

Date: 24 August 2021

Swissmedic, Swiss Agency for Therapeutic Products

## ***Swiss Public Assessment Report***

### **INREBIC**

**International non-proprietary name:** fedratinib as fedratinib dihydrochloride monohydrate

**Pharmaceutical form:** hard capsule

**Dosage strength:** 100 mg

**Route(s) of administration:** oral

**Marketing Authorisation Holder:** Celgene GmbH

**Marketing Authorisation No.:** 67792

**Decision and Decision date:** approved (temporary authorisation in accordance with Art. 9a TPA) on 1<sup>st</sup> July 2021

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

**About Swissmedic**

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

**About the Swiss Public Assessment Report (SwissPAR)**

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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## 1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC <sub>0-24h</sub>	Area under the plasma concentration-time curve for the 24-hour dosing interval
C <sub>max</sub>	Maximum observed plasma/serum concentration of drug
CSR	Clinical study report
CYP	Cytochrome P450
EOC6	End of Cycle 6
ERA	Environmental Risk Assessment
GI	Gastro-intestinal
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IPSS	International Prognostic Scoring System
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MF	Myelofibrosis
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression Free Survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PMF	Primary myelofibrosis
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
RR	Response rate
SVR	Spleen volume reduction
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21))
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
WE	Wernicke's encephalopathy

## 2 Background Information on the Procedure

### 2.1 Applicant's Request(s)

#### **New Active Substance status**

The applicant requested the status of a new active entity for the active substance fedratinib as fedratinib dihydrochloride monohydrate of the medicinal product mentioned above.

#### **Orphan drug status**

The applicant requested Orphan Drug Status in accordance with Article 4 a<sup>decies</sup> no. 2 of the TPA. The Orphan Status was granted on 15 October 2019.

#### **Authorisation human medical product under Art. 13 TPA**

The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

#### **Temporary authorisation for human medical products**

The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

## 2.2 Indication and Dosage

### 2.2.1 Requested Indication

Inrebic is a kinase inhibitor indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythaemia vera or post-essential thrombocythaemia) myelofibrosis (MF).

Conduct baseline testing of thiamine (Vitamin B1) levels prior to initiation of Inrebic.

### 2.2.2 Approved Indication

Inrebic is indicated for the treatment of splenomegaly or disease-associated symptoms in intermediate or high risk patients who have failed to respond, or are intolerant, to ruxolitinib (See section "Warnings/precautions"):

- with primary myelofibrosis or
- with secondary myelofibrosis as a complication of polycythaemia vera or essential thrombocythaemia.

The criteria for failure of, and intolerance to, ruxolitinib are described in the section "Properties/Effects".

### 2.2.3 Requested Dosage

The recommended dosage of Inrebic is 400 mg taken orally once daily for patients with a baseline platelet count of greater than or equal to  $50 \times 10^9/L$ .

Inrebic may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting.

Modify the dose for patients using concomitant strong CYP3A4 inhibitors, and in patients with severe renal impairment (creatinine clearance (CLcr) 15 mL/min to 29 mL/min).

### 2.2.4 Approved Dosage

(see appendix)

### 2.3 Regulatory History (Milestones)

Application	29 November 2019
Formal control completed	10 February 2020
List of Questions (LoQ)	4 June 2020
Answers to LoQ	4 October 2020
Predecision	17 December 2020
Answers to Predecision	15 February 2021
2. Predecision	3 May 2021
Answers to 2. Predecision	8 June 2021
Final Decision	1 July 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has not assessed all the primary data of this application and is taking over the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR refers to the publicly available Assessment Report INREBIC, application number 212327 (approval date: 16 August 2019) issued by the FDA.

### **3 Medical Context**

Myelofibrosis (MF) is a serious and life-threatening, stem-cell derived clonal myeloproliferative neoplasm. It can present either de novo as primary myelofibrosis (PMF) or following previously diagnosed polycythaemia vera (PV) and essential thrombocythaemia (ET).

First line therapy of myelofibrosis depends on the risk score (IPSS) of the disease. For patients with intermediate-2 risk and high-risk aged under 70 years the preferred therapy is an allogeneic stem cell transplantation (allo-SCT), which is the only potentially curative treatment option. However, allo-SCT is associated with high morbidity and mortality rates of 20-30% and a relapse rate after 5 years of 29%.

If allo-SCT is not possible, therapy depends on the occurrence of splenomegaly or other symptoms of the disease. In case of splenomegaly or other symptoms of disease, ruxolitinib or symptom-oriented therapy are preferred options.

There is no approved therapy for patients previously treated with ruxolitinib. The prognosis for these patients is poor, with a median overall survival (OS) between 6 – 28 months.

#### **4 Quality Aspects**

Swissmedic has not assessed the primary data relating to quality aspects of this application and is taking over the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to quality aspects refers to the publicly available Assessment Report INREBIC, application number 212327 (approval date: 16 August 2019) issued by the FDA.

#### **5 Nonclinical Aspects**

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority, the FDA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report INREBIC, application number 212327 (approval date: 16 August 2019) issued by the FDA.



## **6 Clinical and Clinical Pharmacology 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 FDA. The available assessment reports and approved product information from the FDA were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology aspects, see section 8.1 of this report.

### **6.2 Dose Finding and Dose Recommendation**

The evaluation of dose recommendation of this application has been carried out in reliance on a previous regulatory decision by FDA. The available assessment reports and approved product information from the FDA were used as a basis for the evaluation of the recommended dose.

### **6.3 Efficacy**

The evaluation of the clinical efficacy and safety data of this application has been carried out in reliance on a previous regulatory decision by FDA. The fedratinib clinical development programme, including JAKARTA and JAKARTA 2, was placed on full clinical hold on November 15, 2013, due to reports of several cases consistent with events of Wernicke's encephalopathy (WE) and heart failure. Therefore, the evaluation focused on specific adverse events, such as encephalopathy, including Wernicke's encephalopathy (WE), gastrointestinal toxicity and cardiac safety in particular, taking into account the limited efficacy data due to premature termination of the studies.

The applicant submitted two clinical studies for evaluation of efficacy, Study EFC12153 (JAKARTA) and Study ARD12181 (JAKARTA2).

The evaluation of second-line treatment was based on the results of JAKARTA2, which was an open-label, single-arm Phase 2 study in subjects previously exposed to ruxolitinib with intermediate-1 with symptoms, intermediate-2 or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis with splenomegaly and platelet count  $\geq 50 \times 10^9/L$ .

The definitions and assessments of ruxolitinib resistance and intolerance per the investigators' assessments were not pre-specified in the study protocol. Post-hoc specific criteria for ruxolitinib resistance and intolerance were defined with the help of myelofibrosis (MF) experts. Of the 97 patients enrolled in the JAKARTA2 study, 79 were identified as having met at least one of the stringent criteria.

