

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Inrebic 100 mg hard capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains fedratinib dihydrochloride monohydrate equivalent to 100 mg fedratinib.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Hard capsule.

Reddish-brown opaque capsules, 21.4 - 22.0 mm (size 0), printed with “FEDR” on the cap and “100 mg” on the body in white ink.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

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.

### **4.2 Posology and method of administration**

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

#### Posology

Patients who are on treatment with ruxolitinib, prior to starting treatment with Inrebic, must taper and discontinue ruxolitinib according to the ruxolitinib prescribing information.

Baseline testing of thiamine (vitamin B1) levels, complete blood count, hepatic panel, amylase/lipase, blood urea nitrogen (BUN) and creatinine should be obtained prior to starting treatment with Inrebic, periodically during treatment and as clinically indicated. Inrebic treatment should not be started in patients with thiamine deficiency, until thiamine levels have been corrected (see section 4.4). Initiating treatment with Inrebic is not recommended in patients with a baseline platelet count below  $50 \times 10^9/L$  and  $ANC < 1.0 \times 10^9/L$ .

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 4.4). Administration of Inrebic with a high fat meal may reduce the incidence of nausea and vomiting.

The recommended dose of Inrebic is 400 mg once daily.

Treatment may be continued for as long as patients derive clinical benefit. Dose modifications should be considered for haematologic and non-haematologic toxicities (Table 1). Inrebic should be discontinued in patients who are unable to tolerate a dose of 200 mg daily.

If a dose 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 modifications

Dose modifications for haematologic toxicities, non-haematologic toxicities and management of Wernicke's encephalopathy (WE) are shown in Table 1.

#### *Dose management of thiamine levels*

Before treatment initiation and during treatment, thiamine levels should be replenished if they are low. While on treatment, all patients should receive prophylaxis with daily 100 mg oral thiamine and should have thiamine levels assessed.

#### *Dose modifications 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 (see sections 4.4 and 4.5).

In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, the Inrebic dose should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor and then 400 mg once daily thereafter as tolerated. Additional dose adjustments should be made as needed, based upon monitoring of Inrebic-related safety and efficacy.

#### *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,  $\geq$  Grade 3 alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin elevation, or reoccurrence of a Grade 4 haematologic toxicity.

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

| Haematologic toxicity                                                                                                                                   | Dose reduction                                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade 3 thrombocytopenia with active bleeding (platelet count $< 50 \times 10^9/L$ ) or Grade 4 thrombocytopenia (platelet count $< 25 \times 10^9/L$ ) | Interrupt Inrebic dose until resolved to $\leq$ Grade 2 (platelet count $< 75 \times 10^9/L$ ) or baseline. Restart dose at 100 mg daily below the last given dose.                                                                                        |
| Grade 4 neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9/L$ )                                                                            | Interrupt Inrebic dose until resolved to $\leq$ Grade 2 (ANC $< 1.5 \times 10^9/L$ ) or baseline. Restart dose at 100 mg daily below the last given dose. Granulocyte growth factors may be used at the physician's discretion (see sections 4.4 and 4.5). |
| Grade 3 and higher anaemia, transfusion indicated (haemoglobin level $< 8.0$ g/dL)                                                                      | Interrupt Inrebic dose until resolved to $\leq$ 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 upper limit of normal [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.<br><br>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.<br><br>Monitor amylase/lipase 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 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 (74 to 222 nmol/L)* 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.                                                                                                                                                                                                                                                                                                     |

\*the normal thiamine range may differ depending on the methods used by the laboratory.

### Special populations

#### *Renal impairment*

For patients with severe renal impairment (creatinine clearance [CL<sub>cr</sub>] 15 mL/min to 29 mL/min by Cockcroft-Gault [C-G]), the dose should be reduced to 200 mg. 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 C-G). Due to potential increase of exposure, patients with pre-existing moderate renal impairment may require at least weekly safety monitoring and if necessary, dose modifications based on adverse reactions.

#### *Hepatic impairment*

No modification of the starting dose is required for patients with mild, moderate and severe hepatic impairment, based on the Child-Pugh classification.

#### *Elderly*

No additional dose adjustments are required in elderly patients (> 65 years of age).

#### *Paediatric population*

The safety and efficacy of Inrebic in children and adolescents aged up to 18 years have not been established. No data are available.

#### Method of administration

Inrebic is for oral use.

The capsules should not be opened, broken or chewed. They should be swallowed whole, preferably with water, and may be taken with or without food. Administration with a high fat meal may reduce the incidence of nausea and vomiting, therefore it is recommended to be taken with food.

### **4.3 Contraindications**

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

Pregnancy (see section 4.6).

### **4.4 Special warnings and precautions for use**

#### Encephalopathy, including Wernicke's encephalopathy

In the absence of thiamine supplementation, 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 4.2 and 4.8).

