1. NAME OF THE MEDICINAL PRODUCT

Inrebic capsules 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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 splenomegaly and/or disease related symptoms in adult patients with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, including patients who have been previously exposed to 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 x 10^9/L and ANC < 1.0 x 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. During treatment, thiamine levels should be assessed periodically (e.g. monthly for the first 3 months and every 3 months thereafter) and as clinically indicated (see section 4.4).

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 section 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, ≥ 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 x 10^9/L) or Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)	Interrupt Inrebic dose until resolved to ≤ Grade 2 (platelet count < 75 x 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 x 10^9/L)	Interrupt Inrebic dose until resolved to ≤ Grade 2 (ANC < 1.5 x 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 ≤ 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.
Non--haematologic toxicity	**Dose reduction**
≥ 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. 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 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.
Management of thiamine levels and Wernicke's encephalopathy	**Dose reduction**
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 [CLcr] 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 (CLcr 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

Inrebic pharmacokinetics have not been evaluated in patients with severe hepatic impairment. Use of Inrebic in patients with severe hepatic impairment (Child-Pugh class C or total bilirubin >3 times ULN and any AST increase) should be avoided. No modification of the starting dose is required for patients with mild to moderate hepatic impairment.

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

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, periodically during treatment (e.g. monthly for the first 3 months and every 3 months thereafter) and as clinically indicated. Inrebic treatment should not be started in patients with thiamine deficiency. Before treatment initiation and during treatment, thiamine levels should be replenished if they are low. 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 $< 50 \times 10^9$/L and ANC $< 1.0 \times 10^9$/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 x 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. Consider providing appropriate prophylactic anti-emetic therapy (e.g. 5-HT3 receptor antagonists) during Inrebic treatment. Treat diarrhoea with anti-diarrheal 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 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).

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 and should be avoided in patients receiving Inrebic (see section 4.5).

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 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 section 4.5 and 4.2).

Special populations

Elderly
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.

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 1.2 and 1.1-fold, respectively. Adverse reactions following prolonged co-administration of a moderate CYP3A4 inhibitor cannot be excluded.

Simultaneous inhibition of CYP3A4 and CYP2C19
The effect of concomitant administration of a dual or combination of CYP3A4 and CYP2C19 inhibitors on fedratinib pharmacokinetics has not been studied. The PBPK simulations suggest that co-administration of a dual CYP3A4 and CYP2C19 inhibitor with a single dose of fedratinib can increase the AUC_{inf} of fedratinib by approximately 4-fold and the situation may change with

multiple-dose fedratinib administration due to complex interplay of CYP enzyme autoinhibition and autoinduction. Agents that simultaneously inhibit CYP3A4 and CYP2C19 (e.g. fluconazole, fluvoxamine) or the combination of inhibitors of CYP3A4 and CYP2C19 may increase fedratinib exposure and should be avoided in patients receiving fedratinib.

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 overall safety information of Inrebic was assessed in 608 patients who received continuous doses of Inrebic in Phase 1, 2 and 3 clinical studies.

Primary or secondary myelofibrosis (JAKARTA, JAKARTA2, ARD11936)

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=203), including patients previously exposed to ruxolitinib (N=97; JAKARTA2), the median exposure was 35.6 weeks (range 0.7 to 114.6 weeks) and the median number of cycles (1 cycle = 28 days) initiated was 9 cycles. Sixty-three percent of 203 patients were exposed for 6 months or longer and 38% were exposed for 12 months or longer.

Among the 203 patients with MF treated with a 400 mg dose of Inrebic in the clinical studies, the most frequent non-haematologic adverse reactions were diarrhoea (67.5%), nausea (61.6%), and vomiting (44.8%). The most frequent haematologic adverse reactions were anaemia (99.0%) and thrombocytopenia (68.5%) based on laboratory values (Table 2). The most frequent serious adverse reactions in MF patients treated with 400 mg were 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.