- Relapsed: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared to baseline after an initial response (as defined below).  
Subjects must have had treatment with ruxolitinib for  $\geq 3$  months.  
Response to ruxolitinib was defined as:  $\geq 50\%$  reduction in spleen size for baseline spleen > 10 cm (or  $\geq 35\%$  reduction in spleen volume from baseline); nonpalpable spleen for baseline spleen between 5 and 10 cm; not eligible for spleen response for baseline spleen < 5 cm.
- Refractory: < 30% reduction in spleen size (or < 10% reduction in spleen volume) at the end of ruxolitinib treatment compared to baseline and failure to meet criteria for response (as defined above) during ruxolitinib treatment. Subjects must have had treatment with ruxolitinib for  $\geq 3$  months.
- Intolerant: ruxolitinib treatment for  $\geq 28$  days complicated by either (i) the development of red blood cell (RBC) transfusion requirement ( $\geq 2$  units/month for 2 months), or (ii) toxicity defined as Grade  $\geq 3$  AEs of thrombocytopenia, anaemia, haematoma, and/or haemorrhage while on treatment with ruxolitinib.

Eligible patients received 400 mg/day of fedratinib orally starting on Day 1 of Cycle 1. If there was lack of adequate splenic response and no unacceptable drug toxicity, the study drug dose was up-titrated in 100 mg/day increments up to maximum of 600 mg/day.

Overall, 97 patients who were pre-treated (79% of patients had received  $\geq 2$  prior therapies and 13% had received  $\geq 4$  prior therapies) were enrolled. The median age was 67 years (range: 38 to 83 years) with 46% of patients aged between 65 and 74 years and 17% of patients at least 75 years. Included patients had primary MF (55%), post-polycythaemia vera MF 26% and, in 19% of cases, post-essential thrombocythaemia MF. Sixteen percent (16%) of patients had intermediate-1 with symptoms, 49% had intermediate-2, and 35% had high-risk disease.

The primary endpoint was spleen response rate (RR) defined as the proportion of subjects with a  $\geq 35\%$  spleen volume reduction (SVR) at the end of Cycle 6 (EOC6), as measured by MRI/CT scan relative to baseline.

JAKARTA2 was terminated prematurely due to safety concerns, and all subjects were permanently discontinued from fedratinib treatment. Overall, 64.9% of the subjects had to discontinue treatment due to early termination of the study. Therefore, long-term efficacy beyond the primary endpoint is limited.

The spleen RR at the End of Cycle 6 ( $\geq 35\%$  SVR) for patients with a dose of 400 mg fedratinib was 22.7% (22/97 patients, 95% CI: 14.8%, 32.3%).

After permanent treatment discontinuation, 40 (41.2%) of all 97 subjects received further anticancer therapy. Analysis of survival after initiation of further anticancer therapy was not performed due to the limited data.

## 6.4 Safety

Overall, 97 patients were included in the safety analyses of JAKARTA2. Treatment-emergent adverse events occurring in  $\geq 15\%$  of subjects were diarrhoea (61.9%), nausea (55.7%), anaemia (48.5%), vomiting (41.2%), thrombocytopenia (26.6%), constipation (20.6%), fatigue (15.5%). Grade 3-4 events in  $\geq 15\%$  of patients were anaemia (38.1%), thrombocytopenia (21.6%), lipase increased (6.2%). Overall, 18 deaths occurred during on-treatment period (7 deaths) and post-treatment period (11 deaths). Main cause of death was disease progression. Treatment-emergent serious adverse events reported in two or more subjects were pneumonia (4.1%), pleural effusion (3.1%) and fall (2.1%).

Overall, 13.4% of patients in JAKARTA2 had cardiac failure/cardiomyopathy with peripheral oedema (6.2%), cardiac failure (3.1%) and ascites, cardiorespiratory arrest, diastolic dysfunction, myocardial ischaemia, peripheral swelling and ventricular hypokinesia (each 1%). Of these, three were evaluated as serious, (one cardiac failure, one cardiorespiratory arrest and one myocardial ischaemia) and two adverse events as grade 3-4 (two cardiac failure and one myocardial ischaemia). One event, cardiorespiratory arrest, resulted in death.

Safety signals of encephalopathy, including Wernicke's encephalopathy (WE) adverse reactions, occurred in patients treated with fedratinib. Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with fedratinib. Some patients had predisposing factors (including baseline malnutrition and treatment-emergent GI AEs) that may have led to thiamine deficiency. However, the relationship between fedratinib and thiamine deficiency is not clearly established. Wernicke's encephalopathy is a neurological emergency requiring immediate thiamine replacement. The risk of WE can be potentially mitigated by monitoring the patient's thiamine levels, early recognition of signs and symptoms of WE, and supplementing thiamine as needed, as well as monitoring gastrointestinal toxicity. In the clinical database for study JAKARTA2, 17 (17.5%) patients had at least one TEAE that could be associated with WE. Signs and symptoms in these patients were

peripheral neuropathy (4.1%), blurred vision (4.1%), dysgeusia (3.1%), Herpes zoster (2.1%) and amnesia, encephalopathy (serious), hypogeusia, paraesthesia, paraesthesia oral, peripheral sensory neuropathy, photopsia (each 1%). Of these, one event was evaluated as serious (encephalopathy) and two events as grade 3-4 (encephalopathy and peripheral neuropathy).

## 6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The supporting trial (JAKARTA-2) results showed that treatment with 400 mg fedratinib resulted in an SVR at EOC6 compared to baseline in patients previously treated with ruxolitinib.

The fedratinib clinical development programme, including JAKARTA 2, was placed on full clinical hold on November 15, 2013, due to reports of several cases consistent with events of Wernicke's encephalopathy (WE) and heart failure and, in consequence, the marketing authorisation holder terminated the development of fedratinib on November 18, 2013. Therefore, data are limited, with no long-term efficacy results beyond the primary endpoint, in particular with no results for Progression-Free Survival (PFS) or Overall Survival (OS). In addition, the definition of ruxolitinib resistance and intolerance was not pre-specified in the study protocol and was determined by the investigator. The applicant published a sensitivity analysis with more stringent criteria for ruxolitinib resistance or intolerance (see above). However, these criteria were defined post-hoc, and analyses for patients that fulfilled these criteria are exploratory.

Therapy with fedratinib is associated with relevant toxicity. In particular, cardiac toxicity and cases of WE are of concern. Currently no (long-term) data are available showing that thiamine supplementation can prevent cardiac events or WE.

Two clinical trials, FREEDOM (NCT03755518) and FREEDOM-2 (NCT03952039), are ongoing and will provide relevant long-term data on efficacy and safety and clarify whether thiamine supplementation will prevent cardiac disorders and cases of WE.