Thiamine levels and nutritional status in patients should be assessed before starting treatment with Inrebic. Inrebic treatment should not be started in patients with thiamine deficiency. Before treatment initiation, thiamine levels should be replenished if they are low. While on treatment, all patients should receive prophylaxis with oral thiamine and should have thiamine levels assessed as clinically indicated. If encephalopathy is suspected, Inrebic treatment should be discontinued immediately and parenteral thiamine treatment should be initiated while evaluating for all possible causes. Patients should be monitored until symptoms have resolved or improved and thiamine levels have normalised (see sections 4.2 and 4.8).

#### 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 4.2 and 4.8). Inrebic has not been studied in patients with a baseline platelet count < 50 x 10<sup>9</sup>/L and ANC < 1.0 x 10<sup>9</sup>/L.

#### 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 for the first month until haemoglobin levels improve). 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 4.2 and 4.8).

#### 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 for the first month until platelet count improves) (see sections 4.2 and 4.8). 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.

#### Neutropenia

Neutropenia was generally reversible and was managed by temporarily withholding Inrebic (see sections 4.2 and 4.8).

#### Gastrointestinal events

Nausea, vomiting and diarrhoea are among the most frequent adverse reactions in Inrebic-treated patients. Most of the adverse reactions are Grade 1 or 2 and typically occur within the first 2 weeks of treatment. Prophylactic anti-emetic therapy (e.g. 5-HT<sub>3</sub> receptor antagonists) should be provided 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 4.2 and 4.8).

#### 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 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 (see sections 4.2 and 4.8).

#### Elevated amylase/lipase

Elevations of amylase and/or lipase have been reported with Inrebic treatment and one case of pancreatitis was reported. 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, dose modifications are recommended (see sections 4.2 and 4.8).

#### Elevated creatinine

Elevations of creatinine have been reported with Inrebic treatment (see section 4.8). Patients with myelofibrosis treated with fedratinib at 400 mg had an approximately 30% increase in serum creatinine (SCr) in the first cycle after initiating treatment, which remained stable throughout treatment duration. 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 (CLcr 15 mL/min to 29 mL/min by C-G), dose modifications are recommended (see section 4.2). Inrebic has been shown to increase serum creatinine (SCr) due to inhibition of renal transporters. Therefore, change of SCr as the marker for renal function should be used with caution. Other renal markers may be considered.

## Uveitis

Uveitis has been observed in post-approval clinical studies (see section 4.8). Fedratinib-associated uveitis is a late-onset adverse event, with the first episode occurring at a median of 14 months after starting treatment, with a range of 8 to 22 months.

Patients should be advised on the risks of developing (recurring episodes of) uveitis before starting Inrebic therapy. Common uveitis symptoms include eye pain, redness, photophobia, floaters, and decreased vision. In case of symptoms, prompt comprehensive ophthalmologic evaluation is recommended. Most cases manifest as anterior uveitis. No dose modifications are required for uveitis as long as effective topical corticosteroid treatment can control ocular inflammation. If uveitis does not respond to local ocular therapy, systemic treatment may be indicated and Inrebic should be withheld until resolution of ocular inflammation.

## Interactions

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 4.2 and 4.5).

Agents that simultaneously inhibit CYP3A4 and CYP2C19 (e.g. fluconazole, fluvoxamine) or the combination of inhibitors of CYP3A4 and CYP2C19 may increase Inrebic exposure. Therefore, patients taking concomitant dual inhibitors of CYP3A4 and CYP2C19 may require more intensive safety monitoring and if necessary, dose modifications of Inrebic based on adverse reactions (see sections 4.2 and 4.5).

Agents that strongly or moderately induce CYP3A4 (e.g. phenytoin, rifampicin, efavirenz) may decrease Inrebic exposure and should be avoided in patients receiving Inrebic (see section 4.5).

If Inrebic is to be co-administered with substrate of CYP3A4 (e.g. midazolam, simvastatin), CYP2C19 (e.g. omeprazole, S-mephenytoin) or CYP2D6 (e.g. metoprolol, dextromethorphan), dose modifications of co-administered medicines should be made as needed with close monitoring of safety and efficacy (see section 4.5).

If Inrebic is to be co-administered with agents that are renally excreted via organic cation transporter (OCT)2 and multidrug and toxin extrusion (MATE)1/2-K (e.g. metformin), caution should be exercised and dose modifications should be made as needed (see section 4.5).

The concomitant use of haematopoietic growth factors with Inrebic has not been studied. The safety and efficacy of these co-administrations are not known (see sections 4.2 and 4.5).

## Major adverse cardiac events (MACE)

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

Events of MACE have been reported in patients receiving Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly

in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors.

### Thrombosis

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

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly in patients with cardiovascular factors (see also section 4.4 “Major adverse cardiovascular events (MACE)”).

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, Inrebic should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder.

Patients should be re-evaluated periodically during Inrebic treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue Inrebic in patients with suspected VTE, regardless of dose.

### Secondary malignancies

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

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older and patients who are current or past long-time smokers.

### Special populations

#### Elderly

Among patients with myelofibrosis who received an Inrebic dose of 400 mg in the clinical studies, 58.4% were older than 65 years of age and 14.8 % were greater than 75 years of age. All safety parameters had a higher incidence in patients > 65 years of age than patients ≤ 65 years of age.

