SUMMARY OF PRODUCT CHARACTERISTICS

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Omjjara 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains momelotinib dihydrochloride monohydrate equivalent to 100 mg momelotinib.

Excipient with known effect

50.8 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Brown, round tablets, of approximately 8.7 mm diameter, with an underlined "M" debossed on one side and "100" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Omjjara is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with moderate to severe anaemia who have primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis and who are Janus Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

4.2 Posology and method of administration

Treatment should be initiated and monitored by physicians experienced in the use of anti-cancer medicinal products.

Posology

Omjjara should not be used in combination with other JAK inhibitors.

The recommended dose is 200 mg once daily.

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Complete blood cell count and liver function tests must be performed before initiating treatment, periodically during treatment, and as clinically indicated (see section 4.4).

Dose modifications

Dose modifications should be considered for haematologic and non-haematologic toxicities (table 1).

Table 1: Dose modifications for adverse reactions

Haematologic toxicities		
Thrombocytopenia		**Dose modification[a]**
Baseline platelet count	**Platelet count**	
≥100 × 10^9/L	20 × 10^9/L to <50 × 10^9/L	Reduce daily dose by 50 mg from the last given dose
	<20 × 10^9/L	Interrupt treatment until platelets recover to 50 × 10^9/L Restart Omjjara at a daily dose of 50 mg below the last given dose[b]
≥50 × 10^9/L to <100 × 10^9/L	<20 × 10^9/L	Interrupt treatment until platelets recover to 50 × 10^9/L Restart Omjjara at a daily dose of 50 mg below the last given dose[b]
<50 × 10^9/L	<20 × 10^9/L	Interrupt treatment until platelets recover to baseline Restart Omjjara at a daily dose of 50 mg below the last given dose[b]
Neutropenia		**Dose modification[a]**
ANC <0.5 × 10^9/L		Interrupt treatment until ANC ≥0.75 × 10^9/L Restart Omjjara at a daily dose of 50 mg below the last given dose[b]
Non-haematologic toxicities		
Hepatotoxicity (unless other apparent causes)		**Dose modification[a]**
ALT and/or AST >5 × ULN (or >5 × baseline, if baseline is abnormal) and/or total bilirubin >2 × ULN (or >2 × baseline, if baseline is abnormal)		Interrupt treatment until AST and ALT ≤2 × ULN or baseline and total bilirubin ≤1.5 × ULN or baseline Restart Omjjara at a daily dose of 50 mg below the last given dose[b] If reoccurrence of ALT or AST elevations >5 × ULN, permanently discontinue Omjjara

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Other non-haematologic	Dose modification[a]
Grade 3 or higher[c] Grade 2 or higher[c] bleeding	Interrupt treatment until the toxicity resolves to Grade 1 or lower (or baseline) Restart Omjjara at a daily dose of 50 mg below the last given dose[b]

ANC = absolute neutrophil count; ALT = alanine transaminase; AST = aspartate transaminase;

ULN = upper limit of normal.

[a] Reinitiate or escalate treatment up to starting dosage as clinically appropriate.

[b] May reinitiate treatment at 100 mg if previously dosed at 100 mg.

[c] Graded using the National Cancer Institute Common Terminology Criteria for Adverse Events per (CTCAE).

Treatment with Omjjara should be discontinued in patients unable to tolerate 100 mg once daily.

Duration of use

Treatment may be continued for as long as the benefit-risk remains positive for patients, as assessed by the treating physician.

Missed dose

If a dose of Omjjara is missed, the next scheduled dose should be taken the following day. Two doses should not be taken at the same time to make up for the missed dose.

Special populations

Elderly

No dose adjustment is required for patients who are aged 65 years and older (see section 5.2).

Renal impairment

No dose adjustment is required for patients with renal impairment (>15 mL/min).

Omjjara has not been studied in patients with end-stage renal disease.

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see section 4.4). The recommended starting dose of Omjjara is 150 mg once daily in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Paediatric population

The safety and efficacy of Omjjara in children and adolescents less than 18 years of age have not been established. No data are available.

Method of administration

Omjjara is for oral use only and can be taken with or without meals (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Infections

Infections, including serious and fatal bacterial and viral infections (including COVID-19), have occurred in patients treated with Omjjara (see section 4.8). Omjjara should not be initiated in patients with active infections. Physicians should carefully observe patients receiving Omjjara for signs and symptoms of infection (including but not limited to fever, cough, diarrhoea, vomiting, nausea, and pain upon urination) and initiate appropriate treatment promptly.