Due to the limited size of the efficacy population, including uncertainties due to the single-arm nature of the submitted study, the presently limited efficacy (without PFS or OS data) and safety data (including relevant toxicity), the current data are not sufficient for a regular approval.

No therapies are available for patients with primary myelofibrosis or secondary myelofibrosis who have failed to respond, or are intolerant, to ruxolitinib. Therefore, current results of JAKARTA2 with 22.7% of patients achieving a  $\geq 35\%$  SVR (400 mg) at EOC6 were accepted for a temporary approval of fedratinib.

The applicant will submit results of the following studies as a condition of the temporary approval:

FREEDOM-2, a Phase 3 randomised study in the post ruxolitinib setting, is designed to confirm the findings of JAKARTA 2. The planned date of the clinical study report (CSR) for the primary analysis of the FREEDOM 2 study is December 2022, and final CSR is planned in May 2025.

FREEDOM is a Phase 3b, single-arm, open-label study in patients previously treated with ruxolitinib. The primary endpoint is the proportion of patients achieving a  $\geq 35\%$  SVR. The planned date of the clinical study report (CSR) for the FREEDOM study is August 2023, which will include 1 year of follow-up after 1 year of treatment with fedratinib.

A key serious safety concern of fedratinib is the risk of encephalopathy, including WE. Therefore, a black box warning for encephalopathy, including WE, with an adequate description of the risk and risk minimisation measures, including evaluation of thiamine levels and substitution, was included in the product information for healthcare professionals.

**6.6 Approved Indication and Dosage**

See information for healthcare professionals in the Appendix.

## **7 Risk Management Plan Summary**

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

## **8 Appendix**

### **8.1 Approved Information for Healthcare Professionals**

Please be aware that the following version of the information for healthcare professionals relating to Inrebic 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch)).

**Note:**

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

- ▼ 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.

Inrebic is approved for a limited period of time, see section "Properties/effects".

### **Inrebic®**

**IMPORTANT WARNING** for the use of Inrebic: Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with Inrebic. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue Inrebic and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize. See Sections "Dosage/Administration", "Warnings/Precautions" and "Adverse Reactions".

### **Composition**

#### *Active substances*

Fedratinib (as dihydrochloride monohydrate)

#### *Excipients*

Silicified microcrystalline cellulose (contains microcrystalline cellulose and colloidal silicon dioxide), sodium stearyl fumarate, gelatin, titanium dioxide (E171), red iron oxide (E172), printing ink (shellac, titanium dioxide (E171), propylene glycol (E1520))

Contains 0.18 mg of sodium per hard capsule.

### **Pharmaceutical form and active substance quantity per unit**

Hard capsules containing 100 mg of fedratinib (equivalent to 117.30 mg of fedratinib dihydrochloride monohydrate).

### **Indications/Uses**

Inrebic is indicated for the treatment of splenomegaly or disease-associated symptoms in intermediate or high risk patients who have failed or are intolerant to ruxolitinib (See section "Warnings/precautions").

- with primary myelofibrosis or
- with secondary myelofibrosis a complication of polycythaemia vera or essential thrombocythemia.

The criteria for failure of and intolerance to ruxolitinib are described in the section “Properties/Effects”.

### **Dosage/Administration**

Treatment with Inrebic should be initiated and monitored under the supervision of physicians experienced in the use of anti-cancer medicinal products.

#### *Prior to treatment initiation*

Before initiation of the treatment with Inrebic patients that are on treatment with ruxolitinib must taper and discontinue ruxolitinib.

Obtain the following blood tests prior to starting treatment with Inrebic, periodically during treatment, and as clinically indicated (see section “Warnings and precautions”):

- Thiamine (Vitamin B1) level;
- Complete blood count with platelets;
- Blood Urea Nitrogen (BUN) and Creatinine;
- Hepatic panel;
- Amylase and lipase.

Do not start Inrebic in patients with thiamine deficiency; replete thiamine prior to treatment initiation. Initiating treatment with Inrebic is not recommended in patients with a baseline platelet count below  $50 \times 10^9/L$  and  $ANC < 1.0 \times 10^9/L$ .

#### *Dosing*

The recommended dose of Inrebic is 400 mg taken orally once daily for patients with a baseline platelet count of  $\geq 50 \times 10^9/L$ .

Inrebic may be taken with or without food. Administration with a high fat meal may reduce the incidence of nausea and vomiting.

It is recommended that prophylactic anti-emetics be used according to local practice for the first 8 weeks of treatment and continued thereafter as clinically indicated (see section “Warnings and precautions”).

If a dose of Inrebic is missed, the next scheduled dose should be taken the following day. Extra capsules should not be taken to make up for the missed dose.



*Dose adjustment following undesirable effects/interactions*

Dose Modification with Concomitant Use of Strong CYP3A4 Inhibitors

If concomitant strong CYP3A4 inhibitors cannot be avoided, the dose of Inrebic should be reduced to 200 mg. Patients should be carefully monitored (e.g. at least weekly) for safety-

In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, Inrebic dosage should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter as tolerated (see sections “Warnings and Precautions” and “Interactions”).

Dose modification for adverse reactions

Dose modifications for haematologic toxicities, non-haematologic toxicities and management of Wernicke’s encephalopathy (WE) are shown in Table 1. Discontinue Inrebic in patients unable to tolerate a dose of 200 mg daily; See section “Warnings and precautions” for other mitigating strategies.

**Table 1: Dose reductions for haematologic, non-haematologic treatment emergent toxicities and management of Wernicke’s encephalopathy**

<b>Haematologic toxicity</b>	<b>Dose reduction</b>
Grade 3 thrombocytopenia with active bleeding (platelet count < 50 x 10 <sup>9</sup> /L) or Grade 4 thrombocytopenia (platelet count < 25 x 10 <sup>9</sup> /L)	Interrupt Inrebic dose until resolved to ≤ Grade 2 (platelet count < 75 x 10 <sup>9</sup> /L) or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5 x 10 <sup>9</sup> /L)	Interrupt Inrebic dose until resolved to ≤ Grade 2 (ANC < 1.5 x 10 <sup>9</sup> /L) or baseline. Restart dose at 100 mg daily below the last given dose. Granulocyte growth factors may be used at the physician’s discretion.
Grade 3 and higher anaemia, transfusion indicated (haemoglobin level < 8.0 g/dL)	Interrupt Inrebic dose until resolved to ≤ Grade 2 (haemoglobin level < 10.0 g/dL) or baseline. Restart dose at 100 mg daily below the last given dose.
Recurrence of a Grade 4 haematologic toxicity	Inrebic discontinuation as per physician’s discretion.
<b>Non-haematologic toxicity</b>	<b>Dose reduction</b>
≥ Grade 3 nausea, vomiting or diarrhoea not responding to supportive measures within 48 hours	Interrupt Inrebic dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
≥ Grade 3 ALT/ AST (> 5.0 to 20.0 x ULN*) or bilirubin (> 3.0 to 10.0 ULN)	Interrupt Inrebic dose until resolved to ≤ Grade 1 (AST/ALT (> ULN - 3.0 x ULN) or bilirubin (> ULN - 1.5 x ULN)) or baseline. Restart dose at 100 mg daily below the last given dose.