### Excipients

Inrebic capsules contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium free’.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### Effect of other medicinal products on fedratinib

Fedratinib is metabolised by multiple CYPs *in vitro* with the predominant contribution from CYP3A4 and with a lesser contribution from CYP2C19, and flavin-containing monooxygenases (FMOs).

#### 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. (see section 4.2).

Based on physiologically based pharmacokinetic (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 1.1-fold.

Adverse reactions following prolonged co-administration of a moderate CYP3A4 inhibitor cannot be excluded.

#### Simultaneous inhibition of CYP3A4 and CYP2C19

Co-administration of fluconazole (dual inhibitor of CYP3A4 and CYP2C19, 200 mg once daily) with a single dose of fedratinib (100 mg) increased  $AUC_{inf}$  of fedratinib by 1.7-fold.

Based on PBPK simulations, co-administration of fluconazole (200 mg once daily) with fedratinib 400 mg once daily is predicted to increase fedratinib AUC at steady state by 1.5-fold.

Due to potential increase in exposure of fedratinib, patients taking concomitant dual inhibitors of CYP3A4 and CYP2C19 may require more intensive safety monitoring and if necessary, dose modifications of Inrebic based on adverse reactions (see section 4.2).

#### 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.

#### Proton pump inhibitors

Co-administration of pantoprazole (proton pump inhibitor: 40 mg daily) with a single dose of fedratinib (500 mg) increased fedratinib  $AUC_{inf}$  to a clinically insignificant extent (by 1.15-fold).

Therefore, an increase in gastric pH is not expected to have clinically meaningful impact on fedratinib exposure and no dose adjustment is needed for concomitant administration of fedratinib with agents that increase gastric pH.

#### Effect of fedratinib on other medicinal products

##### Effects on enzymes: CYP3A4, CYP2C19 or CYP2D6 substrates

Concomitant administration of fedratinib with the CYP3A4 substrate, midazolam (2 mg), the CYP2C19 substrate, omeprazole (20 mg), and the CYP2D6 substrate, metoprolol (100 mg), increases midazolam, omeprazole, and metoprolol  $AUC_{inf}$  by 3.8-, 2.8-, 1.8- fold and peak concentrations ( $C_{max}$ ) by 1.8-, 1.1- and 1.6-fold, respectively. Therefore, dose modifications of medicinal products that are CYP3A4, CYP2C19, or CYP2D6 substrates should be made as needed with close monitoring of safety and efficacy.

##### Effects on transporters

In *in vitro* studies, fedratinib inhibits P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), MATE1, MATE2-K, organic anion transporting polypeptide (OATP)1B1, OATP1B3 and OCT2.

Co-administration of a single dose of fedratinib (600 mg) with a single dose of digoxin (P-gp substrate: 0.25 mg), rosuvastatin (OATP1B1/1B3 and BCRP substrate: 10 mg), and metformin (OCT2 and MATE1/2-K substrate: 1000 mg) had no clinically meaningful effect on the  $AUC_{inf}$  of digoxin, rosuvastatin, and metformin. Renal clearance of metformin was decreased by 36% in the presence of fedratinib. The glucose-lowering pharmacodynamic effect of metformin in the presence of fedratinib appears reduced, with the glucose  $AUC_{0-3h}$  being 17% higher. Caution should be exercised and dose modifications should be made as needed for agents that are renally excreted via OCT2 and MATE1/2-K.

### Haematopoietic growth factors

The concurrent use of haematopoietic growth factors and fedratinib has not been studied. It is not known whether the JAK inhibition by fedratinib reduces the efficacy of haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of fedratinib (see sections 4.2 and 4.4).

## **4.6 Fertility, pregnancy and lactation**

### Women of childbearing potential/Contraception

Females of reproductive potential should be advised to avoid becoming pregnant whilst receiving Inrebic and should use effective contraception during treatment with Inrebic and for at least 1 month after the last dose.

### Pregnancy

There are no data from the use of Inrebic in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3); exposure in these studies was lower than human exposure at the recommended dose. Based on its mechanism of action, Inrebic may cause foetal harm. Inrebic belongs to a class of drugs, JAK inhibitors, that has been shown in pregnant rats and rabbits to cause embryo-foetal mortality and teratogenicity at clinically-relevant exposures. Inrebic is contraindicated during pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during treatment and for at least 1 month after the last dose. If Inrebic is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be advised of the potential hazard to the foetus.

### Breast-feeding

It is unknown whether fedratinib/metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded.

Women should not breastfeed during treatment with Inrebic and for at least 1 month after the last dose of Inrebic.

### Fertility

There are no human data on the effect of fedratinib on fertility. There are no data on effects on fertility in animals at clinically-relevant exposure levels (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

### Summary of the safety profile

The safety data is pooled for 486 patients (at 400 mg daily dose) previously treated with ruxolitinib. This analysis combines data from six studies: three pre-approval trials (JAKARTA, JAKARTA2, ARD11936) and three post-approval trials (FEDR-MF-001, FEDR-MF-002, FEDR-MF-003).