Hepatitis B reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking JAK inhibitors, including Omjjara. The effect of Omjjara on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection who receive Omjjara should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Thrombocytopenia and neutropenia

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New onset of severe (Grade ≥3) thrombocytopenia and neutropenia was observed in patients treated with Omjjara (see section 4.8). A complete blood count including platelet count should be obtained before initiating treatment with Omjjara, periodically during treatment, and as clinically indicated. Dose interruption or reduction may be required (see section 4.2).

Hepatic monitoring

Liver function tests should be obtained before initiating treatment with Omjjara, periodically during treatment, and as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, dose interruption or reduction may be required (see section 4.2).

Major adverse cardiovascular events (MACE)

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors.

Events of MACE have been reported in patients receiving Omjjara, however, a causal relationship has not been established. Prior to initiating or continuing therapy with Omjjara, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors.

Thrombosis

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

Events of DVT and PE have been reported in patients receiving Omjjara. However, a causal association has not been established. In patients with myelofibrosis treated with Omjjara in clinical trials, the rates of thromboembolic events were similar in Omjjara and control-treated patients. Prior to initiating or continuing therapy with Omjjara, the benefits and risks for the individual patient should be considered particularly in patients with cardiovascular risk factors (see also section 4.4 Major adverse cardiovascular events [MACE]).

Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

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Second primary malignancies

In a large randomised active controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors.

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Omjjara. However, a causal association has not been established.

Interactions

Based on the potential of Omjjara to increase the plasma concentrations of certain medicinal products (e.g., sensitive breast cancer resistance protein [BCRP] substrates, such as rosuvastatin and sulfasalazine), patients should be monitored for adverse reactions with co-administration (see section 4.5).

Co-administration of strong cytochrome P450 (CYP) 3A4 inducers may lead to decreased exposure of Omjjara and consequently a risk for reduced efficacy. Therefore, additional monitoring of the clinical signs and symptoms of myelofibrosis is recommended with concomitant use of Omjjara and strong CYP3A4 inducers (including but not limited to carbamazepine, phenobarbital, phenytoin, and St John's wort [*Hypericum perforatum*]) (see section 4.5).

Women of childbearing potential

Given uncertainties whether Omjjara may reduce the effectiveness of hormonal contraceptives, women using oral hormonal contraceptives should add a barrier method during treatment and for at least 1 week after the last dose of Omjjara (see sections 4.5 and 4.6).

Excipients with known effect

Omjjara contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on momelotinib

Momelotinib undergoes metabolism though multiple CYP enzymes (including CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP1A2) and aldehyde oxidase, with CYP3A4 having the greatest contribution.

Strong CYP3A4 inducers

Multiple doses of rifampicin (600 mg daily for 7 days) decreased momelotinib C_{max} by 29.4% and AUC_{inf} by 46.1% when compared with momelotinib (200 mg single dose) plus rifampicin single-dose (600 mg), to capture the induction effect of rifampicin. Co-administration of strong CYP3A4 inducers may lead to decreased momelotinib exposure and consequently a risk for reduced efficacy. Therefore, additional monitoring of the clinical signs and symptoms of myelofibrosis is recommended with concomitant use of momelotinib and strong CYP3A4 inducers (including but not limited to carbamazepine, phenobarbital, phenytoin, and St John's wort [*Hypericum perforatum*]).

Multiple doses of rifampicin (600 mg daily for 7 days) did not change momelotinib C_{max} and decreased momelotinib AUC_{inf} by 15.3% when compared with momelotinib alone (200 mg single dose), capturing the combined effect of CYP3A4 induction and organic anion transporting peptide (OATP)1B1 and OATP1B3 inhibition. Momelotinib can be co-administered with rifampicin without a dose modification.

Transporters

Momelotinib is a substrate of OATP1B1 and OATP1B3 transporters. Co-administration with a single dose of rifampicin, capturing the OATP1B1/1B3 inhibition effect, moderately increased momelotinib exposure (C_{max} by 40.4% and AUC_{inf} by 57.1%). Therefore, caution and monitoring for adverse reactions is advised with concomitant use of OATP1B1/1B3 inhibitors, including ciclosporin.

