8 February 2021
EMADOC-1700519818-608960
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Inrebic (fedratinib)
Sponsor: Celgene Europe B.V.

Note

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

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Introductory comment:

The approved therapeutic indication "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", 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

Orphan medicinal product designation procedural history

EU/3/10/794

Product	
Active substances at the time of orphan designation	N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate
International Non-Proprietary Name	Fedratinib
Tradename	Inrebic
Orphan condition	Treatment of primary myelofibrosis
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Ulrich Granzer
COMP opinion date	16 July 2010
EC decision date	1 October 2010
EC registration number	EU/3/10/794
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dr Ulrich Granzer to Sanofi Aventis EC decision of 4 February 2011
Sponsor's name change	Name change from Sanofi Aventis to Sanofi-Aventis Groupe – EC letter of 30 October 2012
Transfer of sponsorship	Transfer from Sanofi-Aventis Groupe to SynteractHCR Deutschland GmbH – EC decision of 28 April 2017
Transfer of sponsorship	Transfer from SynteractHCR Deutschland GmbH to Celgene Europe B.V. – EC decision of 8 June 2018

EU/3/10/810

Product	
Active substances at the time of orphan designation	N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate
International Non-Proprietary Name	Fedratinib
Tradename	Inrebic
Orphan condition	Treatment of post-essential thrombocythaemia myelofibrosis
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands

Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Ulrich Granzer
COMP opinion date	9 September 2010
EC decision date	26 November 2010
EC registration number	EU/3/10/810
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dr Ulrich Granzer to Sanofi Aventis EC decision of 4 February 2011
Sponsor's name change	Name change from Sanofi Aventis to Sanofi-Aventis Groupe – EC letter of 30 October 2012
Transfer of sponsorship	Transfer from Sanofi-Aventis Groupe to SynteractHCR Deutschland GmbH – EC decision of 28 April 2017
Transfer of sponsorship	Transfer from SynteractHCR Deutschland GmbH to Celgene Europe B.V. – EC decision of 8 June 2018

EU/3/10/811

Product	
Active substances at the time of orphan designation	N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate
International Non-Proprietary Name	Fedratinib
Tradename	Inrebic
Orphan condition	Treatment of post-polycythaemia vera myelofibrosis
Sponsor's details:	Celgene Europe B.V. Winthontlaan 6n 3526 KV Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dr Ulrich Granzer
COMP opinion date	9 September 2010
EC decision date	26 November 2010
EC registration number	EU/3/10/811
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dr Ulrich Granzer to Sanofi Aventis EC decision of 4 February 2011
Sponsor's name change	Name change from Sanofi Aventis to Sanofi-Aventis Groupe – EC letter of 30 October 2012
Transfer of sponsorship	Transfer from Sanofi-Aventis Groupe to SynteractHCR Deutschland GmbH – EC decision of 28 April 2017
Transfer of sponsorship	Transfer from SynteractHCR Deutschland GmbH to Celgene Europe B.V. – EC decision of 8 June 2018

Marketing authorisation procedural history

Rapporteur / Co-rapporteur	Paula Boudewina van Hennik / Tuomo Lapveteläinen
Applicant	Celgene Europe B.V.
Application submission date	20 December 2019
Procedure start date	30 January 2020
Procedure number	EMA/H/C/005026
Invented name	Inrebic
Proposed therapeutic indication	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. Further information on Inrebic can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic
CHMP opinion date	10 December 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Karri Penttila / Dinko Vitezic
Sponsor's report submission date	14 February 2020
COMP discussion and adoption of list of questions	3-5 November 2020
Oral explanation	2 December 2020
COMP opinion date (adopted via written procedure)	16 December 2020

2. Grounds for the COMP opinions

EU/3/10/794

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- 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 due to anaemia, splenomegaly and hepatomegaly, and life-threatening due to its complications resulting in a 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-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate may be of significant benefit to those affected by the condition. This is based on a clinically relevant advantage, on the grounds of a novel mechanism of action which might offer a

therapeutic alternative as supported by results in relevant preclinical models and in preliminary clinical data.

