swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Omjjara

International non-proprietary name:	momelotinib
Pharmaceutical form:	film-coated tablet
Dosage strength(s):	100 mg, 150 mg, 200 mg
Route(s) of administration:	oral use
Marketing authorisation holder:	GlaxoSmithKline AG
Marketing authorisation no.:	69428
Decision and decision date:	approved on 25 September 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ACVR1	Activin A receptor type 1
AE	Adverse event
AUC	Area under the plasma concentration-time curve
BID	Twice daily
C_{max}	Maximum observed plasma/serum concentration of drug
DAN	Danazol
EMA	European Medicines Agency
ERA	Environmental risk assessment
ET	Essential thrombocythaemia
FDA	Food and Drug Administration (USA)
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
INN	International non-proprietary name
JAK	Janus kinase
JAKi	Janus kinase inhibitor
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MF	Myelofibrosis
Min	Minimum
MMB	Momelotinib
NO(A)EL	No observed (adverse) effect level
OS	Overall survival
PMF	Primary myelofibrosis
PV	Polycythaemia vera
QD	Once daily
QSAR	Quantitative structure-activity relationship
RMP	Risk management plan
SMF	Secondary myelofibrosis
STAT	Signal transducer and activator of transcription
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TSS	Total symptom score
UPLC	Ultra-performance liquid chromatography

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for momelotinib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 7 December 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Omjjara is indicated for the treatment of primary myelofibrosis, post-polycythaemia vera myelofibrosis, and post-essential thrombocythaemia myelofibrosis in adults with anaemia.

2.2.2 Approved indication

Omjjara as monotherapy is indicated for the treatment of intermediate or high-risk primary myelofibrosis, myelofibrosis secondary to polycythaemia vera, or myelofibrosis secondary to essential thrombocythaemia in adults with moderate or severe anaemia, who have been treated previously with ruxolitinib or are not eligible for treatment with ruxolitinib, and who are not eligible for allogeneic stem cell transplantation (see "*Clinical efficacy*").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dosage is 200 mg orally once daily. Omjjara may be taken with or without food.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	16 May 2023
Formal objection	5 June 2023
Response to formal objection	13 June 2023
Formal control completed	20 June 2023
List of Questions (LoQ)	17 October 2023
Response to LoQ	15 January 2024

Preliminary decision	12 April 2024
Response to preliminary decision	11 June 2024
Labelling corrections and/or other aspects	11 September 2024
Response to labelling corrections and/or other aspects	20 September 2024
Final decision	25 September 2024
Decision	approval

3 Medical context

Myelofibrosis (MF) is a rare Philadelphia chromosome-negative myeloproliferative neoplasm, which can present as a *de novo,* primary myelofibrosis (PMF) or as secondary MF (SMF) following the progression of polycythaemia vera (PV) and essential thrombocythaemia (ET) [post-PV MF or post-ET MF]. At a biological level, MF is characterised by clonal expansion of malignant haematopoietic stem and progenitor cells, with aberrant trafficking to extramedullary sites of haematopoiesis and secretion of inflammatory cytokines. The histopathological consequences are bone marrow hypercellularity, and reticulin and collagen fibrosis. The clinical picture is heterogeneous but in general includes progressive cytopenia, organomegaly, debilitating systemic symptoms, and the potential for evolution to acute myeloid leukaemia. Myelocytosis and systemic proinflammatory conditions significantly increase the risk of arterial and venous vascular events.

Therapy of MF is risk-adapted. While observation alone is advised for asymptomatic low-risk disease, allogeneic haematopoietic cell transplant is currently the only known cure for MF and the preferred treatment of choice for high-risk and selected intermediate-risk disease. Drug therapy for MF is palliative and aims at improving the key clinical features anaemia, splenomegaly, and MF-related symptoms. Because hyperactivity of the JAK-STAT signalling pathway is the central biological hallmark of MF, with somatic mutations involving the 3 genes *JAK2*, *CALR,* and *MPL* comprising 90% of driver mutations, JAK inhibitors (JAKi), such as ruxolitinib, are a standard treatment for MF. However, there is currently no convincing evidence regarding disease-modifying effects and impact on long-term efficacy outcomes such as overall survival (OS), and objective responses such as complete or partial responses are hardly ever achieved. In addition, while the currently approved JAKi might be able to address splenomegaly and MF-related symptoms, disease-related cytopenias, remain a therapeutic challenge, and might be even exacerbated or induced by JAKi therapy.

Despite its debilitating character, the management of anaemia is particularly challenging as neither hydroxyurea nor approved JAKi show satisfactory effectiveness against MF-associated anaemia. Other drugs used to treat MF-associated anaemia include danazol, androgens, prednisone, and thalidomide or lenalidomide ± prednisone. Erythropoiesis-stimulating agents are often ineffective in transfusion-dependent patients and could exacerbate splenomegaly. Response rates to the aforementioned drugs are approximately 15 to 25%, and response durations average about 1 to 2 years. In summary, there is still a medical need for the management of MF-associated anaemia, especially when associated with symptomatic splenomegaly or MF-related symptoms.

Hyperactivity of the JAK-STAT signalling pathway leads to hyperactivation of activin A receptor type 1 (ACVR1) and consequently elevated hepcidin levels. Besides JAK 1 and 2, momelotinib (MMB) and its major human circulating metabolite inhibit ACVR1, which produces subsequent inhibition of liver hepcidin expression and increased iron availability, resulting in increased red blood cell production.

4 Quality aspects

4.1 Drug substance

Momelotinib
INN: Momelotinib dihydrochloride monohydrate

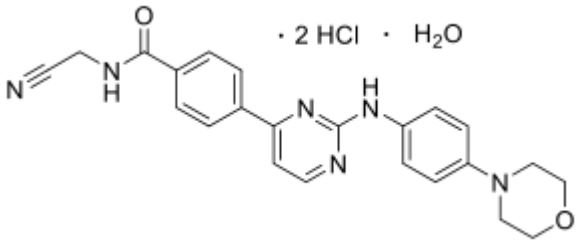
Chemical name:
IUPAC:
N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl] amino}pyrimidin-4-yl)benzamide dihydrochloride hydrate

Other chemical names:
Benzamide, N-(cyanomethyl)-4-[2-[[4-(4-morpholinyl)phenyl]amino]-4-pyrimidinyl]
N-(cyanomethyl)-4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]benzamide dihydrochloride monohydrate

Molecular formula:
$C_{23}H_{22}N_6O_2 \cdot 2HCl \cdot H_2O$
$C_{23}H_{22}N_6O_2$ (free base)

Molecular mass:
Momelotinib dihydrochloride monohydrate = 505.40
Momelotinib free base = 414.47

Molecular structure:



Physicochemical properties:
BCS Class 2.
One polymorphic form for momelotinib dihydrochloride monohydrate (GS-0387-01, Form II) has been observed.

Synthesis:
The manufacturing process of momelotinib dihydrochloride monohydrate drug substance (DS) is composed of 5 steps.

Specification:
Visual appearance, identification (IR and UPLC retention time), identification of crystalline form II, water content, residual solvents by GC, assay by UPLC, related substances by UPLC, hydrochloride content by titration, particle size by laser light scattering, residue on ignition/sulphated ash, microbial limits.

Stability:
The proposed retest period is justified based on the available results of stability studies performed according to ICH requirements.

