25 January 2024
EMA/OD/0000129901
EMADOC-1700519818-1227008
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Omjjara (momelotinib)
Treatment of myelofibrosis
EU/3/11/886 - EU/3/11/887 - EU/3/11/888

Sponsor: GlaxoSmithKline Trading Services Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

Introductory comment:

The therapeutic indication "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", falls within the scope of the three designated orphan conditions "treatment of primary myelofibrosis", "treatment of post-essential thrombocythaemia myelofibrosis" and "treatment of post-polycythaemia vera myelofibrosis" and are covered in this one document.

1. Product and administrative information

EU/3/11/886:

Product	
Designated active substance	N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt
Other name(s)	--
International Non-Proprietary Name	Momelotinib
Tradename	Omjjara
Orphan condition	Treatment of post-polycythaemia vera myelofibrosis
Sponsor's details:	GlaxoSmithKline Trading Services Limited Riverwalk 12 Citywest Business Campus Dublin 24 D24 YK11 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Cres Pharmaceuticals Limited
COMP opinion	5 May 2011
EC decision	5 August 2011
EC registration number	EU/3/11/886
Post-designation procedural history	
Transfers of sponsorship	Transfer from Cres Pharmaceuticals Limited, United Kingdom, to YM BioSciences (UK) Limited, United Kingdom – EC decision of 27 February 2012 Transfer from YM BioSciences (UK) Limited, United Kingdom to Gilead Sciences International Ltd., United Kingdom – EC decision of 15 May 2013 Transfer from Gilead Sciences International Ltd., United Kingdom to Gilead Sciences Ireland UC, Ireland – EC decision of 8 June 2018 Transfer from Gilead Sciences Ireland UC, Ireland to DLRC Pharma Services Ltd., Ireland – EC decision of 21 February 2019 Transfer from to DLRC Pharma Services Ltd., Ireland, to GlaxoSmithKline Trading Services Limited – EC decision of 29 September 2022

Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Christophe Focke / Alexandre Moreau
Applicant	GlaxoSmithKline Trading Services Limited
Application submission	9 November 2022
Procedure start	1 December 2022
Procedure number	EMA/H/C/005768
Invented name	Omjjara
Therapeutic indication	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. Further information on Omjjara can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/omjjara
CHMP opinion	9 November 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	20 February 2023 and 12 July 2023
COMP discussion and adoption of list of questions	7-9 November 2023
Oral explanation	6 December 2023
COMP opinion	7 December 2023

EU/3/11/887:

Product	
Designated active substance	N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt
Other name(s)	--
International Non-Proprietary Name	Momelotinib
Tradename	Omjjara
Orphan condition	Treatment of post-essential thrombocythaemia myelofibrosis
Sponsor's details:	GlaxoSmithKline Trading Services Limited Riverwalk 12 Citywest Business Campus Dublin 24 D24 YK11 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Cres Pharmaceuticals Limited
COMP opinion	5 May 2011

EC decision	5 August 2011
EC registration number	EU/3/11/887
Post-designation procedural history	
Transfers of sponsorship	Transfer from Cres Pharmaceuticals Limited, United Kingdom, to YM BioSciences (UK) Limited, United Kingdom – EC decision of 27 February 2012 Transfer from YM BioSciences (UK) Limited, United Kingdom to Gilead Sciences International Ltd., United Kingdom – EC decision of 15 May 2013 Transfer from Gilead Sciences International Ltd., United Kingdom to Gilead Sciences Ireland UC, Ireland – EC decision of 8 June 2018 Transfer from Gilead Sciences Ireland UC, Ireland to DLRC Pharma Services Ltd., Ireland – EC decision of 21 February 2019 Transfer from to DLRC Pharma Services Ltd., Ireland, to GlaxoSmithKline Trading Services Limited – EC decision of 29 September 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Christophe Focke / Alexandre Moreau
Applicant	GlaxoSmithKline Trading Services Limited
Application submission	9 November 2022
Procedure start	1 December 2022
Procedure number	EMA/H/C/005768
Invented name	Omjjara
Therapeutic indication	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. Further information on Omjjara can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/omjjara
CHMP opinion	9 November 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	20 February 2023 and 12 July 2023
COMP discussion and adoption of list of questions	7-9 November 2023

Oral explanation	6 December 2023
COMP opinion	7 December 2023

EU/3/11/888:

Product	
Designated active substance	N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt
Other name(s)	--
International Non-Proprietary Name	Momelotinib
Tradename	Omjjara
Orphan condition	Treatment of primary myelofibrosis
Sponsor's details:	GlaxoSmithKline Trading Services Limited Riverwalk 12 Citywest Business Campus Dublin 24 D24 YK11 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Cres Pharmaceuticals Limited
COMP opinion	5 May 2011
EC decision	5 August 2011
EC registration number	EU/3/11/888
Post-designation procedural history	
Transfers of sponsorship	Transfer from Cres Pharmaceuticals Limited, United Kingdom, to YM BioSciences (UK) Limited, United Kingdom – EC decision of 27 February 2012 Transfer from YM BioSciences (UK) Limited, United Kingdom to Gilead Sciences International Ltd., United Kingdom – EC decision of 15 May 2013 Transfer from Gilead Sciences International Ltd., United Kingdom to Gilead Sciences Ireland UC, Ireland – EC decision of 8 June 2018 Transfer from Gilead Sciences Ireland UC, Ireland to DLRC Pharma Services Ltd., Ireland – EC decision of 21 February 2019 Transfer from to DLRC Pharma Services Ltd., Ireland, to GlaxoSmithKline Trading Services Limited – EC decision of 29 September 2022

Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Christophe Focke / Alexandre Moreau
Applicant	GlaxoSmithKline Trading Services Limited
Application submission	9 November 2022
Procedure start	1 December 2022
Procedure number	EMA/H/C/005768
Invented name	Omjjara
Therapeutic indication	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. Further information on Omjjara can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/omjjara
CHMP opinion	9 November 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	20 February 2023 and 12 July 2023
COMP discussion and adoption of list of questions	7-9 November 2023
Oral explanation	6 December 2023
COMP opinion	7 December 2023

2. Grounds for the COMP opinion

2.1. EU/3/11/886

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

The sponsor, Cres Pharmaceuticals Limited, submitted on 28 February 2011 an application for designation of a medicinal product containing N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt as an orphan medicinal product for treatment of post-polycythaemia vera myelofibrosis.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- post-polycythaemia vera myelofibrosis (hereinafter referred to as "the condition") was estimated to be affecting less than 0.15 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to pancytopenia, splenomegaly, hepatomegaly and reduced life expectancy;

- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, as an orphan medicinal product for the orphan indication: treatment of post-polycythaemia vera myelofibrosis.

2.2. EU/3/11/887

The sponsor, Cres Pharmaceuticals Limited, submitted on 28 February 2011 an application for designation of a medicinal product containing N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt as an orphan medicinal product for treatment of post-essential thrombocythaemia myelofibrosis.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- post-essential thrombocythaemia myelofibrosis (hereinafter referred to as "the condition") was estimated to be affecting less than 0.15 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to pancytopenia, splenomegaly and hepatomegaly, and reduced life expectancy;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, as an orphan medicinal product for the orphan indication: treatment of post-essential thrombocythaemia myelofibrosis.

2.3. EU/3/11/888

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- primary myelofibrosis (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.3 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to pancytopenia, splenomegaly, hepatomegaly and reduced life expectancy;;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on a new mechanism of action that could result in improved clinical outcome for patients. This is in line with the available preclinical and preliminary clinical data presented by the sponsor.

The COMP recommends the designation of this medicinal product, containing N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, as an orphan medicinal product for the orphan indication: treatment of primary myelofibrosis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Myelofibrosis (MF) is a Philadelphia chromosome (Ph)-negative myeloproliferative neoplasm (MPN) that is characterised by unregulated, clonogenic proliferation of a myeloid precursor cell in the bone marrow (BM) and amplification of cytokine-producing megakaryocytes and macrophages. In MF, fibrosis is mediated by increased deposition of reticulin and collagen fibres leading to anaemia and insufficient haematopoiesis, thereby leading to migration of haematopoietic stem cells from the bone marrow to the spleen. Clinically it is a condition of middle-age to older adults, with a clinical presentation of fatigue, thrombotic events, splenomegaly and hepatomegaly, extramedullary erythropoiesis and manifestations of the bones and joints, while transformation to acute leukaemia may also be seen in a minority of patients.

MF can arise de novo (primary MF [PMF]) or after diagnosis and treatment for essential thrombocythemia (ET) or polycythaemia vera (PV), which are considered relatively benign MPNs. MF develops as these diseases evolve, resulting in post–ET-MF or post–PV-MF. The underlying cause of PMF is unknown. Patients with PMF have monoclonal increases in myeloid, lymphoid, or erythroid lineages suggesting that the disease is initiated by a mutant clone of stem cell origin.

With reference to the WHO 2022 classification of tumours of haematopoietic and lymphoid tissues (Khoury et al. Leukemia 2022), under the category of myeloproliferative neoplasms (MPNs), eight subcategories are listed: chronic myeloid leukaemia, chronic neutrophilic leukaemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukaemia, juvenile myelomonocytic leukaemia, and myeloproliferative neoplasm-not otherwise specified.

