abdominal tissue, gall bladder, skin, fat and muscle tissue and in the following body fluids: Synovial, peritoneal and pleural fluid, bile, sputum, pus.

Both active substances diffuse through the placental barrier; reproduction studies in animals showed no adverse effects; limited clinical experience in humans.

The concentrations of amoxicillin in breast milk are low. Traces of clavulanic acid have also been found in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this excretion, there are no known adverse effects for the infant.

Metabolism

Amoxicillin is 10-25% metabolized into the corresponding inactive penicilloic acid, which is excreted renally. 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are predominantly excreted renally. After oral administration, approximately 60 - 70% of the administered amoxicillin and 40 - 65% of clavulanic acid are excreted unchanged in active form in the urine within 6 hours.

The elimination half-lives of amoxicillin and clavulanic acid are approx. 1 - 1½ hours with normal kidney function.

Kinetics of special patient groups

Renal dysfunction

Renal insufficiency delays the renal elimination of both active substances; the dose must be adjusted accordingly. Plasma concentrations of both active substances are greatly reduced by hemodialysis.

Preclinical data

Administration of amoxicillin and clavulanate in combination (2:1) or clavulanate alone showed no effect in the F0 generation in rats or mice with regard to mating behavior, fertility, gestation (including embryonic and fetal development) or parturition. In addition, no adverse effects on embryo-fetal development and no adverse effects on viability, growth, development, behavior or reproductive function of the F1 offspring were observed.

Potassium clavulanate was tested alone and in combination with amoxicillin (1:2 or 1:4) in an extensive series of genotoxicity tests under in vitro and in vivo conditions, which were able to measure very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate does not entail any genotoxic risks.

Other notes

Incompatibilities

None known.

Influencing diagnostic methods

Possibly falsified results of estriol determination in pregnant women.

Due to the high concentration of amoxicillin in the urine, the glucose determination with chemical methods (Benedict or Fehling solution as well as with Clinitest) can be influenced (false positive results). It is therefore recommended that glucose determination is carried out using enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).

The direct Coombs test can be positive, but without hemolysis occurring.

In amino acid chromatography of urine, amoxicillin or its degradation products can result in ninhydrin-positive stains.

Possible interference with urine and serum total protein determinations using color reaction (ninhydrin reaction according to Ehrlich).

Possible false positive color reaction in the glycosuria determinations.

Falsely elevated serum uric acid concentrations can result if the copper chelate method is used. The tungsten phosphate and uricase methods for uric acid determination are not affected by amoxicillin.

Durability

The medicinal product may only be used until the date marked "EXP" on the container.

Shelf life after reconstitution

The 457 mg/5 mL (400/57) suspension can be stored in the refrigerator (2 - 8°C) for 7 days after reconstitution.

Special storage instructions

Store in a dry place at room temperature (15 - 25°C) and out of the reach of children.

Handling instructions

Preparation of the suspension:

The suspension is normally prepared by the pharmacist.

Shake the bottle with the powder. Carefully fill with tap water (in 2 portions) up to the line on the label (31 mL for 35 mL, 62 mL for 70 mL or 124 mL for 140 mL suspension). Shake the bottle well and leave to stand for a short time. If necessary, add more water up to the line. This results in 35, 70 or 140 mL of ready-to-use suspension. Shake bottle before each use. 2.5 mL = 228.5 mg active ingredients (200 mg amoxicillin, 28.5 mg clavulanic acid). 5 mL = 457 mg active ingredients (400 mg amoxicillin, 57 mg clavulanic acid).

Approval number

53’974 (Swissmedic).

Packs

Only intended for distribution abroad.

Marketing authorization holder

GlaxoSmithKline AG, 3053 Münchenbuchsee.

Status of the information

May 2024

swissmedic
Text approved
Text approve
May 29, 2024
Taking into account the corrections

Augmentin

Suspension

Composition

Active ingredients

Amoxicillin anhydrous and Amoxicillin trihydrate

clavulanic acid and potassium clavulanate.

Auxiliary materials

Suspension 457 mg/5 ml (400/57): Aromatics: Vanillin and other aromatics, Aspartame; Excipients in powder form

Dosage form and amount of active substance per unit

Galenische Form	Amoxicillin anhydrous and Amoxicillin trihydrate	clavulanic acid and potassium clavulanate	Ratio Amoxicillin: clavulanic acid
5 mL suspension 457 mg (400/57)	400 mg	57 mg	7 : 1

Indications/possible applications

Augmentin should be used in accordance with the official local recommendations for the use of antibiotics and taking into account local sensitivity data.

Augmentin is indicated for Gram-positive and Gram-negative bacterial infections with Augmentin-susceptible pathogens (especially germs that are resistant to amoxicillin due to their β-lactamase production, see "Properties/effects").

Tonsillitis

Infections of the lower airways

Otitis media

The sensitivity of pathogens to Augmentin may vary geographically and may change over time. Local susceptibility data should therefore be taken into account and, if necessary, susceptibility tests should be carried out.

Dosage / Application

The dose depends on the patient's age, body weight and kidney function as well as the severity of the infection

Usual dosage

Adults and children over 40 kg

For the treatment of infections in adults and children over 40 kg, see the Information for healthcare professionals for Augmentin film-coated tablets.

Children up to 40 kg

a) General dosage guidelines

The general dosage guidelines per kg and day (see below) must be observed!

The daily dose should be divided into 2 single doses.

Augmentin should only be used for the infections listed here.

Age	**Daily dose**
Under 2 years	***Acute otitis media:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
Over 2 years	***Tonsillitis and mild to moderate lower respiratory tract infections:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
	Otitis media: **51 - 80 mg/kg/day (44.6 mg AMX/6.4 mg CLV to 70 mg/10 mg)**

b) Dosage recommendations

Augmentin 457 mg (400/57) Suspension is used for certain infections in children from 2 months of age (see "General dosing guidelines ”).

The 35 mL suspension pack contains a dosing pipette graduated in 0.2 mL increments up to 5 mL. The 70 mL and 140 mL packs contain a dosing cup with the following graduations: 2.5; 5; 7.5 and 10 mL.

Tonsillitis and mild to moderate lower respiratory tract infections:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
13 – 15 kg	2 - 3 years	2x daily 2,5 mL
16 – 18 kg	3 - 5 years	2x daily 3 mL
19 – 21 kg	5 - 6 years	2x daily 3,5 mL
22 – 30 kg	6 - 10 years	2x daily 5 mL
31 - 40 kg	10 - 12 years	2x daily 7,5 mL

Acute otitis media:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
4 - 6 kg	2 - 6 months	2x daily 1 mL
7 - 9 kg	6 - 12 months	2x daily 1,6 mL
10 - 12 kg	1 - 2 years	2x daily 2 mL
13 – 17 kg	2 - 4 years	2x daily 5 mL
18 – 26 kg	4 - 8 years	2x daily 7,5 mL
27 – 35 kg	8 - 10 years	2x daily 10 mL
36 – 40 kg	10 - 12 years	2x daily 12,5 mL

Special dosing instructions

Patients with renal dysfunction

Augmentin should not be administered to patients with a creatinine clearance of less than 30 mL/min.

If creatinine clearance is above 30 mL/min, no dose adjustment is required.

Type of application

Augmentin should preferably be taken at the beginning of a meal to optimize absorption and gastrointestinal tolerance.

The dose depends on the patient's age, body weight and kidney function, as well as the severity of the infection. Parenteral therapies can be continued orally.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins or to any ingredient of Augmentin, as well as in patients who developed jaundice or hepatic dysfunction during previous Augmentin therapy.

Infectious mononucleosis, lymphocytic leukemia: Patients suffering from these diseases are particularly predisposed to exanthema formation during amoxicillin therapy.

Warnings and precautions

- Augmentin should not be administered to patients with impaired renal function (creatinine clearance of less than 30 mL/min) (see "Special dosing instructions ").
- Before starting treatment with Augmentin, it should be ascertained whether hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens have already been detected.
    - Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction. Symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin clavulanate (see "Adverse reactions"). If an allergic reaction occurs, Augmentin should be discontinued and appropriate alternative therapy initiated.
- Emergency measures should be prepared in the event of anaphylactic or anaphylactoid reactions. These reactions require the immediate injection of adrenaline (caution: cardiac arrhythmia). Adrenaline administration can be repeated if necessary. Then intravenous administration of glucocorticoids (e.g. 250 - 1000 mg prednisolone). The glucocorticoid administration can be repeated if necessary. Oxygen, intravenous steroids and ventilation, including intubation, may also be required. In children, the dosage of the preparations should be adjusted according to body weight or age. Further therapeutic measures such as intravenous administration of antihistamines and volume substitution should be considered. Careful monitoring of the patient is necessary as the symptoms may recur.
  Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalized exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Adverse reactions"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered
- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Adverse reactions"). DIES is an allergic reaction with the main symptom of persistent vomiting (1-4 hours after ingestion of the drug) in the absence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy,

diarrhea, hypotension or leukocytosis with neutrophilia. Severe cases including progression to shock have occurred.

- If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and suitable alternative therapy initiated.
- If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
- Long-term use can lead to the proliferation of non-susceptible germs. In such a case, appropriate clarification and therapy must be initiated.
- The occurrence of diarrhea during or after treatment with Augmentin, especially if it is severe, persistent and/or bloody, may be a symptom of Clostridium difficile infection. The most severe form is pseudomembranous colitis. If such a complication is suspected, treatment with Augmentin should be discontinued immediately and the patient should be examined in detail so that specific antibiotic therapy (e.g. metronidazole, vancomycin) can be used if necessary. The use of peristaltic inhibitors is contraindicated in this clinical situation.
- During long-term therapy, periodic monitoring of renal, hepatic and hematopoietic functions is recommended.
- In patients taking amoxicillin-clavulanate and oral anticoagulants, an abnormal prolongation of the prothrombin time (increased INR) has rarely been reported. If anticoagulants are prescribed at the same time, appropriate monitoring should therefore be carried out. In order to maintain the desired level of anticoagulation, the dose of oral anticoagulants may need to be adjusted.
- Augmentin should only be used with caution in cases of liver dysfunction.
- The suspensions contain aspartame and should therefore be used with caution in patients with phenylketonuria.
- In the case of severe gastrointestinal disorders with vomiting and diarrhea, adequate absorption of Augmentin is no longer guaranteed. Parenteral application should then be considered.
- Crystalluria has been observed very rarely in patients with reduced urine output, especially with parenteral treatment. Acute renal failure may occur as a possible consequence of crystal formation. When administering high doses of amoxicillin, ensure sufficient fluid intake and appropriate urine excretion to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate in the bladder catheter at room temperature. Therefore, the normal urine flow in the catheter should be checked regularly.

Interactions

Probenecid inhibits the renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.

Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives can be reduced or completely eliminated due to the impairment of the intestinal flora. This reduces the effectiveness of the contraceptives.

Because amoxicillin only acts on bacteria in the growth phase, there is an interaction with bacteriostatic antibiotics.

There is a possibility of interaction with glycosides (e.g. digoxin) because antibiotics can cause damage to the intestinal flora, leading to increased absorption of glycosides in some patients.

The concomitant use of allopurinol during treatment with amoxicillin may increase the likelihood of allergic skin reactions. No data are available on the combination of Augmentin with allopurinol.

The literature describes rare cases of an increased International Normalized Ratio (INR) in patients taking acenocoumarol or warfarin who are prescribed amoxicillin therapy. If concomitant administration is necessary, the prothrombin time or International Normalized Ratio should be carefully monitored when adding or discontinuing amoxicillin.

In patients taking mycophenolate mofetil, a decrease of approximately 50% in the concentration of the active metabolite mycophenolic acid prior to administration was reported after initiation of treatment with an oral amoxicillin-clavulanic acid combination. The change in pre-administration concentration may not accurately reflect changes in total MPA exposure.

Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy, breastfeeding

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times higher than in humans) with orally and parenterally administered Augmentin showed no teratogenic effects.

In a study in women with premature rupture of the fetal membrane, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in newborns (incidence of proven necrotizing enterocolitis in newborns of 1.5% with Augmentin treatment versus 0.5% without Augmentin treatment).

Augmentin should therefore not be used during pregnancy unless clearly necessary.

Breastfeeding

Since traces of Augmentin pass into breast milk, there is a possibility of a hypersensitivity reaction in sensitive newborns. An impairment of the intestinal flora of infants is theoretically conceivable, but has not yet been observed at the recommended dosages. Breastfeeding should therefore be avoided during treatment with Augmentin.

Effect on the ability to drive and operate machinery

Certain drug reactions which vary from individual to individual (see "Undesirable effects") may impair the patient's concentration and reaction to such an extent that the ability to drive or operate machinery may be impaired.

Undesirable effects

The frequencies of the very common to rare adverse effects were taken from the data material of large clinical studies. The frequencies of the remaining adverse reactions (i.e. with an incidence <1/10,000) are mainly derived from the data of the post-marketing reports and therefore refer to the frequency of reporting and not to the actual frequency of occurrence.

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Very common (≥1/10)

Common (<1/10, ≥1/100)

Uncommon (<1/100, ≥1/1000)

rare (<1/1000, ≥1/10’000)

very rare (<1/10‘000)

Not known (cannot be estimated from the available data)

Infections and parasitic diseases

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding time and prothrombin time (Quick value). (see "Warnings and precautions" and "Interactions).

Testimonials (Post-Marketing Data)

Rare: Thrombocytosis.

Diseases of the immune system

Very rare: Angioneurotic edema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see Diseases of the skin and subcutaneous tissue).

Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions “).

Data from clinical studies

Common: reversible eosinophilia (hypersensitivity reaction).

Testimonials (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, itchy erythema, angioneurotic oedema; abdominal pain, vomiting and other abdominal signs; dyspnoea with bronchospasm or laryngeal oedema; circulatory symptoms such as drop in blood pressure up to anaphylactic shock). A Herxheimer reaction is possible during the treatment of typhoid fever, lues or leptospirosis. If a hypersensitivity reaction occurs, treatment must be discontinued immediately (see also "Diseases of the skin and subcutaneous cell tissue").

Diseases of the nervous system

Uncommon: Dizziness, headaches.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired renal function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Testimonials (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioral changes, drowsiness, dysesthesia.

Heart diseases

Testimonials (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Diseases of the gastrointestinal tract

Very common: Diarrhea.

Common: Nausea, vomiting.

Nausea occurs more frequently with higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the beginning of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare:

- Antibiotic-induced colitis (including pseudomembranous colitis and hemorrhagic colitis) (see "Warnings and precautions “).
- There are reports of superficial tooth discoloration in children after use of the suspension. Good oral hygiene could prevent the occurrence of tooth discoloration, as this can generally be removed by brushing your teeth.
- Black hair tongue (only after use of the oral forms).
- A cohort study of 576 nine-year-old children showed that the administration of amoxicillin at the age of 0 - 9 months significantly increased the risk of fluorosis of the definitive maxillary incisors. Fluorosis can manifest itself as white streaks, cosmetically unpleasant discoloration, enamel indentations and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions")

Drug-induced enterocolitis syndrome (DIES)

(Testimonials (Post-Marketing Data).

Data from clinical studies

Very common: loose stool.

Common: Abdominal pain.

Liver and biliary diseases

Uncommon:

- A moderate increase in AST and/or ALT levels was observed in patients receiving Augmentin.
- Temporary increase in lactate dehydrogenases and alkaline phosphatases.

Rare: Hepatitis and cholestatic jaundice.

The risk appears to be slightly increased with longer treatment duration, age ≥ 65 years and in men. Such side effects have been reported extremely rarely in children. The incidence of these side effects with Augmentin is approx. 5 times higher than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, but in some cases may not be noticed until several weeks after the end of treatment and are usually reversible. Liver events can be serious and, in extremely rare circumstances, can even lead to death. However, these cases occurred almost exclusively in patients with a serious underlying disease or who were also taking medication with a known potential for side effects in the liver.

Diseases of the skin and subcutaneous tissue

Uncommon: Skin rash (in the form of maculopapular or morbiliform exanthema) and Drug Reaction, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and Drug Reaction exanthema with eosinophilia and systemic symptoms (DRESS). (see Diseases of the immune system).

If dermatitis occurs as a hypersensitivity reaction, treatment should be discontinued (see also "Warnings and precautions “).

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome).

Frequency unknown: Linear IgA disease.

Diseases of the kidneys and urinary tract

Very rare: Interstitial nephritis.

Renal dysfunction with increased urea nitrogen and creatinine concentrations in serum.

Frequency unknown: Crystalluria (including acute kidney injury)

The reporting of suspected adverse reactions after authorization is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

In the event of an overdose, gastrointestinal symptoms and a disturbance of the fluid and electrolyte balance may occur. It can be treated symptomatically with activated charcoal and fluid intake.

Augmentin can be removed from the body by hemodialysis.

Severe overdoses of amoxicillin result in very high urine levels, especially after parenteral administration.

Amoxicillin crystalluria and concomitant acute renal failure have been reported (see "Warnings and precautions ”).

Properties/effects

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semi-synthetic aminopenicillin from the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative germs. The bactericidal effect of amoxicillin is based on the inhibition of bacterial cell wall synthesis by blocking the transpeptidases. Amoxicillin is acid-stable, but sensitive to penicillinases.

Clavulanic acid is a β-lactam that has a mild antibacterial effect against some strains of bacteria. The main effect of clavulanic acid lies in its enzyme-inhibiting activity against many types of β-lactamases.

Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases, which are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.

This inhibition protects amoxicillin from destruction by β-lactamases and thus allows amoxicillin to fully develop its antibiotic effect.

The combination of amoxicillin and clavulanic acid makes many germs sensitive that would be resistant to amoxicillin due to their β-lactamase formation. This synergistic effect is seen at clavulanic acid concentrations reached in the body after parenteral or oral administration.

Pharmacodynamics

Spectrum of action

In vitro susceptibility of the pathogens

In the following list, the germs are categorized according to their in vitro sensitivity to Augmentin.

* Clinical efficacy against Augmentin has been proven in clinical studies.

+ Germs that do not produce β-lactamases. If an isolate is sensitive to amoxicillin, it can be considered sensitive to Augmentin.

Usually sensitive germs:

Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides

- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+
- Streptococcus agalactiae*+
- Streptococcus viridans +
- Streptococcus spp. (other β-hemolytic streptococci)*+
- Staphylococcus aureus (methicillin-sensitive) *
- Staphylococcus saprophyticus (methicillin-sensitive)
- Coagulase-negative staphylococci (methicillin-sensitive))

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp..

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Germs for which acquired resistance can be a problem:

Gram-negative aerobes:

- Escherichia coli *
    - Klebsiella oxytoca

- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant germs:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

Not specified.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are well absorbed in the intestine. For optimal absorption, it is recommended to take them at the beginning of a meal. The absorption curves of the two components are similar; the maximum serum levels of amoxicillin and clavulanic acid are reached approx. 1 to 1½ hours after oral administration. After ingestion of a 375 mg tablet (250/125), they are around 5 mg/L (amoxicillin) and 3 mg/L (clavulanic acid).

The total absorbed amounts are usually 80% for amoxicillin and 70% for clavulanic acid.

Distribution

Amoxicillin is bound to plasma proteins to approx. 18%, clavulanic acid to approx. 25%. The distribution volumes are 22 liters for amoxicillin and 16 liters for clavulanic acid.

Since high serum concentrations of amoxicillin and clavulanic acid are achieved after oral administration of Augmentin, good penetration into body fluids can be expected.

Therapeutic concentrations of both active substances were found in abdominal tissue, gall bladder, skin, fat and muscle tissue and in the following body fluids: Synovial, peritoneal and pleural fluid, bile, sputum, pus.

Both active substances diffuse through the placental barrier; reproduction studies in animals showed no adverse effects; limited clinical experience in humans.

The concentrations of amoxicillin in breast milk are low. Traces of clavulanic acid have also been found in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this excretion, there are no known adverse effects for the infant.

Metabolism

Amoxicillin is 10-25% metabolized into the corresponding inactive penicilloic acid, which is excreted renally. 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are predominantly excreted renally. After oral administration, approximately 60 - 70% of the administered amoxicillin and 40 - 65% of clavulanic acid are excreted unchanged in active form in the urine within 6 hours.

The elimination half-lives of amoxicillin and clavulanic acid are approx. 1 - 1½ hours with normal kidney function.

Kinetics of special patient groups

Renal dysfunction

Renal insufficiency delays the renal elimination of both active substances; the dose must be adjusted accordingly. Plasma concentrations of both active substances are greatly reduced by hemodialysis.

Preclinical data

Administration of amoxicillin and clavulanate in combination (2:1) or clavulanate alone showed no effect in the F0 generation in rats or mice with regard to mating behavior, fertility, gestation (including embryonic and fetal development) or parturition. In addition, no adverse effects on embryo-fetal development and no adverse effects on viability, growth, development, behavior or reproductive function of the F1 offspring were observed.

Potassium clavulanate was tested alone and in combination with amoxicillin (1:2 or 1:4) in an extensive series of genotoxicity tests under in vitro and in vivo conditions, which were able to measure very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate does not entail any genotoxic risks.

Other notes

Incompatibilities

None known.

Influencing diagnostic methods

Possibly falsified results of estriol determination in pregnant women.

Due to the high concentration of amoxicillin in the urine, the glucose determination with chemical methods (Benedict or Fehling solution as well as with Clinitest) can be influenced (false positive results). It is therefore recommended that glucose determination is carried out using enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).

The direct Coombs test can be positive, but without hemolysis occurring.

In amino acid chromatography of urine, amoxicillin or its degradation products can result in ninhydrin-positive stains.

Possible interference with urine and serum total protein determinations using color reaction (ninhydrin reaction according to Ehrlich).

Possible false positive color reaction in the glycosuria determinations.

Falsely elevated serum uric acid concentrations can result if the copper chelate method is used. The tungsten phosphate and uricase methods for uric acid determination are not affected by amoxicillin.

Durability

The medicinal product may only be used until the date marked "EXP" on the container.

Shelf life after reconstitution

The 457 mg/5 mL (400/57) suspension can be stored in the refrigerator (2 - 8°C) for 7 days after reconstitution.

Special storage instructions

Store in a dry place at room temperature (15 - 25°C) and out of the reach of children.

Handling instructions

Preparation of the suspension:

The suspension is normally prepared by the pharmacist.

Shake the bottle with the powder. Carefully fill with tap water (in 2 portions) up to the line on the label (31 mL for 35 mL, 62 mL for 70 mL or 124 mL for 140 mL suspension). Shake the bottle well and leave to stand for a short time. If necessary, add more water up to the line. This results in 35, 70 or 140 mL of ready-to-use suspension. Shake bottle before each use. 2.5 mL = 228.5 mg active ingredients (200 mg amoxicillin, 28.5 mg clavulanic acid). 5 mL = 457 mg active ingredients (400 mg amoxicillin, 57 mg clavulanic acid).

Approval number

53’974 (Swissmedic).

Packs

Only intended for distribution abroad.

Marketing authorization holder

GlaxoSmithKline AG, 3053 Münchenbuchsee.

Status of the information

May 2024

swissmedic
Text approved
Text approve
May 29, 2024
Taking into account the corrections

Augmentin

Suspension

Composition

Active ingredients

Amoxicillin anhydrous and Amoxicillin trihydrate

clavulanic acid and potassium clavulanate.

Auxiliary materials

Suspension 457 mg/5 ml (400/57): Aromatics: Vanillin and other aromatics, Aspartame; Excipients in powder form

Dosage form and amount of active substance per unit

Galenische Form	Amoxicillin anhydrous and Amoxicillin trihydrate	clavulanic acid and potassium clavulanate	Ratio Amoxicillin: clavulanic acid
5 mL suspension 457 mg (400/57)	400 mg	57 mg	7 : 1

Indications/possible applications

Augmentin should be used in accordance with the official local recommendations for the use of antibiotics and taking into account local sensitivity data.

Augmentin is indicated for Gram-positive and Gram-negative bacterial infections with Augmentin-susceptible pathogens (especially germs that are resistant to amoxicillin due to their β-lactamase production, see "Properties/effects").

Tonsillitis

Infections of the lower airways

Otitis media

The sensitivity of pathogens to Augmentin may vary geographically and may change over time. Local susceptibility data should therefore be taken into account and, if necessary, susceptibility tests should be carried out.

Dosage / Application

The dose depends on the patient's age, body weight and kidney function as well as the severity of the infection

Usual dosage

Adults and children over 40 kg

For the treatment of infections in adults and children over 40 kg, see the Information for healthcare professionals for Augmentin film-coated tablets.

Children up to 40 kg

a) General dosage guidelines

The general dosage guidelines per kg and day (see below) must be observed!

The daily dose should be divided into 2 single doses.