4.2 Drug product

Description and composition:
Momelotinib tablets are manufactured in strengths of 100 mg, 150 mg, and 200 mg.
Momelotinib tablets, 100 mg, are brown, round, film-coated tablets, debossed with an underscored M on one side and 100 on the other side.

Momelotinib tablets, 150 mg, are brown, triangle-shaped, film-coated tablets, debossed with an underscored M on one side and 150 on the other side.

Momelotinib tablets, 200 mg, are brown, capsule-shaped, film-coated tablets, debossed with an underscored M on one side and 200 on the other side.

Excipients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, silica colloidal anhydrous, propyl gallate. Film coating: polyvinyl alcohol, macrogol 3350, titanium dioxide, talc, yellow iron oxide, red iron oxide.

Pharmaceutical development:
An overview of the formulations employed in clinical trials throughout the development of momelotinib is provided.
There were no process changes between Phase 3 and commercial process.

Manufacture:
The manufacturing process utilises conventional steps to produce a powder blend by dry granulation. Tablet production involves tablet compression and tablet coating.

Specification:
Appearance, identification (UV and UPLC retention time), water content by Karl Fischer, assay by UPLC, degradation products by UPLC, uniformity of dosage units, dissolution, propyl gallate content, microbial limits.

Container closure system:
High-density polyethylene (HDPE) bottle with silica gel desiccant and polyester coil. Capped with a white, continuous thread, child resistant polypropylene cap fitted with an induction-sealed, aluminium-faced liner.

Stability:
The proposed shelf life of 36 months is supported by sufficient data.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Momelotinib is a potent inhibitor of Janus kinase 1 and 2 (JAK 1 and JAK 2) with IC_{50} values in a low nanomolar range. In comparison with JAK2, its affinity for JAK3 and tyrosine kinase 2 (TYK2) was at least 4.5 and 1.3 times lower. In the ATP-independent competitive binding assay, M21 (the major human metabolite) exhibited similar activities for members of JAK family as momelotinib. The applicant did not clearly clarify the selectivity of momelotinib and M21 for other JAK family members.

In vitro, momelotinib and M21 inhibited intracellular Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling in activated primary human peripheral blood mononuclear cells, mediated by JAK homo- or heterodimers with EC_{50} values of 59.6 to 725 nM. Momelotinib treatment inhibited hepcidin RNA transcription stimulated by bone morphogenetic protein 6 (BMP6) in a concentration-dependent manner, with an EC50 value of 652 nM. M21 was 2.2 times less potent. These data indicate that momelotinib and M21 may restore iron homeostasis via regulation of activin A receptor type 1 (ACVR1)-mediated hepcidin expression. Momelotinib inhibited the nuclear factor-κB reporter activity with an IC_{50} of 600 nM *in vitro*. M21 was 5-fold less potent. These data suggest that momelotinib may have a beneficial role in myelofibrosis (MF) inflammation, via a JAK-independent mechanism.
In a mouse model of myeloproliferative neoplasm, oral administration of momelotinib at 50 mg/kg (i.e. 240 mg human equivalent dose for an adult of 60 kg) normalised white cell counts, haematocrit, spleen size, and restored physiologic levels of inflammatory cytokines in addition to significantly reducing the concentration of inflammatory cytokines IL-17, IL-3, and IP-10 relative to control animals.
In a rat model of anaemia, oral momelotinib treatment (5 to 25 mg/day for 21 days) normalised haemoglobin and red blood cell numbers, reduced STAT3 levels in the liver and serum hepcidin, and increased serum iron as well as mature red blood cells in the bone marrow.
Secondary pharmacodynamics studies revealed a significant inhibition of UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) at clinically relevant concentration. The clinical consequence of this interaction seems to be minimal.
In safety pharmacology studies, momelotinib did not show any cardiovascular, respiratory, or central nervous system (CNS) effects up to exposure levels corresponding to 3.3-fold (cardiac function) and 6-fold (respiratory and CNS function), when compared to human exposure at therapeutic dosing. In the 26-week study in rats, a reversible, mild slowing of caudal and digital nerve conduction velocity was observed at exposure levels corresponding to 11-fold human exposure based on AUC. No adverse effects, however, were observed in the observational test battery in this study. In clinical trials, peripheral neuropathy was frequently observed and is mentioned in the Information for healthcare professionals and RMP.

5.2 Pharmacokinetics

The pharmacokinetics of momelotinib and its metabolites was investigated in *in vitro* studies and after single intravenous and oral administration in mice, rats, and dogs. Momelotinib dihydrochloride salt was selected for nonclinical and clinical development.
In dogs, rats, and mice, momelotinib salt was rapidly absorbed following oral administration, with T_{max} ≤3 hours post-dose. $T_{1/2}$ was normally ≤ 1.8 hours (similar to humans: T_{max}: 1.8 hours and $T_{1/2}$: 5.1h). The oral bioavailability was approx. 20% in dogs and 50-70% in rats. The volume of distribution was higher in rats than in dogs (6.8 L/kg vs 2.4 L/kg). Momelotinib, M19, M20, and M21 exposure normally increased in a greater than dose-proportional manner. No sex-dependency in pharmacokinetics was observed.
Momelotinib plasma binding was 97.5% in rats, 88.2% in mice, and 80.8% in dogs and humans *in vitro*. In clinical studies, the fraction of bound momelotinib was 91%. The applicant calculated the

safety margins based on the comparison of animal momelotinib exposure to human momelotinib plus M21 exposure.
Wide tissue distribution of ^{14}C-momelotinib was observed with C_{max} at 4 h post-dose, and the highest concentrations of radioactivity were found in the alimentary canals in non-pigmented (Sprague Dawley) and pigmented (Long Evans) rats. No radioactivity was found in bone, brain, spinal cord, and testes. Radioactivity was cleared from tissues by 72 hours post-dose except for pigmented skin and the uveal tract in Long Evans rats, where radioactivity was still quantifiable at 168 hours post-dose.
Placental and milk transfer of momelotinib and its metabolites were not studied. In the PPND study, momelotinib and its metabolites were found in the plasma of the pups, suggesting that momelotinib is secreted in milk.
Momelotinib was moderately metabolised in liver microsomes and in hepatocytes from humans, mice, rats, and dogs. The primary metabolism pathways were oxidation and hydrolysis following a single oral administration of ^{14}C-momelotinib in all three nonclinical species. There were no unique human metabolites. Thiocyanate is generated in rats and dogs as a consequence of hydrolysis of momelotinib to M19. M19 is a major metabolite in animals, but a minor metabolite in humans. Clinically relevant thiocyanate plasma levels were not detected in humans. The pharmacological activity of M21 is similar to momelotinib and its toxicity is adequately assessed in nonclinical species.
In mice, rats, and dogs, ^{14}C-momelotinib-related radioactivity was excreted predominantly in faeces (≥70% of dose), similarly to humans (69.3% via faeces).