EU/3/10/810

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- 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 anaemia, 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.

EU/3/10/811

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- 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;
- condition is chronically debilitating and life-threatening, in particular due to anaemia, 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.

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 is a disease in which fibrous tissue forms in the bone marrow, interfering with normal blood cell production. This causes some immature blood cells to move from the bone marrow to other organs, such as the spleen and liver, which become enlarged. Symptoms of the disease include bone pain, tiredness, weakness, weight loss, fever and bleeding.

Primary myelofibrosis is characterized by the presence of bone marrow fibrosis that cannot be attributed to another myeloid disorder. Secondary forms of myelofibrosis arise from essential thrombocythemia or polycythemia vera.

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 proposed therapeutic indication "Treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis who are JAK inhibitor naïve or have been treated with ruxolitinib." falls within the scope of the 3 designated orphan conditions "post-polycythaemia vera myelofibrosis", "Treatment of Primary Myelofibrosis" and "Treatment of Post-Essential Thrombocythaemia 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 fedratinib in 2010, one product was approved in the EU for the treatment of myelofibrosis: Jakavi (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 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, ruxolitinib it is not recommended as a standard second-line option and it is unclear how common this strategy is in practice. Patients who progress on ruxolitinib represent an unmet need. Survival in these patients has been reported to be 6 to 16 months (Kuykendall,2017; Kuykendall,2018; Newberry,2017; Schain, 2019).

Therefore, despite authorisation of ruxolitinib, 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 (Cervantes 2009).

Number of people affected or at risk

Based on literature and on an American patient registry the sponsor prepared a table of incidence and prevalence values found in Europe and worldwide. The data from MPN Registry (2008 and 2010) show that post-PVMF and post-ET MF account for a smaller proportion of the MF population.

Table 1. Data from MPN Registry

	IMPACT per 100,000			MARKETSCAN per 100,000		
	2008	2009	2010	2008	2009	2010
Any MF	4.93	5.73	5.69	3.56	3.69	4.16
Primary MF	1.69	2.03	2.25	1.44	1.34	1.72
post-PV MF	0.47	0.70	0.62	0.29	0.33	0.29
post-ET MF	0.71	0.89	1.08	0.46	0.55	0.55
PMF, post-PV MF, and post-ET MF	2.78	3.44	3.82	2.12	2.15	2.52

MF = myelofibrosis; MPN = myeloproliferative neoplasm; PMF = primary myelofibrosis; post-ET MF = post-essential thrombocythemia myelofibrosis; post-PV MF = post-polycythemia vera myelofibrosis.

The literature discussed for the estimation of the prevalence of MF included Roaldsnes et al. 2016, Titmarsh et al. 2014, Moulard et al. 2014, HMRN Registry, Dupriez et al. 2016, Heinrich et al. 2014, Kaifie et al. 2016 Steinmetz et al. 2018, Kousoulakou et al. 2014 and Devos et al. 2015.

The number of expected cases of post-PV MF and post-ET MF was derived by annualizing the 15-year cumulative incidence estimates of 6% for post-PV (Passamonte, 2008) and 15% for post-ET (Cervantes, 2002).

Median survival estimates of PMF and post-PV MF are 5.8 years (Tefferi, 2007) and 5.7 years (Passamonti, 2008), respectively. No survival estimate of post-ET MF is available, so the MF estimate of 5.7 years (Pastor-Galán, 2019) is applied to patients with post-ET MF.

The prevalence of each designated condition was calculated and was estimated at 0.3 in 10,000 for PMF, 0.1 in 10,000 for PPV-MF, and 0.1 in 10,000 for PET-MT. This was accepted based on the literature and methodology used.