Augmentin should only be used for the infections listed here.

Age	**Daily dose**
Under 2 years	***Acute otitis media:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
Over 2 years	***Tonsillitis and mild to moderate lower respiratory tract infections:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
	Otitis media: **51 - 80 mg/kg/day (44.6 mg AMX/6.4 mg CLV to 70 mg/10 mg)**

b) Dosage recommendations

Augmentin 457 mg (400/57) Suspension is used for certain infections in children from 2 months of age (see "General dosing guidelines ”).

The 35 mL suspension pack contains a dosing pipette graduated in 0.2 mL increments up to 5 mL. The 70 mL and 140 mL packs contain a dosing cup with the following graduations: 2.5; 5; 7.5 and 10 mL.

Tonsillitis and mild to moderate lower respiratory tract infections:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
13 – 15 kg	2 - 3 years	2x daily 2,5 mL
16 – 18 kg	3 - 5 years	2x daily 3 mL
19 – 21 kg	5 - 6 years	2x daily 3,5 mL
22 – 30 kg	6 - 10 years	2x daily 5 mL
31 - 40 kg	10 - 12 years	2x daily 7,5 mL

Acute otitis media:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
4 - 6 kg	2 - 6 months	2x daily 1 mL
7 - 9 kg	6 - 12 months	2x daily 1,6 mL
10 - 12 kg	1 - 2 years	2x daily 2 mL
13 – 17 kg	2 - 4 years	2x daily 5 mL
18 – 26 kg	4 - 8 years	2x daily 7,5 mL
27 – 35 kg	8 - 10 years	2x daily 10 mL
36 – 40 kg	10 - 12 years	2x daily 12,5 mL

Special dosing instructions

Patients with renal dysfunction

Augmentin should not be administered to patients with a creatinine clearance of less than 30 mL/min.

If creatinine clearance is above 30 mL/min, no dose adjustment is required.

Type of application

Augmentin should preferably be taken at the beginning of a meal to optimize absorption and gastrointestinal tolerance.

The dose depends on the patient's age, body weight and kidney function, as well as the severity of the infection. Parenteral therapies can be continued orally.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins or to any ingredient of Augmentin, as well as in patients who developed jaundice or hepatic dysfunction during previous Augmentin therapy.

Infectious mononucleosis, lymphocytic leukemia: Patients suffering from these diseases are particularly predisposed to exanthema formation during amoxicillin therapy.

Warnings and precautions

- Augmentin should not be administered to patients with impaired renal function (creatinine clearance of less than 30 mL/min) (see "Special dosing instructions ").
- Before starting treatment with Augmentin, it should be ascertained whether hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens have already been detected.
    - Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction. Symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin clavulanate (see "Adverse reactions"). If an allergic reaction occurs, Augmentin should be discontinued and appropriate alternative therapy initiated.
- Emergency measures should be prepared in the event of anaphylactic or anaphylactoid reactions. These reactions require the immediate injection of adrenaline (caution: cardiac arrhythmia). Adrenaline administration can be repeated if necessary. Then intravenous administration of glucocorticoids (e.g. 250 - 1000 mg prednisolone). The glucocorticoid administration can be repeated if necessary. Oxygen, intravenous steroids and ventilation, including intubation, may also be required. In children, the dosage of the preparations should be adjusted according to body weight or age. Further therapeutic measures such as intravenous administration of antihistamines and volume substitution should be considered. Careful monitoring of the patient is necessary as the symptoms may recur.
  Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalized exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Adverse reactions"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered
- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Adverse reactions"). DIES is an allergic reaction with the main symptom of persistent vomiting (1-4 hours after ingestion of the drug) in the absence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy,

diarrhea, hypotension or leukocytosis with neutrophilia. Severe cases including progression to shock have occurred.

- If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and suitable alternative therapy initiated.
- If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
- Long-term use can lead to the proliferation of non-susceptible germs. In such a case, appropriate clarification and therapy must be initiated.
- The occurrence of diarrhea during or after treatment with Augmentin, especially if it is severe, persistent and/or bloody, may be a symptom of Clostridium difficile infection. The most severe form is pseudomembranous colitis. If such a complication is suspected, treatment with Augmentin should be discontinued immediately and the patient should be examined in detail so that specific antibiotic therapy (e.g. metronidazole, vancomycin) can be used if necessary. The use of peristaltic inhibitors is contraindicated in this clinical situation.
- During long-term therapy, periodic monitoring of renal, hepatic and hematopoietic functions is recommended.
- In patients taking amoxicillin-clavulanate and oral anticoagulants, an abnormal prolongation of the prothrombin time (increased INR) has rarely been reported. If anticoagulants are prescribed at the same time, appropriate monitoring should therefore be carried out. In order to maintain the desired level of anticoagulation, the dose of oral anticoagulants may need to be adjusted.
- Augmentin should only be used with caution in cases of liver dysfunction.
- The suspensions contain aspartame and should therefore be used with caution in patients with phenylketonuria.
- In the case of severe gastrointestinal disorders with vomiting and diarrhea, adequate absorption of Augmentin is no longer guaranteed. Parenteral application should then be considered.
- Crystalluria has been observed very rarely in patients with reduced urine output, especially with parenteral treatment. Acute renal failure may occur as a possible consequence of crystal formation. When administering high doses of amoxicillin, ensure sufficient fluid intake and appropriate urine excretion to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate in the bladder catheter at room temperature. Therefore, the normal urine flow in the catheter should be checked regularly.

Interactions

Probenecid inhibits the renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.

Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives can be reduced or completely eliminated due to the impairment of the intestinal flora. This reduces the effectiveness of the contraceptives.

Because amoxicillin only acts on bacteria in the growth phase, there is an interaction with bacteriostatic antibiotics.

There is a possibility of interaction with glycosides (e.g. digoxin) because antibiotics can cause damage to the intestinal flora, leading to increased absorption of glycosides in some patients.

The concomitant use of allopurinol during treatment with amoxicillin may increase the likelihood of allergic skin reactions. No data are available on the combination of Augmentin with allopurinol.

The literature describes rare cases of an increased International Normalized Ratio (INR) in patients taking acenocoumarol or warfarin who are prescribed amoxicillin therapy. If concomitant administration is necessary, the prothrombin time or International Normalized Ratio should be carefully monitored when adding or discontinuing amoxicillin.

In patients taking mycophenolate mofetil, a decrease of approximately 50% in the concentration of the active metabolite mycophenolic acid prior to administration was reported after initiation of treatment with an oral amoxicillin-clavulanic acid combination. The change in pre-administration concentration may not accurately reflect changes in total MPA exposure.

Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy, breastfeeding

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times higher than in humans) with orally and parenterally administered Augmentin showed no teratogenic effects.

In a study in women with premature rupture of the fetal membrane, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in newborns (incidence of proven necrotizing enterocolitis in newborns of 1.5% with Augmentin treatment versus 0.5% without Augmentin treatment).

Augmentin should therefore not be used during pregnancy unless clearly necessary.

Breastfeeding

Since traces of Augmentin pass into breast milk, there is a possibility of a hypersensitivity reaction in sensitive newborns. An impairment of the intestinal flora of infants is theoretically conceivable, but has not yet been observed at the recommended dosages. Breastfeeding should therefore be avoided during treatment with Augmentin.

Effect on the ability to drive and operate machinery

Certain drug reactions which vary from individual to individual (see "Undesirable effects") may impair the patient's concentration and reaction to such an extent that the ability to drive or operate machinery may be impaired.

Undesirable effects

The frequencies of the very common to rare adverse effects were taken from the data material of large clinical studies. The frequencies of the remaining adverse reactions (i.e. with an incidence <1/10,000) are mainly derived from the data of the post-marketing reports and therefore refer to the frequency of reporting and not to the actual frequency of occurrence.

The following definitions were used to classify the frequency of adverse effects:

Very common (≥1/10)

Common (<1/10, ≥1/100)

Uncommon (<1/100, ≥1/1000)

rare (<1/1000, ≥1/10’000)

very rare (<1/10‘000)

Not known (cannot be estimated from the available data)

Infections and parasitic diseases

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding time and prothrombin time (Quick value). (see "Warnings and precautions" and "Interactions).

Testimonials (Post-Marketing Data)

Rare: Thrombocytosis.

Diseases of the immune system

Very rare: Angioneurotic edema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see Diseases of the skin and subcutaneous tissue).

Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions “).

Data from clinical studies

Common: reversible eosinophilia (hypersensitivity reaction).

Testimonials (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, itchy erythema, angioneurotic oedema; abdominal pain, vomiting and other abdominal signs; dyspnoea with bronchospasm or laryngeal oedema; circulatory symptoms such as drop in blood pressure up to anaphylactic shock). A Herxheimer reaction is possible during the treatment of typhoid fever, lues or leptospirosis. If a hypersensitivity reaction occurs, treatment must be discontinued immediately (see also "Diseases of the skin and subcutaneous cell tissue").

Diseases of the nervous system

Uncommon: Dizziness, headaches.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired renal function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Testimonials (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioral changes, drowsiness, dysesthesia.

Heart diseases

Testimonials (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Diseases of the gastrointestinal tract

Very common: Diarrhea.

Common: Nausea, vomiting.

Nausea occurs more frequently with higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the beginning of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare:

- Antibiotic-induced colitis (including pseudomembranous colitis and hemorrhagic colitis) (see "Warnings and precautions “).
- There are reports of superficial tooth discoloration in children after use of the suspension. Good oral hygiene could prevent the occurrence of tooth discoloration, as this can generally be removed by brushing your teeth.
- Black hair tongue (only after use of the oral forms).
- A cohort study of 576 nine-year-old children showed that the administration of amoxicillin at the age of 0 - 9 months significantly increased the risk of fluorosis of the definitive maxillary incisors. Fluorosis can manifest itself as white streaks, cosmetically unpleasant discoloration, enamel indentations and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions")

Drug-induced enterocolitis syndrome (DIES)

(Testimonials (Post-Marketing Data).

Data from clinical studies

Very common: loose stool.

Common: Abdominal pain.

Liver and biliary diseases

Uncommon:

- A moderate increase in AST and/or ALT levels was observed in patients receiving Augmentin.
- Temporary increase in lactate dehydrogenases and alkaline phosphatases.

Rare: Hepatitis and cholestatic jaundice.

The risk appears to be slightly increased with longer treatment duration, age ≥ 65 years and in men. Such side effects have been reported extremely rarely in children. The incidence of these side effects with Augmentin is approx. 5 times higher than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, but in some cases may not be noticed until several weeks after the end of treatment and are usually reversible. Liver events can be serious and, in extremely rare circumstances, can even lead to death. However, these cases occurred almost exclusively in patients with a serious underlying disease or who were also taking medication with a known potential for side effects in the liver.

Diseases of the skin and subcutaneous tissue

Uncommon: Skin rash (in the form of maculopapular or morbiliform exanthema) and Drug Reaction, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and Drug Reaction exanthema with eosinophilia and systemic symptoms (DRESS). (see Diseases of the immune system).

If dermatitis occurs as a hypersensitivity reaction, treatment should be discontinued (see also "Warnings and precautions “).

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome).

Frequency unknown: Linear IgA disease.

Diseases of the kidneys and urinary tract

Very rare: Interstitial nephritis.

Renal dysfunction with increased urea nitrogen and creatinine concentrations in serum.

Frequency unknown: Crystalluria (including acute kidney injury)

The reporting of suspected adverse reactions after authorization is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

In the event of an overdose, gastrointestinal symptoms and a disturbance of the fluid and electrolyte balance may occur. It can be treated symptomatically with activated charcoal and fluid intake.

Augmentin can be removed from the body by hemodialysis.

Severe overdoses of amoxicillin result in very high urine levels, especially after parenteral administration.

Amoxicillin crystalluria and concomitant acute renal failure have been reported (see "Warnings and precautions ”).

Properties/effects

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semi-synthetic aminopenicillin from the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative germs. The bactericidal effect of amoxicillin is based on the inhibition of bacterial cell wall synthesis by blocking the transpeptidases. Amoxicillin is acid-stable, but sensitive to penicillinases.

Clavulanic acid is a β-lactam that has a mild antibacterial effect against some strains of bacteria. The main effect of clavulanic acid lies in its enzyme-inhibiting activity against many types of β-lactamases.

Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases, which are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.

This inhibition protects amoxicillin from destruction by β-lactamases and thus allows amoxicillin to fully develop its antibiotic effect.

The combination of amoxicillin and clavulanic acid makes many germs sensitive that would be resistant to amoxicillin due to their β-lactamase formation. This synergistic effect is seen at clavulanic acid concentrations reached in the body after parenteral or oral administration.

Pharmacodynamics

Spectrum of action

In vitro susceptibility of the pathogens

In the following list, the germs are categorized according to their in vitro sensitivity to Augmentin.

* Clinical efficacy against Augmentin has been proven in clinical studies.

+ Germs that do not produce β-lactamases. If an isolate is sensitive to amoxicillin, it can be considered sensitive to Augmentin.

Usually sensitive germs:

Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides

- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+
- Streptococcus agalactiae*+
- Streptococcus viridans +
- Streptococcus spp. (other β-hemolytic streptococci)*+
- Staphylococcus aureus (methicillin-sensitive) *
- Staphylococcus saprophyticus (methicillin-sensitive)
- Coagulase-negative staphylococci (methicillin-sensitive))

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp..

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Germs for which acquired resistance can be a problem:

Gram-negative aerobes:

- Escherichia coli *
    - Klebsiella oxytoca

- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant germs:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

Not specified.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are well absorbed in the intestine. For optimal absorption, it is recommended to take them at the beginning of a meal. The absorption curves of the two components are similar; the maximum serum levels of amoxicillin and clavulanic acid are reached approx. 1 to 1½ hours after oral administration. After ingestion of a 375 mg tablet (250/125), they are around 5 mg/L (amoxicillin) and 3 mg/L (clavulanic acid).

The total absorbed amounts are usually 80% for amoxicillin and 70% for clavulanic acid.

Distribution

Amoxicillin is bound to plasma proteins to approx. 18%, clavulanic acid to approx. 25%. The distribution volumes are 22 liters for amoxicillin and 16 liters for clavulanic acid.

Since high serum concentrations of amoxicillin and clavulanic acid are achieved after oral administration of Augmentin, good penetration into body fluids can be expected.

Therapeutic concentrations of both active substances were found in abdominal tissue, gall bladder, skin, fat and muscle tissue and in the following body fluids: Synovial, peritoneal and pleural fluid, bile, sputum, pus.

Both active substances diffuse through the placental barrier; reproduction studies in animals showed no adverse effects; limited clinical experience in humans.

The concentrations of amoxicillin in breast milk are low. Traces of clavulanic acid have also been found in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this excretion, there are no known adverse effects for the infant.

Metabolism

Amoxicillin is 10-25% metabolized into the corresponding inactive penicilloic acid, which is excreted renally. 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are predominantly excreted renally. After oral administration, approximately 60 - 70% of the administered amoxicillin and 40 - 65% of clavulanic acid are excreted unchanged in active form in the urine within 6 hours.

The elimination half-lives of amoxicillin and clavulanic acid are approx. 1 - 1½ hours with normal kidney function.

Kinetics of special patient groups

Renal dysfunction

Renal insufficiency delays the renal elimination of both active substances; the dose must be adjusted accordingly. Plasma concentrations of both active substances are greatly reduced by hemodialysis.

Preclinical data

Administration of amoxicillin and clavulanate in combination (2:1) or clavulanate alone showed no effect in the F0 generation in rats or mice with regard to mating behavior, fertility, gestation (including embryonic and fetal development) or parturition. In addition, no adverse effects on embryo-fetal development and no adverse effects on viability, growth, development, behavior or reproductive function of the F1 offspring were observed.

Potassium clavulanate was tested alone and in combination with amoxicillin (1:2 or 1:4) in an extensive series of genotoxicity tests under in vitro and in vivo conditions, which were able to measure very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate does not entail any genotoxic risks.

Other notes

Incompatibilities

None known.

Influencing diagnostic methods

Possibly falsified results of estriol determination in pregnant women.

Due to the high concentration of amoxicillin in the urine, the glucose determination with chemical methods (Benedict or Fehling solution as well as with Clinitest) can be influenced (false positive results). It is therefore recommended that glucose determination is carried out using enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).

The direct Coombs test can be positive, but without hemolysis occurring.

In amino acid chromatography of urine, amoxicillin or its degradation products can result in ninhydrin-positive stains.

Possible interference with urine and serum total protein determinations using color reaction (ninhydrin reaction according to Ehrlich).

Possible false positive color reaction in the glycosuria determinations.

Falsely elevated serum uric acid concentrations can result if the copper chelate method is used. The tungsten phosphate and uricase methods for uric acid determination are not affected by amoxicillin.

Durability

The medicinal product may only be used until the date marked "EXP" on the container.

Shelf life after reconstitution

The 457 mg/5 mL (400/57) suspension can be stored in the refrigerator (2 - 8°C) for 7 days after reconstitution.

Special storage instructions

Store in a dry place at room temperature (15 - 25°C) and out of the reach of children.

Handling instructions

Preparation of the suspension:

The suspension is normally prepared by the pharmacist.

Shake the bottle with the powder. Carefully fill with tap water (in 2 portions) up to the line on the label (31 mL for 35 mL, 62 mL for 70 mL or 124 mL for 140 mL suspension). Shake the bottle well and leave to stand for a short time. If necessary, add more water up to the line. This results in 35, 70 or 140 mL of ready-to-use suspension. Shake bottle before each use. 2.5 mL = 228.5 mg active ingredients (200 mg amoxicillin, 28.5 mg clavulanic acid). 5 mL = 457 mg active ingredients (400 mg amoxicillin, 57 mg clavulanic acid).

Approval number

53’974 (Swissmedic).

Packs

Only intended for distribution abroad.

Marketing authorization holder

GlaxoSmithKline AG, 3053 Münchenbuchsee.

Status of the information

May 2024

swissmedic
Text approved
Text approve
May 29, 2024
Taking into account the corrections

Augmentin

Suspension

Composition

Active ingredients

Amoxicillin anhydrous and Amoxicillin trihydrate

clavulanic acid and potassium clavulanate.

Auxiliary materials

Suspension 457 mg/5 ml (400/57): Aromatics: Vanillin and other aromatics, Aspartame; Excipients in powder form

Dosage form and amount of active substance per unit

Galenische Form	Amoxicillin anhydrous and Amoxicillin trihydrate	clavulanic acid and potassium clavulanate	Ratio Amoxicillin: clavulanic acid
5 mL suspension 457 mg (400/57)	400 mg	57 mg	7 : 1

Indications/possible applications

Augmentin should be used in accordance with the official local recommendations for the use of antibiotics and taking into account local sensitivity data.

Augmentin is indicated for Gram-positive and Gram-negative bacterial infections with Augmentin-susceptible pathogens (especially germs that are resistant to amoxicillin due to their β-lactamase production, see "Properties/effects").

Tonsillitis

Infections of the lower airways

Otitis media

The sensitivity of pathogens to Augmentin may vary geographically and may change over time. Local susceptibility data should therefore be taken into account and, if necessary, susceptibility tests should be carried out.

Dosage / Application

The dose depends on the patient's age, body weight and kidney function as well as the severity of the infection

Usual dosage

Adults and children over 40 kg

For the treatment of infections in adults and children over 40 kg, see the Information for healthcare professionals for Augmentin film-coated tablets.

Children up to 40 kg

a) General dosage guidelines

The general dosage guidelines per kg and day (see below) must be observed!

The daily dose should be divided into 2 single doses.

Augmentin should only be used for the infections listed here.

Age	**Daily dose**
Under 2 years	***Acute otitis media:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
Over 2 years	***Tonsillitis and mild to moderate lower respiratory tract infections:*** ***29 - 51 mg/kg/day (25.4 mg AMX/3.6 mg CLV to 44.6 mg/6.4 mg)***
	Otitis media: **51 - 80 mg/kg/day (44.6 mg AMX/6.4 mg CLV to 70 mg/10 mg)**

b) Dosage recommendations

Augmentin 457 mg (400/57) Suspension is used for certain infections in children from 2 months of age (see "General dosing guidelines ”).

The 35 mL suspension pack contains a dosing pipette graduated in 0.2 mL increments up to 5 mL. The 70 mL and 140 mL packs contain a dosing cup with the following graduations: 2.5; 5; 7.5 and 10 mL.

Tonsillitis and mild to moderate lower respiratory tract infections:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
13 – 15 kg	2 - 3 years	2x daily 2,5 mL
16 – 18 kg	3 - 5 years	2x daily 3 mL
19 – 21 kg	5 - 6 years	2x daily 3,5 mL
22 – 30 kg	6 - 10 years	2x daily 5 mL
31 - 40 kg	10 - 12 years	2x daily 7,5 mL

Acute otitis media:

Weight	**Approx. age**	**Dosage** **Augmentin 457 mg/5 mL (400/57) suspension**
4 - 6 kg	2 - 6 months	2x daily 1 mL
7 - 9 kg	6 - 12 months	2x daily 1,6 mL
10 - 12 kg	1 - 2 years	2x daily 2 mL
13 – 17 kg	2 - 4 years	2x daily 5 mL
18 – 26 kg	4 - 8 years	2x daily 7,5 mL
27 – 35 kg	8 - 10 years	2x daily 10 mL
36 – 40 kg	10 - 12 years	2x daily 12,5 mL

Special dosing instructions

Patients with renal dysfunction

Augmentin should not be administered to patients with a creatinine clearance of less than 30 mL/min.

If creatinine clearance is above 30 mL/min, no dose adjustment is required.

Type of application

Augmentin should preferably be taken at the beginning of a meal to optimize absorption and gastrointestinal tolerance.

The dose depends on the patient's age, body weight and kidney function, as well as the severity of the infection. Parenteral therapies can be continued orally.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins or to any ingredient of Augmentin, as well as in patients who developed jaundice or hepatic dysfunction during previous Augmentin therapy.

Infectious mononucleosis, lymphocytic leukemia: Patients suffering from these diseases are particularly predisposed to exanthema formation during amoxicillin therapy.

Warnings and precautions

- Augmentin should not be administered to patients with impaired renal function (creatinine clearance of less than 30 mL/min) (see "Special dosing instructions ").
- Before starting treatment with Augmentin, it should be ascertained whether hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens have already been detected.
    - Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can result in myocardial infarction. Symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin clavulanate (see "Adverse reactions"). If an allergic reaction occurs, Augmentin should be discontinued and appropriate alternative therapy initiated.
- Emergency measures should be prepared in the event of anaphylactic or anaphylactoid reactions. These reactions require the immediate injection of adrenaline (caution: cardiac arrhythmia). Adrenaline administration can be repeated if necessary. Then intravenous administration of glucocorticoids (e.g. 250 - 1000 mg prednisolone). The glucocorticoid administration can be repeated if necessary. Oxygen, intravenous steroids and ventilation, including intubation, may also be required. In children, the dosage of the preparations should be adjusted according to body weight or age. Further therapeutic measures such as intravenous administration of antihistamines and volume substitution should be considered. Careful monitoring of the patient is necessary as the symptoms may recur.
  Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalized exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Adverse reactions"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered
- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Adverse reactions"). DIES is an allergic reaction with the main symptom of persistent vomiting (1-4 hours after ingestion of the drug) in the absence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy,

diarrhea, hypotension or leukocytosis with neutrophilia. Severe cases including progression to shock have occurred.

- If an allergic reaction occurs, amoxicillin-clavulanate therapy should be discontinued and suitable alternative therapy initiated.
- If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
- Long-term use can lead to the proliferation of non-susceptible germs. In such a case, appropriate clarification and therapy must be initiated.
- The occurrence of diarrhea during or after treatment with Augmentin, especially if it is severe, persistent and/or bloody, may be a symptom of Clostridium difficile infection. The most severe form is pseudomembranous colitis. If such a complication is suspected, treatment with Augmentin should be discontinued immediately and the patient should be examined in detail so that specific antibiotic therapy (e.g. metronidazole, vancomycin) can be used if necessary. The use of peristaltic inhibitors is contraindicated in this clinical situation.
- During long-term therapy, periodic monitoring of renal, hepatic and hematopoietic functions is recommended.
- In patients taking amoxicillin-clavulanate and oral anticoagulants, an abnormal prolongation of the prothrombin time (increased INR) has rarely been reported. If anticoagulants are prescribed at the same time, appropriate monitoring should therefore be carried out. In order to maintain the desired level of anticoagulation, the dose of oral anticoagulants may need to be adjusted.
- Augmentin should only be used with caution in cases of liver dysfunction.
- The suspensions contain aspartame and should therefore be used with caution in patients with phenylketonuria.
- In the case of severe gastrointestinal disorders with vomiting and diarrhea, adequate absorption of Augmentin is no longer guaranteed. Parenteral application should then be considered.
- Crystalluria has been observed very rarely in patients with reduced urine output, especially with parenteral treatment. Acute renal failure may occur as a possible consequence of crystal formation. When administering high doses of amoxicillin, ensure sufficient fluid intake and appropriate urine excretion to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate in the bladder catheter at room temperature. Therefore, the normal urine flow in the catheter should be checked regularly.