5.3 Toxicology

The applicant conducted the toxicological evaluation of momelotinib dihydrochloride salt by single-dose and repeat-dose administration in mice, rats, rabbits, and dogs. Repeat-dose oral administration studies were conducted in mice (up to 56 days with 14-day recovery period), once daily or twice daily (BID) for up to 26 weeks in Sprague Dawley rats (with10-week recovery), once daily for 7 days in New Zealand White (NZW) nonpregnant rabbits, and once daily or BID for up to 39 weeks in beagle dogs (with a 6-week recovery period). The oral route of administration and the duration of the studies in rodents and non-rodents support the clinical use. Mortality was observed in all species or animals had to be prematurely terminated, mostly because of weakness and debilitation and/or clinical signs of continued inappetence, thin appearance, reduced activity, and weight loss.
Momelotinib treatment resulted in a dose-dependent reduction of body weight gain in all species. The main target organs for toxicity were the haematopoietic system and the reproductive organs. In all species, momelotinib treatment was associated with a reduction in red blood cell count, haemoglobin, and haematocrit, as well as a lower white blood cell count, which correlated with dose-related cellular depletion in the bone marrow and lymphoid depletion in the spleen, lymph nodes, thymus, and/or gut-associated lymphoid tissue. There was a trend to recovery from the cellular and lymphoid depletion in the off-dose period. These findings are consistent with the pharmacological activity of momelotinib on Janus kinases involved in haematopoiesis and immune response. No infections were identified in the nonclinical species, although in the clinical trials with momelotinib, infection was a very common adverse reaction, in line with the class effect reported with other JAK inhibitors.
Cataracts were observed in the 39-week study in dogs at 50 mg/kg/day (approx. 1-fold human unbound AUC) and were still present after the recovery period. The clinical relevance of this finding is unknown. In the 26-week study in rats, minimal renal tubular degeneration/regeneration was observed with NOAEL at doses corresponding to 4.5-fold human exposure based on free AUC.

Momelotinib (dihydrochloride salt) was not genotoxic. There were no momelotinib-related neoplasms in animals administered up to 100 mg/kg/day in the 26-week transgenic mouse carcinogenicity study. In the 104-week rat carcinogenicity study, in which rats were treated with either momelotinib (up to 15 mg/kg/day) or with momelotinib (5 mg/kg/day) and M21 (25 mg/kg/day), a momelotinib-related increased incidence of testicular interstitial (Leydig) cell adenoma was observed. This effect is related to the JAK2-mediated inhibition of prolactin signalling pathways in rats and therefore irrelevant for

humans. However, JAK inhibitors carry a risk of carcinogenicity, which is followed by the pharmacovigilance department.

In the fertility and early embryonic development study in rats, momelotinib irreversibly affected male and female reproductive system at ≥ 25 mg/kg/day in a dose-dependent manner. The NOAEL for males and the NOEL for early embryonic development was 5 mg/kg/day, which corresponds to a safety margin of 1-fold based on free AUC in humans at the therapeutic dose.
Momelotinib exerted embryo-fetal toxicity in embryo-fetal growth and development studies in rats and rabbits (no safety margin). JAK2 is involved in embryonal development. Given the known class effects of other marketed JAK inhibitors, momelotinib is to be contra-indicated in pregnancy.
In a pre- and post-natal development study momelotinib maternal toxicity and embryotoxicity was observed at ≥6 mg/kg/day. Pup survival was reduced from birth to weaning by 15% and 11% in pups from the dams administered 6 and 12 mg/kg/day, respectively. This finding was considered a direct effect on the offspring via exposure through the milk. In the post-weaning F1 generation, there were no momelotinib-related clinical findings or effects on any of the developmental landmarks or neurobehavioral parameters. The exposure at NOAEL was lower than the AUC observed at the recommended dose of 200 mg daily. Considering that exposure to momelotinib through the milk was observed at clinically relevant exposure levels and the proven toxic profile of approved JAK inhibitors, momelotinib is contraindicated during breast-feeding.
In a study with juvenile rats treated orally from post-natal day 7 to 21 with up to 30 mg/kg/day, no additional clinical signs were observed in juvenile animals except for a reversible deficit in learning in males. The NOAEL for juvenile toxicity was 3 mg/kg/day (no safety margin).

No immunotoxicology or immunophenotyping studies were conducted with momelotinib as immune suppression is an expected pharmacological effect of JAK inhibitors. This is acceptable.
Impurities are controlled by the toxicity studies, QSAR analysis, and literature. There are no concerns with regard to the excipients.

The submitted ERA is incomplete; an updated assessment is requested as a post-approval requirement.

The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

5.4 Nonclinical conclusions

The pharmaco-toxicological profile of momelotinib is considered sufficiently characterised. The submitted nonclinical data support the approval of Omjjara in the proposed indication. The identified safety concerns in pharmacologically relevant animal species relate to the haematopoietic system and to reproduction. The relevant information has been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on a previous regulatory decision by the US FDA. The available assessment reports and the Information for healthcare professionals from the US FDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, please see section 8 of this report.

6.2 Dose finding and dose recommendation

Overall, 4 clinical studies conducted in patients with PMF or post PV/ET MF and healthy subjects contributed to the selection of the dose for the pivotal study. In addition, supportive exposure-response analyses were submitted. However, these were based on studies which had used no other dosage than 200 mg once daily (QD). Despite this limitation, the dose finding based on 4 Phase 1 and 2 studies and leading to the proposed dosage of 200 mg QD momelotinib (MMB), which was subsequently used in 3 Phase 3 studies, including the pivotal MOMENTUM study, was considered acceptable.

6.3 Efficacy

The pivotal double-blind, randomised Phase 3 MOMENTUM study was conducted in symptomatic and anaemic (haemoglobin <10 g/dl) patients with MF, who had received prior JAK inhibitor (JAKi) therapy. While all patients had received prior therapy with ruxolitinib, 3.6% of patients had also been treated with fedratinib. In total 195 patients were randomly assigned 2:1 to either 200 mg QD MMB or 300 mg twice daily (BID) danazol (DAN). Following the 24-week double-blind treatment phase, all patients received open-label MMB.

The median age of patients was 71 years (range 38 to 86 years); 79% were 65 years or older, and 63% were male. Sixty-four percent had PMF, 19% had post-PV MF, and 17 % had post-ET MF. While 5% of patients had intermediate-1 risk MF, 57% had intermediate-2 risk, and 35% high-risk MF. All patients had a symptomatic MF at screening, with a total symptom score (TSS) ≥10 based on Myelofibrosis Symptom Assessment Form (MFSAF) v4.0; the average TSS at baseline was 27. Median haemoglobin at baseline was 8 g/dl; 79% of patients had received red blood cell transfusions within 8 weeks prior to entering the study. Median platelet count at baseline was 96 × 10^9/l.

The MOMENTUM study met its first primary endpoint, demonstrating a statistically significant improvement in the TSS response rate at Week 24, i.e. the proportion of patients whose TSS decreased (improved) by at least 50% compared to baseline: 25% (95% CI: 17, 33) in the MMB arm vs 9% (95% CI: 3, 19) in the DAN arm; the treatment difference was 16% (95% CI: 6, 26).

Noninferiority could be demonstrated for the second primary endpoint of transfusion independency rate at Week 24, defined as the absence of any red blood cell transfusions along with a haemoglobin level of at least 8 g/dl during the 12-week interval prior to Week 24. The delta for noninferiority was 14% (95% CI: 2, 25); the transfusion independency rate increased from 13% at baseline to 30% at Week 24 in the MMB treatment arm, and from 15% at baseline to 20% at Week 24 in the DAN treatment arm.

In addition, a statistically significant higher proportion of patients in the MMB group vs DAN treatment had no need to receive any transfusion units during treatment and up to Week 24 (35% vs 17%, respectively), which was a secondary efficacy endpoint.