Effect of momelotinib on other medicinal products

Transporters

Momelotinib is an inhibitor of BCRP *in vitro*. Co-administration of a single dose of rosuvastatin at 10 mg (a BCRP substrate) with multiple doses of momelotinib (200 mg once daily) increased rosuvastatin C_{max} by 3.2-fold and AUC by 2.7-fold, which may increase the risk of adverse reactions of rosuvastatin. T_{max} and $t_{1/2}$ of rosuvastatin remained unchanged. Momelotinib may increase exposure to other sensitive BCRP substrates, including sulfasalazine.

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Momelotinib may inhibit P-gp in the gut and increase exposure to P-gp substrates. Therefore, caution is advised when administering momelotinib with P-gp substrates with a narrow therapeutic index.

Momelotinib may inhibit organic cation transporter 1 (OCT1). The active metabolite of momelotinib, M21, may inhibit multidrug and toxic compound extrusion transporter 1 (MATE1). Momelotinib and M21 have not been evaluated for MATE2-K inhibition. Therefore, caution is advised when administering momelotinib with sensitive substrates of OCT1, MATE1 and MATE2-K (e.g., metformin).

CYP450 substrates

Momelotinib may induce CYP1A2 and CYP2B6 and may inhibit CYP2B6. Therefore, narrow therapeutic index or sensitive substrate medicinal products of CYP1A2 (e.g., theophylline, tizanidine) or CYP2B6 (e.g., cyclophosphamide) should be co-administered with momelotinib with caution.

Hormonal contraceptives

Multiple doses of momelotinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. However, a risk for induction of other pregnane X receptor (PXR) regulated enzymes apart from CYP3A4 cannot be completely excluded and the effectiveness of concomitant administration of oral contraceptives may be reduced (see sections 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should be advised to avoid becoming pregnant whilst receiving Omjjara. It is currently unknown whether Omjjara may reduce the effectiveness of systemically acting hormonal contraceptives, therefore women using systemically acting hormonal contraceptives should add a barrier method during treatment and for at least 1 week after the last dose of Omjjara (see sections 4.4 and 4.5).

Pregnancy

There are no data from the use of momelotinib in pregnant women. Studies in animals have shown embryo-foetal toxicity at exposures lower than human exposure at the recommended dose (see section 5.3). Based on its mechanism of action, Omjjara may cause foetal harm. As a JAK inhibitor, Omjjara has been shown to cause embryo-foetal mortality and teratogenicity in pregnant rats and rabbits at clinically-relevant exposures. Omjjara is contraindicated during pregnancy (see section 4.3). If Omjjara is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should discontinue treatment and be advised of the potential hazard to the foetus.

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Breast-feeding

It is unknown whether momelotinib/metabolites are excreted in human milk. Momelotinib was present in rat pups following nursing from treated dams with adverse events in the offspring (see section 5.3). A risk to the breast-fed child cannot be excluded. Omjjara is contraindicated during breast-feeding (see section 4.3).

Fertility

There are no data on the effects of momelotinib on human male or female fertility. In animal studies, momelotinib impaired fertility in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Omjjara may have a minor influence on the ability to drive and use machines, dizziness or blurred vision may occur. Patients who experience dizziness or blurred vision after taking Omjjara should observe caution when driving or using machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of Omjjara, evaluated in three randomised, active-controlled, multicentre studies in adults with myelofibrosis (MOMENTUM, SIMPLIFY-1, and SIMPLIFY-2), is presented below (table 2). Among patients treated with Omjjara 200 mg daily in the randomised treatment period of the clinical trials (n = 448), the most common adverse reactions were diarrhoea (23%), thrombocytopenia (21%), nausea (17%), headache (13%), dizziness (13%), fatigue (12%), asthenia (11%), abdominal pain (11%), and cough (10%).

The most common severe adverse reaction (≥ Grade 3) was thrombocytopenia (11%). The most common adverse reaction leading to discontinuation of Omjjara was thrombocytopenia (2%). The most common adverse reaction requiring dosage reduction and/or treatment interruption was thrombocytopenia (7%).