Interactions

Probenecid inhibits the renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.

Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives can be reduced or completely eliminated due to the impairment of the intestinal flora. This reduces the effectiveness of the contraceptives.

Because amoxicillin only acts on bacteria in the growth phase, there is an interaction with bacteriostatic antibiotics.

There is a possibility of interaction with glycosides (e.g. digoxin) because antibiotics can cause damage to the intestinal flora, leading to increased absorption of glycosides in some patients.

The concomitant use of allopurinol during treatment with amoxicillin may increase the likelihood of allergic skin reactions. No data are available on the combination of Augmentin with allopurinol.

The literature describes rare cases of an increased International Normalized Ratio (INR) in patients taking acenocoumarol or warfarin who are prescribed amoxicillin therapy. If concomitant administration is necessary, the prothrombin time or International Normalized Ratio should be carefully monitored when adding or discontinuing amoxicillin.

In patients taking mycophenolate mofetil, a decrease of approximately 50% in the concentration of the active metabolite mycophenolic acid prior to administration was reported after initiation of treatment with an oral amoxicillin-clavulanic acid combination. The change in pre-administration concentration may not accurately reflect changes in total MPA exposure.

Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy, breastfeeding

Pregnancy

Reproduction studies in animals (mice and rats at doses up to 10 times higher than in humans) with orally and parenterally administered Augmentin showed no teratogenic effects.

In a study in women with premature rupture of the fetal membrane, it was reported that prophylactic treatment with Augmentin may be associated with an increased risk of necrotizing enterocolitis in newborns (incidence of proven necrotizing enterocolitis in newborns of 1.5% with Augmentin treatment versus 0.5% without Augmentin treatment).

Augmentin should therefore not be used during pregnancy unless clearly necessary.

Breastfeeding

Since traces of Augmentin pass into breast milk, there is a possibility of a hypersensitivity reaction in sensitive newborns. An impairment of the intestinal flora of infants is theoretically conceivable, but has not yet been observed at the recommended dosages. Breastfeeding should therefore be avoided during treatment with Augmentin.

Effect on the ability to drive and operate machinery

Certain drug reactions which vary from individual to individual (see "Undesirable effects") may impair the patient's concentration and reaction to such an extent that the ability to drive or operate machinery may be impaired.

Undesirable effects

The frequencies of the very common to rare adverse effects were taken from the data material of large clinical studies. The frequencies of the remaining adverse reactions (i.e. with an incidence <1/10,000) are mainly derived from the data of the post-marketing reports and therefore refer to the frequency of reporting and not to the actual frequency of occurrence.

The following definitions were used to classify the frequency of adverse effects:

Very common (≥1/10)

Common (<1/10, ≥1/100)

Uncommon (<1/100, ≥1/1000)

rare (<1/1000, ≥1/10’000)

very rare (<1/10‘000)

Not known (cannot be estimated from the available data)

Infections and parasitic diseases

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and hemolytic anemia. Prolongation of bleeding time and prothrombin time (Quick value). (see "Warnings and precautions" and "Interactions).

Testimonials (Post-Marketing Data)

Rare: Thrombocytosis.

Diseases of the immune system

Very rare: Angioneurotic edema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see Diseases of the skin and subcutaneous tissue).

Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions “).

Data from clinical studies

Common: reversible eosinophilia (hypersensitivity reaction).

Testimonials (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, itchy erythema, angioneurotic oedema; abdominal pain, vomiting and other abdominal signs; dyspnoea with bronchospasm or laryngeal oedema; circulatory symptoms such as drop in blood pressure up to anaphylactic shock). A Herxheimer reaction is possible during the treatment of typhoid fever, lues or leptospirosis. If a hypersensitivity reaction occurs, treatment must be discontinued immediately (see also "Diseases of the skin and subcutaneous cell tissue").

Diseases of the nervous system

Uncommon: Dizziness, headaches.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired renal function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Testimonials (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioral changes, drowsiness, dysesthesia.

Heart diseases

Testimonials (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Diseases of the gastrointestinal tract

Very common: Diarrhea.

Common: Nausea, vomiting.

Nausea occurs more frequently with higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the beginning of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare:

- Antibiotic-induced colitis (including pseudomembranous colitis and hemorrhagic colitis) (see "Warnings and precautions “).
- There are reports of superficial tooth discoloration in children after use of the suspension. Good oral hygiene could prevent the occurrence of tooth discoloration, as this can generally be removed by brushing your teeth.
- Black hair tongue (only after use of the oral forms).
- A cohort study of 576 nine-year-old children showed that the administration of amoxicillin at the age of 0 - 9 months significantly increased the risk of fluorosis of the definitive maxillary incisors. Fluorosis can manifest itself as white streaks, cosmetically unpleasant discoloration, enamel indentations and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions")

Drug-induced enterocolitis syndrome (DIES)

(Testimonials (Post-Marketing Data).

Data from clinical studies

Very common: loose stool.

Common: Abdominal pain.

Liver and biliary diseases

Uncommon:

- A moderate increase in AST and/or ALT levels was observed in patients receiving Augmentin.
- Temporary increase in lactate dehydrogenases and alkaline phosphatases.

Rare: Hepatitis and cholestatic jaundice.

The risk appears to be slightly increased with longer treatment duration, age ≥ 65 years and in men. Such side effects have been reported extremely rarely in children. The incidence of these side effects with Augmentin is approx. 5 times higher than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, but in some cases may not be noticed until several weeks after the end of treatment and are usually reversible. Liver events can be serious and, in extremely rare circumstances, can even lead to death. However, these cases occurred almost exclusively in patients with a serious underlying disease or who were also taking medication with a known potential for side effects in the liver.

Diseases of the skin and subcutaneous tissue

Uncommon: Skin rash (in the form of maculopapular or morbiliform exanthema) and Drug Reaction, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and Drug Reaction exanthema with eosinophilia and systemic symptoms (DRESS). (see Diseases of the immune system).

If dermatitis occurs as a hypersensitivity reaction, treatment should be discontinued (see also "Warnings and precautions “).

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome).

Frequency unknown: Linear IgA disease.

Diseases of the kidneys and urinary tract

Very rare: Interstitial nephritis.

Renal dysfunction with increased urea nitrogen and creatinine concentrations in serum.

Frequency unknown: Crystalluria (including acute kidney injury)

The reporting of suspected adverse reactions after authorization is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

In the event of an overdose, gastrointestinal symptoms and a disturbance of the fluid and electrolyte balance may occur. It can be treated symptomatically with activated charcoal and fluid intake.

Augmentin can be removed from the body by hemodialysis.

Severe overdoses of amoxicillin result in very high urine levels, especially after parenteral administration.

Amoxicillin crystalluria and concomitant acute renal failure have been reported (see "Warnings and precautions ”).

Properties/effects

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semi-synthetic aminopenicillin from the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative germs. The bactericidal effect of amoxicillin is based on the inhibition of bacterial cell wall synthesis by blocking the transpeptidases. Amoxicillin is acid-stable, but sensitive to penicillinases.

Clavulanic acid is a β-lactam that has a mild antibacterial effect against some strains of bacteria. The main effect of clavulanic acid lies in its enzyme-inhibiting activity against many types of β-lactamases.

Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases, which are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.

This inhibition protects amoxicillin from destruction by β-lactamases and thus allows amoxicillin to fully develop its antibiotic effect.

The combination of amoxicillin and clavulanic acid makes many germs sensitive that would be resistant to amoxicillin due to their β-lactamase formation. This synergistic effect is seen at clavulanic acid concentrations reached in the body after parenteral or oral administration.

Pharmacodynamics

Spectrum of action

In vitro susceptibility of the pathogens

In the following list, the germs are categorized according to their in vitro sensitivity to Augmentin.

* Clinical efficacy against Augmentin has been proven in clinical studies.

+ Germs that do not produce β-lactamases. If an isolate is sensitive to amoxicillin, it can be considered sensitive to Augmentin.

Usually sensitive germs:

Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides

- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+
- Streptococcus agalactiae*+
- Streptococcus viridans +
- Streptococcus spp. (other β-hemolytic streptococci)*+
- Staphylococcus aureus (methicillin-sensitive) *
- Staphylococcus saprophyticus (methicillin-sensitive)
- Coagulase-negative staphylococci (methicillin-sensitive))

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp..

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Germs for which acquired resistance can be a problem:

Gram-negative aerobes:

- Escherichia coli *
    - Klebsiella oxytoca

- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant germs:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

Not specified.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are well absorbed in the intestine. For optimal absorption, it is recommended to take them at the beginning of a meal. The absorption curves of the two components are similar; the maximum serum levels of amoxicillin and clavulanic acid are reached approx. 1 to 1½ hours after oral administration. After ingestion of a 375 mg tablet (250/125), they are around 5 mg/L (amoxicillin) and 3 mg/L (clavulanic acid).

The total absorbed amounts are usually 80% for amoxicillin and 70% for clavulanic acid.

Distribution

Amoxicillin is bound to plasma proteins to approx. 18%, clavulanic acid to approx. 25%. The distribution volumes are 22 liters for amoxicillin and 16 liters for clavulanic acid.

Since high serum concentrations of amoxicillin and clavulanic acid are achieved after oral administration of Augmentin, good penetration into body fluids can be expected.

Therapeutic concentrations of both active substances were found in abdominal tissue, gall bladder, skin, fat and muscle tissue and in the following body fluids: Synovial, peritoneal and pleural fluid, bile, sputum, pus.

Both active substances diffuse through the placental barrier; reproduction studies in animals showed no adverse effects; limited clinical experience in humans.

The concentrations of amoxicillin in breast milk are low. Traces of clavulanic acid have also been found in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this excretion, there are no known adverse effects for the infant.

Metabolism

Amoxicillin is 10-25% metabolized into the corresponding inactive penicilloic acid, which is excreted renally. 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are predominantly excreted renally. After oral administration, approximately 60 - 70% of the administered amoxicillin and 40 - 65% of clavulanic acid are excreted unchanged in active form in the urine within 6 hours.

The elimination half-lives of amoxicillin and clavulanic acid are approx. 1 - 1½ hours with normal kidney function.

Kinetics of special patient groups

Renal dysfunction

Renal insufficiency delays the renal elimination of both active substances; the dose must be adjusted accordingly. Plasma concentrations of both active substances are greatly reduced by hemodialysis.

Preclinical data

Administration of amoxicillin and clavulanate in combination (2:1) or clavulanate alone showed no effect in the F0 generation in rats or mice with regard to mating behavior, fertility, gestation (including embryonic and fetal development) or parturition. In addition, no adverse effects on embryo-fetal development and no adverse effects on viability, growth, development, behavior or reproductive function of the F1 offspring were observed.

Potassium clavulanate was tested alone and in combination with amoxicillin (1:2 or 1:4) in an extensive series of genotoxicity tests under in vitro and in vivo conditions, which were able to measure very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate does not entail any genotoxic risks.

Other notes

Incompatibilities

None known.

Influencing diagnostic methods

Possibly falsified results of estriol determination in pregnant women.

Due to the high concentration of amoxicillin in the urine, the glucose determination with chemical methods (Benedict or Fehling solution as well as with Clinitest) can be influenced (false positive results). It is therefore recommended that glucose determination is carried out using enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).

The direct Coombs test can be positive, but without hemolysis occurring.

In amino acid chromatography of urine, amoxicillin or its degradation products can result in ninhydrin-positive stains.

Possible interference with urine and serum total protein determinations using color reaction (ninhydrin reaction according to Ehrlich).

Possible false positive color reaction in the glycosuria determinations.

Falsely elevated serum uric acid concentrations can result if the copper chelate method is used. The tungsten phosphate and uricase methods for uric acid determination are not affected by amoxicillin.

Durability

The medicinal product may only be used until the date marked "EXP" on the container.

Shelf life after reconstitution

The 457 mg/5 mL (400/57) suspension can be stored in the refrigerator (2 - 8°C) for 7 days after reconstitution.

Special storage instructions

Store in a dry place at room temperature (15 - 25°C) and out of the reach of children.

Handling instructions

Preparation of the suspension:

The suspension is normally prepared by the pharmacist.

Shake the bottle with the powder. Carefully fill with tap water (in 2 portions) up to the line on the label (31 mL for 35 mL, 62 mL for 70 mL or 124 mL for 140 mL suspension). Shake the bottle well and leave to stand for a short time. If necessary, add more water up to the line. This results in 35, 70 or 140 mL of ready-to-use suspension. Shake bottle before each use. 2.5 mL = 228.5 mg active ingredients (200 mg amoxicillin, 28.5 mg clavulanic acid). 5 mL = 457 mg active ingredients (400 mg amoxicillin, 57 mg clavulanic acid).

Approval number

53’974 (Swissmedic).

Packs

Only intended for distribution abroad.

Marketing authorization holder

GlaxoSmithKline AG, 3053 Münchenbuchsee.

Status of the information

May 2024

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600 mg/42.9 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every mL of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid.

Excipient with known effect

Each mL of oral suspension contains 2.72 mg of aspartame (E951). The flavouring of Augmentin contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and with a body weight of less than 40 kg, caused or suspected to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat a specific infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as described below.

Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
There is no experience with Augmentin oral suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given.

Children < 40 kg (aged ≥ 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day in two divided doses.

There are no clinical data on Augmentin in children under 3 months of age.

Renal impairment
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

In patients with creatinine clearance less than 30 mL/min, the use of Augmentin is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment
Dose with caution and monitor liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake to loosen powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients mentioned in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporins, carbapenems or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, the possibility of previous hypersensitivity reactions to penicillins, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including serious adverse cutaneous and anaphylactoid reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions may also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported, mainly in children on treatment with amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction, the main symptom of which is prolonged vomiting (1–4 hours after administration of the drug) in the absence of skin allergy or respiratory symptoms. Other symptoms may include abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been cases included progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

If an infection is proven to be due to amoxicillin-susceptible organisms, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. They have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician should be consulted and appropriate therapy should be initiated. Anti-peristaltic drugs are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is recommended during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Therefore, appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with reduced urine output, crystalluria (including acute kidney injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA tests in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of infection by this microorganism. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per mL, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or the international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in

humans does not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use of Augmentin should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, causing a need to discontinue breast-feeding. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known

Immune system disorders[9]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Acute pancreatitis	Not known
Black hairy tongue	Not known
Changes to teeth colour[4]	Not known
Hepatobiliary disorders	
Increase in AST and/or ALT values[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear Ig A disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury) [8]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions occur, they may be reduced by administering amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4).
[4] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferably)
or via the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Medicine Line: 800222444 (free-phone)
Email: farmacovigilancia@infarmed.pt

4.9. Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 – Anti-infective drugs. Antibacterial. Combinations of penicillins with beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan. This biopolymer is an integral structural component of the bacterial cell wall whose function is related to maintaining the cellular form and integrity. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are listed below: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus (methicillin-susceptible)$* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other *beta-haemolytic streptococci* Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Streptococcus pneumoniae that are resistant to penicillin should only be treated with this presentation of amoxicillin/clavulanic acid under the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Mean pharmacokinetic parameters are given below for Augmentin administered at 45 mg/3.2 mg/kg every 12 hours to paediatric patients:

Formulation	C_{max} (µg/mL)	T_{max}* (h)	AUC (0-t) (µg,h/mL)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX and 3.2 mg/kg CA 12-hourly	Amoxicillin			
	15.7 +/- 7.7	2.0 (1.0-4.0)	59.8 +/- 20.0	1.4 +/- 0.35
	Clavulanic acid			
	1.7 +/- 0.9	1.1 (1.0-4.0)	4.0 +/- 1.9	1.1 +/- 0.29
AMX – amoxicillin CA – clavulanic acid * Median (range)				

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/ clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug-derived material for any component or its derivatives. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy male and female subjects, gender has shown to have no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Colloidal hydrated silica
Colloidal anhydrous silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavour (including maltodextrin)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions should be stored at 2 °C–8 °C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original container to protect from moisture. Do not store above 25 °C. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Colourless glass bottle containing powder for reconstitution for 50 mL, 75 mL, 100 mL or 150 mL with a child-resistant plastic cap and a removable protective seal. The pack may be provided with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Check that the protective seal of the bottle is intact before using. At the time of preparation, shake the bottle to loosen the powder and remove the protective seal. Add volume of water (as indicated below). Put the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water to just below the mark on the bottle label. Put the cap on the bottle, invert and shake well, then fill with water exactly up to the mark. Put the cap on the bottle, invert and shake well again.

Concentration	Volume of water to be added at reconstitution (mL)	Final volume of reconstituted oral suspension (mL)
600 mg/42.9 mg/5 mL	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Rua Dr. António Loureiro Borges, 3
Arquiparque – Miraflores
1495 – 131 Algés

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5323688 – powder for 50 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323787 – powder for 75 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323886 – powder for 100 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323985 – powder for 150 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2005
Date of latest renewal: 6 March 2015

10. DATE OF REVISION OF THE TEXT

6 July 2024

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600 mg/42.9 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every mL of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid.

Excipient with known effect

Each mL of oral suspension contains 2.72 mg of aspartame (E951). The flavouring of Augmentin contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and with a body weight of less than 40 kg, caused or suspected to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat a specific infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as described below.

Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
There is no experience with Augmentin oral suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given.

Children < 40 kg (aged ≥ 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day in two divided doses.

There are no clinical data on Augmentin in children under 3 months of age.

Renal impairment
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

In patients with creatinine clearance less than 30 mL/min, the use of Augmentin is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment
Dose with caution and monitor liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake to loosen powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients mentioned in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporins, carbapenems or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, the possibility of previous hypersensitivity reactions to penicillins, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including serious adverse cutaneous and anaphylactoid reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions may also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported, mainly in children on treatment with amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction, the main symptom of which is prolonged vomiting (1–4 hours after administration of the drug) in the absence of skin allergy or respiratory symptoms. Other symptoms may include abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been cases included progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

If an infection is proven to be due to amoxicillin-susceptible organisms, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. They have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician should be consulted and appropriate therapy should be initiated. Anti-peristaltic drugs are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is recommended during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Therefore, appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with reduced urine output, crystalluria (including acute kidney injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA tests in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of infection by this microorganism. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per mL, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or the international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in

humans does not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use of Augmentin should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, causing a need to discontinue breast-feeding. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known

Immune system disorders[9]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Acute pancreatitis	Not known
Black hairy tongue	Not known
Changes to teeth colour[4]	Not known
Hepatobiliary disorders	
Increase in AST and/or ALT values[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear Ig A disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury) [8]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions occur, they may be reduced by administering amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4).
[4] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferably)
or via the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Medicine Line: 800222444 (free-phone)
Email: farmacovigilancia@infarmed.pt

4.9. Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 – Anti-infective drugs. Antibacterial. Combinations of penicillins with beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan. This biopolymer is an integral structural component of the bacterial cell wall whose function is related to maintaining the cellular form and integrity. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are listed below: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus (methicillin-susceptible)$* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other *beta-haemolytic streptococci* Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Streptococcus pneumoniae that are resistant to penicillin should only be treated with this presentation of amoxicillin/clavulanic acid under the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Mean pharmacokinetic parameters are given below for Augmentin administered at 45 mg/3.2 mg/kg every 12 hours to paediatric patients:

Formulation	C_{max} (µg/mL)	T_{max}* (h)	AUC (0-t) (µg,h/mL)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX and 3.2 mg/kg CA 12-hourly	Amoxicillin			
	15.7 +/- 7.7	2.0 (1.0-4.0)	59.8 +/- 20.0	1.4 +/- 0.35
	Clavulanic acid			
	1.7 +/- 0.9	1.1 (1.0-4.0)	4.0 +/- 1.9	1.1 +/- 0.29
AMX – amoxicillin CA – clavulanic acid * Median (range)				

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/ clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug-derived material for any component or its derivatives. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy male and female subjects, gender has shown to have no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Colloidal hydrated silica
Colloidal anhydrous silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavour (including maltodextrin)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions should be stored at 2 °C–8 °C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original container to protect from moisture. Do not store above 25 °C. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Colourless glass bottle containing powder for reconstitution for 50 mL, 75 mL, 100 mL or 150 mL with a child-resistant plastic cap and a removable protective seal. The pack may be provided with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Check that the protective seal of the bottle is intact before using. At the time of preparation, shake the bottle to loosen the powder and remove the protective seal. Add volume of water (as indicated below). Put the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water to just below the mark on the bottle label. Put the cap on the bottle, invert and shake well, then fill with water exactly up to the mark. Put the cap on the bottle, invert and shake well again.

Concentration	Volume of water to be added at reconstitution (mL)	Final volume of reconstituted oral suspension (mL)
600 mg/42.9 mg/5 mL	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Rua Dr. António Loureiro Borges, 3
Arquiparque – Miraflores
1495 – 131 Algés

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5323688 – powder for 50 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323787 – powder for 75 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323886 – powder for 100 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323985 – powder for 150 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2005
Date of latest renewal: 6 March 2015

10. DATE OF REVISION OF THE TEXT

6 July 2024

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600 mg/42.9 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every mL of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid.

Excipient with known effect

Each mL of oral suspension contains 2.72 mg of aspartame (E951). The flavouring of Augmentin contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and with a body weight of less than 40 kg, caused or suspected to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat a specific infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as described below.

Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
There is no experience with Augmentin oral suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given.

Children < 40 kg (aged ≥ 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day in two divided doses.

There are no clinical data on Augmentin in children under 3 months of age.

Renal impairment
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

In patients with creatinine clearance less than 30 mL/min, the use of Augmentin is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment
Dose with caution and monitor liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake to loosen powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients mentioned in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporins, carbapenems or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, the possibility of previous hypersensitivity reactions to penicillins, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including serious adverse cutaneous and anaphylactoid reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions may also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported, mainly in children on treatment with amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction, the main symptom of which is prolonged vomiting (1–4 hours after administration of the drug) in the absence of skin allergy or respiratory symptoms. Other symptoms may include abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been cases included progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

If an infection is proven to be due to amoxicillin-susceptible organisms, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. They have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician should be consulted and appropriate therapy should be initiated. Anti-peristaltic drugs are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is recommended during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Therefore, appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with reduced urine output, crystalluria (including acute kidney injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA tests in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of infection by this microorganism. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per mL, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or the international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in

humans does not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use of Augmentin should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, causing a need to discontinue breast-feeding. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known

Immune system disorders[9]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Acute pancreatitis	Not known
Black hairy tongue	Not known
Changes to teeth colour[4]	Not known
Hepatobiliary disorders	
Increase in AST and/or ALT values[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear Ig A disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury) [8]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions occur, they may be reduced by administering amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4).
[4] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferably)
or via the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Medicine Line: 800222444 (free-phone)
Email: farmacovigilancia@infarmed.pt

4.9. Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 – Anti-infective drugs. Antibacterial. Combinations of penicillins with beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan. This biopolymer is an integral structural component of the bacterial cell wall whose function is related to maintaining the cellular form and integrity. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are listed below: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus (methicillin-susceptible)$* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other *beta-haemolytic streptococci* Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Streptococcus pneumoniae that are resistant to penicillin should only be treated with this presentation of amoxicillin/clavulanic acid under the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Mean pharmacokinetic parameters are given below for Augmentin administered at 45 mg/3.2 mg/kg every 12 hours to paediatric patients:

Formulation	C_{max} (µg/mL)	T_{max}* (h)	AUC (0-t) (µg,h/mL)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX and 3.2 mg/kg CA 12-hourly	Amoxicillin			
	15.7 +/- 7.7	2.0 (1.0-4.0)	59.8 +/- 20.0	1.4 +/- 0.35
	Clavulanic acid			
	1.7 +/- 0.9	1.1 (1.0-4.0)	4.0 +/- 1.9	1.1 +/- 0.29
AMX – amoxicillin CA – clavulanic acid * Median (range)				

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/ clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug-derived material for any component or its derivatives. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy male and female subjects, gender has shown to have no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Colloidal hydrated silica
Colloidal anhydrous silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavour (including maltodextrin)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions should be stored at 2 °C–8 °C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original container to protect from moisture. Do not store above 25 °C. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Colourless glass bottle containing powder for reconstitution for 50 mL, 75 mL, 100 mL or 150 mL with a child-resistant plastic cap and a removable protective seal. The pack may be provided with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Check that the protective seal of the bottle is intact before using. At the time of preparation, shake the bottle to loosen the powder and remove the protective seal. Add volume of water (as indicated below). Put the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water to just below the mark on the bottle label. Put the cap on the bottle, invert and shake well, then fill with water exactly up to the mark. Put the cap on the bottle, invert and shake well again.