6.4 Safety

The safety pool is comprised of 725 patients who were treated with MMB monotherapy for MF. The most common adverse events were infections (55.4%), haemorrhages (29%), diarrhoea (26.8%), thrombocytopenia (25%), nausea (19.4%), fatigue (17.5%), cough (17.4%), dizziness (15.4%), peripheral neuropathy (14.6%), abdominal pain (14.1%), headache (13.9%), and asthenia (13.2%). Thrombocytopenia was the most common adverse event of ≥ Grade 3 (16.4%), and is an AE related to the mechanism of action of JAKi. It was also the most frequent AE leading to discontinuation of treatment.

Infections included serious and fatal bacterial and viral infections, mainly due to COVID-19. Haemorrhages included 5 serious gastro-intestinal haemorrhages in patients treated with MMB. Peripheral neuropathy included a significant proportion of cases that were irreversible/unresolved by the time of study cut-off. Peripheral neuropathy is considered an adverse reaction of MMB, which is supported by pertinent findings in preclinical (slowing of nerve conduction velocity in rats) and exposure-response analyses (trend for higher incidence of any grade peripheral neuropathy at higher MMB exposure).

Notably, MMB carries a significant risk of hepatocellular drug-induced liver injury (DILI) in MF patients, and increased transaminases have been commonly reported in patients treated with MMB.

6.5 Final clinical benefit-risk assessment

MF-associated anaemia can be debilitating, represents a significant burden to patients, and is frequently associated with a need for red blood cell transfusions and transfusion dependency. Therefore, improving MF-associated anaemia and related symptoms is of clinical relevance.

Non-haematologic toxicities reported on MMB treatment were mainly known JAKi class effects. Haematological toxicities on MMB treatment included thrombocytopenia, which could result in early treatment discontinuations. However, patients with low platelet counts were also treated in the MOMENTUM study, and few serious bleeding adverse events were reported. One of the notable toxicities is peripheral neuropathy, which was generally of low grade but irreversible or reported as ongoing in a substantial proportion of patients. Overall, the observed safety profile is considered manageable and acceptable for the indication, and is adequately labelled in the Information for healthcare professionals.

Considering the unmet medical need for the management of MF-associated anaemia, and based on the consistent anti-anaemic effects of MMB and the manageable safety profile, the benefit-risk balance was considered positive for the approved indication (*in German*):

Omjjara als Monotherapie ist indiziert zur Behandlung der primären Myelofibrose, der Myelofibrose nach Polycythaemia vera oder der Myelofibrose nach essentieller Thrombozythämie mit intermediärem oder hohem Risiko bei Erwachsenen mit moderater oder schwerer Anämie, die vorgängig mit Ruxolitinib behandelt wurden oder für eine Behandlung mit Ruxolitinib nicht in Frage kommen, und die nicht für eine allogene Stammzelltransplantation vorgesehen sind (siehe "Klinische Wirksamkeit").

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Omjjara was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Omjjara

Composition

Active substances

Momelotinib (as momelotinib dihydrochloride monohydrate).

Excipients

Tablet core:
Microcrystalline cellulose (E460i), lactose monohydrate, carboxymethyl starch (type A), magnesium stearate (E470b), highly dispersed silicon dioxide (E551), propyl gallate (E310).
Film coating:
Poly(vinyl alcohol) (E1203), macrogol 3350 (E1521), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), iron oxide red (E172).

Each 100 mg film-coated tablet contains 50.76 mg lactose monohydrate and max. 0.76 mg sodium.
Each 150 mg film-coated tablet contains 76.14 mg lactose monohydrate and max. 1.13 mg sodium.
Each 200 mg film-coated tablet contains 101.52 mg lactose monohydrate and max. 1.51 mg sodium.

Pharmaceutical form and active substance quantity per unit

200 mg, 150 mg or 100 mg film-coated tablets of momelotinib (as momelotinib dihydrochloride monohydrate).

- Brown, capsule-shaped 200 mg film-coated tablets with an embossed and underlined “M” on one side and “200” on the other side.
- Brown, triangular 150 mg film-coated tablets with an embossed and underlined “M” on one side and “150” on the other side.
- Brown, round 100 mg film-coated tablets with an embossed and underlined “M” on one side and “100” on the other side.

Indications/Uses

Omjjara as monotherapy is indicated for the treatment of intermediate or high-risk primary myelofibrosis, myelofibrosis secondary to polycythaemia vera, or myelofibrosis secondary to essential thrombocythaemia in adults with moderate or severe anaemia, who have been treated previously with ruxolitinib or are not eligible for treatment with ruxolitinib, and who are not eligible for allogeneic stem cell transplantation (see "*Clinical efficacy*").

Dosage/Administration

Usual dosage

Adults

The recommended dose of Omjjara is 200 mg orally once daily.

Omjjara may be taken with or without food.

Missed doses

If a dose of Omjjara was missed, the next planned dose should be taken the following day.

Monitoring

A complete blood cell count as well as liver function tests must be performed before initiating treatment with Omjjara, at regular intervals during treatment, and as clinically indicated.

Dose adjustment

Dose adjustment should be considered in the event of haematological or non-haematological toxicity (Table 1). Omjjara must be stopped for patients who are unable to tolerate 100 mg once daily.

Table 1. Dose adjustment following undesirable effects

Haematological toxicities		
Thrombocytopenia		Dose adjustment[a]
Baseline platelet count	Platelet count	
≥100 × 10^9/L	20 × 10^9/L to <50 × 10^9/L	Reduce the daily dose by 50 mg compared to the last dose administered
	<20 × 10^9/L	Interrupt treatment until the platelet count recovers to 50 × 10^9/L Resume treatment at a daily dose of 50 mg below the last dose administered[b]

≥50 × 10^9/L to <100 × 10^9/L	<20 × 10^9/L	Interrupt treatment until the platelet count recovers to 50 × 10^9/L Resume treatment at a daily dose of 50 mg below the last dose administered [b]
<50 × 10^9/L	<20 × 10^9/L	Interrupt treatment until the platelet count recovers to baseline. Resume treatment at a daily dose of 50 mg below the last dose administered[b]
Neutropenia		Dose adjustment[a]
Absolute neutrophil count (ANC) <0.5 × 10^9/L		Interrupt treatment until ANC ≥0.75 × 10^9/L Resume treatment at a daily dose of 50 mg below the last dose administered[b]
Non-haematological toxicities		
Hepatotoxicity (if no other obvious causes)		Dose adjustment[a]
ALT and/or AST >5 × upper limit of normal (ULN) (or >5 × baseline, if baseline is abnormal) and/or total bilirubin >2 × ULN (or >2 × baseline, if baseline is abnormal)		Interrupt treatment until the AST and ALT is ≤2 × ULN or baseline and total bilirubin is ≤1.5 × ULN or baseline Resume treatment at a daily dose of 50 mg below the last dose administered[b] In the event of a recurrence of ALT or AST increase >5 × ULN, discontinue Omjjara permanently
Other non-haematological toxicities		Dose adjustment[a]
Grade 3 or higher[c] Grade 2 or higher[c] bleeding		Interrupt treatment until the toxicity has decreased to Grade 1 or lower (or baseline). Resume treatment at a daily dose of 50 mg below the last dose administered[b]

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

ULN = upper limit of normal

[a] Resumption of treatment or escalation of treatment up to the starting dose, if clinically appropriate.

[b] A possible alternative is to resume treatment with 100 mg if 100 mg was previously administered.

[c] Assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute.

Special dosage instructions

Patients with renal disorders

The dose does not need to be adjusted for patients with renal disorders (see *"Kinetics in specific patient groups"*). No data are available for patients with end-stage renal disease.