Tabulated list of adverse reactions

The following adverse reactions have been identified in 448 patients exposed to Omjjara during a median duration of 24 weeks during clinical trials (see section 5.1). Adverse reactions are listed by MedDRA system organ classification (SOC) and by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as:

Very common: ≥1/10

Common: ≥1/100 to <1/10

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Uncommon: ≥1/1 000 to <1/100

Rare: ≥1/10 000 to <1/1 000

Table 2: Summary of adverse reactions reported in Phase 3 studies in adults with myelofibrosis

System organ class (SOC)	Adverse reaction	Frequency category
Infections and infestations	Urinary tract infection, upper respiratory tract infection, pneumonia, nasopharyngitis, COVID-19, cystitis, bronchitis, oral herpes, sinusitis, herpes zoster, cellulitis, respiratory tract infection, sepsis, lower respiratory tract infection, oral candidiasis, skin infection, gastroenteritis	Common
	COVID-19 pneumonia	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia[a]	Very common
	Neutropenia[b]	Common
Metabolism and nutrition disorders	Vitamin B1 deficiency	Common
Nervous system disorders	Dizziness, headache	Very common
	Syncope, peripheral neuropathy[c], paraesthesia	Common
Eye disorders	Blurred vision	Common
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension, haematoma, flushing	Common
Respiratory, thoracic and mediastinal disorders	Cough	Very common
Gastrointestinal disorders	Diarrhoea, abdominal pain, nausea	Very common
	Vomiting, constipation	Common
Musculoskeletal and connective tissue disorders	Arthralgia, pain in extremity	Common
General disorders and administration site conditions	Asthenia, fatigue	Very common
	Pyrexia	Common
Investigations	Alanine transaminase (ALT) increased, aspartate transaminase (AST) increased	Common
Injury, poisoning and procedural complications	Contusion	Common

[a] Thrombocytopenia includes platelet count decreased.

[b] Neutropenia includes neutrophil count decreased.

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c Peripheral neuropathy includes peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy peripheral, peripheral sensorimotor neuropathy, neuralgia, and polyneuropathy.

Description of selected adverse reactions

Infections

In the three randomised clinical trials, the most common infections were urinary tract infection (6%), upper respiratory tract infection (4.9%), pneumonia (3.6%), nasopharyngitis (2.9%), COVID-19 (2.7%), cystitis (2.7%), bronchitis (2.5%), and oral herpes (2.5%). The majority of infections were mild or moderate; the most frequently reported severe (≥ Grade 3) infections were pneumonia, sepsis, urinary tract infection, cellulitis, COVID-19 pneumonia, COVID-19, herpes zoster, cystitis, and skin infection. The proportion of patients discontinuing treatment due to an infection was 2% (9/448). Fatal infections were reported in 2.2% (10/448) of patients (most frequently reported COVID-19 and COVID-19 pneumonia).

Thrombocytopenia

In the three randomised clinical trials, 21% (94/448) of patients treated with Omjjara experienced thrombocytopenia; 12% (54/448) of patients treated with Omjjara experienced severe thrombocytopenia (≥ Grade 3). The proportion of patients discontinuing treatment due to thrombocytopenia was 2.5% (11/448).

Peripheral neuropathy

In the three randomised clinical trials, 8.7% (39/448) of patients treated with Omjjara experienced peripheral neuropathy. The majority of cases were mild or moderate, while one of the 39 cases was severe (≥ Grade 3). The proportion of patients discontinuing treatment due to peripheral neuropathy was 0.7% (3/448).

Elevated ALT/AST

In the three randomised clinical trials, new or worsening elevations of ALT and AST (all grades) occurred in 20% (88/448) and 20% (90/448), respectively, of patients treated with Omjjara; Grade 3 and 4 transaminase elevations occurred in 1.1% (5/448) and 0.2% (1/448) of patients, respectively. Reversible drug-induced liver injury has been reported in patients with myelofibrosis treated with Omjjara in clinical trials.