Concentration	Volume of water to be added at reconstitution (mL)	Final volume of reconstituted oral suspension (mL)
600 mg/42.9 mg/5 mL	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Rua Dr. António Loureiro Borges, 3
Arquiparque – Miraflores
1495 – 131 Algés

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5323688 – powder for 50 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323787 – powder for 75 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323886 – powder for 100 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323985 – powder for 150 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2005
Date of latest renewal: 6 March 2015

10. DATE OF REVISION OF THE TEXT

6 July 2024

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600 mg/42.9 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every mL of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid.

Excipient with known effect

Each mL of oral suspension contains 2.72 mg of aspartame (E951). The flavouring of Augmentin contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and with a body weight of less than 40 kg, caused or suspected to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat a specific infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as described below.

Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
There is no experience with Augmentin oral suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given.

Children < 40 kg (aged ≥ 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day in two divided doses.

There are no clinical data on Augmentin in children under 3 months of age.

Renal impairment
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

In patients with creatinine clearance less than 30 mL/min, the use of Augmentin is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment
Dose with caution and monitor liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake to loosen powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients mentioned in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporins, carbapenems or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, the possibility of previous hypersensitivity reactions to penicillins, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including serious adverse cutaneous and anaphylactoid reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions may also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported, mainly in children on treatment with amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction, the main symptom of which is prolonged vomiting (1–4 hours after administration of the drug) in the absence of skin allergy or respiratory symptoms. Other symptoms may include abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been cases included progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

If an infection is proven to be due to amoxicillin-susceptible organisms, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. They have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician should be consulted and appropriate therapy should be initiated. Anti-peristaltic drugs are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is recommended during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Therefore, appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with reduced urine output, crystalluria (including acute kidney injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA tests in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of infection by this microorganism. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per mL, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or the international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in

humans does not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use of Augmentin should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, causing a need to discontinue breast-feeding. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known

Immune system disorders[9]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Acute pancreatitis	Not known
Black hairy tongue	Not known
Changes to teeth colour[4]	Not known
Hepatobiliary disorders	
Increase in AST and/or ALT values[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear Ig A disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury) [8]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions occur, they may be reduced by administering amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4).
[4] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferably)
or via the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Medicine Line: 800222444 (free-phone)
Email: farmacovigilancia@infarmed.pt

4.9. Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 – Anti-infective drugs. Antibacterial. Combinations of penicillins with beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan. This biopolymer is an integral structural component of the bacterial cell wall whose function is related to maintaining the cellular form and integrity. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are listed below: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus (methicillin-susceptible)$* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other *beta-haemolytic streptococci* Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Streptococcus pneumoniae that are resistant to penicillin should only be treated with this presentation of amoxicillin/clavulanic acid under the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Mean pharmacokinetic parameters are given below for Augmentin administered at 45 mg/3.2 mg/kg every 12 hours to paediatric patients:

Formulation	C_{max} (µg/mL)	T_{max}* (h)	AUC (0-t) (µg,h/mL)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX and 3.2 mg/kg CA 12-hourly	Amoxicillin			
	15.7 +/- 7.7	2.0 (1.0-4.0)	59.8 +/- 20.0	1.4 +/- 0.35
	Clavulanic acid			
	1.7 +/- 0.9	1.1 (1.0-4.0)	4.0 +/- 1.9	1.1 +/- 0.29
AMX – amoxicillin CA – clavulanic acid * Median (range)				

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/ clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug-derived material for any component or its derivatives. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy male and female subjects, gender has shown to have no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Colloidal hydrated silica
Colloidal anhydrous silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavour (including maltodextrin)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions should be stored at 2 °C–8 °C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original container to protect from moisture. Do not store above 25 °C. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Colourless glass bottle containing powder for reconstitution for 50 mL, 75 mL, 100 mL or 150 mL with a child-resistant plastic cap and a removable protective seal. The pack may be provided with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Check that the protective seal of the bottle is intact before using. At the time of preparation, shake the bottle to loosen the powder and remove the protective seal. Add volume of water (as indicated below). Put the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water to just below the mark on the bottle label. Put the cap on the bottle, invert and shake well, then fill with water exactly up to the mark. Put the cap on the bottle, invert and shake well again.

Concentration	Volume of water to be added at reconstitution (mL)	Final volume of reconstituted oral suspension (mL)
600 mg/42.9 mg/5 mL	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Rua Dr. António Loureiro Borges, 3
Arquiparque – Miraflores
1495 – 131 Algés

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5323688 – powder for 50 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323787 – powder for 75 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323886 – powder for 100 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323985 – powder for 150 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2005
Date of latest renewal: 6 March 2015

10. DATE OF REVISION OF THE TEXT

6 July 2024

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Augmentin ES 600 mg/42.9 mg/5 mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When reconstituted, every mL of oral suspension contains amoxicillin trihydrate equivalent to 120 mg amoxicillin and potassium clavulanate equivalent to 8.58 mg of clavulanic acid.

Excipient with known effect

Each mL of oral suspension contains 2.72 mg of aspartame (E951). The flavouring of Augmentin contains maltodextrin (glucose) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and with a body weight of less than 40 kg, caused or suspected to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- Acute otitis media
- Community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology
Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat a specific infection should take into account:
- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as described below.

Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
There is no experience with Augmentin oral suspension in adults and children ≥ 40 kg, and therefore no dose recommendation can be given.

Children < 40 kg (aged ≥ 3 months)
The recommended dose of Augmentin oral suspension is 90 mg/6.4 mg/kg/day in two divided doses.

There are no clinical data on Augmentin in children under 3 months of age.

Renal impairment
No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 mL/min.

In patients with creatinine clearance less than 30 mL/min, the use of Augmentin is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment
Dose with caution and monitor liver function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Shake to loosen powder, add water as directed, invert and shake. Shake the bottle before each dose (see section 6.6).

For instructions on reconstitution of the medicinal product before administration see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients mentioned in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporins, carbapenems or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4. Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, the possibility of previous hypersensitivity reactions to penicillins, cephalosporins or beta-lactam agents should be carefully investigated (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including serious adverse cutaneous and anaphylactoid reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions may also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported, mainly in children on treatment with amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction, the main symptom of which is prolonged vomiting (1–4 hours after administration of the drug) in the absence of skin allergy or respiratory symptoms. Other symptoms may include abdominal pain, diarrhoea, hypotension or leukocytosis with neutrophilia. There have been cases included progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

If an infection is proven to be due to amoxicillin-susceptible organisms, consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. The occurrence at the treatment initiation of a feverish generalised erythema associated with pustules may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. They have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician should be consulted and appropriate therapy should be initiated. Anti-peristaltic drugs are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is recommended during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Therefore, appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with reduced urine output, crystalluria (including acute kidney injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is recommended to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using Bio-Rad Laboratories Platelia Aspergillus EIA tests in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of infection by this microorganism. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported.

Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

Augmentin ES powder for oral suspension contains 2.72 mg of aspartame (E951) per mL, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Augmentin ES powder for oral suspension contains maltodextrin (glucose). Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or the international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in

humans does not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use of Augmentin should be avoided during pregnancy, unless considered essential by the physician.

Breast-feeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, causing a need to discontinue breast-feeding. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8. Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the frequencies:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidiasis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known

Immune system disorders[9]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Acute pancreatitis	Not known
Black hairy tongue	Not known
Changes to teeth colour[4]	Not known
Hepatobiliary disorders	
Increase in AST and/or ALT values[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthematous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear Ig A disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury) [8]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions occur, they may be reduced by administering amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4).
[4] Superficial tooth discolouration has been reported very rarely in children. Good oral hygiene may help to prevent tooth discolouration as it can usually be removed by brushing.
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly to INFARMED, I.P.:

Website: http://www.infarmed.pt/web/infarmed/submissaoram (preferably)
or via the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon
Tel: +351 21 798 73 73
Medicine Line: 800222444 (free-phone)
Email: farmacovigilancia@infarmed.pt

4.9. Overdose

Symptoms and signs of overdose
Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication
Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 1.1.5 – Anti-infective drugs. Antibacterial. Combinations of penicillins with beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan. This biopolymer is an integral structural component of the bacterial cell wall whose function is related to maintaining the cellular form and integrity. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:
- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and are listed below: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Staphylococcus aureus (methicillin-susceptible)$* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other *beta-haemolytic streptococci* Aerobic Gram-negative microorganisms *Haemophilus influenzae*[2] *Moraxella catarrhalis*
Species for which acquired resistance may be a problem
Aerobic Gram-negative microorganisms *Klebsiella pneumoniae*
Inherently resistant organisms
Aerobic Gram-negative microorganisms *Legionella pneumophila* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid. [1] Streptococcus pneumoniae that are resistant to penicillin should only be treated with this presentation of amoxicillin/clavulanic acid under the approved indications (see section 4.1). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2. Pharmacokinetic properties

Absorption
Amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (Tmax) in each case is approximately one hour.

Mean pharmacokinetic parameters are given below for Augmentin administered at 45 mg/3.2 mg/kg every 12 hours to paediatric patients:

Formulation	C_{max} (µg/mL)	T_{max}* (h)	AUC (0-t) (µg,h/mL)	T 1/2 (h)
Augmentin dosed at 45 mg/kg AMX and 3.2 mg/kg CA 12-hourly	Amoxicillin			
	15.7 +/- 7.7	2.0 (1.0-4.0)	59.8 +/- 20.0	1.4 +/- 0.35
	Clavulanic acid			
	1.7 +/- 0.9	1.1 (1.0-4.0)	4.0 +/- 1.9	1.1 +/- 0.29
AMX – amoxicillin CA – clavulanic acid * Median (range)				

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/ clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution
About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.
From animal studies there is no evidence for significant tissue retention of drug-derived material for any component or its derivatives. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10-25% of the initial dose. Clavulanic acid is extensively metabolised in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24-hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm new-borns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy male and female subjects, gender has shown to have no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)
Xanthan gum
Colloidal hydrated silica
Colloidal anhydrous silica
Carboxymethylcellulose sodium
Artificial strawberry cream flavour (including maltodextrin)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Powder for oral suspension: 2 years
Reconstituted suspensions should be stored at 2 °C–8 °C (but not frozen) for up to 10 days.

6.4. Special precautions for storage

Store in the original container to protect from moisture. Do not store above 25 °C. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Colourless glass bottle containing powder for reconstitution for 50 mL, 75 mL, 100 mL or 150 mL with a child-resistant plastic cap and a removable protective seal. The pack may be provided with a plastic measuring spoon.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Check that the protective seal of the bottle is intact before using. At the time of preparation, shake the bottle to loosen the powder and remove the protective seal. Add volume of water (as indicated below). Put the cap on the bottle, invert and shake well.

Alternatively, fill the bottle with water to just below the mark on the bottle label. Put the cap on the bottle, invert and shake well, then fill with water exactly up to the mark. Put the cap on the bottle, invert and shake well again.

Concentration	Volume of water to be added at reconstitution (mL)	Final volume of reconstituted oral suspension (mL)
600 mg/42.9 mg/5 mL	50	50
	70	75
	90	100
	135	150

Shake the bottle well before each dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Rua Dr. António Loureiro Borges, 3
Arquiparque – Miraflores
1495 – 131 Algés

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5323688 – powder for 50 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323787 – powder for 75 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323886 – powder for 100 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle
Registration no.: 5323985 – powder for 150 mL of oral suspension,
600 mg/5 mL+42.9 mg/5 mL, colourless glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 February 2005
Date of latest renewal: 6 March 2015

10. DATE OF REVISION OF THE TEXT

6 July 2024

swissmedic
Text genehmigt
Texte approuvé
Testo approvato
Bern, 29 May 2024
Taking corrections into account

Augmentin

Film-coated tablets

Composition

Active substances

Amoxicillin anhydrous as amoxicillin trihydrate.
Clavulanic acid as potassium clavulanate.

Excipients

Excipients per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Pharmaceutical form	Amoxicillin anhydrous as amoxicillin trihydrate	Clavulanic acid as potassium clavulanate	Ratio of amoxicillin to clavulanic acid
625 mg (500/125) film-coated tablets	500 mg	125 mg	4 : 1
1 g (875/125) film-coated tablets (with decorative groove)	875 mg	125 mg	7 : 1

Indications/Uses

Augmentin should be used in accordance with official local recommendations for antibiotics, taking into account local susceptibility data.
Augmentin is indicated for gram-positive and gram-negative bacterial infections with Augmentin-susceptible pathogens (especially bacteria that are resistant to amoxicillin due to their formation of β-lactamase, see "Properties / Effects").

ENT infections:

Tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.*

Lower respiratory tract infections:

Acute bronchitis with bacterial superinfection and acute exacerbation of chronic bronchitis, bacterial pneumonia, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.*

Urinary tract infections:

Acute and chronic pyelonephritis, cystitis, urethritis, etc. caused by *Escherichia coli*.

Venereal diseases:

Gonorrhoea (specific urethritis).

Skin and soft tissue infections:

Caused mainly by *Staphylococcus aureus* and *Streptococcus pyogenes*.

Gynaecological infections:

Salpingitis, adnexitis, endometritis, bacterial vaginitis.

The susceptibility of pathogens to Augmentin may differ geographically, and can change over time. Local susceptibility data should therefore be taken into consideration and, if necessary, susceptibility tests should be performed.

Dosage/Administration

The dose depends on the age, body weight and kidney function of the patient, as well as on the severity of the infection.

Usual dosage

Adults and children over 40 kg:

For mild, moderate and severe infections, the usual posology is 3 x 625 mg (500/125) daily.

In special cases (acute sinusitis, community-acquired pneumonia, acute exacerbations of chronic bronchitis, pyelonephritis and complicated urinary tract infections), the posology is 2 x 1 g (875/125) or 3 x 625 mg (500/125) daily.

If necessary, these posologies can be doubled (up to a maximum of 3 x 1 g (875/125) daily).

Children and adolescents under 40 kg.

Augmentin film-coated tablets are not suitable for the treatment of infections in children. For the treatment of infections in children, see the Summary of Product Characteristics for Augmentin Duo/Augmentin Trio Forte Suspensions.

Special posology guidelines

Patients with impaired renal function

The excretion of amoxicillin and clavulanic acid is slowed in renal insufficiency. The Augmentin dose should therefore be as follows, depending on the degree of renal insufficiency, expressed as creatinine clearance (CrCl):

Adults and children over 40 kg:

Creatinine clearance	Mild, moderate and severe infections
10-30 ml/min	625 mg every 12 hours
less than 10 ml/min	625 mg every 24 hours

2x 1 g (875/125) should not be administered to patients with creatinine clearance below 30 ml/min.
No dose adjustment is necessary for creatinine clearances above 30 ml/min.

Haemodialysis

One additional normal dose should be given during and at the end of dialysis (as the plasma levels of amoxicillin and clavulanic acid are reduced by haemodialysis).
The 1 g film-coated tablets should only be used in patients with creatinine clearance >30 ml/min.

Elderly patients

No dose adjustment is necessary; the dose should be as in adults. In cases of renal insufficiency, the dose should be adjusted as for adults with renal insufficiency.

Method of administration

Augmentin should be taken at the start of a meal, with at least half a glass of water. This will optimise absorption and gastrointestinal tolerance.
Parenteral therapies may be continued orally.
The fracture score on the 1 g film-coated tablet is only intended to make it easier to take the tablet.
The film-coated tablets are not intended for halving the dosage.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins, or to any of the ingredients of Augmentin, as well as in patients who developed jaundice or hepatic impairment during a previous Augmentin therapy.
Infectious mononucleosis, lymphatic leukaemia: when treated with amoxicillin, patients with these conditions are especially predisposed to skin rashes.

Warnings and precautions

Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can lead to a myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin-clavulanate (see "Adverse reactions").
If an allergic reaction occurs, Augmentin should be discontinued and other appropriate therapies initiated. Preparations should be made for emergency measures in the event of anaphylactic or anaphylactoid reactions. Such reactions call for the immediate injection of adrenaline (caution: cardiac arrhythmias). If necessary, the adrenaline may be repeated. Thereafter, IV glucocorticoids should be given (e.g. 250–1000 mg prednisolone). The glucocorticoid injection can be repeated if necessary. Oxygen, intravenous steroids and mechanical ventilation, with intubation, may also be required. (In children, the posology of the preparations must be adapted to their body weight and age.) Further therapeutic measures such as the intravenous injection of antihistamines and volume expanders should be considered. Careful monitoring of the patient is required as symptoms could reoccur.
Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related exanthema with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Undesirable effects"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Undesirable effects"). DIES is an allergic reaction with the main symptom of persistent vomiting (1–4 hours after taking the drug) without the presence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy, diarrhoea, hypotension or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.
If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
In cases of limited kidney function, the time between administrations should be increased based on the severity of the impairment (see "Special dosage instructions").
Long-term use can lead to the proliferation of non-susceptible bacteria. Such cases must be diagnosed appropriately and suitable treatment must be initiated.
The appearance of diarrhoea during or after treatment with Augmentin, especially when severe, persistent and/or bloody, could be a symptom of an infection with Clostridium difficile. The most severe form of such infections is pseudomembranous colitis. If this complication is suspected, the

Augmentin treatment must be discontinued immediately and the patient must be examined thoroughly in order to initiate specific antibiotic therapy (e.g., metronidazole, vancomycin) as needed. The use of peristalsis inhibitors is contraindicated in these clinical situations.
During long-term therapy, kidney, liver and haematopoietic function should be verified regularly.
There have been rare reports of abnormal prolongation of prothrombin time (increased INR) in patients receiving amoxicillin/clavulanic acid and oral anticoagulants. Therefore, appropriate monitoring should be carried out whenever concomitant anticoagulants are prescribed. In order to maintain the desired level of anticoagulation, the dose of the oral anticoagulants may need to be adjusted.
Augmentin should be used with caution in cases of hepatic impairment.
In severe gastrointestinal disturbances, with vomiting and diarrhoea, adequate absorption of Augmentin is no longer guaranteed. Parenteral use should be considered in such cases.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. A possible consequence of the formation of crystals is acute kidney failure. When high doses of amoxicillin are administered, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate at room temperature in the bladder catheter. Therefore, normal urine flow in the catheter should be monitored regularly.
Because oral antibiotics could reduce the efficacy of oral contraceptives, patients should be advised to take additional contraceptive measures during treatment with Augmentin.

Interactions

Probenecid inhibits renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.
Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives may be reduced or completely eliminated due to impairment of the intestinal flora. The efficacy of contraceptives is reduced as a result.
Because amoxicillin only acts on bacteria during their growth phase, there is an interaction with bacteriostatic antibiotics.
There is a possible interaction with glycosides (e.g. digoxin), as glycoside absorption is increased in certain patients due to damage to the intestinal flora during treatment with antibiotics.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no available data on the combination of Augmentin with allopurinol.
Rare cases of an increased International Normalised Ratio (INR) have been reported in the literature in patients treated with acenocoumarol or warfarin in whom amoxicillin was prescribed. If concomitant administration is necessary, the prothrombin time or International Normalised Ratio should be monitored carefully when amoxicillin is added or discontinued.

In patients receiving mycophenolate mofetil, reduction by approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose levels may not accurately represent changes in overall MPA exposure.
Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy/Lactation

Pregnancy

Reproduction studies in animals (mice and rats, with doses up to 10 times higher than in humans) with Augmentin administered orally and parenterally showed no teratogenic effects.
In a study in women with premature rupture of the foetal membrane, prophylactic treatment with Augmentin was reported to be associated with an elevated risk of necrotising enterocolitis in neonates (1.5% incidence of proven necrotising enterocolitis in neonates with Augmentin treatment versus 0.5% without Augmentin treatment).
During pregnancy, Augmentin should therefore not be used unless clearly necessary.

Breastfeeding

Traces of Augmentin pass into breast milk and therefore hypersensitivity reactions may occur in sensitive neonates. Though impairment of the intestinal flora of infants is theoretically possible, it has not been found at the recommended doses.
Breastfeeding is therefore not recommended during treatment with Augmentin.

Effects on ability to drive and use machines

Certain drug reactions that vary depending on the individual (see "Undesirable effects") may affect the concentration and reaction in the patient to an extent that impairs the ability to drive and use machines.

Undesirable effects

The frequencies from very common to rare undesirable effects come from datasets in major clinical trials. The frequencies of the remaining adverse reactions (i.e. with incidence < 1/10,000) derive mainly from data during use (post-marketing reports) and therefore relate to the reporting frequency and not the actual number of occurrences.
The frequencies of the undesirable effects are classified as follows: Very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

Infections and infestations

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (Quick value) (see "Warnings and precautions" and "Interactions").

Data during use (Post-Marketing Data)

Rare: Thrombocytosis.

Immune system disorders

Very rare: Angioneurotic oedema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see "Skin and subcutaneous tissue disorders"). Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions").

Data from clinical studies

Common: Reversible eosinophilia (hypersensitivity reaction).

Data during use (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, pruritic erythema, angioneurotic oedema, abdominal pain, vomiting among other abdominal symptoms, dyspnoea in bronchospasm or laryngeal oedema, circulatory symptoms such as hypotension and even anaphylactic shock). A Herxheimer reaction may occur during therapy for typhus, syphilis or leptospirosis. The treatment must be immediately discontinued if a hypersensitivity reaction occurs (see "Skin and subcutaneous tissue disorders").

Nervous system disorders

Uncommon: Dizziness, headache.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired kidney function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Data during use (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioural changes, dizziness, dysaesthesia.

Cardiac disorders

Data during use (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Gastrointestinal disorders

Very common: Diarrhoea.

Common: Nausea, vomiting.

Nausea is more commonly observed at higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the start of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see "Warnings and precautions").

There have been reports of superficial tooth discolouration in children, especially following use of the suspension. Good oral hygiene could prevent the occurrence of tooth discolouration, as it can generally be removed by brushing.

Black hairy tongue (only after use of the oral forms).

A cohort study of 576 nine-year-old children showed that the administration of amoxicillin between the ages of 0 and 9 months significantly increases the risk of fluorosis of the definitive maxillary incisors. The fluorosis may present as white streaks, cosmetically disturbing discolouration, dents in the enamel and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions"), drug-induced enterocolitis syndrome *(DIES)* (post-marketing data).

Data from clinical studies

Very common: Loose stools.

Common: Stomach pain.

Liver and bile diseases

Uncommon: A moderate rise in AST and/or ALT levels has been noted in patients receiving Augmentin.

Transient increase of lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic icterus.

The risk appears to be slightly higher with prolonged treatment, age ≥65 years and in men. Reports of such adverse effects are extremely rare in children. The incidence of these adverse effects with Augmentin is approximately 5 times greater than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, and can also be observed up to several weeks after the end of treatment in individual cases. They are usually reversible. Liver disorders can be severe and even fatal in extremely rare situations. However, these cases occurred almost exclusively in patients with a serious underlying disease or using concomitant medicinal products known to have potential adverse effects on the liver.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash (in the form of maculo-papular or morbilliform rashes) and erythema, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug-related exanthema with eosinophilia and systemic symptoms (DRESS) (see "Immune system disorders").
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see also "Warnings and precautions").
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)

Frequency unknown: Linear Ig A disease.

Renal and urinary disorders

Very rare: Interstitial nephritis,
Renal impairment with increased BUN and serum creatinine concentration.

Frequency unknown: Crystalluria (including acute renal damage)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, gastrointestinal symptoms and fluid and electrolyte balance disturbances may occur. These can be treated symptomatically with activated charcoal and hydration.
Augmentin can be removed from the body by haemodialysis.
Large overdoses of amoxicillin, especially when administered parenterally, lead to very high urine levels.
Amoxicillin crystalluria and accompanying acute kidney failure have been observed (see "Warnings and precautions").

Properties/Effects

ATC code

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semisynthetic aminopenicillin in the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative bacteria. The bactericidal effect of amoxicillin relies on the inhibition of bacterial cell wall synthesis by blocking the transpeptidase. Amoxicillin is stable in the presence of acid, but is sensitive to penicillinases.
Clavulanic acid is a β-lactam, which has a mild antibacterial effect against some bacteria strains. The principal action of clavulanic acid is its enzyme-inhibiting activity against many types of β-lactamases. Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases that are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.
This inhibition protects amoxicillin from destruction by β-lactamases, thereby allowing amoxicillin to mediate its full antibiotic effect.
Many bacteria that are resistant to amoxicillin because they produce β-lactamase are susceptible to this combination of amoxicillin and clavulanic acid. This synergistic effect is achieved at clavulanic acid concentrations reached in the body following parenteral or oral administration.