Patients with hepatic disorders
No dose adjustment is recommended in patients with mild to moderate hepatic disorders. The recommended starting dose of Omjjara for patients with severe hepatic disorders (Child-Pugh class C) is 150 mg once daily (see *"Kinetics in specific patient groups"*).

Elderly patients
The dose does not need to be adjusted for patients aged 65 years or over (see *"Kinetics in specific patient groups"*).

Paediatric population
Omjjara is not authorised for use in the paediatric population.

Contraindications

Hypersensitivity to the active substance or one of the excipients as per composition.
Lactation (see section "Pregnancy, lactation").

Warnings and precautions

Infections
Infections, including serious and sometimes fatal bacterial and viral infections (including COVID-19), have occurred in patients treated with Omjjara (see *"Undesirable effects"*). Patients with active infections should not be started on treatment with Omjjara. Doctors should carefully monitor patients receiving Omjjara for signs and symptoms of infection and initiate suitable treatment immediately as required.

Hepatitis B reactivation
Increases in hepatitis B viral load (HBV DNA titre), with or without associated increases in alanine transaminase (ALT) or aspartate transaminase (AST), have been observed in patients with chronic hepatitis B viral (HBV) infection. The effect of Omjjara on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection receiving Omjjara should be treated and monitored according to clinical guidelines for HBV.

Thrombocytopenia and neutropenia
There were reports of new cases of severe thrombocytopenia and neutropenia (Grade ≥3) in patients treated with Omjjara (see *"Undesirable effects"*). A complete blood count, including platelet count, should be obtained before initiating treatment with Omjjara, at regular intervals during treatment, and

as clinically indicated. It may be necessary to suspend treatment or reduce the dose (see *“Dosage/Administration”*).

Hepatotoxicity and hepatic monitoring

Cases of reversible drug-induced liver injury (DILI) and frequent elevations in liver function tests (see “Undesirable effects”) have been reported in patients after taking Omjjara. If there is uncontrolled acute or chronic liver disease, therapy with Omjjara should only be started after the causes have been examined and treatment has been tailored to the patient’s needs. Liver function tests should be performed prior to initiating treatment with Omjjara, at regular intervals during treatment, and as clinically indicated. If treatment-related elevations in ALT, AST or bilirubin are suspected, dose interruption or reduction may be necessary (see “Dosage/Administration”).

Peripheral neuropathy

Peripheral neuropathy was very frequently reported in patients after taking Omjjara, some of which had not resolved by the end of the observation period (see “Undesirable effects”). Patients with peripheral neuropathy greater than Grade 1 were excluded from the Phase 3 studies with Omjjara. The incidence of peripheral neuropathy in these Phase 3 studies was lower than in the early Phase 1/2 studies, which had no exclusion criteria in this regard. Patients should be examined for the presence of peripheral neuropathy before starting therapy with Omjjara, and the results of the examination should be taken into account when making treatment decisions.

Major adverse cardiovascular events (MACE)

In a large, randomised, active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients aged 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 and non-fatal stroke, was observed under treatment with tofacitinib compared with tumour necrosis factor (TNF) inhibitors.

Cases of MACE have been reported in patients receiving Omjjara. Before starting or continuing therapy with Omjjara, the benefits and risks for the individual patient should be considered, particularly in the case of:

- Patients aged 65 years and over,
- Patients who currently smoke or have smoked in the past,
- Patients with other cardiovascular risk factors.

Thrombosis

In a large, randomised, active-controlled study of tofacitinib (another JAK inhibitor) in patients with rheumatoid arthritis aged 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 under treatment with tofacitinib compared to TNF inhibitors.
Cases of DVT and PE have been reported in patients receiving Omjjara. In patients with myelofibrosis treated with Omjjara in clinical trials, rates of thromboembolic events were similar between Omjjara and control patients. Before 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 the section "*Major adverse cardiovascular events (MACE")*).
Patients with symptoms of thrombosis should be examined immediately and treated accordingly.

Second primary malignancies
In a large, randomised, active-controlled study of tofacitinib (another JAK inhibitor) in patients with rheumatoid arthritis aged 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 under treatment with tofacitinib compared to TNF inhibitors.
Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Omjjara. Before starting or continuing therapy with Omjjara, the benefits and risks for the individual patient should be considered, particularly in the case of:

- Patients aged 65 years and over,
- Patients who currently smoke or have smoked in the past,
- Patients with other risk factors for malignancies (e.g., current malignant disease or a previous history of such diseases, with the exception of successfully treated non-melanoma skin cancer (NMSC)).

Pregnancy
In animal reproduction studies, Omjjara exposures less than the recommended human daily dose of 200 mg resulted in embryo-foetal toxicity (see "*Reproductive toxicity*"). Therefore, Omjjara should only be used in pregnancy if the expected benefit to the mother outweighs the potential risks to the unborn child (see "*Pregnancy, lactation"*).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., it is virtually "sodium-free".

Lactose
Patients with rare hereditary galactose intolerance, e.g., galactosaemia or glucose-galactose malabsorption, should not use this medicinal product.

Interactions

Pharmacokinetic interactions

In-vitro studies

Cytochrome P450 (CYP) enzymes:
Momelotinib is a weak, reversible, time-independent inhibitor of CYP2B6, but does not inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6 or 3A4/5. The M21 metabolite does not inhibit any of these CYP enzymes. Momelotinib and M21 do not induce CYP3A4, CYP2C8, CYP2C9 or P-glycoprotein (P-gp).

Uridine diphosphate glucuronosyltransferase (UGT):
Momelotinib is an inhibitor of UGT1A1 and UGT1A9. The M21 metabolite is an inducer of UGT1A1.

Transporter systems:
Momelotinib and M21 are in-vitro substrates for the efflux transporters P-gp and BCRP, and the hepatic uptake transporters OATP1B1/1B3. Momelotinib is an inhibitor of BCRP.

Clinical pharmacokinetic interactions
Effect of other agents on the pharmacokinetics of momelotinib

Strong CYP3A4 inducers
Multiple doses of rifampicin (600 mg daily for 7 days) decreased momelotinib C_{max} by 29.4% and AUC by 46.1% compared to momelotinib (200 mg single dose) plus single rifampicin dose (600 mg), in order to detect the induction effect of rifampicin. The concomitant administration of strong CYP3A4 inducers may result in decreased momelotinib exposure, and thus to a risk of reduced efficacy. Therefore, when momelotinib and strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin and St. John's wort [*Hypericum perforatum*]) are administered concomitantly, additional monitoring is recommended (see "Clinical efficacy").
Multiple doses of rifampicin (600 mg daily for 7 days) did not change the C_{max} of momelotinib and decreased the AUC of momelotinib by 15.3% compared to momelotinib alone (200 mg single dose), reflecting the combined effect of CYP3A4 induction and the inhibition of the organic anion transporting peptides (OATP)1B1 and OATP1B3. Momelotinib can be administered with rifampicin without dose adjustment.

OATP 1B1/1B3 inhibitors

Momelotinib is a substrate of the organic anion transporting polypeptides (OATP) 1B1 and 1B3. Concomitant administration with a single dose of rifampicin, which captures the OATP1B1/1B3 inhibitory effect, moderately increased momelotinib exposure (C_{max} by 40.4% and AUC by 57.1%). Therefore, in the event of the concomitant use of OATP1B1/1B3 inhibitors, including ciclosporin, caution is advised and monitoring for undesirable effects is required.