In the past the COMP designated primary and secondary forms of myelofibrosis separately, and this has changed to reflect the similarities in the clinical management of these three conditions. Since the sponsor obtained 3 independent orphan designations for primary and secondary forms of the condition, the sponsor presented 3 maintenance reports that jointly cover the proposed treatment indication.

The approved therapeutic indication "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" falls within the scope of the designated orphan condition "Treatment of post-polycythaemia vera myelofibrosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Since the original orphan designations of momelotinib in 2011, new treatments for MF have been approved in the EU, specifically the JAK inhibitors ruxolitinib (Jakavi;23 August 2012) and fedratinib (Inrebic; 08 February 2021). However, MF continues to be a life-threatening and debilitating disease.

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy.

While the JAK inhibitors have improved MF-related symptoms and splenomegaly, disease- as well as treatment-related cytopenias contribute to morbidity and mortality. With ruxolitinib, improvement of survival compared with best available treatment (BAT) was demonstrated based on the 3-year follow up data from the COMFORT-II study (Cervantes, 2013). The Kaplan Meier estimated probability of survival at 144 weeks was 81% in the ruxolitinib arm and 61% in the best alternative treatment (BAT) arm. However, in COMFORT-I and COMFORT-II, ruxolitinib discontinuation rates were approximately 50% by 3 years (Cervantes, 2013; Verstovsek, 2013). Due to the limited benefits of ruxolitinib re-challenge, it is not recommended as a standard second-line option in treatment guidelines and frequency of use in routine practice is unknown (Harrison, 2020). The European Society for Medical Oncology guidelines recommend that ruxolitinib should be discontinued in the event of progression and tapered gradually to prevent withdrawal syndrome, which has been associated with cytokine storm (Vannucchi, 2015a).

Therefore, despite authorisation of treatments, all forms of myelofibrosis still remain chronically debilitating due to symptoms such as bone pain, tiredness, weakness, weight loss, fever and bleeding and life threatening with the estimated median survival of 69 months (Guglielmelli 2017, Rumi 2017).

Number of people affected or at risk

In the initial ODD (Orphan Drug Designation) in 2011, this product was granted orphan designations in 3 myelofibrosis (MF) indications: post-polycythemia vera myelofibrosis (post-PV MF), post-essential thrombocythemia myelofibrosis (post-ET MF), and primary myelofibrosis (PMF). The COMP agreed on a prevalence estimate for post-PV MF of 0.15 per 10,000 persons, post-ET MF of 0.15 per 10,000 persons, and PMF of 0.3 per 10,000 persons. As part of the prevalence calculation in the context of the maintenance of the orphan designation, the sponsor estimates the prevalence of myelofibrosis as a whole through a systematic literature review from publicly available registries and databases.

According to the sponsor there is limited published data on the incidence or prevalence of MF. Most studies would not provide adequate information to differentiate between studies that have estimated the prevalence of PMF only, versus studies that have included both PMF and secondary MF (i.e., post-PV MF and post-ET MF).

To estimate the prevalence of MF, the most recently published studies that included a representative sample of the population were selected. Three articles were identified that reported the prevalence of MF including primary and secondary MF. The prevalence of MF from these studies ranged from 0.1 to 0.9 per 10,000 (Kousoulakou, 2014; Roaldsnes, 2017). Table 1 summarizes all identified EU studies and global databases (that included European countries) reporting the prevalence of myelofibrosis including patients with primary and secondary MF.

Table 1. Estimates of PMF incidence and prevalence from the literature/

Author, Publication Year; Country	Study period	Incidence [a] (per 10 000 person-years)	Prevalence (per 10 000)
HMRN, 2022; UK[b]	2019	0.06	0.1 – 0.31
Hultcrantz, 2020; Sweden[b]	2000 - 2014	0.054	NA
Devos, 2015; Belgium	2011	NA	0.27
Titmarsh, 2014; Europe	1935 - 2013	0.046[c]	NA
Solans, 2022; Spain[b]	2002 - 2013	0.036	NA

HMRN, Haematological Malignancy Research Network; NA, not available; PMF, primary myelofibrosis; UK, United Kingdom.
[a] crude incidence rate
[b] patient registry
[c] pooled annual incidence rate for Europe

Estimates for duration of PMF were obtained from median OS reported in published data. Four studies were identified and reported the following estimates for median OS: 7.2 years (Guglielmelli, 2017), 4.6 years (Htun, 2022), 4.4 years (Szuber, 2019) and 3.6 years (Verstovsek, 2022b) (range 3.6 to 7.2 years). Therefore, a median OS across all 4 studies for patients with PMF was calculated as 4.5 years and was used in combination incidence rates provided in Table 1. The prevalence of PMF was calculated to be 0.22 per 10,000 persons.