Pharmacodynamics

Scope of action
In vitro susceptibility of pathogens
The following list classifies the bacteria by their *in-vitro* susceptibility to Augmentin.

* Clinical efficacy of Augmentin has been demonstrated in clinical studies.
+ Bacteria that do not produce β-lactamases. If an isolate is susceptible to amoxicillin, it can be considered as susceptible to Augmentin.

Commonly susceptible bacteria:
Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides
- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+

- Streptococcus agalactiae*+
- Streptococcus viridans+
- Streptococcus spp. (other β-haemolytic streptococci)*+
- Staphylococcus aureus (methicillin-susceptible)*
- Staphylococcus saprophyticus (methicillin-susceptible)
- Coagulase-negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp.

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Bacteria for which acquired resistance may be a problem:

Gram-negative aerobes:

- Escherichia coli*
- Klebsiella oxytoca
- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant bacteria:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are readily absorbed in the intestines. Absorption is optimised when taken at the start of a meal. The absorption curves of both components are similar. The maximum serum levels of amoxicillin and clavulanic acid are reached within approximately 1 to 1½ hours following oral intake. After taking one 375 mg tablet (250/125), the serum levels are about 5 mg/l (amoxicillin) and 3 mg/l (clavulanic acid).
The total quantities absorbed are generally 80% for amoxicillin and 70% for clavulanic acid.

Distribution

About 18% of amoxicillin and 25% of clavulanic acid are bound to plasma proteins. The volume of distribution is 22 litres for amoxicillin and 16 litres for clavulanic acid.
Because high serum levels of amoxicillin and clavulanic acid are reached following oral administration of Augmentin, good penetration into bodily fluids can be expected.
Therapeutic concentrations of both active substances have been found in abdominal tissue, the gall bladder, skin, fat and muscle tissues and in the following bodily fluids: synovial, peritoneal and pleural fluids, bile, sputum and pus.
Both active substances cross the placental barrier. Reproduction studies in animals did not find harmful effects. Clinical experience in humans is limited.
Small quantities of amoxicillin are found in breast milk. Only trace quantities of clavulanic acid are detected in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this type of excretion, no adverse effects are known in the infant.

Metabolism

Up to 10-25% of amoxicillin is metabolised into the corresponding inactive form penicilloic acid and excreted via the kidneys. Up to 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are chiefly eliminated via the kidneys. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in active form in the urine within the first 6 h after oral administration.
The elimination half-life of amoxicillin and clavulanic acid is approximately 1–1½ hours in subjects with normal kidney function.

Kinetics in special patient groups

Renal impairment

In renal insufficiency, the renal elimination of both active substances is delayed, and therefore the dose must be adjusted accordingly. The plasma levels of both active substances are greatly reduced by haemodialysis.

Preclinical data

Administration of the combination of amoxicillin and clavulanate (2:1) or of clavulanate alone was not found to have an effect in the F0 generation of rats or mice with regard to mating behaviour, fertility, gestation (including embryonic and foetal development) or birthing. Furthermore, studies have not revealed any adverse effects on embryo-foetal development or negative effects on the viability, growth, development, behaviour or reproductive function of the F1 progeny.
Potassium clavulanate was detected when tested alone and in combination with amoxicillin (1:2 or 1:4) in a wide range of genotoxicity tests under *in-vitro* and *in-vivo* conditions, with very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate poses no genotoxic dangers.

Other information

Incompatibilities

None known.

Influence on diagnostic methods

Possible falsification of results of oestriol tests in pregnant women.
The high concentration of amoxicillin in the urine can affect (false-positive results) glucose tests by chemical methods (Benedict's or Fehling's solution as well as Clinitest). Therefore, glucose tests should be performed by enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).
The direct Coombs test can come back positive, though haemolysis has not occurred.
In the amino acid chromatography of urine, amoxicillin or its degradation products could give ninhydrin-positive spots.
Possible interference with urine and serum total protein tests by a colour reaction (Ehrlich's ninhydrin reaction).
Possible false-positive colour reaction in glycosuria tests.
Falsely elevated serum uric acid levels can occur when the copper-chelating method is used. The Wolfram phosphate and uricase methods for uric acid are not affected by amoxicillin.

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store in a dry place in the original package, at room temperature (15–25 °C). Keep out of the reach of children.

Marketing authorisation number

625 mg film-coated tablets: 45,674 (Swissmedic)
1 g film-coated tablets: 53,692 (Swissmedic)

Packs

Augmentin 625 mg (500/125) film-coated tablets: Pack of 20 film-coated tablets **(A).**
Augmentin 1 g (875/125) film-coated tablets (with decorative groove): Packs of 12 and 20 film-coated tablets **(A).**

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

May 2024

swissmedic
Text genehmigt
Texte approuvé
Testo approvato
Bern, 29 May 2024
Taking corrections into account

Augmentin

Film-coated tablets

Composition

Active substances

Amoxicillin anhydrous as amoxicillin trihydrate.
Clavulanic acid as potassium clavulanate.

Excipients

Excipients per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Pharmaceutical form	Amoxicillin anhydrous as amoxicillin trihydrate	Clavulanic acid as potassium clavulanate	Ratio of amoxicillin to clavulanic acid
625 mg (500/125) film-coated tablets	500 mg	125 mg	4 : 1
1 g (875/125) film-coated tablets (with decorative groove)	875 mg	125 mg	7 : 1

Indications/Uses

Augmentin should be used in accordance with official local recommendations for antibiotics, taking into account local susceptibility data.
Augmentin is indicated for gram-positive and gram-negative bacterial infections with Augmentin-susceptible pathogens (especially bacteria that are resistant to amoxicillin due to their formation of β-lactamase, see "Properties / Effects").

ENT infections:

Tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.*

Lower respiratory tract infections:

Acute bronchitis with bacterial superinfection and acute exacerbation of chronic bronchitis, bacterial pneumonia, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.*

Urinary tract infections:

Acute and chronic pyelonephritis, cystitis, urethritis, etc. caused by *Escherichia coli*.

Venereal diseases:

Gonorrhoea (specific urethritis).

Skin and soft tissue infections:

Caused mainly by *Staphylococcus aureus* and *Streptococcus pyogenes*.

Gynaecological infections:

Salpingitis, adnexitis, endometritis, bacterial vaginitis.

The susceptibility of pathogens to Augmentin may differ geographically, and can change over time. Local susceptibility data should therefore be taken into consideration and, if necessary, susceptibility tests should be performed.

Dosage/Administration

The dose depends on the age, body weight and kidney function of the patient, as well as on the severity of the infection.

Usual dosage

Adults and children over 40 kg:

For mild, moderate and severe infections, the usual posology is 3 x 625 mg (500/125) daily.
In special cases (acute sinusitis, community-acquired pneumonia, acute exacerbations of chronic bronchitis, pyelonephritis and complicated urinary tract infections), the posology is 2 x 1 g (875/125) or 3 x 625 mg (500/125) daily.
If necessary, these posologies can be doubled (up to a maximum of 3 x 1 g (875/125) daily).

Children and adolescents under 40 kg.

Augmentin film-coated tablets are not suitable for the treatment of infections in children. For the treatment of infections in children, see the Summary of Product Characteristics for Augmentin Duo/Augmentin Trio Forte Suspensions.

Special posology guidelines

Patients with impaired renal function

The excretion of amoxicillin and clavulanic acid is slowed in renal insufficiency. The Augmentin dose should therefore be as follows, depending on the degree of renal insufficiency, expressed as creatinine clearance (CrCl):

Adults and children over 40 kg:

Creatinine clearance	Mild, moderate and severe infections
10-30 ml/min	625 mg every 12 hours
less than 10 ml/min	625 mg every 24 hours

2x 1 g (875/125) should not be administered to patients with creatinine clearance below 30 ml/min.
No dose adjustment is necessary for creatinine clearances above 30 ml/min.

Haemodialysis

One additional normal dose should be given during and at the end of dialysis (as the plasma levels of amoxicillin and clavulanic acid are reduced by haemodialysis).
The 1 g film-coated tablets should only be used in patients with creatinine clearance >30 ml/min.

Elderly patients

No dose adjustment is necessary; the dose should be as in adults. In cases of renal insufficiency, the dose should be adjusted as for adults with renal insufficiency.

Method of administration

Augmentin should be taken at the start of a meal, with at least half a glass of water. This will optimise absorption and gastrointestinal tolerance.
Parenteral therapies may be continued orally.
The fracture score on the 1 g film-coated tablet is only intended to make it easier to take the tablet.
The film-coated tablets are not intended for halving the dosage.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins, or to any of the ingredients of Augmentin, as well as in patients who developed jaundice or hepatic impairment during a previous Augmentin therapy.
Infectious mononucleosis, lymphatic leukaemia: when treated with amoxicillin, patients with these conditions are especially predisposed to skin rashes.

Warnings and precautions

Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can lead to a myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin-clavulanate (see "Adverse reactions").
If an allergic reaction occurs, Augmentin should be discontinued and other appropriate therapies initiated. Preparations should be made for emergency measures in the event of anaphylactic or anaphylactoid reactions. Such reactions call for the immediate injection of adrenaline (caution: cardiac arrhythmias). If necessary, the adrenaline may be repeated. Thereafter, IV glucocorticoids should be given (e.g. 250–1000 mg prednisolone). The glucocorticoid injection can be repeated if necessary. Oxygen, intravenous steroids and mechanical ventilation, with intubation, may also be required. (In children, the posology of the preparations must be adapted to their body weight and age.) Further therapeutic measures such as the intravenous injection of antihistamines and volume expanders should be considered. Careful monitoring of the patient is required as symptoms could reoccur.
Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related exanthema with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Undesirable effects"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Undesirable effects"). DIES is an allergic reaction with the main symptom of persistent vomiting (1–4 hours after taking the drug) without the presence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy, diarrhoea, hypotension or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.
If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
In cases of limited kidney function, the time between administrations should be increased based on the severity of the impairment (see "Special dosage instructions").
Long-term use can lead to the proliferation of non-susceptible bacteria. Such cases must be diagnosed appropriately and suitable treatment must be initiated.
The appearance of diarrhoea during or after treatment with Augmentin, especially when severe, persistent and/or bloody, could be a symptom of an infection with Clostridium difficile. The most severe form of such infections is pseudomembranous colitis. If this complication is suspected, the

Augmentin treatment must be discontinued immediately and the patient must be examined thoroughly in order to initiate specific antibiotic therapy (e.g., metronidazole, vancomycin) as needed. The use of peristalsis inhibitors is contraindicated in these clinical situations.
During long-term therapy, kidney, liver and haematopoietic function should be verified regularly.
There have been rare reports of abnormal prolongation of prothrombin time (increased INR) in patients receiving amoxicillin/clavulanic acid and oral anticoagulants. Therefore, appropriate monitoring should be carried out whenever concomitant anticoagulants are prescribed. In order to maintain the desired level of anticoagulation, the dose of the oral anticoagulants may need to be adjusted.
Augmentin should be used with caution in cases of hepatic impairment.
In severe gastrointestinal disturbances, with vomiting and diarrhoea, adequate absorption of Augmentin is no longer guaranteed. Parenteral use should be considered in such cases.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. A possible consequence of the formation of crystals is acute kidney failure. When high doses of amoxicillin are administered, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate at room temperature in the bladder catheter. Therefore, normal urine flow in the catheter should be monitored regularly.
Because oral antibiotics could reduce the efficacy of oral contraceptives, patients should be advised to take additional contraceptive measures during treatment with Augmentin.

Interactions

Probenecid inhibits renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.
Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives may be reduced or completely eliminated due to impairment of the intestinal flora. The efficacy of contraceptives is reduced as a result.
Because amoxicillin only acts on bacteria during their growth phase, there is an interaction with bacteriostatic antibiotics.
There is a possible interaction with glycosides (e.g. digoxin), as glycoside absorption is increased in certain patients due to damage to the intestinal flora during treatment with antibiotics.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no available data on the combination of Augmentin with allopurinol.
Rare cases of an increased International Normalised Ratio (INR) have been reported in the literature in patients treated with acenocoumarol or warfarin in whom amoxicillin was prescribed. If concomitant administration is necessary, the prothrombin time or International Normalised Ratio should be monitored carefully when amoxicillin is added or discontinued.

In patients receiving mycophenolate mofetil, reduction by approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose levels may not accurately represent changes in overall MPA exposure.
Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy/Lactation

Pregnancy

Reproduction studies in animals (mice and rats, with doses up to 10 times higher than in humans) with Augmentin administered orally and parenterally showed no teratogenic effects.
In a study in women with premature rupture of the foetal membrane, prophylactic treatment with Augmentin was reported to be associated with an elevated risk of necrotising enterocolitis in neonates (1.5% incidence of proven necrotising enterocolitis in neonates with Augmentin treatment versus 0.5% without Augmentin treatment).
During pregnancy, Augmentin should therefore not be used unless clearly necessary.

Breastfeeding

Traces of Augmentin pass into breast milk and therefore hypersensitivity reactions may occur in sensitive neonates. Though impairment of the intestinal flora of infants is theoretically possible, it has not been found at the recommended doses.
Breastfeeding is therefore not recommended during treatment with Augmentin.

Effects on ability to drive and use machines

Certain drug reactions that vary depending on the individual (see "Undesirable effects") may affect the concentration and reaction in the patient to an extent that impairs the ability to drive and use machines.

Undesirable effects

The frequencies from very common to rare undesirable effects come from datasets in major clinical trials. The frequencies of the remaining adverse reactions (i.e. with incidence < 1/10,000) derive mainly from data during use (post-marketing reports) and therefore relate to the reporting frequency and not the actual number of occurrences.
The frequencies of the undesirable effects are classified as follows: Very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

Infections and infestations

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (Quick value) (see "Warnings and precautions" and "Interactions").

Data during use (Post-Marketing Data)

Rare: Thrombocytosis.

Immune system disorders

Very rare: Angioneurotic oedema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see "Skin and subcutaneous tissue disorders"). Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions").

Data from clinical studies

Common: Reversible eosinophilia (hypersensitivity reaction).

Data during use (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, pruritic erythema, angioneurotic oedema, abdominal pain, vomiting among other abdominal symptoms, dyspnoea in bronchospasm or laryngeal oedema, circulatory symptoms such as hypotension and even anaphylactic shock). A Herxheimer reaction may occur during therapy for typhus, syphilis or leptospirosis. The treatment must be immediately discontinued if a hypersensitivity reaction occurs (see "Skin and subcutaneous tissue disorders").

Nervous system disorders

Uncommon: Dizziness, headache.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired kidney function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Data during use (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioural changes, dizziness, dysaesthesia.

Cardiac disorders

Data during use (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Gastrointestinal disorders

Very common: Diarrhoea.

Common: Nausea, vomiting.

Nausea is more commonly observed at higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the start of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see "Warnings and precautions").

There have been reports of superficial tooth discolouration in children, especially following use of the suspension. Good oral hygiene could prevent the occurrence of tooth discolouration, as it can generally be removed by brushing.

Black hairy tongue (only after use of the oral forms).

A cohort study of 576 nine-year-old children showed that the administration of amoxicillin between the ages of 0 and 9 months significantly increases the risk of fluorosis of the definitive maxillary incisors. The fluorosis may present as white streaks, cosmetically disturbing discolouration, dents in the enamel and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions"), drug-induced enterocolitis syndrome *(DIES)* (post-marketing data).

Data from clinical studies

Very common: Loose stools.

Common: Stomach pain.

Liver and bile diseases

Uncommon: A moderate rise in AST and/or ALT levels has been noted in patients receiving Augmentin.

Transient increase of lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic icterus.

The risk appears to be slightly higher with prolonged treatment, age ≥65 years and in men. Reports of such adverse effects are extremely rare in children. The incidence of these adverse effects with Augmentin is approximately 5 times greater than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, and can also be observed up to several weeks after the end of treatment in individual cases. They are usually reversible. Liver disorders can be severe and even fatal in extremely rare situations. However, these cases occurred almost exclusively in patients with a serious underlying disease or using concomitant medicinal products known to have potential adverse effects on the liver.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash (in the form of maculo-papular or morbilliform rashes) and erythema, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug-related exanthema with eosinophilia and systemic symptoms (DRESS) (see "Immune system disorders").
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see also "Warnings and precautions").
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)

Frequency unknown: Linear Ig A disease.

Renal and urinary disorders

Very rare: Interstitial nephritis,
Renal impairment with increased BUN and serum creatinine concentration.

Frequency unknown: Crystalluria (including acute renal damage)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, gastrointestinal symptoms and fluid and electrolyte balance disturbances may occur. These can be treated symptomatically with activated charcoal and hydration.
Augmentin can be removed from the body by haemodialysis.
Large overdoses of amoxicillin, especially when administered parenterally, lead to very high urine levels.
Amoxicillin crystalluria and accompanying acute kidney failure have been observed (see "Warnings and precautions").

Properties/Effects

ATC code

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semisynthetic aminopenicillin in the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative bacteria. The bactericidal effect of amoxicillin relies on the inhibition of bacterial cell wall synthesis by blocking the transpeptidase. Amoxicillin is stable in the presence of acid, but is sensitive to penicillinases.
Clavulanic acid is a β-lactam, which has a mild antibacterial effect against some bacteria strains. The principal action of clavulanic acid is its enzyme-inhibiting activity against many types of β-lactamases. Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases that are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.
This inhibition protects amoxicillin from destruction by β-lactamases, thereby allowing amoxicillin to mediate its full antibiotic effect.
Many bacteria that are resistant to amoxicillin because they produce β-lactamase are susceptible to this combination of amoxicillin and clavulanic acid. This synergistic effect is achieved at clavulanic acid concentrations reached in the body following parenteral or oral administration.

Pharmacodynamics

Scope of action
In vitro susceptibility of pathogens
The following list classifies the bacteria by their *in-vitro* susceptibility to Augmentin.

* Clinical efficacy of Augmentin has been demonstrated in clinical studies.
+ Bacteria that do not produce β-lactamases. If an isolate is susceptible to amoxicillin, it can be considered as susceptible to Augmentin.

Commonly susceptible bacteria:
Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides
- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+

- Streptococcus agalactiae*+
- Streptococcus viridans+
- Streptococcus spp. (other β-haemolytic streptococci)*+
- Staphylococcus aureus (methicillin-susceptible)*
- Staphylococcus saprophyticus (methicillin-susceptible)
- Coagulase-negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp.

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Bacteria for which acquired resistance may be a problem:

Gram-negative aerobes:

- Escherichia coli*
- Klebsiella oxytoca
- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant bacteria:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are readily absorbed in the intestines. Absorption is optimised when taken at the start of a meal. The absorption curves of both components are similar. The maximum serum levels of amoxicillin and clavulanic acid are reached within approximately 1 to 1½ hours following oral intake. After taking one 375 mg tablet (250/125), the serum levels are about 5 mg/l (amoxicillin) and 3 mg/l (clavulanic acid).
The total quantities absorbed are generally 80% for amoxicillin and 70% for clavulanic acid.

Distribution

About 18% of amoxicillin and 25% of clavulanic acid are bound to plasma proteins. The volume of distribution is 22 litres for amoxicillin and 16 litres for clavulanic acid.
Because high serum levels of amoxicillin and clavulanic acid are reached following oral administration of Augmentin, good penetration into bodily fluids can be expected.
Therapeutic concentrations of both active substances have been found in abdominal tissue, the gall bladder, skin, fat and muscle tissues and in the following bodily fluids: synovial, peritoneal and pleural fluids, bile, sputum and pus.
Both active substances cross the placental barrier. Reproduction studies in animals did not find harmful effects. Clinical experience in humans is limited.
Small quantities of amoxicillin are found in breast milk. Only trace quantities of clavulanic acid are detected in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this type of excretion, no adverse effects are known in the infant.

Metabolism

Up to 10-25% of amoxicillin is metabolised into the corresponding inactive form penicilloic acid and excreted via the kidneys. Up to 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are chiefly eliminated via the kidneys. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in active form in the urine within the first 6 h after oral administration.
The elimination half-life of amoxicillin and clavulanic acid is approximately 1–1½ hours in subjects with normal kidney function.

Kinetics in special patient groups

Renal impairment

In renal insufficiency, the renal elimination of both active substances is delayed, and therefore the dose must be adjusted accordingly. The plasma levels of both active substances are greatly reduced by haemodialysis.

Preclinical data

Administration of the combination of amoxicillin and clavulanate (2:1) or of clavulanate alone was not found to have an effect in the F0 generation of rats or mice with regard to mating behaviour, fertility, gestation (including embryonic and foetal development) or birthing. Furthermore, studies have not revealed any adverse effects on embryo-foetal development or negative effects on the viability, growth, development, behaviour or reproductive function of the F1 progeny.
Potassium clavulanate was detected when tested alone and in combination with amoxicillin (1:2 or 1:4) in a wide range of genotoxicity tests under *in-vitro* and *in-vivo* conditions, with very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate poses no genotoxic dangers.

Other information

Incompatibilities

None known.

Influence on diagnostic methods

Possible falsification of results of oestriol tests in pregnant women.
The high concentration of amoxicillin in the urine can affect (false-positive results) glucose tests by chemical methods (Benedict's or Fehling's solution as well as Clinitest). Therefore, glucose tests should be performed by enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).
The direct Coombs test can come back positive, though haemolysis has not occurred.
In the amino acid chromatography of urine, amoxicillin or its degradation products could give ninhydrin-positive spots.
Possible interference with urine and serum total protein tests by a colour reaction (Ehrlich's ninhydrin reaction).
Possible false-positive colour reaction in glycosuria tests.
Falsely elevated serum uric acid levels can occur when the copper-chelating method is used. The Wolfram phosphate and uricase methods for uric acid are not affected by amoxicillin.

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store in a dry place in the original package, at room temperature (15–25 °C). Keep out of the reach of children.

Marketing authorisation number

625 mg film-coated tablets: 45,674 (Swissmedic)
1 g film-coated tablets: 53,692 (Swissmedic)

Packs

Augmentin 625 mg (500/125) film-coated tablets: Pack of 20 film-coated tablets **(A).**
Augmentin 1 g (875/125) film-coated tablets (with decorative groove): Packs of 12 and 20 film-coated tablets **(A).**

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

May 2024

swissmedic
Text genehmigt
Texte approuvé
Testo approvato
Bern, 29 May 2024
Taking corrections into account

Augmentin

Film-coated tablets

Composition

Active substances

Amoxicillin anhydrous as amoxicillin trihydrate.
Clavulanic acid as potassium clavulanate.

Excipients

Excipients per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Pharmaceutical form	Amoxicillin anhydrous as amoxicillin trihydrate	Clavulanic acid as potassium clavulanate	Ratio of amoxicillin to clavulanic acid
625 mg (500/125) film-coated tablets	500 mg	125 mg	4 : 1
1 g (875/125) film-coated tablets (with decorative groove)	875 mg	125 mg	7 : 1

Indications/Uses

Augmentin should be used in accordance with official local recommendations for antibiotics, taking into account local susceptibility data.
Augmentin is indicated for gram-positive and gram-negative bacterial infections with Augmentin-susceptible pathogens (especially bacteria that are resistant to amoxicillin due to their formation of β-lactamase, see "Properties / Effects").

ENT infections:

Tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.*

Lower respiratory tract infections:

Acute bronchitis with bacterial superinfection and acute exacerbation of chronic bronchitis, bacterial pneumonia, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.*

Urinary tract infections:

Acute and chronic pyelonephritis, cystitis, urethritis, etc. caused by *Escherichia coli*.

Venereal diseases:

Gonorrhoea (specific urethritis).

Skin and soft tissue infections:

Caused mainly by *Staphylococcus aureus* and *Streptococcus pyogenes*.

Gynaecological infections:

Salpingitis, adnexitis, endometritis, bacterial vaginitis.

The susceptibility of pathogens to Augmentin may differ geographically, and can change over time. Local susceptibility data should therefore be taken into consideration and, if necessary, susceptibility tests should be performed.

Dosage/Administration

The dose depends on the age, body weight and kidney function of the patient, as well as on the severity of the infection.

Usual dosage

Adults and children over 40 kg:

For mild, moderate and severe infections, the usual posology is 3 x 625 mg (500/125) daily.
In special cases (acute sinusitis, community-acquired pneumonia, acute exacerbations of chronic bronchitis, pyelonephritis and complicated urinary tract infections), the posology is 2 x 1 g (875/125) or 3 x 625 mg (500/125) daily.
If necessary, these posologies can be doubled (up to a maximum of 3 x 1 g (875/125) daily).