Primary or secondary myelofibrosis (JAKARTA, JAKARTA2, ARD11936, FEDR-MF-001, FEDR-MF-002, FEDR-MF-003)

In clinical studies of patients with primary myelofibrosis (MF), post polycythaemia vera myelofibrosis (post-PV MF), or post essential thrombocythemia myelofibrosis (post-ET MF), treated with Inrebic 400 mg (N = 486), including patients previously exposed to ruxolitinib (N = 97; JAKARTA2, N=38; FEDR-MF-001, N=182; FEDR-MF-002). The median exposure was 43.9 weeks (range 0.1 to 264.0 weeks). The median number of cycles (1 cycle = 28 days) initiated was 11 cycles (range 1 to 66 cycles).

Among the 486 patients with MF treated with a 400 mg dose of Inrebic in the clinical studies, the most frequent non-haematologic adverse reactions were diarrhoea (55.3%), nausea (49.6%), and vomiting (32.5%). The most frequent haematologic adverse reactions were anaemia (51.4%) and thrombocytopenia (28.8%) based on laboratory values (Table 2). The most frequent serious adverse reactions in MF patients treated with 400 mg were anaemia (2.3%) and neutropenia (0.4%) based on reported adverse events and not laboratory values. Permanent discontinuation due to adverse event regardless of causality occurred in 20.2% of patients receiving 400 mg of Inrebic.

Tabulated list of adverse reactions

Adverse reactions from clinical studies for entire treatment duration (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); and not known (cannot be estimated from available data).

**Table 2: All adverse reactions by system organ class and preferred term**

| System organ class                          | Adverse reaction                   | All grades frequency |
|---------------------------------------------|------------------------------------|----------------------|
| <b>Infections and infestations</b>          | Urinary tract infection            | Very common          |
| <b>Blood and lymphatic system disorders</b> | Anaemia <sup>a</sup>               | Very common          |
|                                             | Thrombocytopenia <sup>a</sup>      | Very common          |
|                                             | Bleeding <sup>b</sup>              | Very common          |
|                                             | Neutropenia                        | Common               |
| <b>Metabolism and nutrition disorders</b>   | Low thiamine <sup>d</sup>          | Very common          |
|                                             | Lipase increased <sup>a</sup>      | Common               |
|                                             | Amylase increased <sup>a</sup>     | Common               |
|                                             | Hyperkalaemia                      | Common               |
| <b>Nervous system disorders</b>             | Headache                           | Very common          |
|                                             | Dizziness                          | Very Common          |
|                                             | Peripheral neuropathy <sup>c</sup> | Common               |
|                                             | Wernicke's encephalopathy          | Uncommon             |
| <b>Eye disorders</b>                        | Uveitis                            | Common               |
| <b>Vascular disorders</b>                   | Hypertension                       | Common               |

| System organ class                                          | Adverse reaction                                  | All grades frequency |
|-------------------------------------------------------------|---------------------------------------------------|----------------------|
| <b>Gastrointestinal disorders</b>                           | Diarrhoea                                         | Very common          |
|                                                             | Vomiting                                          | Very common          |
|                                                             | Nausea                                            | Very common          |
|                                                             | Constipation                                      | Very common          |
|                                                             | Dyspepsia                                         | Common               |
| <b>Hepatobiliary disorders</b>                              | Alanine aminotransferase increased <sup>a</sup>   | Very common          |
|                                                             | Aspartate aminotransferase increased <sup>a</sup> | Very common          |
| <b>Musculoskeletal and connective tissue disorders</b>      | Muscle spasms                                     | Very common          |
|                                                             | Bone pain                                         | Common               |
|                                                             | Pain in extremity                                 | Common               |
| <b>Renal and urinary disorders</b>                          | Blood creatinine increased <sup>a</sup>           | Very common          |
|                                                             | Dysuria                                           | Common               |
| <b>General disorders and administration site conditions</b> | Fatigue/<br>Asthenia                              | Very common          |
| <b>Investigations</b>                                       | Weight increased                                  | Common               |

MedDRA = Medical dictionary of regulatory activities

SMQ = Standardized MedDRA Query (a grouping of several MedDRA preferred terms to capture a medical concept).

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

<sup>b</sup> Bleeding of any type including GI haemorrhage, subdural hematoma, haematoma, contusion, and epistaxis).

<sup>c</sup> Peripheral neuropathy (narrow scope).

<sup>d</sup> Low thiamine values below 70 nmol/l, based on laboratory values in FEDR-MF-002 data, for further explanation, see below.

### Description of selected adverse reactions

#### Wernicke's encephalopathy, Low Thiamine

Historical data indicate a higher risk of Wernicke's encephalopathy (WE) in the absence of thiamine supplementation particularly in subjects treated with doses higher than 400 mg FEDR daily in the pre-approval clinical program (refer to Section 4.9, Overdose). However, additional long-term evidence obtained in the post-approval program indicates a lower risk of WE with thiamine supplementation (1/486 (0.2%)) and clinical monitoring and laboratory evaluation for low thiamine as clinically indicated at the approved dose of 400 mg.