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	Monitor ALT, AST and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with Inrebic.
≥ Grade 3 amylase / lipase (> 2.0 to 5.0 x ULN)	Interrupt Inrebic dose until resolved to Grade 1 (> ULN - 1.5 x ULN) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor amylase / lipase every 2 weeks for at least 3 months following the dose reduction. If reoccurrence of a Grade 3 or higher elevation, discontinue treatment with Inrebic.
≥ Grade 3 other non-haematologic toxicities	Interrupt Inrebic dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
<b>Management of thiamine levels and Wernicke's encephalopathy</b>	<b>Dose reduction</b>
For thiamine levels < normal range but ≥ 30 nmol/L without signs or symptoms of WE	Interrupt Inrebic treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range. Consider re-starting Inrebic treatment when thiamine levels are within normal range.
For thiamine levels < 30 nmol/L without signs or symptoms of WE	Interrupt Inrebic treatment. Initiate treatment with parenteral thiamine at therapeutic dosages until thiamine levels are restored to normal range. Consider re-starting Inrebic treatment when thiamine levels are within normal range.
For signs or symptoms of WE regardless of thiamine levels	Discontinue Inrebic treatment and immediately administer parenteral thiamine at therapeutic dosages.

\*ULN (Upper limit of Normal)

### Dose re-escalation

If the adverse reaction due to Inrebic that resulted in a dose reduction is controlled with effective management and the toxicity is resolved for at least 28 days, the dose level may be re-escalated to one dose level higher per month up to the original dose level. Dose re-escalation is not recommended if the dose reduction was due to a Grade 4 non haematologic toxicity, ≥ Grade 3 ALT, AST, or total bilirubin elevation, or reoccurrence of a Grade 4 haematologic toxicity.

### *Patients with impaired hepatic function*

Inrebic pharmacokinetics has not been evaluated in patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST). Avoid use of Inrebic in patients with severe hepatic impairment (Child-Pugh class C or total bilirubin >3 times upper limit of normal [ULN] and any AST increase).

No modification of the starting dose is required for patients with mild to moderate hepatic impairment (see section “Warnings and Precautions”).

### *Patients with impaired renal function*

Reduce Inrebic dose to 200 mg once daily in patients with severe renal impairment (creatinine clearance (CL<sub>cr</sub>) 15 mL/min to 29 mL/min as estimated by Cockcroft-Gault (C-G) equation).

No modification of the starting dose is recommended for patients with mild to moderate renal impairment (CL<sub>cr</sub> 30 mL/min to 89 mL/min by Cockcroft-Gault). Due to potential increase of exposure, patients with pre-existing moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions (see section “Warnings and Precautions”).

### *Elderly patients*

No additional dose adjustments are required in elderly patients (> 65 years of age). The experience in the age group 75 years and older is limited. In clinical studies, 13.8% (28/203) of patients treated with Inrebic were 75 years and older and serious adverse reactions and adverse reactions leading to treatment discontinuation occurred more frequently.

### *Children and adolescents*

The safety and efficacy of Inrebic in pediatric or adolescent patients (< 18 years) have not been established. There are no data available.

## **Contraindications**

- Pregnancy.
- Hypersensitivity to fedratinib or any of the excipients.

## **Warnings and precautions**

### *Encephalopathy, including Wernicke’s*

Cases of serious and fatal encephalopathy, including Wernicke’s, were reported in patients taking Inrebic. Wernicke’s encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke’s encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including Wernicke’s, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging (see sections “Dosage/Administration” and “Undesirable effects”).

Assess thiamine levels and nutritional status in all patients prior to starting Inrebic, periodically during treatment (e.g. monthly for the first 3 months and every 3 months thereafter), and as clinically relevant. Do not start Inrebic in patients with thiamine deficiency. Before treatment initiation and during treatment, thiamine levels should be replenished if they are low. If encephalopathy is suspected, immediately discontinue Inrebic and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize (see sections “Dosage/Administration” and “Undesirable effects”).

### *Anaemia, thrombocytopenia and neutropenia*

Treatment with Inrebic may cause anaemia, thrombocytopenia and neutropenia. Complete blood counts should be obtained at baseline, periodically during treatment and as clinically indicated (see sections “Dosage/Administration” and “Undesirable effects”).

### *Anaemia*

Anaemia generally occurs within the first 3 months of treatment. Patients with a haemoglobin level below 10.0 g/dL at the start of therapy are more likely to develop anaemia of Grade 3 or above during treatment and should be carefully monitored (e.g. once weekly). Patients developing anaemia may require blood transfusions. Consider dose reduction for patients developing anaemia particularly for those who become red blood cell transfusion dependent (see sections “Dosage/Administration” and “Undesirable effects”).

### *Thrombocytopenia*

Thrombocytopenia generally occurs within the first 3 months of treatment. Patients with low platelet counts ( $< 100 \times 10^9/L$ ) at the start of therapy are more likely to develop thrombocytopenia of Grade 3 or above during treatment and should be carefully monitored (e.g. once weekly) (see sections “Dosage/Administration” and “Undesirable effects”). Thrombocytopenia is generally reversible and is usually managed by supportive treatment such as dose interruptions, dose reduction and/or platelet transfusions if necessary. Patients should be made aware of the increased risk of bleeding associated with thrombocytopenia (see sections “Dosage/Administration” and “Undesirable effects”). Inrebic has not been studied in patients with a baseline platelet count  $< 50 \times 10^9/L$ .

### *Neutropenia*

Neutropenia was generally reversible and was managed by temporarily withholding Inrebic (see sections “Dosage/Administration” and “Undesirable effects”).

### *Gastrointestinal events*

Nausea, vomiting and diarrhoea are among the most frequent adverse reactions in patients treated with Inrebic.

Most of the events are Grade 1 or 2 and typically occur within the first 2 weeks of treatment. Consider providing appropriate prophylactic anti-emetic therapy (e.g. 5-HT<sub>3</sub> receptor antagonists) during Inrebic treatment. Treat diarrhoea with anti-diarrhoeal medicinal products promptly at the first onset of symptoms. For cases of Grade 3 or higher nausea, vomiting, and diarrhoea that are not responsive to supportive measures within 48 hours, the dose of Inrebic should be interrupted until resolved to Grade 1 or less/baseline. The dose should be restarted at 100 mg daily below the last given dose. Thiamine levels should be monitored and replenished as needed (see sections “Dosage/Administration” and “Undesirable effects”).