Children and adolescents under 40 kg.

Augmentin film-coated tablets are not suitable for the treatment of infections in children. For the treatment of infections in children, see the Summary of Product Characteristics for Augmentin Duo/Augmentin Trio Forte Suspensions.

Special posology guidelines

Patients with impaired renal function

The excretion of amoxicillin and clavulanic acid is slowed in renal insufficiency. The Augmentin dose should therefore be as follows, depending on the degree of renal insufficiency, expressed as creatinine clearance (CrCl):

Adults and children over 40 kg:

Creatinine clearance	Mild, moderate and severe infections
10-30 ml/min	625 mg every 12 hours
less than 10 ml/min	625 mg every 24 hours

2x 1 g (875/125) should not be administered to patients with creatinine clearance below 30 ml/min.
No dose adjustment is necessary for creatinine clearances above 30 ml/min.

Haemodialysis

One additional normal dose should be given during and at the end of dialysis (as the plasma levels of amoxicillin and clavulanic acid are reduced by haemodialysis).
The 1 g film-coated tablets should only be used in patients with creatinine clearance >30 ml/min.

Elderly patients

No dose adjustment is necessary; the dose should be as in adults. In cases of renal insufficiency, the dose should be adjusted as for adults with renal insufficiency.

Method of administration

Augmentin should be taken at the start of a meal, with at least half a glass of water. This will optimise absorption and gastrointestinal tolerance.
Parenteral therapies may be continued orally.
The fracture score on the 1 g film-coated tablet is only intended to make it easier to take the tablet.
The film-coated tablets are not intended for halving the dosage.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins, or to any of the ingredients of Augmentin, as well as in patients who developed jaundice or hepatic impairment during a previous Augmentin therapy.
Infectious mononucleosis, lymphatic leukaemia: when treated with amoxicillin, patients with these conditions are especially predisposed to skin rashes.

Warnings and precautions

Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can lead to a myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin-clavulanate (see "Adverse reactions").
If an allergic reaction occurs, Augmentin should be discontinued and other appropriate therapies initiated. Preparations should be made for emergency measures in the event of anaphylactic or anaphylactoid reactions. Such reactions call for the immediate injection of adrenaline (caution: cardiac arrhythmias). If necessary, the adrenaline may be repeated. Thereafter, IV glucocorticoids should be given (e.g. 250–1000 mg prednisolone). The glucocorticoid injection can be repeated if necessary. Oxygen, intravenous steroids and mechanical ventilation, with intubation, may also be required. (In children, the posology of the preparations must be adapted to their body weight and age.) Further therapeutic measures such as the intravenous injection of antihistamines and volume expanders should be considered. Careful monitoring of the patient is required as symptoms could reoccur.
Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related exanthema with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Undesirable effects"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Undesirable effects"). DIES is an allergic reaction with the main symptom of persistent vomiting (1–4 hours after taking the drug) without the presence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy, diarrhoea, hypotension or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.
If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
In cases of limited kidney function, the time between administrations should be increased based on the severity of the impairment (see "Special dosage instructions").
Long-term use can lead to the proliferation of non-susceptible bacteria. Such cases must be diagnosed appropriately and suitable treatment must be initiated.
The appearance of diarrhoea during or after treatment with Augmentin, especially when severe, persistent and/or bloody, could be a symptom of an infection with Clostridium difficile. The most severe form of such infections is pseudomembranous colitis. If this complication is suspected, the

Augmentin treatment must be discontinued immediately and the patient must be examined thoroughly in order to initiate specific antibiotic therapy (e.g., metronidazole, vancomycin) as needed. The use of peristalsis inhibitors is contraindicated in these clinical situations.
During long-term therapy, kidney, liver and haematopoietic function should be verified regularly.
There have been rare reports of abnormal prolongation of prothrombin time (increased INR) in patients receiving amoxicillin/clavulanic acid and oral anticoagulants. Therefore, appropriate monitoring should be carried out whenever concomitant anticoagulants are prescribed. In order to maintain the desired level of anticoagulation, the dose of the oral anticoagulants may need to be adjusted.
Augmentin should be used with caution in cases of hepatic impairment.
In severe gastrointestinal disturbances, with vomiting and diarrhoea, adequate absorption of Augmentin is no longer guaranteed. Parenteral use should be considered in such cases.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. A possible consequence of the formation of crystals is acute kidney failure. When high doses of amoxicillin are administered, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate at room temperature in the bladder catheter. Therefore, normal urine flow in the catheter should be monitored regularly.
Because oral antibiotics could reduce the efficacy of oral contraceptives, patients should be advised to take additional contraceptive measures during treatment with Augmentin.

Interactions

Probenecid inhibits renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.
Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives may be reduced or completely eliminated due to impairment of the intestinal flora. The efficacy of contraceptives is reduced as a result.
Because amoxicillin only acts on bacteria during their growth phase, there is an interaction with bacteriostatic antibiotics.
There is a possible interaction with glycosides (e.g. digoxin), as glycoside absorption is increased in certain patients due to damage to the intestinal flora during treatment with antibiotics.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no available data on the combination of Augmentin with allopurinol.
Rare cases of an increased International Normalised Ratio (INR) have been reported in the literature in patients treated with acenocoumarol or warfarin in whom amoxicillin was prescribed. If concomitant administration is necessary, the prothrombin time or International Normalised Ratio should be monitored carefully when amoxicillin is added or discontinued.

In patients receiving mycophenolate mofetil, reduction by approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose levels may not accurately represent changes in overall MPA exposure.
Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy/Lactation

Pregnancy

Reproduction studies in animals (mice and rats, with doses up to 10 times higher than in humans) with Augmentin administered orally and parenterally showed no teratogenic effects.
In a study in women with premature rupture of the foetal membrane, prophylactic treatment with Augmentin was reported to be associated with an elevated risk of necrotising enterocolitis in neonates (1.5% incidence of proven necrotising enterocolitis in neonates with Augmentin treatment versus 0.5% without Augmentin treatment).
During pregnancy, Augmentin should therefore not be used unless clearly necessary.

Breastfeeding

Traces of Augmentin pass into breast milk and therefore hypersensitivity reactions may occur in sensitive neonates. Though impairment of the intestinal flora of infants is theoretically possible, it has not been found at the recommended doses.
Breastfeeding is therefore not recommended during treatment with Augmentin.

Effects on ability to drive and use machines

Certain drug reactions that vary depending on the individual (see "Undesirable effects") may affect the concentration and reaction in the patient to an extent that impairs the ability to drive and use machines.

Undesirable effects

The frequencies from very common to rare undesirable effects come from datasets in major clinical trials. The frequencies of the remaining adverse reactions (i.e. with incidence < 1/10,000) derive mainly from data during use (post-marketing reports) and therefore relate to the reporting frequency and not the actual number of occurrences.
The frequencies of the undesirable effects are classified as follows: Very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

Infections and infestations

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (Quick value) (see "Warnings and precautions" and "Interactions").

Data during use (Post-Marketing Data)

Rare: Thrombocytosis.

Immune system disorders

Very rare: Angioneurotic oedema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see "Skin and subcutaneous tissue disorders"). Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions").

Data from clinical studies

Common: Reversible eosinophilia (hypersensitivity reaction).

Data during use (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, pruritic erythema, angioneurotic oedema, abdominal pain, vomiting among other abdominal symptoms, dyspnoea in bronchospasm or laryngeal oedema, circulatory symptoms such as hypotension and even anaphylactic shock). A Herxheimer reaction may occur during therapy for typhus, syphilis or leptospirosis. The treatment must be immediately discontinued if a hypersensitivity reaction occurs (see "Skin and subcutaneous tissue disorders").

Nervous system disorders

Uncommon: Dizziness, headache.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired kidney function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Data during use (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioural changes, dizziness, dysaesthesia.

Cardiac disorders

Data during use (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Gastrointestinal disorders

Very common: Diarrhoea.

Common: Nausea, vomiting.

Nausea is more commonly observed at higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the start of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see "Warnings and precautions").

There have been reports of superficial tooth discolouration in children, especially following use of the suspension. Good oral hygiene could prevent the occurrence of tooth discolouration, as it can generally be removed by brushing.

Black hairy tongue (only after use of the oral forms).

A cohort study of 576 nine-year-old children showed that the administration of amoxicillin between the ages of 0 and 9 months significantly increases the risk of fluorosis of the definitive maxillary incisors. The fluorosis may present as white streaks, cosmetically disturbing discolouration, dents in the enamel and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions"), drug-induced enterocolitis syndrome *(DIES)* (post-marketing data).

Data from clinical studies

Very common: Loose stools.

Common: Stomach pain.

Liver and bile diseases

Uncommon: A moderate rise in AST and/or ALT levels has been noted in patients receiving Augmentin.

Transient increase of lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic icterus.

The risk appears to be slightly higher with prolonged treatment, age ≥65 years and in men. Reports of such adverse effects are extremely rare in children. The incidence of these adverse effects with Augmentin is approximately 5 times greater than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, and can also be observed up to several weeks after the end of treatment in individual cases. They are usually reversible. Liver disorders can be severe and even fatal in extremely rare situations. However, these cases occurred almost exclusively in patients with a serious underlying disease or using concomitant medicinal products known to have potential adverse effects on the liver.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash (in the form of maculo-papular or morbilliform rashes) and erythema, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug-related exanthema with eosinophilia and systemic symptoms (DRESS) (see "Immune system disorders").
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see also "Warnings and precautions").
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)

Frequency unknown: Linear Ig A disease.

Renal and urinary disorders

Very rare: Interstitial nephritis,
Renal impairment with increased BUN and serum creatinine concentration.

Frequency unknown: Crystalluria (including acute renal damage)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, gastrointestinal symptoms and fluid and electrolyte balance disturbances may occur. These can be treated symptomatically with activated charcoal and hydration.
Augmentin can be removed from the body by haemodialysis.
Large overdoses of amoxicillin, especially when administered parenterally, lead to very high urine levels.
Amoxicillin crystalluria and accompanying acute kidney failure have been observed (see "Warnings and precautions").

Properties/Effects

ATC code

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semisynthetic aminopenicillin in the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative bacteria. The bactericidal effect of amoxicillin relies on the inhibition of bacterial cell wall synthesis by blocking the transpeptidase. Amoxicillin is stable in the presence of acid, but is sensitive to penicillinases.
Clavulanic acid is a β-lactam, which has a mild antibacterial effect against some bacteria strains. The principal action of clavulanic acid is its enzyme-inhibiting activity against many types of β-lactamases. Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases that are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.
This inhibition protects amoxicillin from destruction by β-lactamases, thereby allowing amoxicillin to mediate its full antibiotic effect.
Many bacteria that are resistant to amoxicillin because they produce β-lactamase are susceptible to this combination of amoxicillin and clavulanic acid. This synergistic effect is achieved at clavulanic acid concentrations reached in the body following parenteral or oral administration.

Pharmacodynamics

Scope of action
In vitro susceptibility of pathogens
The following list classifies the bacteria by their *in-vitro* susceptibility to Augmentin.

* Clinical efficacy of Augmentin has been demonstrated in clinical studies.
+ Bacteria that do not produce β-lactamases. If an isolate is susceptible to amoxicillin, it can be considered as susceptible to Augmentin.

Commonly susceptible bacteria:
Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides
- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+

- Streptococcus agalactiae*+
- Streptococcus viridans+
- Streptococcus spp. (other β-haemolytic streptococci)*+
- Staphylococcus aureus (methicillin-susceptible)*
- Staphylococcus saprophyticus (methicillin-susceptible)
- Coagulase-negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp.

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Bacteria for which acquired resistance may be a problem:

Gram-negative aerobes:

- Escherichia coli*
- Klebsiella oxytoca
- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant bacteria:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are readily absorbed in the intestines. Absorption is optimised when taken at the start of a meal. The absorption curves of both components are similar. The maximum serum levels of amoxicillin and clavulanic acid are reached within approximately 1 to 1½ hours following oral intake. After taking one 375 mg tablet (250/125), the serum levels are about 5 mg/l (amoxicillin) and 3 mg/l (clavulanic acid).
The total quantities absorbed are generally 80% for amoxicillin and 70% for clavulanic acid.

Distribution

About 18% of amoxicillin and 25% of clavulanic acid are bound to plasma proteins. The volume of distribution is 22 litres for amoxicillin and 16 litres for clavulanic acid.
Because high serum levels of amoxicillin and clavulanic acid are reached following oral administration of Augmentin, good penetration into bodily fluids can be expected.
Therapeutic concentrations of both active substances have been found in abdominal tissue, the gall bladder, skin, fat and muscle tissues and in the following bodily fluids: synovial, peritoneal and pleural fluids, bile, sputum and pus.
Both active substances cross the placental barrier. Reproduction studies in animals did not find harmful effects. Clinical experience in humans is limited.
Small quantities of amoxicillin are found in breast milk. Only trace quantities of clavulanic acid are detected in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this type of excretion, no adverse effects are known in the infant.

Metabolism

Up to 10-25% of amoxicillin is metabolised into the corresponding inactive form penicilloic acid and excreted via the kidneys. Up to 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are chiefly eliminated via the kidneys. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in active form in the urine within the first 6 h after oral administration.
The elimination half-life of amoxicillin and clavulanic acid is approximately 1–1½ hours in subjects with normal kidney function.

Kinetics in special patient groups

Renal impairment

In renal insufficiency, the renal elimination of both active substances is delayed, and therefore the dose must be adjusted accordingly. The plasma levels of both active substances are greatly reduced by haemodialysis.

Preclinical data

Administration of the combination of amoxicillin and clavulanate (2:1) or of clavulanate alone was not found to have an effect in the F0 generation of rats or mice with regard to mating behaviour, fertility, gestation (including embryonic and foetal development) or birthing. Furthermore, studies have not revealed any adverse effects on embryo-foetal development or negative effects on the viability, growth, development, behaviour or reproductive function of the F1 progeny.
Potassium clavulanate was detected when tested alone and in combination with amoxicillin (1:2 or 1:4) in a wide range of genotoxicity tests under *in-vitro* and *in-vivo* conditions, with very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate poses no genotoxic dangers.

Other information

Incompatibilities

None known.

Influence on diagnostic methods

Possible falsification of results of oestriol tests in pregnant women.
The high concentration of amoxicillin in the urine can affect (false-positive results) glucose tests by chemical methods (Benedict's or Fehling's solution as well as Clinitest). Therefore, glucose tests should be performed by enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).
The direct Coombs test can come back positive, though haemolysis has not occurred.
In the amino acid chromatography of urine, amoxicillin or its degradation products could give ninhydrin-positive spots.
Possible interference with urine and serum total protein tests by a colour reaction (Ehrlich's ninhydrin reaction).
Possible false-positive colour reaction in glycosuria tests.
Falsely elevated serum uric acid levels can occur when the copper-chelating method is used. The Wolfram phosphate and uricase methods for uric acid are not affected by amoxicillin.

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store in a dry place in the original package, at room temperature (15–25 °C). Keep out of the reach of children.

Marketing authorisation number

625 mg film-coated tablets: 45,674 (Swissmedic)
1 g film-coated tablets: 53,692 (Swissmedic)

Packs

Augmentin 625 mg (500/125) film-coated tablets: Pack of 20 film-coated tablets **(A).**
Augmentin 1 g (875/125) film-coated tablets (with decorative groove): Packs of 12 and 20 film-coated tablets **(A).**

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

May 2024

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Text genehmigt
Texte approuvé
Testo approvato
Bern, 29 May 2024
Taking corrections into account

Augmentin

Film-coated tablets

Composition

Active substances

Amoxicillin anhydrous as amoxicillin trihydrate.
Clavulanic acid as potassium clavulanate.

Excipients

Excipients per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Pharmaceutical form	Amoxicillin anhydrous as amoxicillin trihydrate	Clavulanic acid as potassium clavulanate	Ratio of amoxicillin to clavulanic acid
625 mg (500/125) film-coated tablets	500 mg	125 mg	4 : 1
1 g (875/125) film-coated tablets (with decorative groove)	875 mg	125 mg	7 : 1

Indications/Uses

Augmentin should be used in accordance with official local recommendations for antibiotics, taking into account local susceptibility data.
Augmentin is indicated for gram-positive and gram-negative bacterial infections with Augmentin-susceptible pathogens (especially bacteria that are resistant to amoxicillin due to their formation of β-lactamase, see "Properties / Effects").

ENT infections:

Tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.*

Lower respiratory tract infections:

Acute bronchitis with bacterial superinfection and acute exacerbation of chronic bronchitis, bacterial pneumonia, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.*

Urinary tract infections:

Acute and chronic pyelonephritis, cystitis, urethritis, etc. caused by *Escherichia coli*.

Venereal diseases:

Gonorrhoea (specific urethritis).

Skin and soft tissue infections:

Caused mainly by *Staphylococcus aureus* and *Streptococcus pyogenes*.

Gynaecological infections:

Salpingitis, adnexitis, endometritis, bacterial vaginitis.

The susceptibility of pathogens to Augmentin may differ geographically, and can change over time. Local susceptibility data should therefore be taken into consideration and, if necessary, susceptibility tests should be performed.

Dosage/Administration

The dose depends on the age, body weight and kidney function of the patient, as well as on the severity of the infection.

Usual dosage

Adults and children over 40 kg:

For mild, moderate and severe infections, the usual posology is 3 x 625 mg (500/125) daily.
In special cases (acute sinusitis, community-acquired pneumonia, acute exacerbations of chronic bronchitis, pyelonephritis and complicated urinary tract infections), the posology is 2 x 1 g (875/125) or 3 x 625 mg (500/125) daily.
If necessary, these posologies can be doubled (up to a maximum of 3 x 1 g (875/125) daily).

Children and adolescents under 40 kg.

Augmentin film-coated tablets are not suitable for the treatment of infections in children. For the treatment of infections in children, see the Summary of Product Characteristics for Augmentin Duo/Augmentin Trio Forte Suspensions.

Special posology guidelines

Patients with impaired renal function

The excretion of amoxicillin and clavulanic acid is slowed in renal insufficiency. The Augmentin dose should therefore be as follows, depending on the degree of renal insufficiency, expressed as creatinine clearance (CrCl):

Adults and children over 40 kg:

Creatinine clearance	Mild, moderate and severe infections
10-30 ml/min	625 mg every 12 hours
less than 10 ml/min	625 mg every 24 hours

2x 1 g (875/125) should not be administered to patients with creatinine clearance below 30 ml/min.
No dose adjustment is necessary for creatinine clearances above 30 ml/min.

Haemodialysis
One additional normal dose should be given during and at the end of dialysis (as the plasma levels of amoxicillin and clavulanic acid are reduced by haemodialysis).
The 1 g film-coated tablets should only be used in patients with creatinine clearance >30 ml/min.

Elderly patients

No dose adjustment is necessary; the dose should be as in adults. In cases of renal insufficiency, the dose should be adjusted as for adults with renal insufficiency.

Method of administration

Augmentin should be taken at the start of a meal, with at least half a glass of water. This will optimise absorption and gastrointestinal tolerance.
Parenteral therapies may be continued orally.
The fracture score on the 1 g film-coated tablet is only intended to make it easier to take the tablet.
The film-coated tablets are not intended for halving the dosage.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins, or to any of the ingredients of Augmentin, as well as in patients who developed jaundice or hepatic impairment during a previous Augmentin therapy.
Infectious mononucleosis, lymphatic leukaemia: when treated with amoxicillin, patients with these conditions are especially predisposed to skin rashes.

Warnings and precautions

Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can lead to a myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin-clavulanate (see "Adverse reactions").
If an allergic reaction occurs, Augmentin should be discontinued and other appropriate therapies initiated. Preparations should be made for emergency measures in the event of anaphylactic or anaphylactoid reactions. Such reactions call for the immediate injection of adrenaline (caution: cardiac arrhythmias). If necessary, the adrenaline may be repeated. Thereafter, IV glucocorticoids should be given (e.g. 250–1000 mg prednisolone). The glucocorticoid injection can be repeated if necessary. Oxygen, intravenous steroids and mechanical ventilation, with intubation, may also be required. (In children, the posology of the preparations must be adapted to their body weight and age.) Further therapeutic measures such as the intravenous injection of antihistamines and volume expanders should be considered. Careful monitoring of the patient is required as symptoms could reoccur.
Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related exanthema with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Undesirable effects"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Undesirable effects"). DIES is an allergic reaction with the main symptom of persistent vomiting (1–4 hours after taking the drug) without the presence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy, diarrhoea, hypotension or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.
If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
In cases of limited kidney function, the time between administrations should be increased based on the severity of the impairment (see "Special dosage instructions").
Long-term use can lead to the proliferation of non-susceptible bacteria. Such cases must be diagnosed appropriately and suitable treatment must be initiated.
The appearance of diarrhoea during or after treatment with Augmentin, especially when severe, persistent and/or bloody, could be a symptom of an infection with Clostridium difficile. The most severe form of such infections is pseudomembranous colitis. If this complication is suspected, the

Augmentin treatment must be discontinued immediately and the patient must be examined thoroughly in order to initiate specific antibiotic therapy (e.g., metronidazole, vancomycin) as needed. The use of peristalsis inhibitors is contraindicated in these clinical situations.
During long-term therapy, kidney, liver and haematopoietic function should be verified regularly.
There have been rare reports of abnormal prolongation of prothrombin time (increased INR) in patients receiving amoxicillin/clavulanic acid and oral anticoagulants. Therefore, appropriate monitoring should be carried out whenever concomitant anticoagulants are prescribed. In order to maintain the desired level of anticoagulation, the dose of the oral anticoagulants may need to be adjusted.
Augmentin should be used with caution in cases of hepatic impairment.
In severe gastrointestinal disturbances, with vomiting and diarrhoea, adequate absorption of Augmentin is no longer guaranteed. Parenteral use should be considered in such cases.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. A possible consequence of the formation of crystals is acute kidney failure. When high doses of amoxicillin are administered, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate at room temperature in the bladder catheter. Therefore, normal urine flow in the catheter should be monitored regularly.
Because oral antibiotics could reduce the efficacy of oral contraceptives, patients should be advised to take additional contraceptive measures during treatment with Augmentin.

Interactions

Probenecid inhibits renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.
Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives may be reduced or completely eliminated due to impairment of the intestinal flora. The efficacy of contraceptives is reduced as a result.
Because amoxicillin only acts on bacteria during their growth phase, there is an interaction with bacteriostatic antibiotics.
There is a possible interaction with glycosides (e.g. digoxin), as glycoside absorption is increased in certain patients due to damage to the intestinal flora during treatment with antibiotics.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no available data on the combination of Augmentin with allopurinol.
Rare cases of an increased International Normalised Ratio (INR) have been reported in the literature in patients treated with acenocoumarol or warfarin in whom amoxicillin was prescribed. If concomitant administration is necessary, the prothrombin time or International Normalised Ratio should be monitored carefully when amoxicillin is added or discontinued.

In patients receiving mycophenolate mofetil, reduction by approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose levels may not accurately represent changes in overall MPA exposure.
Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy/Lactation

Pregnancy

Reproduction studies in animals (mice and rats, with doses up to 10 times higher than in humans) with Augmentin administered orally and parenterally showed no teratogenic effects.
In a study in women with premature rupture of the foetal membrane, prophylactic treatment with Augmentin was reported to be associated with an elevated risk of necrotising enterocolitis in neonates (1.5% incidence of proven necrotising enterocolitis in neonates with Augmentin treatment versus 0.5% without Augmentin treatment).
During pregnancy, Augmentin should therefore not be used unless clearly necessary.

Breastfeeding

Traces of Augmentin pass into breast milk and therefore hypersensitivity reactions may occur in sensitive neonates. Though impairment of the intestinal flora of infants is theoretically possible, it has not been found at the recommended doses.
Breastfeeding is therefore not recommended during treatment with Augmentin.

Effects on ability to drive and use machines

Certain drug reactions that vary depending on the individual (see "Undesirable effects") may affect the concentration and reaction in the patient to an extent that impairs the ability to drive and use machines.

Undesirable effects

The frequencies from very common to rare undesirable effects come from datasets in major clinical trials. The frequencies of the remaining adverse reactions (i.e. with incidence < 1/10,000) derive mainly from data during use (post-marketing reports) and therefore relate to the reporting frequency and not the actual number of occurrences.
The frequencies of the undesirable effects are classified as follows: Very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

Infections and infestations

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (Quick value) (see "Warnings and precautions" and "Interactions").

Data during use (Post-Marketing Data)

Rare: Thrombocytosis.

Immune system disorders

Very rare: Angioneurotic oedema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see "Skin and subcutaneous tissue disorders"). Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions").