The prevalence of secondary MF was calculated using the same formula and assumptions as above. The incidence of MF (15-year cumulative) from PV and ET, has been reported to be 5% to 14% and 1.6% to 9%, respectively (Masarova, 2017). Based on this data, the cumulative incidence was selected based on the median value of the reported range of the 15-year cumulative incidence (i.e., 9.5% for post-PV MF and 5.3% for post-ET MF). This translated to an annual incidence rate of 0.063 per 10 000 person-years for post-PV MF and 0.035 per 10,000 person-years for post-ET MF. The median survival of patients with secondary MF has been estimated to be 4 years (post-PV MF) and 6.1 years (post-ET MF) (Masarova, 2017). Therefore, the prevalence of secondary MF was calculated as 0.25 per 10,000 persons for Post-PV MF, and 0.21 per 10,000 persons for Post-ET MF. Hence, the overall prevalence of MF (primary and secondary) to be 0.68 per 10,000 persons.

An additional calculation was performed using most recent data from a German claims database. In a recent study by Junker et al, the epidemiology of MF in Germany was investigated from January 2010 to December 2021. The standardized point prevalence on December 2021 was 1.1 per 10,000 persons; alternative MF identification strategies used in the study resulted in lower and upper bounds of MF prevalence of 0.9 and 1.2 per 10,000 persons.

In summary, the prevalence estimates of MF (primary and secondary) that were derived based on incidence and duration (i.e., 0.34 and 0.68 per 10 000 population) were within range of the studies that evaluated the prevalence of MF including primary and secondary cases, while prevalence estimates obtained from most recent data (based on a German claims database) were generally higher. These higher estimates may be explained by improved diagnostics, increased offerings for preventive checkups, and the classification change to include prefibrotic (early stage) MF by WHO in 2016. Based on these methods, and in a conservative approach the sponsor opted for the highest estimate of 1.1 per 10,000 is still far below the orphan threshold.

For the sake of completeness and accuracy, the sponsor wasasked to provide conservative individual prevalence estimates for three separate orphan designations.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Treatment of PMF and SMF is similar and requires an individualized approach, considering each patient's age, comorbidities, symptom profile, prognostic risk category, performance status, treatment preference, and other factors.

Existing treatment options are primarily symptom oriented. Treatment goals include reduction of spleen size, improvement of cytopenias and symptom burden, reduction of bone marrow fibrosis, restoration of transfusion-independence, and prevention and delay of progression to acute myeloid leukemia (AML) (Stahl, 2017; Vannucchi, 2015).

In the EU, ruxolitinib and fedratinib are centrally approved products for the treatment of MF (Table 2). Hydroxyurea and busulfan are approved on a national basis in a few countries (e.g., Italy, Ireland and Netherlands) and are used to control excessive myeloproliferation.

Table 2. Medicinal products authorised centrally in the EU for the treatment of myelofibrosis.

Active Substance (Product Names)	**Pharmacotherapeutic Group**	**Indication**
Fedratinib (Inrebic)	Antineoplastic agents (JAK 2 inhibitor)	Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.
Ruxolitinib (Jakavi)	Antineoplastic agent (JAK 1/2 inhibitor)	Jakavi is indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis

Non-pharmacological interventions used in the course of MF treatment for highly selected patient populations, only, include splenectomy, splenic irradiation and haematopoietic stem cell transplantation.

For the purpose of the review of the orphan criteria at the time of marketing authorisation, ruxolitinib, fedratinib, hydroxyurea and busulfan are considered satisfactory methods.

Significant benefit

The therapeutic indication of Omjjara is: 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.

The therapeutic indication of Fedratinib is: Inrebic is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve or have been treated with ruxolitinib.

The therapeutic indication of Jakavi is: Jakavi is indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

The sponsor claims that momelotinib is differentiated from currently available therapies in that it addresses the disease-related symptoms, splenomegaly, and anaemia in MF patients without exacerbation of cytopenias. The significant benefit claim is based on a clinically relevant advantage of improvements in anaemia and in providing a treatment option for thrombocytopenic and anaemic patients.

Significant Benefit Over Ruxolitinib

The sponsor argues that ruxolitinib addresses splenomegaly and constitutional symptoms associated with MF; however, it does not address MF-related anaemia and other cytopenias and instead is myelosuppressive and often worsens anaemia and thrombocytopenia (Naymagon, 2017; Jakavi SmPC; NCCN, 2023).