Strong CYP3A4 inhibitors
Concomitant administration with multiple doses of ritonavir (a strong CYP3A4 inhibitor) increased momelotinib C_{max} by 23.3% and AUC by 13.5%. These changes are not considered clinically relevant.

Proton pump inhibitors
Concomitant administration with multiple doses of omeprazole (a proton pump inhibitor) reduced momelotinib C_{max} by 36% and AUC by 33%. These changes are not considered clinically relevant.

Effect of momelotinib on the pharmacokinetics of other agents

Sensitive substrates of the breast cancer resistance protein (BCRP)
Momelotinib is an inhibitor of the breast cancer resistance protein (BCRP) in vitro. Concomitant administration of a single dose of 10 mg rosuvastatin (a sensitive BCRP substrate) with multiple doses of momelotinib (200 mg once a day) increased the C_{max} of rosuvastatin to 3.2-fold and AUC to 2.7-fold, which may also increase the risk of side effects associated with rosuvastatin. The T_{max} and $t_{1/2}$ of rosuvastatin remained unchanged. Momelotinib may increase the exposure to other sensitive BCRP substrates, including sulfasalazine. In the case of concomitant administration, patients should be monitored for undesirable effects.

Sensitive CYP3A4 substrates
Concomitant administration of multiple doses of momelotinib decreased midazolam (sensitive CYP3A4 substrate) C_{max} by 8.2% and AUC by 16.2%. These changes are not considered clinically relevant.

Pregnancy, lactation

Reproduction
Animal experimental data indicate embryofoetal toxicity. Miscarriage, embryonic death and foetal anomalies were observed in rats and rabbits at exposures below a clinical dose of 200 mg daily (see "*Preclinical data"*). Women of childbearing age who are not pregnant should be advised to avoid pregnancy during treatment with Omjjara and to use a highly effective form of contraception during therapy and for at least one week after discontinuation of therapy.

Pregnancy

There are no data on the effects of momelotinib on pregnancy in humans.

Based on the embryofoetal toxicity observed in the animal reproduction studies, Omjjara may only be used during pregnancy if the expected benefit to the mother outweighs the potential risks to the unborn child (see “Warnings and precautions”).

Lactation

There are no data on whether momelotinib passes into human breast milk. Momelotinib was detected in suckling rat pups of treated dams and had negative effects on offspring (see “Preclinical data”). A risk to breastfed children cannot be ruled out.

Patients should not breastfeed during treatment with momelotinib or for at least one week after discontinuation of treatment (see *“Contraindications”*).

Fertility

Animal experiments indicated harmful effects on fertility. There are no data on the effects of momelotinib on male or female fertility. Women of childbearing age who are not pregnant should be advised to avoid pregnancy during treatment with Omjjara and to use a highly effective form of contraception during therapy and for at least one week after discontinuation of therapy.

Effects on ability to drive and use machines

There have been no studies to investigate the influence of Omjjara on the ability to drive and use machines. Patients who experience nausea, dizziness or blurred vision after taking Omjjara should, however, exercise caution when driving or using machines (see *“Undesirable effects”*).

Undesirable effects

Clinical trial data

Summary of the safety profile

The safety of Omjjara, which was investigated in three multicentre studies in adults (n = 725) with myelofibrosis, is presented below (Table 2). Patients were treated with Omjjara 200 mg daily for a median duration of 49 weeks. The median duration of follow-up was 11.9 months.

The most common undesirable effects were infections (55.4%), haemorrhages (29%), diarrhoea (26.8%), thrombocytopenia (25%), nausea (19.4%), fatigue (17.5%), cough (17.4%), dizziness (15.4%), peripheral neuropathy (14.6%), abdominal pain (14.1%), headache (13.9%) and asthenia

(13.2%). The most common serious side effect (≥ Grade 3) was thrombocytopenia (16.4%). Refer to Table 2 below for more information on infection types.

The undesirable effects of Omjjara, as identified, are listed by MedDRA system organ class and frequency, according to the following convention:
Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1,000
Not known (frequency cannot be estimated from the available data)

Table 2: Tabulated summary of undesirable effects

System organ class (SOC)	**Frequency category**	**Undesirable effect**	
Infections and infestations	Very common	Urinary tract infection	
		All grades[a]	**Grade ≥3[a]**
		12.1%	2.5%
		Pneumonia	
		All grades[a]	**Grade ≥3[a]**
		11.4%	7.6%
		Upper respiratory tract infections	
		All grades[a]	**Grade ≥3[a]**
		10.1%	0.4%
	Common	Nasopharyngitis, oral herpes, sinusitis, herpes zoster, respiratory tract infections, gastroenteritis, cystitis, sepsis, COVID-19, cellulitis, lower respiratory tract infections, influenza, oral candidiasis, skin infections, bronchitis	
Blood and lymphatic system disorders	Very common	Thrombocytopenia	
		All grades[a]	**Grade ≥3[a]**
		25%	16.4%
	Common	Neutropenia	
Metabolic and nutritional disorders	Common	Vitamin B1 deficiency	
Nervous system disorders	Very common	Dizziness	
		All grades[a]	**Grade ≥3[a]**
		15.4%	0.6%
		Peripheral neuropathy[b]	
		All grades[a]	**Grade ≥3[a]**
		14.6%	1.2%
		Headache	
		All grades[a]	**Grade ≥3[a]**
		13.9%	0.8%
	Common	Paraesthesia Syncope	
Ear and inner ear disorders	Common	Vertigo	
Eye disorders	Common	Blurred vision Cataract	
Vascular disorders	Very common	Haemorrhage	
		All grades[a]	**Grade ≥3[a]**

System organ class (SOC)	Frequency category	Undesirable effect	
		29%	6.8%
	Common	Reddened skin Haematoma Hypotension	
Respiratory, thoracic and mediastinal disorders	Very common	Cough	
		All grades[a]	**Grade ≥3[a]**
		17.4%	0.7%
Gastrointestinal disorders	Very common	Diarrhoea	
		All grades[a]	**Grade ≥3[a]**
		26.8%	2.6%
		Nausea	
		All grades[a]	**Grade ≥3[a]**
		19.4%	1.1%
		Abdominal pain	
		All grades[a]	**Grade ≥3[a]**
		14.1%	1.8%
	Common	Constipation Vomiting	
Hepatobiliary disorders	Common	Alanine transaminase (ALT) raised Aspartate transaminase (AST) raised	
Musculoskeletal, connective tissue and bone disorders	Common	Arthralgia Pain in the extremities	
General disorders and administration site conditions	Very common	Asthenia	
		All grades[a]	**Grade ≥3[a]**
		13.2%	2.2%
		Fatigue	
		All grades[a]	**Grade ≥3[a]**
		17.5%	2.5%
	Common	Fever	
Injury, poisoning and complications due to surgery	Common	Contusion	

[a] Assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute.

[b] Peripheral neuropathy includes peripheral sensory neuropathy, peripheral motor neuropathy, peripheral neuropathy, peripheral sensorimotor neuropathy, neuralgia and polyneuropathy.