Data from clinical studies

Common: Reversible eosinophilia (hypersensitivity reaction).

Data during use (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, pruritic erythema, angioneurotic oedema, abdominal pain, vomiting among other abdominal symptoms, dyspnoea in bronchospasm or laryngeal oedema, circulatory symptoms such as hypotension and even anaphylactic shock). A Herxheimer reaction may occur during therapy for typhus, syphilis or leptospirosis. The treatment must be immediately discontinued if a hypersensitivity reaction occurs (see "Skin and subcutaneous tissue disorders").

Nervous system disorders

Uncommon: Dizziness, headache.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired kidney function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Data during use (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioural changes, dizziness, dysaesthesia.

Cardiac disorders

Data during use (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Gastrointestinal disorders

Very common: Diarrhoea.

Common: Nausea, vomiting.

Nausea is more commonly observed at higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the start of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see "Warnings and precautions").

There have been reports of superficial tooth discolouration in children, especially following use of the suspension. Good oral hygiene could prevent the occurrence of tooth discolouration, as it can generally be removed by brushing.

Black hairy tongue (only after use of the oral forms).

A cohort study of 576 nine-year-old children showed that the administration of amoxicillin between the ages of 0 and 9 months significantly increases the risk of fluorosis of the definitive maxillary incisors. The fluorosis may present as white streaks, cosmetically disturbing discolouration, dents in the enamel and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions"), drug-induced enterocolitis syndrome *(DIES)* (post-marketing data).

Data from clinical studies

Very common: Loose stools.

Common: Stomach pain.

Liver and bile diseases

Uncommon: A moderate rise in AST and/or ALT levels has been noted in patients receiving Augmentin.

Transient increase of lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic icterus.

The risk appears to be slightly higher with prolonged treatment, age ≥65 years and in men. Reports of such adverse effects are extremely rare in children. The incidence of these adverse effects with Augmentin is approximately 5 times greater than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, and can also be observed up to several weeks after the end of treatment in individual cases. They are usually reversible. Liver disorders can be severe and even fatal in extremely rare situations. However, these cases occurred almost exclusively in patients with a serious underlying disease or using concomitant medicinal products known to have potential adverse effects on the liver.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash (in the form of maculo-papular or morbilliform rashes) and erythema, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug-related exanthema with eosinophilia and systemic symptoms (DRESS) (see "Immune system disorders").
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see also "Warnings and precautions").
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)

Frequency unknown: Linear Ig A disease.

Renal and urinary disorders

Very rare: Interstitial nephritis,
Renal impairment with increased BUN and serum creatinine concentration.

Frequency unknown: Crystalluria (including acute renal damage)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, gastrointestinal symptoms and fluid and electrolyte balance disturbances may occur. These can be treated symptomatically with activated charcoal and hydration.
Augmentin can be removed from the body by haemodialysis.
Large overdoses of amoxicillin, especially when administered parenterally, lead to very high urine levels.
Amoxicillin crystalluria and accompanying acute kidney failure have been observed (see "Warnings and precautions").

Properties/Effects

ATC code

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semisynthetic aminopenicillin in the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative bacteria. The bactericidal effect of amoxicillin relies on the inhibition of bacterial cell wall synthesis by blocking the transpeptidase. Amoxicillin is stable in the presence of acid, but is sensitive to penicillinases.
Clavulanic acid is a β-lactam, which has a mild antibacterial effect against some bacteria strains. The principal action of clavulanic acid is its enzyme-inhibiting activity against many types of β-lactamases. Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases that are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.
This inhibition protects amoxicillin from destruction by β-lactamases, thereby allowing amoxicillin to mediate its full antibiotic effect.
Many bacteria that are resistant to amoxicillin because they produce β-lactamase are susceptible to this combination of amoxicillin and clavulanic acid. This synergistic effect is achieved at clavulanic acid concentrations reached in the body following parenteral or oral administration.

Pharmacodynamics

Scope of action
In vitro susceptibility of pathogens
The following list classifies the bacteria by their *in-vitro* susceptibility to Augmentin.

* Clinical efficacy of Augmentin has been demonstrated in clinical studies.
+ Bacteria that do not produce β-lactamases. If an isolate is susceptible to amoxicillin, it can be considered as susceptible to Augmentin.

Commonly susceptible bacteria:
Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides
- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+

- Streptococcus agalactiae*+
- Streptococcus viridans+
- Streptococcus spp. (other β-haemolytic streptococci)*+
- Staphylococcus aureus (methicillin-susceptible)*
- Staphylococcus saprophyticus (methicillin-susceptible)
- Coagulase-negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp.

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Bacteria for which acquired resistance may be a problem:

Gram-negative aerobes:

- Escherichia coli*
- Klebsiella oxytoca
- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant bacteria:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are readily absorbed in the intestines. Absorption is optimised when taken at the start of a meal. The absorption curves of both components are similar. The maximum serum levels of amoxicillin and clavulanic acid are reached within approximately 1 to 1½ hours following oral intake. After taking one 375 mg tablet (250/125), the serum levels are about 5 mg/l (amoxicillin) and 3 mg/l (clavulanic acid).
The total quantities absorbed are generally 80% for amoxicillin and 70% for clavulanic acid.

Distribution

About 18% of amoxicillin and 25% of clavulanic acid are bound to plasma proteins. The volume of distribution is 22 litres for amoxicillin and 16 litres for clavulanic acid.
Because high serum levels of amoxicillin and clavulanic acid are reached following oral administration of Augmentin, good penetration into bodily fluids can be expected.
Therapeutic concentrations of both active substances have been found in abdominal tissue, the gall bladder, skin, fat and muscle tissues and in the following bodily fluids: synovial, peritoneal and pleural fluids, bile, sputum and pus.
Both active substances cross the placental barrier. Reproduction studies in animals did not find harmful effects. Clinical experience in humans is limited.
Small quantities of amoxicillin are found in breast milk. Only trace quantities of clavulanic acid are detected in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this type of excretion, no adverse effects are known in the infant.

Metabolism

Up to 10-25% of amoxicillin is metabolised into the corresponding inactive form penicilloic acid and excreted via the kidneys. Up to 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are chiefly eliminated via the kidneys. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in active form in the urine within the first 6 h after oral administration.
The elimination half-life of amoxicillin and clavulanic acid is approximately 1–1½ hours in subjects with normal kidney function.

Kinetics in special patient groups

Renal impairment

In renal insufficiency, the renal elimination of both active substances is delayed, and therefore the dose must be adjusted accordingly. The plasma levels of both active substances are greatly reduced by haemodialysis.

Preclinical data

Administration of the combination of amoxicillin and clavulanate (2:1) or of clavulanate alone was not found to have an effect in the F0 generation of rats or mice with regard to mating behaviour, fertility, gestation (including embryonic and foetal development) or birthing. Furthermore, studies have not revealed any adverse effects on embryo-foetal development or negative effects on the viability, growth, development, behaviour or reproductive function of the F1 progeny.
Potassium clavulanate was detected when tested alone and in combination with amoxicillin (1:2 or 1:4) in a wide range of genotoxicity tests under *in-vitro* and *in-vivo* conditions, with very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate poses no genotoxic dangers.

Other information

Incompatibilities

None known.

Influence on diagnostic methods

Possible falsification of results of oestriol tests in pregnant women.
The high concentration of amoxicillin in the urine can affect (false-positive results) glucose tests by chemical methods (Benedict's or Fehling's solution as well as Clinitest). Therefore, glucose tests should be performed by enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).
The direct Coombs test can come back positive, though haemolysis has not occurred.
In the amino acid chromatography of urine, amoxicillin or its degradation products could give ninhydrin-positive spots.
Possible interference with urine and serum total protein tests by a colour reaction (Ehrlich's ninhydrin reaction).
Possible false-positive colour reaction in glycosuria tests.
Falsely elevated serum uric acid levels can occur when the copper-chelating method is used. The Wolfram phosphate and uricase methods for uric acid are not affected by amoxicillin.

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store in a dry place in the original package, at room temperature (15–25 °C). Keep out of the reach of children.

Marketing authorisation number

625 mg film-coated tablets: 45,674 (Swissmedic)
1 g film-coated tablets: 53,692 (Swissmedic)

Packs

Augmentin 625 mg (500/125) film-coated tablets: Pack of 20 film-coated tablets **(A).**
Augmentin 1 g (875/125) film-coated tablets (with decorative groove): Packs of 12 and 20 film-coated tablets **(A).**

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

May 2024

swissmedic
Text genehmigt
Texte approuvé
Testo approvato
Bern, 29 May 2024
Taking corrections into account

Augmentin

Film-coated tablets

Composition

Active substances

Amoxicillin anhydrous as amoxicillin trihydrate.
Clavulanic acid as potassium clavulanate.

Excipients

Excipients per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

Pharmaceutical form	Amoxicillin anhydrous as amoxicillin trihydrate	Clavulanic acid as potassium clavulanate	Ratio of amoxicillin to clavulanic acid
625 mg (500/125) film-coated tablets	500 mg	125 mg	4 : 1
1 g (875/125) film-coated tablets (with decorative groove)	875 mg	125 mg	7 : 1

Indications/Uses

Augmentin should be used in accordance with official local recommendations for antibiotics, taking into account local susceptibility data.
Augmentin is indicated for gram-positive and gram-negative bacterial infections with Augmentin-susceptible pathogens (especially bacteria that are resistant to amoxicillin due to their formation of β-lactamase, see "Properties / Effects").

ENT infections:

Tonsillitis, pharyngitis, laryngitis, otitis media, sinusitis, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pyogenes.*

Lower respiratory tract infections:

Acute bronchitis with bacterial superinfection and acute exacerbation of chronic bronchitis, bacterial pneumonia, caused mainly by *Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.*

Urinary tract infections:

Acute and chronic pyelonephritis, cystitis, urethritis, etc. caused by *Escherichia coli*.

Venereal diseases:

Gonorrhoea (specific urethritis).

Skin and soft tissue infections:

Caused mainly by *Staphylococcus aureus* and *Streptococcus pyogenes*.

Gynaecological infections:

Salpingitis, adnexitis, endometritis, bacterial vaginitis.

The susceptibility of pathogens to Augmentin may differ geographically, and can change over time. Local susceptibility data should therefore be taken into consideration and, if necessary, susceptibility tests should be performed.

Dosage/Administration

The dose depends on the age, body weight and kidney function of the patient, as well as on the severity of the infection.

Usual dosage

Adults and children over 40 kg:

For mild, moderate and severe infections, the usual posology is 3 x 625 mg (500/125) daily.
In special cases (acute sinusitis, community-acquired pneumonia, acute exacerbations of chronic bronchitis, pyelonephritis and complicated urinary tract infections), the posology is 2 x 1 g (875/125) or 3 x 625 mg (500/125) daily.
If necessary, these posologies can be doubled (up to a maximum of 3 x 1 g (875/125) daily).

Children and adolescents under 40 kg.

Augmentin film-coated tablets are not suitable for the treatment of infections in children. For the treatment of infections in children, see the Summary of Product Characteristics for Augmentin Duo/Augmentin Trio Forte Suspensions.

Special posology guidelines

Patients with impaired renal function

The excretion of amoxicillin and clavulanic acid is slowed in renal insufficiency. The Augmentin dose should therefore be as follows, depending on the degree of renal insufficiency, expressed as creatinine clearance (CrCl):

Adults and children over 40 kg:

Creatinine clearance	Mild, moderate and severe infections
10-30 ml/min	625 mg every 12 hours
less than 10 ml/min	625 mg every 24 hours

2x 1 g (875/125) should not be administered to patients with creatinine clearance below 30 ml/min.
No dose adjustment is necessary for creatinine clearances above 30 ml/min.

Haemodialysis

One additional normal dose should be given during and at the end of dialysis (as the plasma levels of amoxicillin and clavulanic acid are reduced by haemodialysis).
The 1 g film-coated tablets should only be used in patients with creatinine clearance >30 ml/min.

Elderly patients

No dose adjustment is necessary; the dose should be as in adults. In cases of renal insufficiency, the dose should be adjusted as for adults with renal insufficiency.

Method of administration

Augmentin should be taken at the start of a meal, with at least half a glass of water. This will optimise absorption and gastrointestinal tolerance.
Parenteral therapies may be continued orally.
The fracture score on the 1 g film-coated tablet is only intended to make it easier to take the tablet.
The film-coated tablets are not intended for halving the dosage.

Contraindications

Augmentin is contraindicated in patients with known hypersensitivity to penicillins and cephalosporins, or to any of the ingredients of Augmentin, as well as in patients who developed jaundice or hepatic impairment during a previous Augmentin therapy.
Infectious mononucleosis, lymphatic leukaemia: when treated with amoxicillin, patients with these conditions are especially predisposed to skin rashes.

Warnings and precautions

Before initiating therapy with Augmentin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, clavulanic acid, cephalosporins or other allergens.
Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients treated with penicillins. Hypersensitivity reactions can also lead to Kounis syndrome, a severe allergic reaction that can lead to a myocardial infarction. The first symptoms of such reactions may include chest pain associated with an allergic reaction to amoxicillin-clavulanate (see "Adverse reactions").
If an allergic reaction occurs, Augmentin should be discontinued and other appropriate therapies initiated. Preparations should be made for emergency measures in the event of anaphylactic or anaphylactoid reactions. Such reactions call for the immediate injection of adrenaline (caution: cardiac arrhythmias). If necessary, the adrenaline may be repeated. Thereafter, IV glucocorticoids should be given (e.g. 250–1000 mg prednisolone). The glucocorticoid injection can be repeated if necessary. Oxygen, intravenous steroids and mechanical ventilation, with intubation, may also be required. (In children, the posology of the preparations must be adapted to their body weight and age.) Further therapeutic measures such as the intravenous injection of antihistamines and volume expanders should be considered. Careful monitoring of the patient is required as symptoms could reoccur.
Severe cutaneous drug reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-related exanthema with eosinophilia and systemic symptoms (DRESS), erythema multiforme and acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with beta-lactam antibiotics, including amoxicillin trihydrate potassium clavulanate (see also "Undesirable effects"). If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children who have received amoxicillin/clavulanic acid (see "Undesirable effects"). DIES is an allergic reaction with the main symptom of persistent vomiting (1–4 hours after taking the drug) without the presence of allergic skin or respiratory symptoms. Other symptoms may include abdominal pain, lethargy, diarrhoea, hypotension or leukocytosis with neutrophilia. Severe cases have occurred, including progression to shock.
If such reactions occur, Augmentin should be discontinued immediately and alternative therapy should be considered.
In cases of limited kidney function, the time between administrations should be increased based on the severity of the impairment (see "Special dosage instructions").
Long-term use can lead to the proliferation of non-susceptible bacteria. Such cases must be diagnosed appropriately and suitable treatment must be initiated.
The appearance of diarrhoea during or after treatment with Augmentin, especially when severe, persistent and/or bloody, could be a symptom of an infection with Clostridium difficile. The most severe form of such infections is pseudomembranous colitis. If this complication is suspected, the

Augmentin treatment must be discontinued immediately and the patient must be examined thoroughly in order to initiate specific antibiotic therapy (e.g., metronidazole, vancomycin) as needed. The use of peristalsis inhibitors is contraindicated in these clinical situations.
During long-term therapy, kidney, liver and haematopoietic function should be verified regularly.
There have been rare reports of abnormal prolongation of prothrombin time (increased INR) in patients receiving amoxicillin/clavulanic acid and oral anticoagulants. Therefore, appropriate monitoring should be carried out whenever concomitant anticoagulants are prescribed. In order to maintain the desired level of anticoagulation, the dose of the oral anticoagulants may need to be adjusted.
Augmentin should be used with caution in cases of hepatic impairment.
In severe gastrointestinal disturbances, with vomiting and diarrhoea, adequate absorption of Augmentin is no longer guaranteed. Parenteral use should be considered in such cases.
In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. A possible consequence of the formation of crystals is acute kidney failure. When high doses of amoxicillin are administered, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. At high concentrations in the urine, amoxicillin can precipitate at room temperature in the bladder catheter. Therefore, normal urine flow in the catheter should be monitored regularly.
Because oral antibiotics could reduce the efficacy of oral contraceptives, patients should be advised to take additional contraceptive measures during treatment with Augmentin.

Interactions

Probenecid inhibits renal tubular elimination of amoxicillin, but not of clavulanic acid. Concomitant use with Augmentin may result in increased and prolonged blood levels of amoxicillin. Concomitant use is not recommended.
Oral contraceptives: During treatment with amoxicillin, the enterohepatic circulation of oral contraceptives may be reduced or completely eliminated due to impairment of the intestinal flora. The efficacy of contraceptives is reduced as a result.
Because amoxicillin only acts on bacteria during their growth phase, there is an interaction with bacteriostatic antibiotics.
There is a possible interaction with glycosides (e.g. digoxin), as glycoside absorption is increased in certain patients due to damage to the intestinal flora during treatment with antibiotics.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no available data on the combination of Augmentin with allopurinol.
Rare cases of an increased International Normalised Ratio (INR) have been reported in the literature in patients treated with acenocoumarol or warfarin in whom amoxicillin was prescribed. If concomitant administration is necessary, the prothrombin time or International Normalised Ratio should be monitored carefully when amoxicillin is added or discontinued.

In patients receiving mycophenolate mofetil, reduction by approximately 50% in the pre-dose concentration of the active metabolite mycophenolic acid (MPA) has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose levels may not accurately represent changes in overall MPA exposure.
Penicillins can reduce the excretion of methotrexate, which can lead to a potential increase in toxicity.

Pregnancy/Lactation

Pregnancy

Reproduction studies in animals (mice and rats, with doses up to 10 times higher than in humans) with Augmentin administered orally and parenterally showed no teratogenic effects.
In a study in women with premature rupture of the foetal membrane, prophylactic treatment with Augmentin was reported to be associated with an elevated risk of necrotising enterocolitis in neonates (1.5% incidence of proven necrotising enterocolitis in neonates with Augmentin treatment versus 0.5% without Augmentin treatment).
During pregnancy, Augmentin should therefore not be used unless clearly necessary.

Breastfeeding

Traces of Augmentin pass into breast milk and therefore hypersensitivity reactions may occur in sensitive neonates. Though impairment of the intestinal flora of infants is theoretically possible, it has not been found at the recommended doses.
Breastfeeding is therefore not recommended during treatment with Augmentin.

Effects on ability to drive and use machines

Certain drug reactions that vary depending on the individual (see "Undesirable effects") may affect the concentration and reaction in the patient to an extent that impairs the ability to drive and use machines.

Undesirable effects

The frequencies from very common to rare undesirable effects come from datasets in major clinical trials. The frequencies of the remaining adverse reactions (i.e. with incidence < 1/10,000) derive mainly from data during use (post-marketing reports) and therefore relate to the reporting frequency and not the actual number of occurrences.
The frequencies of the undesirable effects are classified as follows: Very common (≥1/10), common (<1/10 to ≥1/100), uncommon (<1/100 to ≥1/1,000), rare (<1/1,000 to ≥1/10,000), very rare (<1/10,000), unknown (frequency cannot be estimated on the basis of the available data).

Infections and infestations

Common: Mucocutaneous candidiasis.

Diseases of the blood and lymphatic system

Rare: Reversible leukopenia (including severe neutropenia) and thrombocytopenia.

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time (Quick value) (see "Warnings and precautions" and "Interactions").

Data during use (Post-Marketing Data)

Rare: Thrombocytosis.

Immune system disorders

Very rare: Angioneurotic oedema, anaphylactic reaction, serum sickness-like syndrome, hypersensitivity vasculitis (see "Skin and subcutaneous tissue disorders"). Anaphylactic shock requires the immediate injection of adrenaline (see "Warnings and precautions").

Data from clinical studies

Common: Reversible eosinophilia (hypersensitivity reaction).

Data during use (Post-Marketing Data)

Very rare: Anaphylactic reactions (with symptoms such as urticaria, pruritic erythema, angioneurotic oedema, abdominal pain, vomiting among other abdominal symptoms, dyspnoea in bronchospasm or laryngeal oedema, circulatory symptoms such as hypotension and even anaphylactic shock). A Herxheimer reaction may occur during therapy for typhus, syphilis or leptospirosis. The treatment must be immediately discontinued if a hypersensitivity reaction occurs (see "Skin and subcutaneous tissue disorders").

Nervous system disorders

Uncommon: Dizziness, headache.

Very rare: Reversible hyperactivity, clonic convulsions. Clonic convulsions may occur in patients with impaired kidney function or in patients receiving high doses.

Frequency unknown: Aseptic meningitis

Data during use (Post-Marketing Data)

Very rare: Agitation, anxiety, insomnia, confusion, behavioural changes, dizziness, dysaesthesia.

Cardiac disorders

Data during use (Post-Marketing Data)

Frequency unknown: Kounis syndrome (see "Warnings and precautions").

Gastrointestinal disorders

Very common: Diarrhoea.

Common: Nausea, vomiting.

Nausea is more commonly observed at higher oral doses. If gastrointestinal reactions occur, they can be reduced by taking Augmentin at the start of a meal.

Uncommon: Dyspepsia, loss of appetite, stomach pressure, flatulence.

Rare: Glossitis, stomatitis.

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see "Warnings and precautions").

There have been reports of superficial tooth discolouration in children, especially following use of the suspension. Good oral hygiene could prevent the occurrence of tooth discolouration, as it can generally be removed by brushing.

Black hairy tongue (only after use of the oral forms).

A cohort study of 576 nine-year-old children showed that the administration of amoxicillin between the ages of 0 and 9 months significantly increases the risk of fluorosis of the definitive maxillary incisors. The fluorosis may present as white streaks, cosmetically disturbing discolouration, dents in the enamel and even tooth deformation.

Frequency unknown: Acute pancreatitis (see "Warnings and precautions"), drug-induced enterocolitis syndrome *(DIES)* (post-marketing data).

Data from clinical studies

Very common: Loose stools.

Common: Stomach pain.

Liver and bile diseases

Uncommon: A moderate rise in AST and/or ALT levels has been noted in patients receiving Augmentin.

Transient increase of lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic icterus.

The risk appears to be slightly higher with prolonged treatment, age ≥65 years and in men. Reports of such adverse effects are extremely rare in children. The incidence of these adverse effects with Augmentin is approximately 5 times greater than with amoxicillin alone.

The signs and symptoms usually occur during or shortly after treatment, and can also be observed up to several weeks after the end of treatment in individual cases. They are usually reversible. Liver disorders can be severe and even fatal in extremely rare situations. However, these cases occurred almost exclusively in patients with a serious underlying disease or using concomitant medicinal products known to have potential adverse effects on the liver.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash (in the form of maculo-papular or morbilliform rashes) and erythema, pruritus, urticaria.

Rare: Erythema multiforme.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) and drug-related exanthema with eosinophilia and systemic symptoms (DRESS) (see "Immune system disorders").
If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see also "Warnings and precautions").
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)

Frequency unknown: Linear Ig A disease.

Renal and urinary disorders

Very rare: Interstitial nephritis,
Renal impairment with increased BUN and serum creatinine concentration.

Frequency unknown: Crystalluria (including acute renal damage)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In case of overdose, gastrointestinal symptoms and fluid and electrolyte balance disturbances may occur. These can be treated symptomatically with activated charcoal and hydration.
Augmentin can be removed from the body by haemodialysis.
Large overdoses of amoxicillin, especially when administered parenterally, lead to very high urine levels.
Amoxicillin crystalluria and accompanying acute kidney failure have been observed (see "Warnings and precautions").

Properties/Effects

ATC code

J01CR02

Mechanism of action

Augmentin is a bactericidal antibiotic. Amoxicillin is a semisynthetic aminopenicillin in the group of β-lactam antibiotics and has bactericidal activity against gram-positive and gram-negative bacteria. The bactericidal effect of amoxicillin relies on the inhibition of bacterial cell wall synthesis by blocking the transpeptidase. Amoxicillin is stable in the presence of acid, but is sensitive to penicillinases.
Clavulanic acid is a β-lactam, which has a mild antibacterial effect against some bacteria strains. The principal action of clavulanic acid is its enzyme-inhibiting activity against many types of β-lactamases. Clavulanic acid has high activity against clinically relevant plasmid-mediated β-lactamases that are often responsible for transmitted antibiotic resistance, but is generally less effective against chromosomally mediated type 1 β-lactamases.
This inhibition protects amoxicillin from destruction by β-lactamases, thereby allowing amoxicillin to mediate its full antibiotic effect.
Many bacteria that are resistant to amoxicillin because they produce β-lactamase are susceptible to this combination of amoxicillin and clavulanic acid. This synergistic effect is achieved at clavulanic acid concentrations reached in the body following parenteral or oral administration.