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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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
Infections and infestations	Urinary tract infection	Very common
Blood and lymphatic system disorders	Anaemia[a]	Very common
	Thrombocytopenia[a]	Very common
	Neutropenia[a]	Very common
	Bleeding[b]	Very common
Metabolism and nutrition disorders	Lipase increased[a]	Very common
	Amylase increased[a]	Very common
Nervous system disorders	Headache	Very common
	Wernicke's encephalopathy	Common
	Dizziness	Common
Vascular disorders	Hypertension	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Constipation	Very common
	Dyspepsia	Common
Hepatobiliary disorders	Alanine aminotransferase increased[a]	Very common
	Aspartate aminotransferase increased[a]	Very common
Musculoskeletal and connective tissue disorders	Bone pain	Common
	Muscle spasms	Very common
	Pain in extremity	Common
Renal and urinary disorders	Blood creatinine increased[a]	Very common
	Dysuria	Common
General disorders and administration site conditions	Fatigue/ Asthenia	Very common
Investigations	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).

[a] Frequency is based on laboratory value.

[b] Bleeding includes any type associated with thrombocytopenia requiring clinical intervention. Bleeding is evaluated using the MedDRA SMQ haemorrhage terms (broad scope).

Description of selected adverse reactions

Encephalopathy, including Wernicke's
Serious cases of encephalopathy, including 1 established case of Wernicke's, were reported in 1.3% (8/608) of patients treated with Inrebic in clinical studies; 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%). This was a patient with head and neck cancer, brain metastasis, difficulty eating, and weight loss who received fedratinib 500 mg in a study for another indication (see sections 4.2 and 4.4 for monitoring and management guidance and section 4.9).

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 11% and 9% of patients, respectively. Permanent discontinuation of 400 mg Inrebic occurred due to gastrointestinal toxicity in 4% of patients (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, 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 sections 4.2 and 4.4 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 sections 4.2 and 4.4 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 sections 4.2 and 4.4 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 sections 4.2 and 4.4 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 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 sections 4.2 and 4.4 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 sections 4.2 and 4.4).

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 aswell 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

Two key clinical studies (JAKARTA and JAKARTA2) 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 naive
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 ≥ 50 x 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 x 10^9/L (range 23.0 to 1155.0 x 10^9/L); 16.3% of patients had a platelet count < 100 x 10^9/L and 83.7% of patients had a platelet count ≥ 100 x 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 ≥ 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 ≥ 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 N=96 n (%)	Placebo N=96 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 ≥ 35% reduction from baseline in spleen volume regardless of the presence or absence of the JAK^{V617F} 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 ≥ 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 ≥ 50 x 10^9/L. A total of 97 patients who were heavily pre-treated (79% of patients had received ≥ 2 prior therapies and 13% had received ≥ 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 x 10^9/L (range 48.0 to 929.0 x 10^9/L) at baseline; 34.0% of patients had a platelet count < 100 x 10^9/L, and 66.0% of patients had a platelet count ≥ 100 x 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 ≥ 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 ≥ 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%)

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 1804 ng/mL (49%) and $AUC_{tau,ss}$ is 26870 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 α1-acid glycoprotein.

Biotransformation

Fedratinib is metabolized 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_{inf} of fedratinib increased by 1.5-fold in subjects with moderate renal impairment (CLcr 30 mL/min to 59 mL/min by C-G) and 1.9-fold in subjects with severe renal impairment (CLcr 15 mL/min to 29 mL/min by C-G), compared to that in subjects with normal renal function (CLcr ≥ 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 ≤CLcr <90 mL/min).

Hepatic impairment
The safety and pharmacokinetics of a single oral 300 mg dose of fedratinib were evaluated in a study in subjects with normal hepatic function and with mild hepatic impairment (Child-Pugh class A). No clinically meaningful effect on the pharmacokinetics of fedratinib was observed in subjects with mild hepatic impairment compared to that in subjects with normal hepatic function.

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.

Fedratinib pharmacokinetics has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.2).

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

36 months.

6.4 Special precautions for storage

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

Do not store above 30°C.

6.5 Nature and contents of container

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

Each bottle contains 120 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. Product Registrant

Bristol-Myers Squibb (S) Pte Ltd
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#20-01/09 Parkway Parade,
Singapore 449269

8. DATE OF REVISION OF THE TEXT

23 September 2022