### *Hepatic toxicity*

Elevations of ALT and AST have been reported with Inrebic treatment and one case of hepatic failure was reported. Patients should have their hepatic function monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed hepatic toxicity, patients should be monitored at least every 2 weeks until resolution. ALT and AST elevations were generally reversible with dose modifications or permanent treatment discontinuation. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt Inrebic dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with Inrebic (see sections “Dosage/Administration” and “Undesirable effects”).

### *Amylase and lipase elevation*

Elevations of amylase and/or lipase and one case of pancreatitis was reported with Inrebic treatment. Patients should have their amylase and lipase monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. After observed toxicity, patients should be monitored at least every 2 weeks until resolution.. For Grade 3 or higher amylase and/or lipase elevations, interrupt Inrebic until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose (see sections “Dosage/Administration” and “Undesirable effects”).

### *Elevated creatinine*

Elevations of creatinine have been reported with Inrebic treatment (see section “Undesirable effects”). Patients should have their creatinine levels monitored at baseline, at least monthly for the first 3 months, periodically during treatment and as clinically indicated. For severe renal impairment (CL<sub>cr</sub> 15 mL/min to 29 mL/min by C-G), dose modifications are recommended (see section “Dosage/Administration”).

### *Concomitant administration with strong and moderate CYP3A4 inhibitors*

Concomitant administration of Inrebic with strong CYP3A4 inhibitors increases Inrebic exposure. Increased exposure of Inrebic may increase the risk of adverse reactions. In place of strong CYP3A4 inhibitors, consider alternative therapies that do not strongly inhibit CYP3A4 activity. If strong CYP3A4 inhibitors cannot be replaced, the dose of Inrebic should be reduced when administering with strong CYP3A4 inhibitors, (e.g. ketoconazole, ritonavir). Patients should be carefully monitored (e.g. at least weekly) for safety. Prolonged co-administration of a moderate CYP3A4 inhibitor may require close safety monitoring and if necessary, dose modifications based on adverse reactions (see sections “Dosage/Administration” and “interactions”).

### *Concomitant administration with strong and moderate CYP3A4 inducers*

Agents that strongly or moderately induce CYP3A4 (e.g. phenytoin, rifampicin, efavirenz) can decrease Inrebic exposure and should be avoided in patients receiving Inrebic (see section “Interactions”).

### *Cardiac disorders*

Cardiac failure was reported as a serious adverse event in 6 (3.0%) of patients receiving Inrebic 400 mg daily. Cardiogenic shock was reported as a fatal adverse event in 1 (0.5%) patient receiving Inrebic 400 mg daily. Cardiac failure led to permanent discontinuation in 3 (1.5%) of patients receiving Inrebic 400 mg daily. Patients with a previous cardiac history should be monitored as clinically indicated.

### *Other warning*

This medicine contains less than 1 mmol sodium (23 mg) per capsule, i.e. it is almost “free of sodium”.

## **Interactions**

### *Effect of Inrebic on other medicinal products*

#### CYP3A4, CYP2C19, or CYP2D6 substrate drugs

Co-administration of a single dose of midazolam (CYP3A4 substrate: 2 mg), omeprazole (CYP2C19 substrate: 20 mg), and metoprolol (CYP2D6 substrate: 100 mg) increased midazolam, omeprazole, or metoprolol AUC<sub>inf</sub> by 4-, 3-, and 2-fold, respectively. Therefore, monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when co-administered with Inrebic.

### *Effect of other medicinal products on Inrebic*

#### Strong and moderate CYP3A4 inhibitors

Co-administration of ketoconazole (strong CYP3A4 inhibitor: 200 mg twice daily) with a single dose of fedratinib (300 mg) increased the fedratinib area under the plasma concentration time curve from time zero to infinity ( $AUC_{inf}$ ) by approximately 3-fold. Based on physiologically based pharmacokinetic (PBPK) simulations, co-administration of a strong CYP3A4 inhibitor such as ketoconazole (400 mg once daily) with Inrebic 400 mg once daily is predicted to increase fedratinib AUC at steady state by 2-fold (See sections “Dosage/Administration” and “Warnings/Precautions”).

Based on PBPK simulations, co-administration of moderate CYP3A4 inhibitors, erythromycin (500 mg three times daily) or diltiazem (120 mg twice daily), with fedratinib 400 mg once daily is predicted to increase fedratinib AUC at steady state by 1.2- and 1.1-fold, respectively. Adverse reactions following prolonged co-administration of a moderate CYP3A4 inhibitor cannot be excluded (See section “Warnings/Precautions”).

#### Strong and moderate CYP3A4 inducers

Co-administration of rifampicin (strong CYP3A4 inducer: 600 mg once daily) or efavirenz (moderate CYP3A4 inducer: 600 mg once daily) with a single dose of fedratinib (500 mg) decreased  $AUC_{inf}$  of fedratinib by approximately 80% or 50%, respectively. Avoid Inrebic co-administered with strong and moderate CYP3A4 inducers (see section “Warnings/Precautions”).

#### Dual CYP3A4 and CYP2C19 inhibitors

Avoid Inrebic with dual CYP3A4 and CYP2C19 inhibitor. The effect of concomitant administration of a dual CYP3A4 and CYP2C19 inhibitor with Inrebic has not been studied.

#### Gastric acid reducing agents

Co-administration of pantoprazole (proton pump inhibitor: 40 mg once daily) with a single dose of Inrebic (500 mg) increased fedratinib  $AUC_{inf}$  by 1.2-fold. Therefore, it can be assumed that an increase in gastric pH does not have a clinically significant impact on fedratinib exposure, so that no adjustment of fedratinib dosage is required.

### *In vitro studies*

#### Fedratinib as a substrate for transporters

Fedratinib is a substrate of P-glycoprotein (P-gp) but not breast cancer resistance protein (BCRP), BSEP, multidrug resistance protein (MRP)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3.

### Effect of fedratinib on transporter substrates

Fedratinib inhibits P-gp, BCRP, OATP1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE)1, and MATE2-K, but not BSEP, MRP2, and organic anion transporter (OAT)1 and OAT3 in vitro.

### **Pregnancy, lactation**

#### *Women of childbearing potential/contraception*

Advise females of childbearing potential to avoid becoming pregnant whilst receiving Inrebic and to use effective contraception during treatment with Inrebic and for at least 1 month after the last dose.