In a randomised controlled post-marketing study (FEDR-MF-002) of Fedratinib vs. best available therapy (BAT), the incidence of thiamine levels below the lower limit of normal (< 70 nmol/L) was 20.9% for Fedratinib vs 4.5% for BAT. Thiamine levels < 30 nmol/L were not observed in the study. The median time to the first low thiamine level after initiation of Fedratinib was 29.5 days. The frequency of low thiamine levels in participants receiving Fedratinib was 4.8% in those receiving thiamine supplementation 100 mg orally per day vs. 23.9% in those not receiving thiamine supplementation (see sections 4.2 and 4.4 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 55.3% of patients, nausea in 49.6% of patients, and vomiting in 32.5% of patients. Grade 3/4 diarrhoea, nausea, and

vomiting occurred in 3.3%, 1% and 1% of patients, respectively. The median time to onset of any grade nausea, vomiting, and diarrhoea was 8.0, 8.5 and 8.0 days respectively, with 27.6%, 17.9% and 32.1%, respectively, occurring within 2 weeks of starting treatment. Dose interruptions and reductions due to nausea were reported in 3.5% and 3.5% of patients, respectively. Dose interruptions and reductions due to vomiting were reported in 3.7% and 1.4% of subjects, respectively. Dose interruptions and reductions due to diarrhoea were reported in 4.9% and 2.3% of subjects, respectively. Permanent discontinuation of 400 mg Inrebic due to nausea diarrhoea, and vomiting occurred infrequently in 1.0%, 1.2% and 0.4%, respectively (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Anaemia

In patients with primary or secondary myelofibrosis treated with 400 mg of Inrebic, 40.3% of patients developed Grade 3/4 anaemia. The median time to first onset of Grade 3 anaemia event was approximately 43 days with 27.4% of cases occurring within 3 months of starting treatment. Permanent discontinuation of 400 mg Inrebic occurred due to anaemia in 1.2% of patients. With longer exposure in Study FEDR-MF-002, 73% of Inrebic-treated patients (including those who received transfusions before starting Inrebic) received RBC transfusions (with a median number of transfusions of 1.3 units per 28 days (Q1, Q3: 0.451, 3.11)) and permanent discontinuation of 400 mg Inrebic occurred due to anaemia in 0.7% of patients (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Thrombocytopenia/Bleeding

In patients with primary or secondary myelofibrosis treated with 400 mg of Inrebic, 13.8% of patients developed Grade 3 (10.1%) and Grade 4 (3.7%) thrombocytopenia, respectively. The median time to first onset of Grade 3/4 thrombocytopenia was approximately 30 days with 10.1% of cases occurring within 3 months of starting treatment. Permanent discontinuation of treatment due to thrombocytopenia occurred in 2.7% of patients. During the entire treatment duration, bleeding of any type was observed in 29.2%, Grade 3/4 events of any kind in 6.2%. In post-approval clinical studies, in 248 patients, bleeding of any type was observed in 28.2%, Grade 3/4 in 7.7%. (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Neutropenia

Grade 3/4 neutropenia occurred in 4.5% of patients and dose interruption due to neutropenia were reported in 1.0% of patients (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Hepatic toxicity

Elevations of ALT and AST (all Grades) occurred in 8.0% and 5.6%, respectively, with Grade 3/4 in 3.1% and 1.2%, respectively, of 400 mg Inrebic-treated patients. The median time to onset of any Grade transaminase elevation for ALT and AST were approximately 57 days (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Elevated amylase/lipase

Elevations of amylase and/or lipase (all Grades) occurred in 2.5 and 5.1%, respectively, with Grade 3/4 in 0.8% and 2.7% of Inrebic-treated MF patients, respectively. The median time to onset of any Grade amylase or lipase elevation was 43 and 85 days respectively. Permanent discontinuation of treatment due to elevated amylase and/or lipase occurred in 0.2% and 0.6% of patients, respectively, receiving 400 mg of Inrebic (see sections 4.2 and 4.4 for monitoring and management guidance).

#### Elevated creatinine

Elevations of creatinine (all Grades), occurred in 8.0% of MF patients taking 400 mg of Inrebic with Grade 3/4 elevations observed in 0.4% of patients. The median time to onset of any Grade creatinine elevation was 15 days. Dose interruptions and reductions due to elevated creatinine were reported in 1.4% and 1.0% of patients, respectively. Permanent discontinuation of treatment due to elevated creatinine occurred in 0.6% of 400 mg Inrebic-treated patients (see sections 4.2 and 4.4).

### Uveitis

Uveitis occurred in 4.4% of Inrebic-exposed patients in the pooled data from three post-approval clinical studies [FREEDOM (single arm): 0 of 38 patients (0%); FREEDOM2 (controlled): 5 of 182 patients (3%) in the Inrebic arm, 0 of 67 patients (0%) in the control arm; FEDR-MF-003 (single arm): 6 of 31 patients (19%)]. Of note, the FEDR-MF-003 study was conducted exclusively in Japanese patients. Overall, three (27%) of the 11 affected patients discontinued due to uveitis.