In COMFORT-I and COMFORT-II, participants experienced reductions in mean Hgb of approximately 1.0 g/dL below baseline after 8 to 12 weeks of ruxolitinib therapy, which gradually reached a new steady state of approximately 0.5 g/dL below baseline (Jakavi SmPC). In COMFORT-I, 60.6% of participants in the ruxolitinib group and 37.7% of participants in the placebo group received RBC transfusions during randomized treatment. In COMFORT-II, 45.2% of participants treated with ruxolitinib had Grade 3 or 4 events of anaemia (Hgb < 8 g/dL); approximately half of the Grade 3 or 4 events of anaemia occurred during the first 8 weeks of ruxolitinib treatment (Harrison, 2012). As a result, patients with MF often receive lower doses of ruxolitinib, thereby impacting treatment. Some patients may never begin treatment with JAK inhibitors to avoid exacerbating their MF-related bone marrow impairment (Mesa, 2022). Real-world evidence has shown that during the first year of therapy, 40% to 70% of patients will discontinue ruxolitinib, primarily due to anaemia (Mesa, 2022; Harrison, 2020). The median survival after discontinuation of ruxolitinib is poor, ranging from approximately 8 to 23 months (Palandri, 2020; Newberry, 2017).

In contrast, the efficacy of momelotinib in anaemic and thrombocytopenic subpopulations is claimed to be comparable with outcomes observed in the intention-to-treat population. In the MOMENTUM study, which exclusively enrolled participants with prior JAK inhibitor use (mostly prior ruxolitinib), momelotinib showed responses in total symptom score (TSS), transfusion independence (TI), and spleen response rate (SRR) without exacerbating cytopenias, demonstrating activity in patients who have failed or who were intolerant of other approved JAK inhibitors. All subjects (100%) previously received RUX and 9 subjects (4.6%) also received fedratinib.

Ruxolitinib dose attenuation is often necessary to avoid continued exacerbation of cytopenias and can compromise efficacy, contributing to treatment failure (Harrison, 2020). This is also reflected in the studies MOMENTUM and SIMPLIFY-2 in which patients were either pretreated with JAK-inhibitors (mainly ruxolitinib in MOMENTUM) or received ruxolitbinib as best available therapy only at a reduced dose for the majority of patients (SIMPLIFY-2).

The sponsor claims that the benefit of momelotinib over ruxolitinib was demonstrated in the JAK inhibitor-naïve population in SIMPLIFY-1. Compared to ruxolitinib, momelotinib-treated participants required fewer RBC transfusions, were more likely to require zero transfusions, and demonstrated a nominally significant TI rate.

Significant Benefit Over Fedratinib

The sponsor argues that treatment with fedratinib also may be complicated by drug-induced cytopenias. Thrombocytopenia can be a limiting factor when selecting JAK inhibitor treatment in MF, since in patients with thrombocytopenia (platelet count $<50 \times 10^9$/L) fedratinib is not recommended. Therefore, similar claims as with ruxolitinib are made in that momelotinib may provide significant benefit in this severely thrombocytopenic subpopulation as an option for MF patients who are unable to initiate or continue optimal dosing of the approved JAK inhibitors.

It is indicated by the sponsor that fedratinib does not provide anaemia benefit and some MF patients with baseline anaemia or transfusion requirements may never initiate fedratinib treatment due to the risk of worsening anaemia. Momelotinib may also provide significant benefit in this anaemic/TD subpopulation. According to the sponsor momelotinib has demonstrated consistent anaemia benefits, including the ability to achieve transfusion independence, decrease transfusions, and increase Hgb in both JAK inhibitor-experienced and JAK inhibitor-naïve MF patient populations.

The sponsor acknowledges that there is limited data directly comparing momelotinib with fedratinib in MF. Although a majority of participants in the SIMPLIFY-2 BAT arm were treated with other JAK inhibitors, 88.5% were treated with ruxolitinib; no participant was treated with fedratinib during the study. Similarly, there were few participants in the Phase 3 studies who had been previously treated with fedratinib. In MOMENTUM, all 195 randomized and treated participants had received prior treatment with ruxolitinib and an additional 9 participants also received fedratinib as prior approved JAK inhibitor therapy (5.4% MMB vs 3.1% DAN). Although not a prespecified subgroup in MOMENTUM, TSS response rate, TI rate and 2 secondary SRR endpoints were summarized for these participants by treatment arm.

- TSS Response Rate: no participants on the MMB arm and 1 participant on the DAN arm had a TSS response of 50% at Week 24 compared to baseline; however, most participants on the MMB arm, 86% (6/7), experienced some degree of TSS improvement during the randomized treatment phase.
- Transfusion Independence: 1 participant (14.3%) on the MMB arm and both participants (100%) on the DAN arm were transfusion independent at Week 24.
- SRR: 2 participants in the MMB arm and no participants on the DAN arm achieved splenic volume reductions of ³25% and ³35% compared to baseline [SRA-MMB-301 Listing 52d.1b]. These response rates in the MMB arm of this subgroup were consistent with those observed in the ITT population.
- Overall, the subgroup analyses were limited by the small numbers of participants who received fedratinib in addition to ruxolitinib as prior JAK inhibitor therapy and as such, no firm conclusions on the comparison of efficacy results to the ITT population can be drawn. Two of the 7 participants

on the MMB arm achieved splenic response and one achieved TI at Week 24 suggesting that these participants had MF that was not resistant to momelotinib. Additionally, the JAK-inhibitors fedratinib,ruxolitinib and momelotinib have overlapping mechanisms of action and cross resistance of JAK inhibitors have not been characterized in the clinical setting.