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

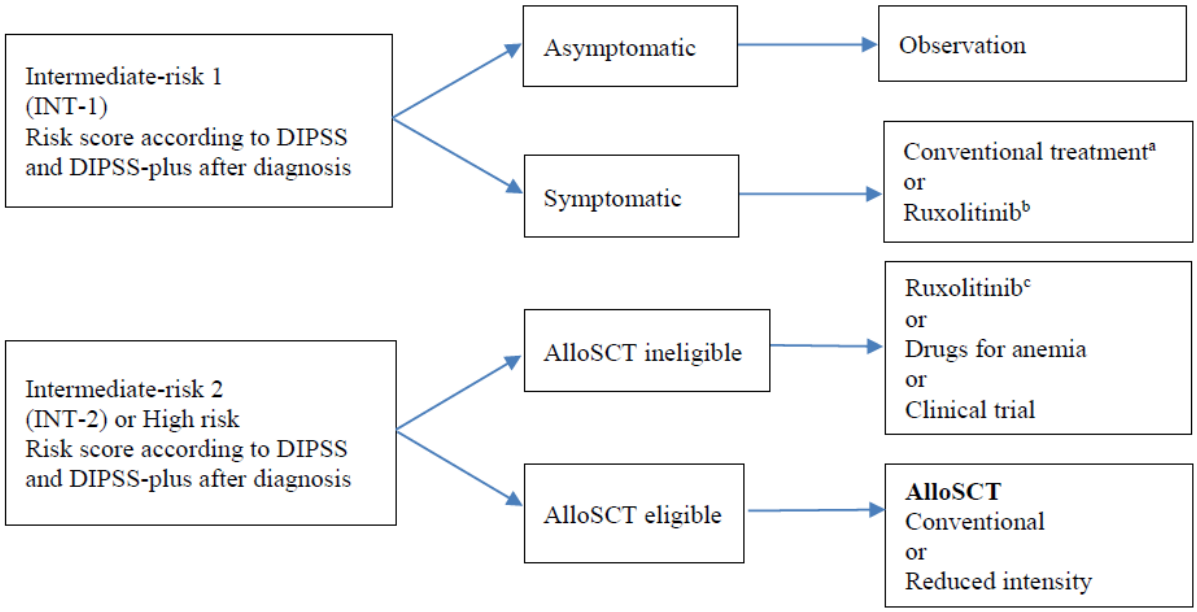
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Allogeneic stem-cell transplantation (SCT) is currently the only treatment that is potentially curative and can induce long term remission in patients with myelofibrosis (Barbui, 2018; Vannucchi, 2017). In the EU, ruxolitinib is the only centrally approved product from the treatment of MF. 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.

The sponsor referred to both, ESMO and NCCN treatment guidelines (Vannucchi, 2015 and NCCN-MPN, 2019) to describe currently recommended treatment algorithms for myelofibrosis.

Figure 1. Treatment Algorithm for Intermediate-1, Intermediate-2, and High-risk Myelofibrosis (Adapted from the ESMO Clinical Practice Guidelines)



AlloSCT = allogeneic stem cell transplantation; DIPSS = Dynamic International Prognostic Scoring System; ESMO = European Society for Medical Oncology.

[a] Hydroxyurea for symptomatic splenomegaly in countries where ruxolitinib is not approved for low-risk patients. If anaemia is the problem, erythropoietin, corticosteroids, danazol, immunomodulators or splenectomy.

[b] For patients presenting with symptomatic splenomegaly and/or constitutional symptoms if allowed by the label.

[c] For patients presenting with symptomatic splenomegaly and/or constitutional symptoms.

Source: Vannucchi, 2015

According to the sponsor there are no products authorised for patients who do not respond to treatment with ruxolitinib. Ruxolitinib 1, 2, and 3-year discontinuation rates are 49%, 71%, and 86%, respectively, with the main reasons for discontinuation of ruxolitinib therapy being loss of therapeutic effect, lack of response, and drug induced cytopenias (Abdelrahman, 2015). More than half of the patients of the patients on ruxolitinib require dose reductions due to myelosuppression (Verstovsek, 2017a). The myelosuppression is a great limitation specifically for patients with low baseline platelet counts (< 100 x 109/L).

Significant benefit

The initial sponsor for these designations received Protocol Assistance from the Committee for Medicinal Products for Human Use (CHMP) in 2011 on the design for clinical Phase 3 study Fedratinib EFC12153 (JAKARTA). At that time, ruxolitinib was not yet approved in the EU, hence the demonstration of significant benefit of fedratinib over ruxolitinib was not discussed.