Reporting of suspected adverse reactions

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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 Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

If overdose is suspected, the patient should be monitored for any signs or symptoms of adverse reactions or effects, and appropriate standard of care measures should be instituted immediately. Further management should be as clinically indicated. Haemodialysis is not expected to enhance the elimination of momelotinib.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors. ATC code: not yet assigned

Mechanism of action

Momelotinib and its major human circulating metabolite (M21), are inhibitors of wild type Janus Kinase 1 and 2 (JAK1/JAK2) and mutant $JAK2^{V617F}$, which contribute to signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. JAK1 and JAK2 recruit and activate STAT (signal transducer and activator of transcription) proteins that control gene transcription impacting inflammation, haematopoiesis, and immune regulation. Myelofibrosis is a myeloproliferative neoplasm associated with constitutive activation and dysregulated JAK signalling that contributes to elevated inflammation and hyperactivation of activin A receptor type 1 (ACVR1), also known as activin receptor-like kinase 2 (ALK-2). Additionally, momelotinib and M21 are direct inhibitors of ACVR1, which further down regulates liver hepcidin expression resulting in increased iron availability and red blood cell production. Momelotinib and M21 potentially inhibit additional kinases, such as other JAK family members, inhibitor of κB kinase (IKK), interleukin-1 receptor-associated kinase 1 (IRAK1), and others.

Pharmacodynamic effects

Momelotinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from patients with myelofibrosis and inhibits hepcidin. Maximal inhibition of STAT3 phosphorylation occurred 2 hours after momelotinib dosing with inhibition persisting for at least 6 hours. An acute and sustained reduction of circulating hepcidin was observed for the duration of the 24-week study, associated with increased iron levels and haemoglobin, following administration of momelotinib to patients with myelofibrosis.

Clinical efficacy and safety

The efficacy of momelotinib in the treatment of patients with myelofibrosis was evaluated in two randomised Phase 3 trials, MOMENTUM and SIMPLIFY-1.

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Myelofibrosis patients who have been treated with ruxolitinib

MOMENTUM was a double-blind, 2:1 randomised, active-controlled Phase 3 study in 195 symptomatic and anaemic patients with myelofibrosis who had previously received a JAK inhibitor. All patients had received ruxolitinib and 3.6% of patients had also received fedratinib; prior JAK inhibitor treatment was for ≥ 90 days or ≥ 28 days if therapy was interrupted by the need for red blood cell transfusions or due to Grade 3 or 4 thrombocytopenia, anaemia, or haematoma. Patients were treated with Omjjara 200 mg once daily or danazol 300 mg twice daily for 24 weeks, followed by open-label treatment with Omjjara. The two primary efficacy endpoints were percentage of patients with total symptom score (TSS) reduction of 50% or greater from baseline to week 24 (as measured by the Myelofibrosis Symptom Assessment Form [MFSAF] v4.0), and the percentage of patients who were transfusion independent (TI) at week 24 (defined as no transfusions and all haemoglobin values ≥8 g/dL in the 12 weeks prior to week 24). A key secondary endpoint measured the percentage of subjects with ≥35% reduction in spleen volume from baseline at week 24.

Per eligibility criteria, patients were symptomatic with a MFSAF TSS of ≥10 points at screening (mean MFSAF TSS 27 at baseline), and anaemic with haemoglobin (Hgb) values <10 g/dL. The MFSAF daily diary captured the core symptoms of MF: night sweats, abdominal discomfort, pain under the left rib, fatigue, early satiety, pruritus, and bone pain. The inactivity item was excluded from the TSS calculation. Each of the symptoms of the MFSAF v.4.0 were measured on a scale of 0 (absent) to 10 (worst imaginable). Eligible patients were also required to have an enlarged spleen at baseline and a minimum baseline platelet count of 25×10^9/L.

Patients had received prior JAK inhibitor therapy for a median duration of 99 weeks. The median age was 71 years (range 38 to 86 years); 79% were 65 years or older, and 31% were aged 75 years or older, and 63% were male. Sixty-four percent (64%) of patients had primary myelofibrosis, 19% had post-PV myelofibrosis, and 17% had post-ET myelofibrosis. Five percent (5%) of patients had intermediate-1 risk, and 57% had intermediate-2 risk, and 35% had high-risk disease, determined by the Dynamic International Prognostic Scoring System (DIPSS). Sixteen percent (16%) of patients had severe thrombocytopenia (defined as platelet values of less than 50×10^9/L). Forty-eight percent (48%) of patients had severe anaemia (defined as baseline Hgb values <8 g/dL). Within the 8 weeks prior to enrolment, 79% had red blood cell transfusions. At baseline, 13% and 15% of patients treated with Omjjara and danazol, respectively, were transfusion independent (no transfusions and all haemoglobin values ≥8 g/dL in the 12 weeks prior to dosing). The baseline median Hgb value was 8.0 g/dL (range 3.8 g/dL to 10.7 g/dL), and the median platelet count was 96×10^9/L (range 24×10^9/L to 733×10^9/L). The baseline median palpable spleen length was 11.0 cm below the left costal margin; the median spleen volume (measured by magnetic resonance imaging [MRI] or computed tomography [CT])] was 2105 cm^3 (range 609 to 9717 cm^3).