Among patients with uveitis, most (55%) experienced more than one episode with grade 1/2 in 60% of episodes, and grade 3/4 in 40%. Topical steroids were sufficient for treatment in 75%, and systemic steroids were required in 25% of episodes.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance website: [www.hpra.ie](http://www.hpra.ie).

## **4.9 Overdose**

Experience with overdose of Inrebic is limited. During clinical studies 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 studies 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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, 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*.

#### Pharmacodynamic effects

Fedratinib inhibits cytokine induced signal transducer and activator of transcription (STAT)3 phosphorylation in whole blood from myelofibrosis patients. A single dose administration of 300, 400, or 500 mg of fedratinib resulted in maximal inhibition of STAT3 phosphorylation approximately 2 hours after dosing, with values returning to near baseline at 24 hours. Similar levels of inhibition were achieved at steady state PK on cycle 1 day 15, after administration of 300, 400 or 500 mg of fedratinib per day.

#### Clinical efficacy and safety

Three key clinical studies (JAKARTA and JAKARTA2 and FEDR-MF-002) were conducted in patients with myelofibrosis. JAKARTA was a randomised placebo-controlled Phase 3 study in

patients who are JAK inhibitor naïve. JAKARTA2 was a single-arm study in patients who have been treated with ruxolitinib.

*JAKARTA: Myelofibrosis patients who are JAK inhibitor naïve*

JAKARTA was a double-blind, randomised, placebo-controlled Phase 3 study in patients with intermediate-2 or high-risk myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis with splenomegaly and platelet count  $\geq 50 \times 10^9/L$ . A total of 289 patients were randomised to receive either Inrebic 500 mg (N = 97), 400 mg (n = 96) or placebo (n = 96) once daily for at least 24 weeks (6 x 28 day cycles). Placebo patients could cross-over after 24 weeks to active treatment. The 400 mg dose appeared to be better tolerated than the 500 mg dose with fewer patients in the 400 mg arm reporting Grade 3 or 4 treatment emergent adverse events (TEAEs), TEAEs leading to dose reduction or dose interruption, and TEAEs leading to permanent treatment discontinuation. Fifty-nine percent (59%) of patients were male and the median age was 65 years (range 27 to 86 years), with 40% of patients between 65 and 74 years and 11% of patients at least 75 years. Sixty-four percent (64%) of patients had primary MF, 26% had post-polycythaemia vera MF, and 10% had post-essential thrombocythemia MF. Fifty-two percent (52%) of patients had intermediate-2 risk, and 48% had high-risk disease. The median haemoglobin count at baseline was 10.2 g/dL (range 4.5 to 17.4 g/dL). The median platelet count was  $213.5 \times 10^9/L$  (range 23.0 to  $1155.0 \times 10^9/L$ ); 16.3% of patients had a platelet count  $< 100 \times 10^9/L$  and 83.7% of patients had a platelet count  $\geq 100 \times 10^9/L$ . Patients had a median palpable spleen length of 15 cm (range 4 to 40 cm) at baseline and a median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) of 2568.0 mL (range of 316 to 8244 mL) at baseline. (The median normal spleen volume is approximately 215 mL).

The primary efficacy endpoint was the proportion of patients achieving  $\geq 35\%$  reduction from baseline in spleen volume at week 24 (end of cycle 6) as measured by MRI or CT confirmed 4 weeks later.

The key secondary endpoint was the proportion of patients with a  $\geq 50\%$  reduction in Total Symptom Score (TSS) from baseline to the end of cycle 6 as measured by the modified Myelofibrosis Symptoms Assessment Form (MFSAF) v2.0 diary.

Analyses of reduction in spleen volume are presented in Table 3.

**Table 3: Percentage of patients achieving spleen volume reduction from baseline to the end of cycle 6 in the Phase 3 study, JAKARTA (intent-to-treat (ITT) Population)**

| Spleen volume and spleen size at the end of cycle 6                                                                            | Inrebic 400 mg<br>N = 96<br>n (%) | Placebo<br>N = 96<br>n (%) |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|----------------------------|
| Spleen volume                                                                                                                  |                                   |                            |
| Number (%) of patients with spleen volume reduction by 35% or more at the end of cycle 6                                       | 45 (46.9)                         | 1 (1.0)                    |
| 95% confidence interval                                                                                                        | 36.9, 56.9                        | 0.0, 3.1                   |
| p-value                                                                                                                        | p < 0.0001                        |                            |
| Number (%) of patients with spleen volume reduction by 35% or more at the end of cycle 6 (with a follow-up scan 4 weeks later) | 35 (36.5)                         | 1 (1.0)                    |
| 95% confidence interval                                                                                                        | 26.8, 46.1                        | 0.0, 3.1                   |
| p-value                                                                                                                        | p < 0.0001                        |                            |

A higher proportion of patients in Inrebic 400 mg group achieved a  $\geq 35\%$  reduction from baseline in spleen volume regardless of the presence or absence of the JAK<sup>V617F</sup> mutation.