Description of specific adverse reactions and additional information

Infections

In the three clinical trials that included both the randomised treatment period and the open-label treatment period with momelotinib, infections occurred in 55.4% (402/725) of patients treated with Omjjara, of which 18.6% (135/725) were classified as severe (≥Grade 3), while most cases, namely 81.4% (590/725), were mild or moderate. The most commonly reported infections (≥ 1% of subjects in the overall MMB group) were urinary tract infections (12.1%), pneumonia (11.4%), upper respiratory tract infections (10.1%), bronchitis (6.1%), nasopharyngitis (5.5%), oral herpes (3.4%), sinusitis (3.4%), herpes zoster (3.2%), respiratory tract infections (3.2%), gastroenteritis (3.2%), bladder infection (2.8%), sepsis (2.5%), COVID-19 (2.3%), cellulitis (2.3%), lower respiratory tract infections

(2.3%), influenza (2.3%), oral candidiasis (1.5%), skin infections (1.1%) and COVID-19 pneumonia (1.0%). The proportion of patients who discontinued treatment due to infection was 2.5% (18/725). Fatal infections were reported in 4.4% (32/725) of patients (most commonly pneumonia). See also section “Warnings and precautions”.

Thrombocytopenia

In the three clinical studies that included the randomised treatment period and the momelotinib open-label treatment period, 25% (181/725) of patients treated with momelotinib experienced thrombocytopenia; 16.4% (119/725) of patients treated with momelotinib suffered severe thrombocytopenia (Grade ≥3). Thrombocytopenia caused 3.9% (28/725) of patients to discontinue treatment. See also section “Warnings and precautions”.

Haemorrhage

In the three clinical studies that included the randomised treatment period and the momelotinib open-label treatment period, 29% (208/725) of patients treated with momelotinib experienced haemorrhages (of those, 1% [7/725] of patients experienced upper gastrointestinal haemorrhages); 6.8% (49/725) of patients treated with momelotinib suffered severe haemorrhages (Grade ≥3). Haemorrhages caused 0.8% (6/725) of patients to discontinue treatment.

Peripheral neuropathy

In the three clinical trials that included both the randomised treatment period and the open-label treatment period with momelotinib, peripheral neuropathy occurred in 14.6% (106/725) of patients treated with Omjjara. The preferred terms in this category were: peripheral sensory neuropathy 12.3% (89/725), peripheral neuropathy 1.0% (7/725), peripheral sensorimotor neuropathy 0.7% (5/725), peripheral motor neuropathy 0.6% (4/725), neuralgia 0.6% (4/725) and polyneuropathy 0.3% (2/725). The majority of cases were mild or moderate, while severe cases (≥ Grade 3) occurred in 1.2% (9/725) of subjects, including peripheral sensory neuropathy 0.7% (5/725), peripheral sensorimotor neuropathy 0.3% (2/725), peripheral neuropathy 0.1% (1/725) and peripheral motor neuropathy 0.1% (1/725). The proportion of patients who discontinued treatment due to peripheral neuropathy was 2.5% (18/725). See also section “Warnings and precautions”.

Elevated ALT/AST

In the three clinical trials that included both the randomised treatment period and the open-label treatment period with momelotinib, new or worsening increases (all grades) of ALT and AST occurred in 28.6% (207/725) and 27.2% (197/725) of patients treated with Omjjara; Grade 3 or 4 transaminase elevations occurred in 1.5% (11/725) and 0.3% (2/725), respectively. There were no cases of transaminase elevations leading to discontinuation of Omjjara. See also “Hepatotoxicity and hepatic monitoring” in the “Warnings and precautions” section.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Currently, there is only limited experience of overdose with Omjjara. If overdose is suspected, the patient is to be monitored for signs or symptoms of adverse reactions or undesirable effects and an appropriate standard treatment is to be initiated without delay. Next steps are guided by clinical requirements and, if available, recommendations from the national poison control centre.

Properties/Effects

ATC Code

L01EJ04

Mechanism of action

Momelotinib and its most important metabolite (M21) circulating in humans are inhibitors of wild-type and JAK2V617F mutant Janus kinase 1 and 2 (JAK1/JAK2), which are involved in signalling 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 with effects on inflammation, haematopoiesis and immune regulation. Myelofibrosis is a myeloproliferative neoplasm associated with constitutively activated JAK signal transmission, which contributes to increased inflammation and hyperactivation of activin A receptor type 1 (ACVR1), also known as activin receptor-like kinase 2 (ALK-2). In addition, momelotinib and M21 are direct inhibitors of ACVR1. This inhibitory effect of ACVR1 leads to further downregulation of hepcidin expression in the liver and thus to increased iron availability and red blood cell production.

Pharmacodynamics

Momelotinib inhibits cytokine-induced STAT3 phosphorylation in the whole blood of MF patients. Maximum inhibition of STAT3 phosphorylation occurred two hours after administration of momelotinib, with inhibition lasting for at least six hours. Momelotinib also induced both an acute and a sustained reduction in circulating hepcidin in MF patients, which resulted in increased iron availability and increased erythropoiesis.

Cardiovascular effects

In a dose equivalent to four times the highest recommended initial dose of 200 mg, momelotinib did not result in any clinically relevant QT prolongation.

Clinical efficacy

MOMENTUM

MOMENTUM was a double-blind, randomised (allocation ratio of 2:1), active-controlled study of 195 symptomatic and anaemic (haemoglobin <10 g/dL) MF patients, who had previously been treated with JAK inhibitors. All patients had received ruxolitinib and 3.6% of the patients had also received fedratinib. The median age was 71 years (ranging from 38 to 86 years); 79% were 65 years or older and 63% were male. Sixty-four per cent (64%) of patients were suffering from primary myelofibrosis, 19% had post-PV MF and 17% had post-ET MF. 5% of patients were allocated to the intermediate-1 risk group, 57% to the intermediate-2 risk group and 35% to the high-risk group. The patients were symptomatic at the time of screening and recorded a total symptom score (TSS) ≥10 in the Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 (mean MFSAF TSS at start of study: 27). The patients were also anaemic, with a haemoglobin (Hb) value <10 g/dL. The main symptoms of MF were to be recorded daily in the MFSAF diary: night sweats, abdominal complaints, pain below the left costal arch, fatigue/tiredness, early satiety, itchiness and bone pain. 79% had received red blood cell transfusions in the eight weeks prior to inclusion in the study. At the start of the study, the median Hb value was 8 g/dL and the median platelet count was 96 × 10^9/L.

The patients were treated over a period of 24 weeks with 200 mg momelotinib once daily or 300 mg danazol twice daily; this was followed by open-label treatment with momelotinib. The two primary efficacy endpoints were the percentage of patients with a 50% or greater reduction in total symptom score (TSS) from baseline to Week 24 (measured using 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). In A numerically higher (non-inferior) percentage of patients achieved transfusion independence with momelotinib compared to danazol at Week 24. A key secondary endpoint was the rate of transfusion-free patients at Week 24. Study results are summarised in Table 3.

Table 3: Percentage of patients with symptom reduction and transfusion independence in Week 24 (MOMENTUM)

	Omjjara n = 130	**Danazol** n = 65
Patients with TSS reduced by ≥ 50% in Week 24 (95% CI)	25% (17, 33)	9% (3, 19)
% difference[a] (95% CI)	16% (6, 26)	
p-value (superiority)	0.0095	

Patients with transfusion independence in Week 24[b] (95% CI)	30% (22, 39)	20% (11, 32)
% difference[c] (95% CI)	14% (2, 25)	
p-value (non-inferiority)	0.0116	
Rate of non-transfusions in Week 24[d], % (95% CI)	35% (27, 44)	17% (9, 28)
% difference (95% CI)	17% (8, 26)	
p-value (superiority)	0.0012	

TSS = total symptom score; CI = confidence interval.