At week 24, a significantly higher percentage of patients treated with Omjjara achieved a TSS reduction of 50% or greater from baseline (superiority, one of the primary endpoints) and a spleen volume reduction by 35% or greater from baseline (superiority, one of the secondary endpoints) (table 3).

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Table 3: Percent of patients achieving symptom reduction and spleen volume reduction at week 24 (MOMENTUM)

	Omjjara n = 130	**Danazol n = 65**
Patients with TSS reduction of 50% or greater, n (%)	32 (25%)	6 (9%)
Treatment difference[a] (95% CI)	16% (6, 26)	
p-value (superiority)	0.0095	
Patients with spleen volume reduction by 35% or greater, n (%)	29 (22%)	2 (3%)
Treatment difference[a] (95% CI)	18% (10, 27)	
p-value (superiority)	0.0011	

TSS = total symptom score; CI = confidence interval.

[a] Superiority based on a stratified Cochran-Mantel-Haenszel test.

A numerically higher percent of patients treated with Omjjara (30%; 39/130) achieved transfusion independence (defined as no transfusions and all Hgb values ≥8 g/dL in the 12 weeks prior to week 24) compared with 20% (13/65) for danazol at week 24.

Myelofibrosis patients who are JAK inhibitor naïve

SIMPLIFY-1 was a double-blind, randomised, active-controlled study in 432 patients with myelofibrosis who had not previously received a JAK inhibitor. Post-hoc analyses were conducted in a subgroup of 181 patients with moderate to severe anaemia (Hgb <10 g/dL). The baseline characteristics and efficacy results are provided for this subgroup.

In the overall population, the primary efficacy endpoint was percentage of patients with spleen volume response (reduction by 35% or greater) at week 24. Secondary endpoints included modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) TSS response rate at week 24 (defined as the percentage of patients with TSS reduction of 50% or greater from baseline to week 24) and transfusion independence at week 24 (defined as no transfusions and all Hgb values ≥8 g/dL in the 12 weeks prior to week 24).

Per eligibility criteria, patient TSS response was measured by the modified MPN-SAF v2.0 diary (mean MPN-SAF TSS 19 at baseline). The inactivity item was excluded from the TSS calculation. Eligible patients were also required to have an enlarged spleen at baseline and a minimum baseline platelet count of 50×10^9/L.

In the anaemic subgroup, the median age was 68 years (range 25 to 86 years) with 67% of patients older than 65 years, and 19% were aged 75 years or older, and 59% male. Sixty-three percent (63%) of patients had primary myelofibrosis, 13% had post-PV myelofibrosis, and 24% had post-ET myelofibrosis. Four percent (4%) of patients had intermediate-1 risk, and 25% had intermediate-2 risk, and 71% had high-risk disease, determined by the International Prognostic Scoring System (IPSS). In this study, 42% of patients had moderate to severe anaemia (defined as baseline Hgb values <10 g/dL). Within the 8 weeks prior to enrolment, 55% of patients had red blood cell transfusions. At baseline, 29% and 44% of patients treated with Omjjara and ruxolitinib, respectively, were transfusion independent (no transfusions and all haemoglobin values ≥8 g/dL in the 12 weeks prior to dosing). The baseline median Hgb value was 8.8 g/dL (range 6 g/dL to 10 g/dL), and the median platelet count was 193 × 10^9/L at baseline (range 54 × 10^9/L to 2865 × 10^9/L). The baseline median palpable spleen length was 12.0 cm below the left costal margin; the median spleen volume (measured by MRI or CT) was 1843 cm^3 (range 352 to 9022 cm^3). The baseline characteristics of the overall population were similar to the anaemic subgroup, with the exception of anaemia severity and transfusion requirements.