- Matching-adjusted indirect comparisons could not be conducted with the transfusion-related outcomes and anaemia efficacy outcomes as they have not been reported in JAKARTA-2, and differences in definitions of reporting of transfusion-related outcomes for JAKARTA make comparisons not feasible.
- Given these differences in study design features, anaemia-related comparisons vs. fedratinib can only be conducted by a comparison of Grade 3/4 anaemia AEs (Hgb <8 g/dl) and any grade anaemia AEs, which are evaluated by standard criteria across studies using the CTCAE and represent new onset and/or worsening AEs. The sponsor reports a large risk difference/risk ration/odds ratios favouring momelotinib for the development of anaemia grade 3-4 after adjustment in both in the JAKi exposed as well as JAKi naïve patient populations. The choice of matching parameters was based on expert clinical input in the absence of literature identifying prognostic factors or effect-modifiers for safety outcomes in MF. Several differences were identified in terms of study design, inclusion/exclusion criteria and baseline characteristics which limit the interpretability of the indirect treatment comparison.

Hydroxyurea and busulfan

- The sponsor also claims a clinically relevant advantage over hydroxyurea and busulfan with regards to improved efficacy based on the randomised comparison to best available therapy in the Simplify2 trial. The sponsor then refers to the preferred treatment options (JAKi for Int-2 and High-risk MF) and the lack of any reference to busulfan according to current treatment guidelines. Furthermore, dose reduction or dose discontinuation recommendations for busulfan indicate thresholds of min 150*109 /L which would strongly limit the use in patients with MF. In addition, busulfan is reserved for late line treatment with limited use.

Conclusion

- While the Committee for Orphan Medicinal Products (COMP) can follow the overall reasoning of the sponsor with respect to the clinical relevance of providing treatment options for patients with MF with anaemia, the non-inferiority of MMB in SIMPLIFY -1 and -2 with respect to the primary endpoint and the inconsistent effect on total symptom score in JAKi-naïve patients (favouring ruxolitinib) deserve further justification before a SB can be accepted. In line with these considerations, there is insufficient justification for SB over ruxolitinib and fedratinib, both with respect to treatment effect size in the JAKi-naïve setting as well as the differential impact of MMB or fedratinib on thrombocytopenia.

Overall COMP conclusion

The COMP adopted a list of questions on the prevalence and on the significant benefit.

The COMP considered that the prevalence estimates should be updated by referring to updated literature and completed with individual prevalence estimates for Primary myelofibrosis (PMF), post-Essential thrombocythemia myelofibrosis (post-ET MF), and Polycythemia vera myelofibrosis (post-PV MF).

In addition, the claim of significant benefit of momelotinib over the authorised satisfactory methods, fedratinib and ruxolitinib was not considered to be established based on the data presented by the sponsor. A list of questions on significant benefit aiming at clarifying the indirect treatment comparisons provided, especially on the magnitude of effect on disease-related symptoms and on the risk of thrombocytopenia was issued in both naïve and insufficiently controlled patients.

Comments on sponsor's response to the COMP list of issues

In the written response, and during an oral explanation before the Committee on 6 of December 2023, the sponsor presented their responses to the COMP list of questions. The sponsor reviewed the prevalence calculation and provided additional arguments to support the claim for significant benefit of momelotinib over ruxolitinib and fedratinib in naïve and patients previously treated patients for the target myelofibrosis population.

As part of the prevalence calculation, the sponsor highlighted that the scarce literature on prevalence of myelofibrosis do not provide adequate information to differentiate between studies that have estimated the prevalence of PMF only versus studies that have included both PMF and secondary MF and no further information was identified in an updated literature search. Therefore, only additional data based on the already identified literature on the upper and lower bound of the incidence estimates is provided.

Based on the published and calculated estimates, the prevalence of PMF ranges from 0.1 to 0.31 per 10,000 population.

Further, the sponsor elaborated on the individual prevalence estimates for Primary myelofibrosis (PMF), post- Essential thrombocythemia myelofibrosis (post-ET MF), and Polycythemia vera myelofibrosis (post-PV MF) following an indirect prevalence calculation based on disease duration and incidence.