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

[b] Transfusion independence is defined as no transfusions and all haemoglobin values ≥8 g/dL in the 12 weeks before Week 24.

[c] Difference in terms of non-inferiority between the response rate for momelotinib and 80% of the response rate for danazol; one-sided p-value.

[d] Percentage of patients who received no transfusions of red blood cells or whole blood during the 24-week treatment period.

Pharmacokinetics

Absorption

Momelotinib is quickly absorbed following oral administration, with the peak concentration in plasma (C_{max}) being reached within three hours after administration and plasma exposure increasing at a disproportionately low rate in relation to the dose, particularly at doses above 300 mg. At a dose of 200 mg once daily at steady state, the mean C_{max} for momelotinib in patients with myelofibrosis is 479 ng/mL (CV% = 61%) and the AUC_{tau} is 3,288 ng•h/mL (CV% = 60%).

After low-fat and high-fat meals, the C_{max} of momelotinib in healthy volunteers was 38% or 28% higher and the AUC 16% or 28% higher than when taken on an empty stomach. These changes in exposure were not clinically significant.

Distribution

In humans, about 91% of momelotinib is bound to plasma proteins. The mean apparent volume of distribution for momelotinib at steady state in patients with myelofibrosis who received 200 mg momelotinib daily was 984 L, which indicates extensive distribution in tissue.

Metabolism

The human metabolism of momelotinib is primarily mediated by several cytochrome P450 (CYP) enzymes, with contributions in the following decreasing order: CYP3A4 (36%), CYP2C8 (19%), CYP2C19 (19%), CYP2C9 (17%) and CYP1A2 (9%). M21 is an active human metabolite that possesses approximately 40% of the pharmacological activity of the parent compound.
M21 is formed by CYP, followed by aldehyde oxidase metabolism of momelotinib. The mean M21-to-momelotinib ratio for AUC ranged from 1.4 to 2.1.

Elimination

Following oral administration of 200 mg momelotinib, the mean terminal half-life ($t_{½}$) for momelotinib was 4 to 8 hours; the half-life for M21 is similar. The apparent total clearance (CL/F) for momelotinib in patients with myelofibrosis was 103 L/h.
Momelotinib is predominantly eliminated via metabolism and then excreted in faeces. Following a single oral dose of [^{14}C]-labelled momelotinib, 69% of the radioactivity was traced in faeces (13% of the dose as the unchanged parent compound) and 28% in urine (<1% of the dose as the unchanged parent compound) in healthy male subjects.

Kinetics in specific patient groups

Hepatic impairment
The AUC for momelotinib was 8% or 97% higher for people with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment than for people with normal hepatic function (see *"Dosage/Administration"*).

Renal impairment
The AUC for momelotinib decreased by 13% in people with moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2) and by 16% in people with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2), both as compared with people with normal renal function (eGFR ≥90 mL/min/1.73 m^2). The AUC for the active metabolite M21 in people with moderate and severe renal impairment was 20% or 41% higher than in people with normal renal function. There are no data available for patients on dialysis with end-stage renal disease (ESRD).
Age, sex, ethnicity and body weight
According to a population pharmacokinetic analysis, age (range: 28 to 92 years), sex (60% male), ethnicity (83% white, 6% Asian, 2% black) and body weight had no clinically significant influence on the pharmacokinetics of momelotinib.

Preclinical Data

Mutagenicity, carcinogenicity

Momelotinib was neither mutagenic in a bacterial reverse mutation test nor clastogenic in an in-vitro chromosome aberration test with human peripheral blood lymphocytes or in an in-vivo micronucleus test with the bone marrow of rats.

The carcinogenic potential of momelotinib was studied as part of a six-month study of transgenic rasH2 mice as well as a two-year study of carcinogenicity in rats. Momelotinib has not been found to be carcinogenic in mice and rats at exposures of up to 12 to 17 times the clinical exposure level at 200 mg once daily, based on the combined AUC of momelotinib and the active human main metabolite M21.

In the two-year carcinogenicity study on Sprague-Dawley rats, oral momelotinib at a dose of 15 mg/kg/day (approximately equivalent to 17 times the maximum recommended dose based on combined momelotinib and M21 AUC) induced benign Leydig cell tumours. An increased risk for human health is regarded as unlikely, as the increase in the incidence of Leydig cell adenomas was thought to be a species-specific mechanistic finding (i.e., prolactin dependence of Leydig cells in rats).

Reproductive toxicity

In fertility studies, momelotinib was administered orally to male and female rats. In male animals, from a dose of 25 mg/kg/day and higher (exposures equivalent to 13-fold the recommended dose of 200 mg daily, based on the combined momelotinib and M21 AUC), momelotinib reduced sperm concentration and motility and reduced the weight of testes and seminal vesicles, which led to reduced fertility at 68 mg/kg/day.

In female animals, at 68 mg/kg/day, decreased ovarian function and a decreased number of pregnancies, increased pre- and post-implantation loss were observed, with complete litter loss being observed in most animals at 25 and 68 mg/kg/day. The NOAEL (no observed adverse effect level) in male and female rats at a dose of 5 mg/kg/day was approximately three times the recommended dose of 200 mg daily (based on the combined momelotinib and M21 AUC).

In animal reproduction studies, oral administration of momelotinib to pregnant rats during the period of organogenesis at 12 mg/kg/day caused maternal toxicity and was associated with embryonic death, visceral malformations and reduced foetal weight; skeletal changes were observed at 6 and 12 mg/kg/day and (approximately 3.5 times the recommended dose of 200 mg daily based on the combined momelotinib and M21 AUC). No developmental effects were observed (NOAEL) at an exposure of 2 mg/kg/day, equivalent to the recommended dose of 200 mg (based on the combined momelotinib and M21 AUC).

In pregnant rabbits, oral administration of momelotinib during organogenesis caused maternal toxicity and indications of embryofoetal toxicity (reduced foetal weight, delayed bone ossification and

miscarriage) at 60 mg/kg/day at an exposure corresponding to less than the recommended dose of 200 mg (based on the combined AUC for momelotinib and M21).
In a study of pre- and postnatal development, rats were treated with oral momelotinib from pregnancy to the end of lactation.
Evidence of maternal toxicity, embryo lethality and reduced birth weight was observed at 6 and 12 mg/kg/day. The survival rate for offspring was significantly reduced at a dose of 12 mg/kg/day from birth to the fourth day of lactation, at exposures similar to or less than those at the recommended dose (based on the combined AUC for momelotinib and M21), which was therefore thought to be a direct effect of momelotinib through exposure via milk.

Other information

Incompatibilities

No incompatibilities were identified.

Shelf life

Do not use this medicinal product after date marked “EXP” on the container.

Special precautions for storage

Do not store above 25°C and keep out of the reach of children.
Each bottle contains a silica gel desiccant that protects the tablets and must not be removed. Keep the container tightly closed to protect the contents from moisture.

Instructions for handling

Any unused medicinal product or waste material is to be disposed of in accordance with national requirements.

Authorisation number

69428 (Swissmedic)

Packs

Pack with 30 200 mg film-coated tablets in a resealable, child-resistant plastic container (A)
Pack with 30 150 mg film-coated tablets in a resealable, child-resistant plastic container (A)
Pack with 30 100 mg film-coated tablets in a resealable, child-resistant plastic container (A)

Marketing authorisation holder

GlaxoSmithKline AG, 3053 Münchenbuchsee

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April 2024