Patients were treated with Omjjara 200 mg daily or ruxolitinib adjusted dose twice daily for 24 weeks, followed by open-label treatment with Omjjara without tapering of ruxolitinib. The efficacy of Omjjara in SIMPLIFY-1 was based on post-hoc analysis of spleen volume response (reduction by 35% or greater) in the subgroup of patients with anaemia (Hgb values <10 g/dL) (table 4). In this subgroup, a numerically lower percent of patients treated with Omjjara (25%) achieved a TSS reduction of 50% or greater at week 24 compared with ruxolitinib (36%).

Table 4: Percent of patients achieving spleen volume reduction at week 24 in the anaemic subgroup (SIMPLIFY-1)

	Omjjara **n = 86**	**Ruxolitinib** **n = 95**
Patients with spleen volume reduction by 35% or greater, n (%)	27 (31%)	31 (33%)
(95% CI)	(22, 42)	(23, 43)

In the overall population, the percent of patients achieving 35% or greater reduction from baseline in spleen volume (non-inferiority, primary endpoint) at week 24 was 27% for Omjjara and 29% for ruxolitinib (treatment difference 9%; 95% CI: 2, 16, p-value: 0.014).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Omjjara in all subsets of the paediatric population in the treatment of myelofibrosis (see 4.2 for information on paediatric use).

SUMMARY OF PRODUCT CHARACTERISTICS

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5.2 Pharmacokinetic properties

Absorption

Momelotinib is rapidly absorbed after oral administration with the maximal plasma concentration (C_{max}) achieved within 3 hours post-dose, with plasma exposures increased in a less than dose-proportional manner, especially at doses above 200 mg. In a clinical study, at the dose of 200 mg once daily at steady state, the mean momelotinib C_{max} (% CV) is 479 ng/mL (61%) and AUC_{tau} is 3288 ng×h/mL (60%) in patients with myelofibrosis.

Following low-fat and high-fat meals in healthy volunteers, the C_{max} of momelotinib was 38% and 28% higher, respectively, and the AUC was 16% and 28% higher, respectively, as compared with those under fasted conditions. These changes in exposure were not clinically meaningful.

Distribution

Plasma protein binding of momelotinib is approximately 91% in humans. Based on population pharmacokinetics, the mean apparent volume of distribution of momelotinib at steady-state was 984 L in patients with myelofibrosis receiving momelotinib 200 mg once daily suggesting extensive tissue distribution.

Biotransformation

Based on *in vitro* assessment, momelotinib is metabolised by multiple CYP enzymes (including CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP1A2). Generation of the active metabolite M21, involves biotransformation by CYP enzymes followed by metabolism by aldehyde oxidase.

Elimination

Following an oral dose of momelotinib 200 mg, the mean terminal half-life ($t_{½}$) of momelotinib was approximately 4 to 8 hours; the half-life of M21 was similar. Based on a clinical study, the apparent total clearance (CL/F) of momelotinib was 103 L/h in patients with myelofibrosis.

Momelotinib is mainly eliminated through metabolism and then excreted to faeces. Following a single oral dose of [^{14}C]-labelled momelotinib in healthy male subjects, 69% of radioactivity was excreted in the faeces (13% of dose as unchanged momelotinib), and 28% in the urine (<1% of dose as unchanged momelotinib).

In vitro evaluation of medicinal product interaction potential (see also section 4.5)

SUMMARY OF PRODUCT CHARACTERISTICS

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Effect of momelotinib on other medicinal products

Effect of momelotinib on UDP-glucuronosyltransferase (UGT)

Momelotinib is an inhibitor of UGT1A1 and UGT1A9 at clinically relevant concentrations, but the clinical relevance is unknown. Momelotinib and its major circulating metabolite are not inhibitors of the other isoforms (UGT1A3/4/6 and 2B7) at clinically relevant concentrations.

Effect of momelotinib on CYP450 enzymes

At clinically relevant concentrations neither momelotinib nor the major circulating metabolite, M21, represent a risk of inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

Effect of momelotinib on drug transporters

In vitro data indicates that momelotinib inhibits OCT1 and the active metabolite, M21, inhibits MATE1 at clinically relevant concentrations. Neither momelotinib nor M21 have been evaluated for MATE2-K inhibition.

In vitro data indicate that neither momelotinib nor its major metabolite, M21, inhibits the following transporters at clinically relevant concentrations: organic anion transporter 1 and 3 (OAT1, OAT3) and OCT2.