Based on Kaplan-Meier estimates, the median duration of spleen response was 18.2 months for the Inrebic 400 mg group.

The modified MFSAF included 6 key MF associated symptoms: night sweats, itching, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. The symptoms were measured on a scale from 0 (absent) to 10 (worst imaginable).

The percentage of patients (95% confidence interval) with a  $\geq 50\%$  reduction in TSS at the end of cycle 6 was 40.4% (36/89, 95% CI:30.3%, 50.6%) in the Inrebic 400 mg arm and 8.6% (7/81, 95% CI: 2.5%, 14.8%) in the placebo arm.

JAKARTA2: Myelofibrosis patients who have been treated with ruxolitinib

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, post-polycythaemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis 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 started treatment with Inrebic 400 mg once daily with dose escalation up to 600 mg permitted. Fifty-five percent (55%) of patients were male and the median age was 67 years (range 38 to 83 years) with 46% of patients between 65 and 74 years and 17% of patients at least 75 years. Fifty-five percent (55%) of patients had primary MF, 26% had post-polycythaemia vera MF, and 19% had post-essential thrombocythemia MF. 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 magnetic resonance imaging (MRI) or computed tomography (CT) of 2893.5 mL (range of 737 to 7815 mL) at baseline.

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  $\geq 35\%$  reduction in spleen volume by MRI or CT at the 400 mg dose at the end of cycle 6 was 22.7% (22/97, 95% CI: 14.8%, 32.3%)

FEDR-MF-002

MF-002 was a Phase 3, multicenter, open-label, randomised study assessing fedratinib versus best available therapy for subjects with DIPSS-intermediate or high-risk MF, post-PV MF, or post-ET MF, all previously treated with ruxolitinib. The study's primary objective was to measure the proportion of subjects achieving at least a 35% reduction in SVR35, as assessed by MRI or CT at the EOC6. The key secondary endpoints were Symptom Response Rate ( $\geq 50\%$  reduction in TSS at EOC6) and spleen volume response rate ( $\geq 25\%$  SVR at EOC6).

Overall, 201 subjects were randomised: 134 to the FEDR arm and 67 to the BAT arm. Among those assigned to BAT, 48 subjects crossed over to FEDR following the End of Cycle 6. The percentage of patients with at least 35% SVR at EOC6 was 35.8% in the FEDR arm and 6.0% in the BAT arm. Both key secondary endpoints ( $\geq 50\%$  reduction in TSS at EOC6,  $\geq 25\%$  SVR at EOC6) showed statistically significant superiority for FEDR over BAT (34.1% vs 11.69% and 47% vs 13.4%, respectively).

## Paediatric population

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

## **5.2 Pharmacokinetic properties**

### Absorption

Fedratinib at 300 mg to 500 mg once daily (0.75 to 1.25 times the recommended dose of 400 mg) results in a dose proportional increase in geometric mean fedratinib  $C_{max}$  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 ratios are similar in adult patients with primary MF, post-PV MF or post-ET MF, ranging from 3- to 4-fold.

At the dose of 400 mg once daily, the geometric mean (coefficient of variation, %CV) fedratinib  $C_{max,ss}$  is 1 804 ng/mL (49%) and  $AUC_{tau,ss}$  is 26 870 ng.hr/mL (43%) in patients with myelofibrosis.

Following 400 mg once daily oral administration, fedratinib is rapidly absorbed, achieving  $C_{max}$  at steady-state in 3 hours (range: 2 to 4 hours). Based on a mass balance study in humans, oral absorption of fedratinib is estimated to be approximately 63-77%.

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  $AUC_{inf}$  up to 24% and  $C_{max}$  up to 14% of a single 500 mg dose of fedratinib. Thus, fedratinib can be taken with or without food since no clinically meaningful effect on the pharmacokinetics of fedratinib was observed with food. Administration with a high fat meal may reduce the incidence of nausea and vomiting and thus fedratinib is recommended to be taken with food.

### Distribution

The mean apparent volume of distribution of fedratinib at steady-state is 1770 L in patients with myelofibrosis at 400 mg once daily dose suggesting extensive tissue distribution. The human plasma protein binding of fedratinib is approximately 95%, mostly to  $\alpha$ 1-acid glycoprotein.

### Biotransformation

Fedratinib is metabolised by multiple CYPs *in vitro*, with the predominant contribution from CYP3A4, and with a lesser contribution from CYP2C19 and FMOs.

Fedratinib was the predominant entity (approximately 80% of plasma radioactivity) in systemic circulation after oral administration of radiolabelled fedratinib. None of the metabolites contribute greater than 10% of total parent substance-related exposure in plasma.

### Elimination

Following a single oral dose of radiolabelled fedratinib, elimination was primarily through metabolism with approximately 77% of radioactivity excreted in faeces and only approximately 5% of the excreted in urine. Unchanged parent substance was the major component *in excreta*, accounting on average for approximately 23% and 3% of the dose in faeces and urine, respectively.

Fedratinib pharmacokinetics is characterised 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.