#### *Pregnancy*

There are no data available on the use of Inrebic in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of fedratinib to pregnant rats during organogenesis at doses considerably lower than the recommended human daily dose of 400 mg/day resulted in adverse developmental outcomes (see section "Preclinical data"). Inrebic must not be used during pregnancy unless treatment with fedratinib is required because of the woman's clinical condition.

#### *Lactation*

There are no data on the presence of fedratinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Inrebic, and for at least 1 month after the last dose.

#### *Fertility*

Fedratinib had no effect on the estrous cycle parameters, mating performance, fertility, pregnancy rate or reproductive parameters in male or female rats at doses up to 30 mg/kg. The exposure (AUC) at the dose of 30 mg/kg/day is approximately 0.10 to 0.13 times the clinical exposure at the recommended daily dose. Thus, there are no data on effects on fertility in animals at clinically-relevant exposure levels (see section "Preclinical Data").



### Effects on ability to drive and use machines

Inrebic has a minor influence on the ability to drive and use machines. Patients who experience dizziness after taking Inrebic should refrain from driving or using machines.

### Undesirable effects

The overall safety information of Inrebic was assessed in 608 patients continuously treated with Inrebic as monotherapy in the clinical trials .

In studies of patients with primary myelofibrosis (MF), and secondary myelofibrosis, a complication of polycythemia vera (PV) or essential thrombocythemia (ET), treated with Inrebic 400 mg (N=203), including patients previously exposed to ruxolitinib, the median drug exposure was 35.6 weeks (range 0.7 to 114.6 weeks) and the median number of cycles initiated was 9 cycles. Sixty-three percent (63%) of 203 patients were exposed for 6 months or longer and 38 % were exposed for 12 months or longer. The most frequent nonhematologic adverse drug reactions were diarrhoea (67.5%), nausea (61.6%), and vomiting (44.8%). The most frequent hematologic adverse reactions were anaemia (99.0%) and thrombocytopenia (68.5%) based on laboratory values. The most frequent serious adverse reactions in patients with myelofibrosis treated with 400 mg are anaemia (2.5% based on reported adverse events and not laboratory values) and diarrhoea (1.5%).

Permanent discontinuation due to adverse event regardless of causality occurred in 24% of patients receiving 400 mg of Inrebic .

Adverse drug reactions from clinical trials with MF for entire treatment duration are listed below by MedDRA system organ class.

The frequencies of the adverse reactions are defined as: very common ( $\geq 1/10$ ); common ( $< 1/10$ ,  $\geq 1/100$ ); uncommon ( $< 1/100$ ,  $\geq 1/1'000$ ); rare ( $< 1/1'000$ ,  $\geq 1/10'000$ ); very rare ( $< 1/10'000$ ).

#### Infections and Infestations

Very common: Urinary tract infection (10.8%).

#### Blood and lymphatic system disorders

Very common: Anaemia<sup>a,d</sup> (99%), thrombocytopenia<sup>a</sup> (68.5%), neutropenia (29.2%), Bleeding (associated with thrombocytopenia requiring clinical intervention) (10.8 %)

#### Metabolism and nutrition disorders

Very common: Lipase increased<sup>a</sup> (39.9%), amylase increased<sup>a</sup> (24.1%).

### Nervous system disorders

Very common: Headache (14.3%), dizziness (14.3%).

Common: Wernicke's encephalopathy<sup>b,c</sup>

### Cardiac disorders

Common Cardiac failure

Uncommon Cardiogenic shock

### Vascular disorders

Common: Hypertension

### Gastrointestinal disorders

Very common: Diarrhoea (67.5%), nausea (61.6%), vomiting (44.8%), obstipation (17.7 %),

Common: Dyspepsia

### Hepatobiliary disorders

Very common: Alanine aminotransferase increased<sup>a</sup> (51.7%),  
aspartate aminotransferase increased<sup>a</sup> (59.1%)

### Musculoskeletal and connective tissue disorders

Very common: Muscle spasms (11.8%),

Common: Pain in extremity, bone pain

### Renal and urinary disorders

Very common: Blood creatinine increased<sup>a</sup> (73.9%)

Common: Dysuria

### General Disorders and administration site conditions

Very common: Fatigue/Asthenia (30.5%)

### Investigations

Common: Weight increased

<sup>a</sup> Frequency is based on laboratory value.

<sup>b</sup> Frequency is based on all patients who received continuous doses of fedratinib in clinical studies (N=608).

<sup>c</sup> Patients reported as having Wernicke's Encephalopathy were all taking a dose of 500 mg at the time of symptoms.

<sup>d</sup> Frequency includes Grade 3 only .

### Description of selected adverse reactions:

#### *Encephalopathy, including Wernicke's*

Serious cases of encephalopathy, including Wernicke's were reported in 1.3% (8/608) of patients treated with Inrebic in clinical trials; 7 patients were taking Inrebic at 500 mg daily prior to the onset of neurologic findings and had predisposing factors such as malnutrition, gastrointestinal adverse events, and other risk factors that could lead to thiamine deficiency. One patient treated with Inrebic at 400 mg was determined to have hepatic encephalopathy. Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment and dizziness, except for one fatal case (1/608; 0.16%). (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

#### *Gastrointestinal toxicity*

Nausea, vomiting, and diarrhoea are among the most frequent adverse reactions in Inrebic treated patients. In MF patients treated with 400 mg of Inrebic, diarrhoea occurred in 68% of patients, nausea in 62% of patients, and vomiting in 45% of patients. Grade 3 diarrhoea, nausea, and vomiting occurred in 5%, 0.5% and 2% of patients, respectively. The median time to onset of any grade nausea, vomiting, and diarrhoea was 2 days, with 75% of cases occurring within 3 weeks of starting treatment. Dose interruptions and reductions due to gastrointestinal toxicity were reported in 14% and 9% of patients, respectively. Permanent discontinuation of 400 mg Inrebic occurred due to gastrointestinal toxicity in 5% of patients (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

#### *Anaemia*

In patients with primary or secondary myelofibrosis treated with 400 mg of Inrebic, 52% of patients developed Grade 3 anaemia. The median time to first onset of Grade 3 anaemia event was approximately 60 days with 75% of cases occurring within 4 months of starting treatment. Red blood cell transfusions were received by 58% of 400 mg Inrebic treated patients and permanent discontinuation of 400 mg Inrebic occurred due to anaemia in 1.5% of patients (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

#### *Thrombocytopenia*

In patients with primary or secondary myelofibrosis treated with 400 mg of Inrebic, 14% and 9% of patients developed Grade 3 and Grade 4 thrombocytopenia, respectively. The median time to first onset of Grade 3 or 4 thrombocytopenia was approximately 70 days with 75% of cases occurring within 7 months of starting treatment. Platelet transfusions were received by 9% of 400 mg Inrebic treated patients. Bleeding (associated with thrombocytopenia), that required clinical intervention

occurred in 11% of patients. Permanent discontinuation of treatment due to thrombocytopenia occurred in 3% of patients (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