There is no data directly comparing fedratinib to ruxolitinib. Following a systematic literature review, an indirect treatment comparison (ITC) was performed to provide preliminary evidence to support the comparative efficacy between fedratinib and ruxolitinib.

Significant benefit of fedratinib over SCT, splenectomy and splenic irradiation will not be discussed because these interventions occur in different patient settings than the intended use of fedratinib.

The sponsor defines patients who are JAK inhibitor naïve as:

- Intermediate risk-1 patients with highly symptomatic spleen
- Intermediate risk-2 or high-risk patients ineligible to transplant

The current standard of care for these patients is the only approved JAK inhibitor: ruxolitinib.

The EFC12153 study of fedratinib was compared to the two registration studies of ruxolitinib COMFORT-I and COMFORT-II. Efficacy endpoints compared were ≥35% reduction in spleen volume reduction (SVR) and ≥50% reduction in TSS from baseline to the end of Week 24 (end of Cycle 6).

Table 2. SVR results (matching-adjust indirect comparison)

Outcome	**EFC12153**		**COMFORT-I**		**COMFORT-II**	
	Placebo	**fedratinib**	**Placebo**	**ruxolitinib**	**BAT**	**ruxolitinib**
≥35% SVR from baseline to Week 24 (EFC12153 ITT population and no confirmation of response 4 weeks later)	1.0% (n=1; N=96)	46.9% (n=45; N=96)	0.7% (n=1; N=153)	41.9% (n=65; N=155)	0% (n=0; N=72)	31.9% (n=46; N=144)
			Δ 400mg Fed–Rux [95% CI]: 7.9% [-5.2, 20.9]		Δ 400mg Fed–Rux [95% CI]: 16.3% [3.5, 29.0]	
			Δ 400mg Fed–Rux [95% CI]: 12.3% [0.6, 24.0]			
≥35% SVR from baseline to Week 24 (subgroup of the EFC12153 ITT population with platelet counts ≥100 x 10^9/L and no confirmation of response 4 weeks later)	1.3% (n=1; N=77)	48.8% (n=40; N=82)	0.7% (n=1; N=153)	41.9% (n=65; N=155)	0% (n=0; N=72)	31.9% (n=46; N=144)
			Δ 400mg Fed–Rux [95% CI]: 10.4% [-3.2, 24.1]		Δ 400mg Fed–Rux [95% CI]: 18.5% [5.1, 31.9]	
			Δ 400mg Fed–Rux [95% CI]: 14.7% [2.4, 27.1]			

Table 3. Total symptom score (TSS) results

Outcome	EFC12153		COMFORT-I		COMFORT-II	
	Placebo	fedratinib	Placebo	ruxolitinib	BAT	ruxolitinib
≥50% reduction in TSS from baseline to Week 24 (EFC12153 symptom analysis population)	8.2% (n=7; N=85)	39.6% (n=36; N=91)	5.3% (n=8; N=152)	45.9% (n=68; N=148)	NA	NA
			Δ 400mg Fed–Rux [95% CI]: -9.4% [-23.9, 5.2]		NA	
≥50% reduction in TSS from baseline to Week 24 (subgroup of the EFC12153 symptom analysis population with platelet counts ≥100 x 10^9/L)	10.4% (n=7; N=67)	41.0% (n=32; N=78)	5.3% (n=8; N=152)	45.9% (n=68; N=148)	NA	NA
			Δ 400mg Fed–Rux [95% CI]: -10.1% [-25.9, 5.7]		NA	

Among patients with PMF, approximately one-quarter has low platelet counts < 100 x 10^9/L as a consequence of their disease (Tefferi,2012) and therefore represents an important subgroup to be treated. As mentioned above, the two registration studies for ruxolitinib COMFORT-I and COMFORT-II did not enrol subjects with platelet count < 100 x 10^9/L while subjects with platelet count ≥ 50 x 109/L were enrolled in the fedratinib study EFC12153. A side-by-side comparison was performed between the EFC12153 subgroup of subjects with platelet count between 50-100 x 10^9/L and the results from an interim analysis of a study (study 258) investigating ruxolitinib inpatients with myelofibrosis and low platelet counts (Talpaz 2013) to understand if fedratinib could be of significant benefit over ruxolitinib in this patient population.