Effect of momelotinib on hormonal contraceptives

Multiple doses of momelotinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. However, a risk for induction of other pregnane X receptor (PXR) regulated enzymes apart from CYP3A4 cannot be completely excluded and the effectiveness of concomitant administration of oral contraceptives may be reduced (see sections 4.4 and 4.5).

Special populations

Age, body weight, gender and race

Gender and race (White vs Asian) do not have a clinically relevant effect on the pharmacokinetics of momelotinib based on exposure (AUC) data in healthy subjects. Exploratory results of population pharmacokinetics analysis in patients did not show any effects of age, weight, or gender on momelotinib pharmacokinetics.

Hepatic impairment

Momelotinib AUC increased by 8% and 97% in subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, respectively, compared to subjects with normal hepatic function (see section 4.2).

SUMMARY OF PRODUCT CHARACTERISTICS

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5.3 Preclinical safety data

Carcinogenesis/mutagenesis

Momelotinib was not carcinogenic in mice and rats at exposures up to 12 and 17 times the clinical exposure level at 200 mg once daily based on combined momelotinib and the active major human metabolite, M21 (minimally produced in mice, rats and rabbits), AUC.

Momelotinib was not mutagenic or genotoxic based on the results of a series of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Reproductive toxicity

Fertility

In fertility studies, momelotinib was administered orally to male and female rats.

In males, momelotinib reduced sperm concentration and motility and reduced testes and seminal vesicle weights at doses of 25 mg/kg/day and greater (exposures 13-times the recommended dose of 200 mg daily based on combined momelotinib and M21 AUC) resulting in reduced fertility at 68 mg/kg/day.

Observations in females included reduced ovarian function at 68 mg/kg/day and decreased number of pregnancies, increased pre- and post-implantation loss with total litter loss in most animals at 25 and 68 mg/kg/day. Exposures at the no adverse effect level in male and female rats at 5 mg/kg/day were approximately 3 times the recommended dose of 200 mg daily (based on combined momelotinib and M21 AUC).

Pregnancy

In animal reproduction studies, oral administration of momelotinib to pregnant rats during the period of organogenesis caused maternal toxicity at 12 mg/kg/day and was associated with embryonic death, visceral malformation, and decreased foetal weights; skeletal variations were observed at 6 and 12 mg/kg/day and (approximately 3.5-fold the recommended dose of 200 mg daily based on combined momelotinib and M21 AUC). There were no developmental effects observed at 2 mg/kg/day at exposures equivalent to the recommended dose of 200 mg (based on combined momelotinib and M21 AUC).

In pregnant rabbits, oral administration of momelotinib during the period of organogenesis caused severe maternal toxicity and evidence of embryo-foetal toxicity (decreased foetal weight, delayed bone ossification, and abortion) at 60 mg/kg/day at less than the exposure equivalent to the recommended dose of 200 mg (based on combined momelotinib and M21 AUC).

SUMMARY OF PRODUCT CHARACTERISTICS

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In an oral pre- and post-natal development study, rats received oral administration of momelotinib from gestation to end of lactation. Evidence of maternal toxicity, embryo-lethality, and decreased birth weights were observed at 6 and 12 mg/kg/day. Pup survival was significantly reduced at 12 mg/kg/day from birth to Day 4 of lactation at exposures similar to or less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC) and was therefore considered a direct effect of momelotinib via exposure through the milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Lactose monohydrate

Sodium starch glycolate (type A)

Magnesium stearate

Silica colloidal anhydrous

Propyl gallate

Tablet coating

Polyvinyl alcohol

Macrogols

Titanium dioxide (E171)

Talc

Iron oxide yellow (E172)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original bottle in order to protect from moisture. Do not remove the desiccant. Do not swallow the desiccant. This medicinal product does not require any special temperature storage conditions.

SUMMARY OF PRODUCT CHARACTERISTICS

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6.5 Nature and contents of container

Each carton contains one white, high-density polyethylene (HDPE) bottle with a child-resistant polypropylene cap and induction-sealed, aluminium faced liner. Each bottle contains 30 film-coated tablets, a silica gel desiccant, and polyester coil.

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

GlaxoSmithKline UK Limited

980 Great West Road

Brentford

Middlesex

TW8 9GS

8 MARKETING AUTHORISATION NUMBER

PLGB 19494/0318

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/01/2024

10 DATE OF REVISION OF THE TEXT

30/01/2024