### *Neutropenia*

Grade 4 neutropenia occurred in 3.5% of patients and dose interruption due to neutropenia were reported in 0.5% of patients (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

### *Hepatic toxicity*

Elevations of ALT and AST (all Grades) occurred in 52% and 59%, respectively, with Grade 3 or 4 in 3% and 2%, respectively, of 400 mg Inrebic treated patients. The median time to onset of any Grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months of starting treatment (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

### *Elevated amylase/lipase*

Elevations of amylase and/or lipase (all Grades) occurred in 24% and 40%, respectively, of Inrebic treated MF patients. Most of these events under treatment with Inrebic 400 mg were Grade 1 or 2, with Grade 3/4 in 2.5% and 12%, respectively (see section 4.2). The median time to onset of any Grade amylase or lipase elevation was 16 days, with 75% of cases occurring within 3 months of starting treatment. Permanent discontinuation of treatment due to elevated amylase and/or lipase occurred in 1.0% of patients receiving 400 mg of Inrebic (see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

### *Elevated creatinine*

Elevations of creatinine (all Grades), occurred in 74% of MF patients taking 400 mg of Inrebic. These elevations were generally asymptomatic Grade 1 or 2 events, with Grade 3 elevations observed in 3% of patients. The median time to onset of any Grade creatinine elevation was 27 days, with 75% of cases occurring within 3 months of starting treatment. Dose interruptions and reductions due to elevated creatinine were reported in 1% and 0.5% of patients, respectively. Permanent discontinuation of treatment due to elevated creatinine occurred in 1.5% of 400 mg Inrebic-treated patients see section "Dosage/ Administration" and "Warning and precautions" for monitoring and management guidance).

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 adverse reactions online via the EIVIS portal (Electronic Vigilance System). You can obtain information about this at [www.swissmedic.ch](http://www.swissmedic.ch).

### **Overdose**

Experience with overdose of Inrebic is limited. During clinical trials of Inrebic in myelofibrosis patients, doses were escalated up to 600 mg per day including 1 accidental overdose at 800 mg. At doses above 400 mg, gastrointestinal toxicity, fatigue and dizziness as well as anaemia and thrombocytopenia tended to occur more commonly. In pooled clinical trial data encephalopathy including Wernicke's encephalopathy was associated with doses of 500 mg. In the event of an overdose, no further Inrebic should be administered; the individual should be monitored clinically and supportive measures should be undertaken as clinically indicated.

### **Properties/Effects**

*ATC code*

*L01EJ02*

*Mechanism of action*

Fedratinib is a kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS like tyrosine kinase 3 (FLT3). Fedratinib is a JAK2 selective inhibitor with higher inhibitory activity for JAK2 over family members JAK1, JAK3 and TYK2. Fedratinib reduced JAK2 mediated phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited malignant cell proliferation in vitro and in vivo.

*Pharmacodynamics*

Fedratinib inhibited cytokine-induced STAT3 phosphorylation in whole blood from patients with myelofibrosis. The inhibition of STAT3 phosphorylation was maximal approximately 2 hours after the first dose, with values returning to near baseline at 24 hours. After daily administration of fedratinib, levels of inhibition at steady state PK were similar to the maximal inhibition reached after the first dose of 300 (0.75 times the recommended dose), 400 or 500 mg (1.25 times the recommended dose) of fedratinib.

*Cardiac Electrophysiology*

The potential for QTc prolongation with fedratinib was evaluated in 31 patients with solid tumors. No large mean increase in the QTc interval (>20 ms) was detected with daily dosing of fedratinib 500 mg (1.25 times the recommended dose) for 14 days.

### *Clinical efficacy*

#### JAKARTA2:

JAKARTA2, was a multicentre, open label, single arm study in patients previously exposed to ruxolitinib with a diagnosis of intermediate 1 with symptoms, intermediate 2 or high risk primary myelofibrosis or secondary myelofibrosis, a complication of PV or ET, with splenomegaly and platelet count  $\geq 50 \times 10^9/L$ . A total of 97 patients who were heavily pre-treated (79% of patients had received  $\geq 2$  prior therapies and 13% had received  $\geq 4$  prior therapies) were enrolled and treated with Inrebic 400 mg once daily. The median age was 67 years (range 38 to 83 years) with 58% of patients older than 65 years and 13.4% of patients older than 75 years and 55% were male. Fifty-five percent (55%) of patients had primary MF, 26% had myelofibrosis as complication of PV, and 19% had myelofibrosis as complication of ET. Sixteen percent (16%) of patients had intermediate-1 with symptoms, 49% had intermediate-2, and 35% had high-risk disease. The median haemoglobin count was 9.8 g/dL (range 6.8 to 15.3 g/dL) at baseline. The median platelet count was  $147.0 \times 10^9/L$  (range 48.0 to  $929.0 \times 10^9/L$ ) at baseline; 34.0% of patients had a platelet count  $< 100 \times 10^9/L$ , and 66.0% of patients had a platelet count  $\geq 100 \times 10^9/L$ . Patients had a median palpable spleen length of 18 cm (range 5 to 36 cm) at baseline and a median spleen volume as measured by MRI or CT of 2'893.5 mL (range of 737 to 7'815 mL) at baseline.

In the JAKARTA-2 study, failure and intolerance to ruxolitinib was based on investigator assessment. A post-hoc analysis was conducted applying specific criteria outlined below to define ruxolitinib failure and intolerance.

1. Relapse: treatment for  $\geq 3$  months with spleen regrowth after initial response, defined as  $< 10\%$  spleen volume reduction (SVR) or  $< 30\%$  decrease in spleen size from baseline or,
2. Refractoriness: treatment for  $\geq 3$  months with  $< 10\%$  SVR or  $< 30\%$  decrease in spleen size from baseline,
3. Intolerance: ruxolitinib treatment for  $\geq 28$  days complicated by:
  - a. Development of RBC transfusion requirement ( $\geq 2$  units per month for 2 months), or
  - b. Grade  $\geq 3$  thrombocytopenia, anemia, hematoma and/or haemorrhage or
  - c. Any unacceptable toxicity.

The median duration of prior exposure to ruxolitinib was 10.7 months (range 0.1 to 62.4 months). Seventy one percent (71%) of patients had received a dose of either 30 mg or 40 mg daily of ruxolitinib prior to study entry.

The primary efficacy endpoint was the proportion of patients achieving a  $\geq 35\%$  reduction in spleen volume from baseline to the end of cycle 6 as measured by MRI or CT.