Pharmacodynamics

Scope of action
In vitro susceptibility of pathogens
The following list classifies the bacteria by their *in-vitro* susceptibility to Augmentin.

* Clinical efficacy of Augmentin has been demonstrated in clinical studies.
+ Bacteria that do not produce β-lactamases. If an isolate is susceptible to amoxicillin, it can be considered as susceptible to Augmentin.

Commonly susceptible bacteria:
Gram-positive aerobes:

- Bacillus anthracis
- Enterococcus faecalis
- Listeria monocytogenes
- Nocardia asteroides
- Streptococcus pneumoniae*+
- Streptococcus pyogenes*+

- Streptococcus agalactiae*+
- Streptococcus viridans+
- Streptococcus spp. (other β-haemolytic streptococci)*+
- Staphylococcus aureus (methicillin-susceptible)*
- Staphylococcus saprophyticus (methicillin-susceptible)
- Coagulase-negative staphylococcus (methicillin susceptible)

Gram-negative aerobes:

- Bordetella pertussis
- Haemophilus influenzae*
- Haemophilus parainfluenzae
- Helicobacter pylori
- Moraxella catarrhalis*
- Neisseria gonorrhoeae
- Pasteurella multocida
- Vibrio cholerae

Other:

- Borrelia burgdorferi
- Leptospira icterohaemorrhagiae
- Treponema pallidum

Gram-positive anaerobes:

- Clostridium spp.
- Peptococcus niger
- Peptostreptococcus magnus
- Peptostreptococcus micros
- Peptostreptococcus spp.

Gram-negative anaerobes:

- Bacteroides fragilis
- Bacteroides spp.
- Capnocytophaga spp.
- Eikenella corrodens
- Fusobacterium nucleatum
- Fusobacterium spp.
- Porphyromonas spp.
- Prevotella spp.

Bacteria for which acquired resistance may be a problem:

Gram-negative aerobes:

- Escherichia coli*
- Klebsiella oxytoca
- Klebsiella pneumoniae*
- Klebsiella spp.
- Proteus mirabilis
- Proteus vulgaris
- Proteus spp.
- Salmonella spp.
- Shigella spp.

Gram-positive aerobes:

- Corynebacterium spp.
- Enterococcus faecium

Inherently resistant bacteria:

Gram-negative aerobes:

- Acinetobacter spp.
- Citrobacter freundii
- Enterobacter spp.
- Hafnia alvei
- Legionella pneumophila
- Morganella morganii
- Providencia spp.
- Pseudomonas spp.
- Serratia spp.
- Stenotrophomonas maltophilia
- Yersinia enterocolitica

Other:

- Chlamydia pneumoniae
- Chlamydia psittaci
- Chlamydia spp.
- Coxiella burnetti
- Mycoplasma spp.

Clinical efficacy

No information.

Pharmacokinetics

Absorption

Amoxicillin and clavulanic acid are readily absorbed in the intestines. Absorption is optimised when taken at the start of a meal. The absorption curves of both components are similar. The maximum serum levels of amoxicillin and clavulanic acid are reached within approximately 1 to 1½ hours following oral intake. After taking one 375 mg tablet (250/125), the serum levels are about 5 mg/l (amoxicillin) and 3 mg/l (clavulanic acid).
The total quantities absorbed are generally 80% for amoxicillin and 70% for clavulanic acid.

Distribution

About 18% of amoxicillin and 25% of clavulanic acid are bound to plasma proteins. The volume of distribution is 22 litres for amoxicillin and 16 litres for clavulanic acid.
Because high serum levels of amoxicillin and clavulanic acid are reached following oral administration of Augmentin, good penetration into bodily fluids can be expected.
Therapeutic concentrations of both active substances have been found in abdominal tissue, the gall bladder, skin, fat and muscle tissues and in the following bodily fluids: synovial, peritoneal and pleural fluids, bile, sputum and pus.
Both active substances cross the placental barrier. Reproduction studies in animals did not find harmful effects. Clinical experience in humans is limited.
Small quantities of amoxicillin are found in breast milk. Only trace quantities of clavulanic acid are detected in breast milk. With the exception of the risk of a hypersensitivity reaction associated with this type of excretion, no adverse effects are known in the infant.

Metabolism

Up to 10-25% of amoxicillin is metabolised into the corresponding inactive form penicilloic acid and excreted via the kidneys. Up to 35-60% of clavulanic acid is converted into inactive metabolites.

Elimination

Amoxicillin and clavulanic acid are chiefly eliminated via the kidneys. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in active form in the urine within the first 6 h after oral administration.
The elimination half-life of amoxicillin and clavulanic acid is approximately 1–1½ hours in subjects with normal kidney function.

Kinetics in special patient groups

Renal impairment

In renal insufficiency, the renal elimination of both active substances is delayed, and therefore the dose must be adjusted accordingly. The plasma levels of both active substances are greatly reduced by haemodialysis.

Preclinical data

Administration of the combination of amoxicillin and clavulanate (2:1) or of clavulanate alone was not found to have an effect in the F0 generation of rats or mice with regard to mating behaviour, fertility, gestation (including embryonic and foetal development) or birthing. Furthermore, studies have not revealed any adverse effects on embryo-foetal development or negative effects on the viability, growth, development, behaviour or reproductive function of the F1 progeny.
Potassium clavulanate was detected when tested alone and in combination with amoxicillin (1:2 or 1:4) in a wide range of genotoxicity tests under *in-vitro* and *in-vivo* conditions, with very different endpoints. The results obtained lead to the conclusion that the administration of amoxicillin or clavulanate poses no genotoxic dangers.

Other information

Incompatibilities

None known.

Influence on diagnostic methods

Possible falsification of results of oestriol tests in pregnant women.
The high concentration of amoxicillin in the urine can affect (false-positive results) glucose tests by chemical methods (Benedict's or Fehling's solution as well as Clinitest). Therefore, glucose tests should be performed by enzymatic (glucose oxidase) methods (Dextrostix, Diastix or Clinistix).
The direct Coombs test can come back positive, though haemolysis has not occurred.
In the amino acid chromatography of urine, amoxicillin or its degradation products could give ninhydrin-positive spots.
Possible interference with urine and serum total protein tests by a colour reaction (Ehrlich's ninhydrin reaction).
Possible false-positive colour reaction in glycosuria tests.
Falsely elevated serum uric acid levels can occur when the copper-chelating method is used. The Wolfram phosphate and uricase methods for uric acid are not affected by amoxicillin.

Shelf life

Do not use this medicine after the expiry date which is stated on the pack after "EXP".

Special precautions for storage

Store in a dry place in the original package, at room temperature (15–25 °C). Keep out of the reach of children.

Marketing authorisation number

625 mg film-coated tablets: 45,674 (Swissmedic)
1 g film-coated tablets: 53,692 (Swissmedic)

Packs

Augmentin 625 mg (500/125) film-coated tablets: Pack of 20 film-coated tablets **(A).**
Augmentin 1 g (875/125) film-coated tablets (with decorative groove): Packs of 12 and 20 film-coated tablets **(A).**

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

Date of revision of the text

May 2024

Certificate Number: PP10185651

SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

Augmentin 625 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval shaped tablet debossed with 'AC' and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Augmentin is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

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The use of alternative presentations of Augmentin (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Augmentin provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
One 500 mg/125 mg dose taken three times a day.

Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with Augmentin tablets, suspensions or paediatric sachets.

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Augmentin tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

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Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.

No clinical data are available on doses of Augmentin 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

Elderly
No dose adjustment is considered necessary.

Renal impairment
Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

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Therapy can be started parenterally according the SPC of the IV formulation and continued with an oral preparation.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Augmentin is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

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The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in

patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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4.7 Effects on ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common

SUMMARY OF PRODUCT CHARACTERISTICS

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Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Drug-induced enterocolitis syndrome	Not known
Pancreatitis acute	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Linear IgA disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury)[8]	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.4
[10] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints (µg/ml)	
	Susceptible	Resistant
Haemophilus influenzae	≤ 0.001[1]	> 2[1]
Moraxella catarrhalis	≤ 1[1]	> 1[1]
Staphylococcus spp.	≤ 0.125[2a, 3a, 3b, 4]	> 0.125[2a, 3a, 3b, 4]
Enterococcus spp.[7]	≤ 4[1, 5]	> 8[1, 5]
Streptococcus groups A, B, C, G [2b, 8] (indications other than meningitis)	≤ 0.25[2b]	> 0.25[2b]
Streptococcus pneumoniae[8]	≤ 0.5[1, 6]	> 1[1, 6]
Enterobacterales in uncomplicated UTIs	≤ 32[1]	> 32[1]
Gram-negative Anaerobes	≤ 4[1]	> 8[1]
Gram-positive Anaerobes (except *Clostridioides difficile*)	≤ 4[1]	> 8[1]
Non-species related breakpoints	≤ 2[1]	> 8[1]
Viridans group streptococci[8]	≤ 0.25[2a, 9]	> 2[2a, 9]
Pasteurella multocida	≤ 1[1]	> 1[1]
Burkholderia pseudomallei	≤ 0.001[1]	> 8[1]

[1] For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.

[2a] Breakpoint values in the table are based on benzylpenicillin breakpoints. The susceptibility is inferred from the benzylpenicillin susceptibility.

[2b] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.

[3a] Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins.

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[3b] Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but methicillin resistance can be detected with cefoxitin as described.

[4] Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[5] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

[6] The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, can be reported susceptible without further testing.

[7] Aminopenicillin breakpoints in enterococci are based on intravenous administration. Oral administration is relevant for urinary tract infections only.

[8] The addition of a beta-lactamase inhibitor does not add clinical benefit.

[9] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed. Isolates categorised as screen positive should be tested for susceptibility to individual agents. For benzylpenicillin screen negative isolates (MIC ≤0.25 mg/L), susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates (MIC >0.25 mg/L), susceptibility is inferred from ampicillin.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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Commonly susceptible species
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus* (methicillin-susceptible)£ Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti*

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Mycoplasma pneumoniae
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

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From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces, and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

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5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Sodium starch glycolate, Type A
Colloidal anhydrous silica
Microcrystalline cellulose

Tablet film-coat
Titanium dioxide (E171)
Hypromellose
Macrogol (4000, 6000)
Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in cold formed aluminium blisters (CFB) and desiccated pouch packs (DPP).

Tablets in desiccated pouch packs should be used within 30 days of opening.

6.4 Special precautions for storage

Store in the original package to protect from moisture.
Do not store above 25 °C.

6.5 Nature and contents of container

PVC/Aluminium/Polyamide laminate with aluminium lidding foil referred to as a cold formed aluminium blister (CFB) containing 4, 10, 12, 14, 16, 20, 24, 30, 100 or 500 tablets.

Aluminium PVC/PVdC blister enclosed within an aluminium laminate pouch containing a desiccant sachet, referred to as a desiccated pouch (DPP) containing 14, 20 or 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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7 MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS

Trading as:
GlaxoSmithKline UK

8. Marketing Authorisation Numbers

PL 00038/0362

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/1991 / 23/11/2005

10 DATE OF REVISION OF THE TEXT

13/06/2023

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1 NAME OF THE MEDICINAL PRODUCT

Augmentin 625 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval shaped tablet debossed with 'AC' and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Augmentin is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

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The use of alternative presentations of Augmentin (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Augmentin provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
One 500 mg/125 mg dose taken three times a day.

Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with Augmentin tablets, suspensions or paediatric sachets.

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Augmentin tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

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Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.

No clinical data are available on doses of Augmentin 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

Elderly
No dose adjustment is considered necessary.

Renal impairment
Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration
Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Therapy can be started parenterally according the SPC of the IV formulation and continued with an oral preparation.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Augmentin is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

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The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in

patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

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4.7 Effects on ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common

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Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Drug-induced enterocolitis syndrome	Not known
Pancreatitis acute	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Linear IgA disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury)[8]	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.4
[10] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:

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www.mhra.gov.uk/yellowcard or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

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- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Breakpoints
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints (µg/ml)	
	Susceptible	Resistant
Haemophilus influenzae	≤ 0.001[1]	> 2[1]
Moraxella catarrhalis	≤ 1[1]	> 1[1]
Staphylococcus spp.	≤ 0.125[2a, 3a, 3b, 4]	> 0.125[2a, 3a, 3b, 4]
Enterococcus spp.[7]	≤ 4[1, 5]	> 8[1, 5]
Streptococcus groups A, B, C, G [2b, 8] (indications other than meningitis)	≤ 0.25[2b]	> 0.25[2b]
Streptococcus pneumoniae[8]	≤ 0.5[1, 6]	> 1[1, 6]
Enterobacterales in uncomplicated UTIs	≤ 32[1]	> 32[1]
Gram-negative Anaerobes	≤ 4[1]	> 8[1]
Gram-positive Anaerobes (except *Clostridioides difficile*)	≤ 4[1]	> 8[1]
Non-species related breakpoints	≤ 2[1]	> 8[1]
Viridans group streptococci[8]	≤ 0.25[2a, 9]	> 2[2a, 9]
Pasteurella multocida	≤ 1[1]	> 1[1]
Burkholderia pseudomallei	≤ 0.001[1]	> 8[1]

[1] For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.

[2a] Breakpoint values in the table are based on benzylpenicillin breakpoints. The susceptibility is inferred from the benzylpenicillin susceptibility.

[2b] The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility (indications other than meningitis) with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.

[3a] Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins.

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[3b] Most coagulase-negative staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. No currently available method can reliably detect penicillinase production in coagulase-negative staphylococci but methicillin resistance can be detected with cefoxitin as described.

[4] Ampicillin susceptible *S. saprophyticus* are *mecA*-negative and susceptible to ampicillin, amoxicillin and piperacillin (without or with a beta-lactamase inhibitor).

[5] Susceptibility to ampicillin, amoxicillin and piperacillin (with and without beta-lactamase inhibitor) can be inferred from ampicillin. Ampicillin resistance is uncommon in *E. faecalis* (confirm with MIC) but common in *E. faecium*.

[6] The oxacillin 1 µg disk screen test or a benzylpenicillin MIC test shall be used to exclude beta-lactam resistance mechanisms. When the screen is negative (oxacillin inhibition zone ≥20 mm, or benzylpenicillin MIC ≤0.06 mg/L) all beta-lactam agents for which clinical breakpoints are available, can be reported susceptible without further testing.

[7] Aminopenicillin breakpoints in enterococci are based on intravenous administration. Oral administration is relevant for urinary tract infections only.

[8] The addition of a beta-lactamase inhibitor does not add clinical benefit.

[9] Benzylpenicillin (MIC or disk diffusion) can be used to screen for beta-lactam resistance in viridans group streptococci. Isolates categorised as screen negative can be reported susceptible to beta-lactam agents for which clinical breakpoints are listed. Isolates categorised as screen positive should be tested for susceptibility to individual agents. For benzylpenicillin screen negative isolates (MIC ≤0.25 mg/L), susceptibility can be inferred from benzylpenicillin or ampicillin. For benzylpenicillin screen positive isolates (MIC >0.25 mg/L), susceptibility is inferred from ampicillin.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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Commonly susceptible species
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus* (methicillin-susceptible)£ Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti*

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Mycoplasma pneumoniae
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

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From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces, and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

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5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Sodium starch glycolate, Type A
Colloidal anhydrous silica
Microcrystalline cellulose

Tablet film-coat
Titanium dioxide (E171)
Hypromellose
Macrogol (4000, 6000)
Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in cold formed aluminium blisters (CFB) and desiccated pouch packs (DPP).

Tablets in desiccated pouch packs should be used within 30 days of opening.

6.4 Special precautions for storage

Store in the original package to protect from moisture.
Do not store above 25 °C.

6.5 Nature and contents of container

PVC/Aluminium/Polyamide laminate with aluminium lidding foil referred to as a cold formed aluminium blister (CFB) containing 4, 10, 12, 14, 16, 20, 24, 30, 100 or 500 tablets.

Aluminium PVC/PVdC blister enclosed within an aluminium laminate pouch containing a desiccant sachet, referred to as a desiccated pouch (DPP) containing 14, 20 or 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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7 MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS

Trading as:
GlaxoSmithKline UK

8. Marketing Authorisation Numbers

PL 00038/0362

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/1991 / 23/11/2005

10 DATE OF REVISION OF THE TEXT

13/06/2023

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1. NAME OF THE MEDICINAL PRODUCT

Augmentin 500/125 (Tablets 625 mg)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off white oval film-coated tablets debossed with 'AC' and a scoreline on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Augmentin is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Augmentin (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

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For adults and children ≥ 40 kg, this formulation of Augmentin provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg
One 500 mg/125 mg dose taken three times a day.

Children < 40 kg
20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with Augmentin tablets, suspensions or paediatric sachets.

As the tablets cannot be divded, children weighing less than 25 kg must not be treated with Augmentin tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.
No clinical data are available on doses of Augmentin 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

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Elderly

No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

Augmentin is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

Therapy can be started parenterally according the SPC of the IV-formulation and continued with an oral preparation.

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4.3 Contra-indications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special Warnings and Precautions for Use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Augmentin is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). This reaction requires Augmentin discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see section 4.2).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may

be severe and, in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see section 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of Clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

4.5 Interaction with other Medicaments and other Forms of Interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see sections 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

4.6 Pregnancy and Lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Lactation
Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable Effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

SUMMARY OF PRODUCT CHARACTERISTICS

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Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders [7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known

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Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[1] See section 4.4
[2] See section 4.4
[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking Augmentin at the start of a meal.
[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[5] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[8] See section 4.9
[9] See section 4.4
[10] See sections 4.3 and 4.4

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.
Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

SUMMARY OF PRODUCT CHARACTERISTICS

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mode of action
Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

PK/PD relationship
The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

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Breakpoints
MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Organism	Susceptibility Breakpoints (μg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2
Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

[1] The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/l.
[2] The reported values are Oxacillin concentrations.
[3] Breakpoint values in the table are based on Ampicillin breakpoints.
[4] The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.
[5] Breakpoint values in the table are based on Benzylpenicillin breakpoints.

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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Commonly susceptible species
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus (*methicillin-susceptible)£ Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms *Chlamydophila pneumoniae* *Chlamydophila psittaci* *Coxiella burnetti*

SUMMARY OF PRODUCT CHARACTERISTICS

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Mycoplasma pneumoniae
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic Properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

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From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination
The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender
Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment
The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

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5.3 Preclinical Safety Data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with Augmentin or its components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Sodium starch glycolate, Type A
Colloidal anhydrous silica
Microcrystalline cellulose

Tablet film-coat
Titanium dioxide (E171)
Hypromellose
Macrogol (4000, 6000)
Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in cold formed aluminium blisters (CFB) and desiccated pouch packs (DPP)

Tablets in desiccated pouch packs should be used within 30 days of opening.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium/Polyamide laminate with aluminium lidding foil referred to as a cold formed aluminium blister (CFB) containing 4, 10, 12, 14, 16, 20, 24, 30, 100 or 500 tablets.

Aluminium PVC/PVdC blister enclosed within an aluminium laminate pouch containing a desiccant sachet, referred to as a desiccated pouch (DPP) containing 14, 20 or 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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7. MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford,
Middlesex, TW8 9GS

Trading as:
Beecham Research or SrnithKline Beecham Pharmaceuticals at Mundells,
Welwyn Garden City, Hertfordshire, AL7 1EY

8. Marketing Authorisation Numbers

Augmentin 500/125 (Tablets 625 mg) PL 00038/0366

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 1993

10 DATE OF REVISION OF THE TEXT

21/12/2012

PI-14395
DOP: February 2025

Certificate Number: PP10189276

SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

Augmentin 625 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval shaped tablet debossed with 'AC' and a score line on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Augmentin is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Augmentin that is selected to treat an individual infection should take into account:

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- The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- The severity and the site of the infection
- The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Augmentin (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of Augmentin provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Augmentin provides a maximum daily dose of 2400 mg amoxicillin/600 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Augmentin is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

Adults and children ≥ 40 kg

One 500 mg/125 mg dose taken three times a day.

Children < 40 kg

20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with Augmentin tablets, suspensions or paediatric sachets.

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with Augmentin tablets.

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The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	12.5	14.3	16.7	20.0	6.67 – 20
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.67 - 5

Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Augmentin suspension or paediatric sachets.

No clinical data are available on doses of Augmentin 4:1 formulations higher than 40 mg/10 mg/kg per day in children under 2 years.

Elderly

No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.
No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

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Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Method of administration

Augmentin is for oral use.

Augmentin should be administered with a meal to minimise potential gastrointestinal intolerance.

Therapy can be started parenterally according the SPC of the IV formulation and continued with an oral preparation.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8).

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanic acid (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain,

diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Augmentin is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires Augmentin discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and, in extremely rare circumstances deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Augmentin may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of *Aspergillus* infection. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia *Aspergillus* EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Methotrexate
Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Probenecid
Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil

SUMMARY OF PRODUCT CHARACTERISTICS

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In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with Augmentin, sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1 000 to <1/100)
Rare (≥1/10 000 to <1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible	Not known

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organisms	
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[8]	
Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[1]	Not known
Aseptic meningitis	Not known
Cardiac disorders	
Kounis syndrome	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[2]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[3]	Not known
Drug-induced enterocolitis syndrome	Not known
Pancreatitis acute	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[4]	Uncommon
Hepatitis[5]	Not known
Cholestatic jaundice[5]	Not known
Skin and subcutaneous tissue disorders[6]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known

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Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known
Acute generalised exanthemous pustulosis (AGEP)[1]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome)	Not known
Linear IgA disease	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria (including acute renal injury)[7]	Not known

[1] See section 4.4
[2] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.
[3] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)
[4] A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.
[5] These events have been noted with other penicillins and cephalosporins (see section 4.4).
[6] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).
[7] See section 4.9
[8] See sections 4.3 and 4.4

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; ATC code: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for amoxicillin/clavulanic acid and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert

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advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms *Enterococcus faecalis* *Gardnerella vaginalis* *Staphylococcus aureus* (methicillin-susceptible)£ Coagulase-negative staphylococci (methicillin-susceptible) *Streptococcus agalactiae* *Streptococcus pneumoniae*[1] *Streptococcus pyogenes* and other beta-haemolytic streptococci *Streptococcus viridans* group Aerobic Gram-negative micro-organisms *Capnocytophaga* spp. *Eikenella corrodens* *Haemophilus influenzae*[2] *Moraxella catarrhalis* *Pasteurella multocida* Anaerobic micro-organisms *Bacteroides fragilis* *Fusobacterium nucleatum* *Prevotella* spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms *Enterococcus faecium* $ Aerobic Gram-negative micro-organisms *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Proteus vulgaris*
Inherently resistant organisms
Aerobic Gram-negative micro-organisms *Acinetobacter* sp. *Citrobacter freundii* *Enterobacter* sp. *Legionella pneumophila* *Morganella morganii* *Providencia* spp. *Pseudomonas* sp. *Serratia* sp. *Stenotrophomonas maltophilia* Other micro-organisms

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Chlamydophila pneumoniae *Chlamydophila psittaci* *Coxiella burnetti* *Mycoplasma pneumoniae*
$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance. £ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid [1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4). [2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10%.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (500 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters

Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 500/125 mg	500	7.19 ± 2.26	1.5 (1.0-2.5)	53.5 ± 8.87	1.15 ± 0.20
Clavulanic acid					
AMX/CA 500 mg/125 mg	125	2.40 ± 0.83	1.5 (1.0-2.0)	15.72 ± 3.86	0.98 ± 0.12

AMX – amoxicillin, CA – clavulanic acid
* Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

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Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (see section 4.6).

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces, and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Augmentin 250 mg/125 mg or 500 mg/125 mg tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see section 4.5).

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must

therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section 4.2).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Sodium starch glycolate, Type A
Colloidal anhydrous silica
Microcrystalline cellulose

Tablet film-coat
Titanium dioxide (E171)
Hypromellose
Macrogol (4000, 6000)
Dimeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in cold formed aluminium blisters (CFB) and desiccated pouch packs (DPP).

Tablets in desiccated pouch packs should be used within 30 days of opening.

6.4 Special precautions for storage

Store in the original package to protect from moisture.
Do not store above 25 °C.

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6.5 Nature and contents of container

PVC/Aluminium/Polyamide laminate with aluminium lidding foil referred to as a cold formed aluminium blister (CFB) containing 4, 10, 12, 14, 16, 20, 24, 30, 100 or 500 tablets.

Aluminium PVC/PVdC blister enclosed within an aluminium laminate pouch containing a desiccant sachet, referred to as a desiccated pouch (DPP) containing 14, 20 or 21 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS

Trading as:
GlaxoSmithKline UK

8. Marketing Authorisation Numbers

PL 00038/0362

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/1991 / 23/11/2005

10 DATE OF REVISION OF THE TEXT

04/07/2024