Several differences were identified in terms of study design, inclusion/exclusion criteria and baseline characteristics. There are indications to suggest that subjects in Study 258 are healthier than in ECF12153. However, comparison of baseline characteristics is limited by the small sample sizes.

Table 4. Efficacy Results in Patients with Low Platelet Counts 50-100 x 10^9/L

	ECF12153		Study 258
	Placebo	**Fedratinib 400 mg**	**Ruxolitinib**
SVR			
≥35% reduction from baseline to week 24 regardless of confirmation	0% (n=0, N=18)	38.5% (CI: 12.0, 64.9) (n=5, N=13)	20% (CI: 7.6, 32.4) (n=8, N=40)
TSS reduction			
≥50% reduction in TSS at week 24	0% (n=0, N=13)	33.3% (CI: 6.7, 60.0) (n=4, N=12)	34.1% (CI: 19.6, 48.7) (n = 14, N=41)

CI = confidence interval; SVR = spleen volume reduction; TSS = total symptom score.

Despite several limitations, including small sample sizes, differences in study design and baseline characteristics, a greater proportion of fedratinib-treated subjects responded in terms of SVR compared to ruxolitinib-treated subjects (38.5% [CI: 12.0, 64.9] compared with 20% [CI: 7.6, 32.4]). For the TSS reduction outcome, the percentage of responders was similar in the fedratinib arm of ECF12153 and the ruxolitinib in Study 258. These results are proposed as relevant considering the unmet need in patients with low platelet counts. In addition, the risk of thrombocytopenia in these patients may be lower. As compared to fedratinib, a higher incidence of dose interruptions and dose reductions due to thrombocytopenia was observed for ruxolitinib (Table 5).

Table 5: Dose modifications due to thrombocytopenia

	Study EFC12153	Study 258
	Fedratinib 400 mg (N=13) First 24 weeks	**Ruxolitinib (N=50)**
	n (%)	**n (%)**
Thrombocytopenia leading to dose interruption	1 (7.7)	8 (16.0)
Thrombocytopenia leading to dose reduction	1 (7.7)	12 (24.0)
Thrombocytopenia / bleeding leading to drug withdrawal	1 (7.7)	2 (4.0)

The COMP agreed to treat these comparisons with caution but nevertheless concluded that fedratinib may bring clinically relevant advantage in low platelet count patients.

As per the approved product information, the recommended starting dose of ruxolitinib is 15 mg twice daily for patients with a platelet count between 100 and 200 x 10^9/L and 20 mg twice daily for patients with a platelet count of > 200 x 10^9/L. The maximum starting dose for patients with platelet counts between 50 and 100 x 10^9/L is 5 mg twice daily and the dose should be titrated cautiously. Treatment should be discontinued for platelet counts less than 50 x 10^9/L or absolute neutrophil counts less than 500/mm3(Novartis Europharm, 2019).

In addition, the product was shown to be efficacious in patients previously treated with ruxolitinib. In this patient population, the ESMO clinical guideline refers to clinical trials and the NCCN guideline specifically refers to fedratinib which was approved in the USA in August 2019. Hydroxyurea and busulfan could still be considered satisfactory methods in this setting as they have a broad indication in MF in some EU countries (e.g. Italy, Ireland and Netherlands).

There are no data comparing directly fedratinib to hydroxyurea or busulfan in patients previously treated with ruxolitinib. Studies in this setting utilized best available therapies (BAT) as comparator. HU or busulfan could be used in the BAT arm. In the two large studies PERSIST-2 (Mascarenhas, 2018) and SIMPLIFY-2 (Harrison, 2018), which investigated BAT in a patient population that had received prior JAK-inhibitor treatment, HU was used in approximately 20% of subjects whereas busulfan was not used at all.

Although detailed responses of each therapies constituting the BAT arm are not published, the sponsor performed an indirect treatment comparison to BAT to demonstrate significant benefit of fedratinib over HU and busulfan in patients with MF previously treated with ruxolitinib.