For the primary endpoint, the percentage of patients (95% confidence interval) who achieved a reduction in spleen volume of  $\geq 35\%$  according to MRI or CT at the end of cycle 6 with the 400 mg dose was 22.7% (22/97, 95% CI: 14.8%, 32.3%).

### *Temporary marketing authorisation*

Due to incomplete clinical data at the time of the assessment of the marketing authorisation application, the medicinal product Inrebic is granted a temporary marketing authorisation (Art. 9a Therapeutic Products Act). The temporary marketing authorisation is compulsorily linked to the timely fulfilment of conditions. Once these conditions have been fulfilled, the temporary marketing authorisation can be converted into a full marketing authorisation.

### **Pharmacokinetics**

Inrebic at 300 mg to 500 mg once daily (0.75 to 1.25 times the recommended dose) results in a dose proportional increase in geometric mean fedratinib peak concentrations ( $C_{max}$ ) and the area under the plasma concentration time curve over the dosing interval ( $AUC_{tau}$ ). The mean steady state levels are achieved within 15 days of daily dosing. The mean accumulation ratio ranged between 3- to 4-fold. At the dose of 400 mg once daily, the geometric mean (coefficient of variation, %CV) fedratinib  $C_{max}$  is 1804 ng/mL (49%) and  $AUC_{tau}$  is 26'870 ng·hr/mL (43%) in patients with myelofibrosis.

### *Absorption*

Following 400 mg once daily, fedratinib median time to peak concentrations ( $T_{max}$ ) at steady-state is 3 hours (range: 2 to 4 hours).

### Effect of Food

A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) or a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased area under the curve over time to infinity ( $AUC_{inf}$ ) up to 24% and  $C_{max}$  up to 14% of a single 500 mg dose of fedratinib.

### *Distribution*

The apparent volume of distribution of fedratinib at steady-state is 1'770 L in patients with myelofibrosis at 400 mg once daily dose. Fedratinib is 92% or greater bound to human plasma proteins.

### Metabolism

Fedratinib is metabolized by CYP3A4, CYP2C19, and flavin-containing monooxygenase 3 (FMO3). Fedratinib accounts for approximately 80% of total circulating drug in plasma after oral administration.

### *Elimination*

Fedratinib pharmacokinetics is characterized by a biphasic disposition with an effective half-life of 41 hours, a terminal half-life of approximately 114 hours, and apparent clearance (CL/F) (%CV) of 13 L/hr (51%) in patients with myelofibrosis.

### *Excretion*

Following a single oral dose of radiolabeled fedratinib, 77% (23% unchanged) of the administered dose was excreted in feces and 5% (3% unchanged) was eliminated in urine.

### *Kinetics in specific patient groups*

Age (20 years to 95 years), race (Caucasian, Asians), sex, body weight (40 kg to 135 kg), mild [total bilirubin  $\leq$  upper limit of normal (ULN) and AST  $>$ ULN or total bilirubin 1 to 1.5 times ULN and any AST] or moderate (total bilirubin  $>$ 1.5 to 3 times ULN and any AST) hepatic impairment, and mild ( $CL_{cr}$  60 mL/min to 89 mL/min by C-G) renal impairment did not have clinically meaningful effects on the pharmacokinetics of fedratinib.

The effect of severe (total bilirubin  $>$ 3 times ULN and any AST) hepatic impairment on fedratinib pharmacokinetics is unknown.

### *Renal impairment*

Following a single 300 mg dose of Inrebic, the  $AUC_{inf}$  of fedratinib increased by 1.5-fold in subjects with moderate ( $CL_{cr}$  30 mL/min to 59 mL/min by C-G) renal impairment and 1.9-fold in subjects with severe ( $CL_{cr}$  15 mL/min to 29 mL/min by C-G) renal impairment, compared to that in subjects with normal renal function ( $CL_{cr}$   $\geq$ 90 mL/min by C-G) (see "Dosage/Administrations" section).

## **Preclinical data**

### *Mutagenicity*

Fedratinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in in vitro chromosomal aberration assay (Chinese hamster ovary cells) or in vivo in a micronucleus test in rats.

### *Carcinogenicity*

Fedratinib was not carcinogenic in the 6-month Tg-rasH2 transgenic mouse model.

### *Reproductive toxicity*

In a fertility study in rats, fedratinib was administered for at least 70 days (males) and 14 days (females) prior to cohabitation and up to the implantation day (gestation day 7). Fedratinib had no



effect on the estrous cycle parameters, mating performance, fertility, pregnancy rate or reproductive parameters in male or female rats at doses up to 30 mg/kg. The exposure (AUC) at the dose of 30 mg/kg/day which is approximately 0.10 to 0.13 times the clinical exposure at the recommended daily dose.

In an embryo-fetal development study in pregnant rats, fedratinib administration at a dose of 30 mg/kg/day during organogenesis (gestation days 6 to 17) was associated with adverse developmental outcomes including skeletal variations (such as additional ossification center of neuronal arches). These effects occurred in rats at approximately 0.1 times the clinical exposure based on AUC at the recommended daily dose. At lower doses of 10 mg/kg/day (0.01 times the clinical exposure at the recommended daily dose), fedratinib administered to pregnant rats resulted in maternal toxicity of decreased gestational weight gain.

In an embryo-fetal development study in pregnant rabbits, fedratinib administration during organogenesis (gestation Days 6 to 18) did not produce developmental or maternal toxicity at doses up to the highest dose level tested, 30 mg/kg/day (approximately 0.08 times the clinical exposure at the recommended daily dose). In a separate study, administration of 80 mg/kg/day fedratinib to rabbits resulted in maternal mortality.

In a pre- and postnatal study in rats, fedratinib was administered to pregnant female rats at doses of 3, 10, or 30 mg/kg/day from Day 6 of gestation through Day 20 of lactation, with weaning on Day 21. A slight decrease in maternal body weight gain during gestation occurred at 30 mg/kg/day. The offspring from the high dose (30 mg/kg) had decreased body weight preweaning in both sexes and postweaning through the maturation phase in males. These effects occurred at exposures approximately 0.1 times the clinical exposure at the recommended daily dose.

*Other data (local toxicity, phototoxicity, immunotoxicity)*

### Animal Toxicology and/or Pharmacology

The JAK/STAT pathway has been implicated in bone formation and metabolism, and its inhibition may cause bone abnormalities, e.g. in developing bone. There is currently no evidence of bone abnormalities in patients who received Inrebic.

## **Other information**

### *Shelf life*

Do not use this medicine after the expiry date ("EXP") stated on the container.

### *Special precautions for storage*

Do not store above 30°C. Keep out of the reach of children.

**Authorisation number**

67792 (Swissmedic)

**Packs**

Inrebic 100 mg: 120 hard capsules (A)

**Marketing authorisation holder**

Celgene GmbH, Zurich

**Date of revision of the text**

July 2021