## Special populations

### Age, body weight, gender and race

In a population pharmacokinetics analysis of cumulative data from 452 patients, no clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regard to age (analysis including 170 patients with age 65-74 years, 54 with age 75-84 years and 4 with age 85+ years), body weight (40 to 135 kg), gender (analysis including 249 males and 203 females) and race (analysis including 399 White, 7 Black, 44 Asian and 2 other).

### Renal impairment

Following a single 300 mg dose of fedratinib, the AUC<sub>inf</sub> of fedratinib increased by 1.5-fold in subjects with moderate renal impairment (CL<sub>cr</sub> 30 mL/min to 59 mL/min by C-G) and 1.9-fold in subjects with severe renal impairment (CL<sub>cr</sub> 15 mL/min to 29 mL/min by C-G), compared to that in subjects with normal renal function (CL<sub>cr</sub> ≥ 90 mL/min by C-G).

In a population pharmacokinetics analysis of cumulative data from 452 patients, no clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regard to mild renal impairment (defined as 60 ≤ CL<sub>cr</sub> < 90 mL/min).

### Hepatic impairment

The safety and pharmacokinetics of a single oral dose of fedratinib were evaluated in subjects with normal hepatic function and with mild to moderate hepatic impairment (Child-Pugh class A, B) at 300 mg; in subjects with normal hepatic function and with severe hepatic impairment (Child-Pugh C) at 200 mg. No clinically meaningful effect on the pharmacokinetics of fedratinib was observed in subjects with mild, moderate and severe hepatic impairment compared to that in subjects with normal hepatic function (see section 4.2).

In a population pharmacokinetics analysis of cumulative data from 452 patients, no clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regard to mild (defined as total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 1.5 times ULN and any AST increase; n = 115) or moderate (defined as total bilirubin > 1.5 to 3 times ULN and any AST; n = 17) hepatic impairment.

## **5.3 Preclinical safety data**

Fedratinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Fedratinib was not genotoxic and not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model. Preclinical studies have demonstrated that at clinically-relevant doses, fedratinib does not inhibit thiamine transport in the gastrointestinal tract or the brain (see sections 4.2 and 4.8)

In repeat-dose toxicity studies of up to 9 months in length, in mice, rats and dogs, the main toxicities observed included bone marrow hypoplasia; bile duct hypertrophy, necrosis and proliferation; lymphoid atrophy/depletion; renal tubular degeneration/necrosis; gastrointestinal tract inflammation; degeneration/necrosis of skeletal and cardiac muscle; histiocytic infiltration of the lung; and evidence of immunosuppression including pneumonia and/or abscesses. The highest plasma exposures achieved in the repeat-dose toxicology studies were associated with significant toxicity, including mortality, and were below the tolerated plasma exposures in patients at the highest recommended dose of 400 mg, suggesting humans are less sensitive than preclinical species to the toxicities of fedratinib. Clinically-relevant exposures were not attained in the species used in the toxicology studies, therefore these studies have a limited value in producing clinically relevant safety data on fedratinib.

### Fertility and early embryonic development

Fedratinib had no effect on the oestrous cycle parameters, mating performance, fertility, pregnancy rate or reproductive parameters in male or female rats. The exposure (AUC) was approximately 0.10 to 0.13 times the clinical exposure at the recommended dose of 400 mg once daily. In a repeat-dose

toxicity study, at exposures approximately equivalent to human clinical exposure, fedratinib caused aspermia, oligospermia and seminiferous tubule degeneration in male dogs (see section 4.6).

#### Embryo-foetal development

Fedratinib administered to pregnant rats during organogenesis (gestation days 6 to 17) was associated with adverse embryo-foetal effects including post-implantation loss, lower foetal body weights, and skeletal variations. These effects occurred in rats at approximately 0.1 times the clinical exposure at the recommended human daily dose of 400 mg/day. In rabbits, fedratinib did not produce developmental toxicity at the highest dose level tested (exposure approximately 0.08 times the clinical exposure at the recommended human daily dose).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content

Silicified microcrystalline cellulose (contains microcrystalline cellulose (E460) and silica colloidal anhydrous (E551)).

Sodium stearyl fumarate

#### Capsule shell

Gelatin (E441)

Titanium dioxide (E171)

Red iron oxide (E172)

#### Printing ink

Shellac (E904)

Titanium dioxide (E171)

Propylene glycol (E1520)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

4 years.

### **6.4 Special precautions for storage**

Keep the bottle tightly closed in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

### **6.5 Nature and contents of container**

High-density polyethylene (HDPE) bottle with polypropylene child resistant cap and heat induction seal.

Each bottle contains 120 hard capsules and is packed in a cardboard carton.

## **6.6 Special precautions for disposal**

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Bristol-Myers Squibb Pharma EEIG  
Plaza 254  
Blanchardstown Corporate Park 2  
Dublin 15, D15 T867  
Ireland

## **8. MARKETING AUTHORISATION NUMBER**

EU/1/20/1514/001

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8 February 2021  
Date of first renewal: 18 December 2025

## **10. DATE OF REVISION OF THE TEXT**

23/07/2026