In summary, for the naïve (i.e., non-adjusted) ITC comparing fedratinib to BAT where the efficacy of BAT was informed by the PERSIST-2 study, fedratinib 400 mg led to a greater proportion of subjects with platelet count < 100 x 10^9/L achieving ≥ 35% reduction in SVR and ≥ 50% reduction in TSS compared to BAT. Specifically, fedratinib 400 mg had a 33.3% (95% CI 15.9, 50.8) greater proportion of subjects with ≥ 35% SVR compared with BAT and had a 21.2% (95%CI:0.7%,41.7%) greater proportion of subjects with ≥50% TSS reduction compared with BAT. After adjustment for baseline ECOG PS using the MAIC methodology, where the efficacy of BAT was informed by the SIMPLIFY-2 study, fedratinib 400 mg had a 27.0% (95%CI:15.7,38.7) greater proportion of subjects with ≥ 35% SVR compared with BAT. After adjustment for ECOG PS and DIPSS, fedratinib 400 mg had a 17.0% (95% CI: 6.2, 28.2) greater proportion of subjects with ≥ 50% TSS reduction compared with BAT. For both endpoints, results were similar when a naïve (i.e., non-adjusted) comparison was performed and when an STC with the same adjustment (adjustment for ECOG PS) was performed.

Taken together, the sponsor provided an indirect comparative analysis of the standard of care vs. fedratinib in treatment naïve and ruxolitinib refractory populations. In treatment naïve population a clinically relevant advantage of improved efficacy was proposed in patients with low platelet counts.

In refractory population, the sponsor provided literature and an indirect comparison, which indicate that the product performed better, especially in spleen volume reductions, compared to the best standard of care. The sponsor did not present any data demonstrating the response that could be seen with the use of busulfan. However, the fact that this product was not used in the published studies with the BAT may indicate that the efficacy is not expected to be of value compared to other available treatment options. Therefore, taken together, the claims of significant benefit of fedratinib in the ruxolitinib pre-treated patients was accepted.

4. COMP position adopted on 16 December 2020

EU/3/10/794

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/3/10/810 and EU/3/10/811), 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 0.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a median survival of 5.75 years, 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, the assumption that Inrebic may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from the clinical trial in patients who were relapsed and refractory to ruxolitinib showing clinically meaningful reductions in spleen volume reductions and total symptom score. Moreover, patients with low platelet counts who were treatment naïve, achieved improved spleen volume reductions as compared to patients treated with ruxolitinib.

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 Inrebic, N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate, fedratinib for treatment of primary myelofibrosis (EU/3/10/794) is not removed from the Community Register of Orphan Medicinal Products.

EU/3/10/810

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/3/10/794 and EU/3/10/811), 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 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a median survival of 5.75 years, 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, the assumption that Inrebic may be of potential significant benefit to those

affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from the clinical trial in patients who were relapsed and refractory to ruxolitinib showing clinically meaningful reductions in spleen volume reductions and total symptom score. Moreover, patients with low platelet counts who were treatment naïve, achieved improved spleen volume reductions as compared to patients treated with ruxolitinib.

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 Inrebic, N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate, fedratinib for treatment of post-essential thrombocythaemia myelofibrosis (EU/3/10/810) is not removed from the Community Register of Orphan Medicinal Products.

EU/3/10/811

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/3/10/794 and EU/3/10/810), 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 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with a median survival of 5.75 years, 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, the assumption that Inrebic may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from the clinical trial in patients who were relapsed and refractory to ruxolitinib showing clinically meaningful reductions in spleen volume reductions and total symptom score. Moreover, patients with low platelet counts who were treatment naïve, achieved improved spleen volume reductions as compared to patients treated with ruxolitinib.

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 Inrebic, N-tert-butyl-3-[(5-methyl-2-{[4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino] benzenesulfonamide dihydrochloride monohydrate, fedratinib for treatment of post-polycythaemia vera myelofibrosis (EU/3/10/811) is not removed from the Community Register of Orphan Medicinal Products.