The duration (median OS of 4.5 years) of PMF was based on the median value from estimates reported in published literature (Guglielmelli, 2017; Htun, 2022; Szuber, 2019; Verstovsek, 2022). Based on published literature, the mean value of the range of incidence rates of PMF is 0.049; the lower bound of the estimates is 0.036 and the upper bound 0.06. Previously, the sponsor had only presented estimates of prevalence of PMF based on the mean value of 0.049. The sponsor now presented additional estimates of the prevalence of PMF that were calculated based on the lower and upper bound reported estimates.

For the prevalence of post-PV MF the sponsor argued that there are no published specific prevalence estimates. The 15-year cumulative incidence of MF from PV has been reported to be 5% to 14% (Masarova, 2017). Based on the calculated estimates, the prevalence of post-ET MF ranges from 0.07 to 0.37 per 10,000 population. In view that post-ET myelofibrosis is considered rarer than PMF, approximately 0.2 is proposed.

For the prevalence of post-ET MF the sponsor argued that there are no published specific prevalence estimates. The 15-year cumulative incidence of MF from ET has been reported to be between 1.6% to

9% (Masarova, 2017). Based on this data, the median value of the reported range of the 15-year cumulative incidence is 5.3%; the lower bound of the estimates is 1.6% and the upper bound 9%. The sponsor presented additional estimates of the prevalence of post-ET MF that include calculations using the lower and upper bound reported estimates of the cumulative incidence. Based on the calculated estimates, the prevalence of post-ET MF ranges from 0.07 to 0.37 per 10,000 population.

As part of the significant benefit, the sponsor upheld the claim of a clinically relevant advantage due to improved efficacy and added further claims of improved safety and major contribution to patient care. Overall, the claim of improved safety is difficult to accept on its own due to the methodological concerns over the matching parameters and the differences in clinical trial design in the indirect treatment comparison. The claim of major contribution to patient care is also difficult to accept on its own in view that the difference in treatment burden associated with the treatment of anaemia is not translated into improvements in quality of life compared to the other JAK inhibitors.

The sponsor further elaborated in more detail on the clinically relevant subgroup of cytopenic patients with myelofibrosis. Cytopenias, and especially anaemia is a disease-related complication that is integrated in current prognostic scores (both at diagnosis as well as during treatment). Currently authorised JAKi (both ruxolitinib and fedratinib) are known to exacerbate anaemia or may not even be started in anaemic or thrombocytopenic patients. In order to support the relevance of these subgroups, the sponsor provided further data on baseline comparisons on transfusion (in)dependence from SIMPLIFY-1 and data from the momelotinib Managed Access Program (MAP). The global MAP was established in September 2022 (December 2022 in Europe) to provide early access. As of November 2023, a total of 755 patients have been approved for MMB treatment, including 684 requests from Europe. The sponsor provides details from 332 patients with 77% had received just ruxolitinib, 21% had received both ruxolitinib and fedratinib and 2% had received just fedratinib. The sponsor highlighted the high proportion of anaemic and thrombocytopenic patients and thereby underlines the clinical relevance of the efficacy within these subpopulations and the importance of the transfusion endpoints.

Furthermore, the MOMENTUM trial was performed in anaemic patients after prior treatment with ruxolitinib and the control treatment was off-label use of danazol which highlights the limited treatment options for this population. In the SIMPLIFY-2 trial, only 12% of patients received ruxolitinib at the intended dose, so that this trial is also reflective of patients requiring dose-reductions with ruxolitinib (i.e., little treatment options). The improved symptom score and spleen response observed in both trials therefore indicate a clinically relevant advantage of improved efficacy in the second line setting.

COMP discussions

The prevalence of 0.5 for PMF, and 0.2 to both post-ET and post-PV would result in 0.9 in 10.000 which is in line with the estimate given for the umbrella term of MF (1 in 10.000).

Given the sponsor’s claims regarding the scarcity of literature on prevalence of myelofibrosis and the difficulty to differentiate between studies that have estimated the prevalence of PMF only versus studies that have included both PMF and secondary MF, only an additional discussion was provided on the already identified literature. For the sake of completeness, the calculation was executed both for the umbrella condition and for each individual subset with different scenarios from less conservative to more conservative approaches.

While the available data was limited, the COMP considered the level of discussion to be acceptable and in line with previous procedures for the applied orphan condition.

On the significant benefit arguments, the COMP concluded that the updated efficacy analysis in the subset of patients with anaemia and thrombocytopenia in the pooled efficacy population of studies SIMPLIFY-1 in JAKi naïve patients, and MOMENTUM in JAKi-experienced patients, showed proof of benefit for those patients who have limited treatment options.

Regarding fedratinib, the COMP acknowledged the limitations in the absence of head-to-head comparison, in combination with the limited number of patients pre-treated with fedratinib prior to momelotinib treatment. However, the outcomes in moderate to severely anaemic or thrombocytopenic patients demonstrated clinically meaningful spleen and symptom responses in addition to attaining high transfusion independence rates. The COMP also considered the ITC indicating that momelotinib was associated with lower risk of Grade 3 or 4 anaemia and any grade anaemia when compared to fedratinib.

Regarding ruxolitinib, while momelotinib is not convincingly superior to ruxolitinib neither in the JAKi-naïve (SIMPLIFY-1) nor in the prior JAK treated patients (SIMPLIFY-2), the totality of results indicate efficacy after failure of ruxolitinib and the possibility to treat a subgroup of anaemic and thrombocytopenic patients, a clinically relevant subgroup of patients with myelofibrosis.

The COMP hence concluded that the symptom control observed in those patients who have limited options justifies the significant benefit in patients with anaemic and thrombocytopenic myelofibrosis.

As also considered by the CHMP, endpoints on anaemia (transfusion independence, zero transfusions, haemoglobin response, grade 3-4 aneamia) in all three trials (including SIMPLIFY-1 in the JAK-naive setting) indicate at least a protective effect against anaemia and therefore shift the patient population eligible for momelotinib to one that cannot benefit from the existing JAK inhibitors according to the dosing recommendations provided by the SmPC. In SIMPLIFY-1, no severely thrombocytopenic patients were included in the head-to-head-comparison to ruxolitinib in line with the SmPC recommendations. The relevance of cytopenias for treatment with fedratinib is acknowledged.

COMP conclusions

In conclusion, the COMP agreed on individual prevalences of 0.5 for PMF, and 0.2 to both post-ET and post-PV, resulting in 0.9 in 10.000 which is in line with the estimate given for the umbrella term of MF (1 in 10.000). In addition, the significant benefit of momelotinib over the authorised fedratinib and ruxolitinib treatments is considered to be established based on symptom control observed in those patients who have limited options, specifically in patients with anaemic and thrombocytopenic myelofibrosis.

4. COMP position adopted on 7 December 2023

EU/3/11/886

The COMP concluded that:

- the proposed therapeutic indication includes the orphan condition of the designated Orphan Medicinal Product. The therapeutic indication is covered entirely by this and two additional orphan designations (EU/3/11/887 and EU/3/11/888), which are covered by separate opinion documents;
- the prevalence of post-polycythaemia vera myelofibrosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with reduced life expectancy, and chronically debilitating due to anaemia, splenomegaly and hepatomegaly;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Omjjara, the assumption that Omjjara may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from three actively controlled clinical trials in JAK inhibitor naïve and JAK inhibitor exposed patients demonstrating symptom control in those who have limited options due to disease- and treatment related anaemia and thrombocytopenia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Omjjara, N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, momelotinib for treatment of post-polycythaemia vera myelofibrosis (EU/3/11/886) is not removed from the Community Register of Orphan Medicinal Products.

EU/3/11/887

The COMP concluded that:

- the proposed therapeutic indication includes the orphan condition of the designated Orphan Medicinal Product. The therapeutic indication is covered entirely by this and two additional orphan designations (EU/3/11/886 and EU/3/11/888), which are covered by separate opinion documents;
- the prevalence of post-essential thrombocythaemia myelofibrosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with reduced life expectancy, and chronically debilitating due to anaemia, splenomegaly and hepatomegaly;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Omjjara, the assumption that Omjjara may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from three actively controlled clinical trials in JAK inhibitor naïve and JAK inhibitor exposed patients demonstrating symptom control in those who have limited options due to disease- and treatment related anaemia and thrombocytopenia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Omjjara, N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, momelotinib for treatment of post-essential thrombocythaemia myelofibrosis (EU/3/11/887) is not removed from the Community Register of Orphan Medicinal Products.

EU/3/11/888

The COMP concluded that:

- the proposed therapeutic indication includes the orphan condition of the designated Orphan Medicinal Product. The therapeutic indication is covered entirely by this and two additional orphan designations (EU/3/11/886 and EU/3/11/887), which are covered by separate opinion documents;
- the prevalence of primary myelofibrosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with reduced life expectancy, and chronically debilitating due to anaemia, splenomegaly and hepatomegaly;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Omjjara, the assumption that Omjjara may be of potential significant benefit to the subset of the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from three actively controlled clinical trials in JAK inhibitor naïve and JAK inhibitor exposed patients demonstrating symptom control in those who have limited options due to disease- and treatment related anaemia and thrombocytopenia.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Omjjara, N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt, momelotinib for treatment of primary myelofibrosis (EU/3/11/888) is not removed from the Community Register of Orphan Medicinal Products.