▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
INREBIC® (FEDRATINIB)

WARNING: Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC (see Section 4.8 Adverse Effects [Undesirable Effects]).

Wernicke's encephalopathy is a neurologic emergency. The risk of Wernicke's encephalopathy is reduced via thiamine monitoring and prophylaxis with daily oral thiamine (see Section 4.2 Dose and Method of Administration and Section 4.4 Special Warnings and Precautions for Use).

1 NAME OF THE MEDICINE

Fedratinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg fedratinib (equivalent to 117.30 mg fedratinib dihydrochloride monohydrate).

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Hard capsule.

Reddish brown, size 0 opaque capsule, with "FEDR" on cap and "100 mg" on 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 DOSE AND METHOD OF ADMINISTRATION

Dosage

Conduct baseline testing of thiamine (vitamin B1) levels and a complete blood count prior to initiation of INREBIC (see Section 4.4 Special Warnings and Precautions for Use).

The recommended dose of INREBIC is 400 mg taken orally once daily for patients with a baseline platelet count of $\geq 50 \times 10^9$/L. Fedratinib has not been studied in patients with a baseline platelet count less than 50×10^9/L.

INREBIC may be taken with or without food. Administration with a high fat meal may reduce the incidence of nausea and vomiting. If a dose is missed, the next scheduled dose should be taken the following day.

Patients that are on treatment with ruxolitinib before the initiation of INREBIC must taper and discontinue ruxolitinib according to the ruxolitinib prescribing information.

Dose Modifications

Haematologic Toxicities and Non-Haematologic Toxicities

Dose modifications should be considered for haematologic and non-haematologic toxicities. Discontinue INREBIC in patients who are unable to tolerate a dose of 200 mg daily.

Table 1: Dose Reduction for Haematologic Toxicities

Haematologic Toxicity	Dose Reduction
Grade 3 Thrombocytopenia with active bleeding or Grade 4 Thrombocytopenia	Interrupt INREBIC dose until resolved to ≤Grade 2 or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 Neutropenia	Interrupt INREBIC dose until resolved to ≤Grade 2 or baseline. Restart dose at 100 mg daily below the last given dose. Granulocyte growth factors may be used at the doctor's discretion.

Dose reductions should also be considered for patients who become transfusion-dependent during treatment with INREBIC.

Table 2: Dose Reduction for Non- Haematologic Toxicities

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, or Bilirubin	Interrupt INREBIC dose until resolved to ≤Grade 1 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 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.

Thiamine Levels and Wernicke's Encephalopathy (WE)

Assess thiamine levels and nutritional status prior to starting INREBIC. Do not start INREBIC treatment in patients with thiamine deficiency; replenish thiamine prior to treatment initiation if thiamine levels are low.

While on treatment, all patients should receive prophylaxis with daily 100 mg oral thiamine and should have thiamine levels assessed periodically as clinically indicated.

If Wernicke's Encephalopathy is suspected, immediately discontinue treatment with INREBIC and initiate parenteral thiamine treatment. Monitor until symptoms resolve or improve and thiamine levels normalise (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects [Undesirable Effects]).

Table 3: Management of Thiamine Levels and Wernicke's Encephalopathy

Thiamine Levels and Wernicke's Encephalopathy	Dose Reduction
For thiamine levels below the normal range but ≥30 nmol/L without signs or symptoms of WE	Interrupt INREBIC treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range. Consider restarting INREBIC when thiamine levels are within normal range.

Thiamine Levels and Wernicke's Encephalopathy	Dose Reduction
For thiamine levels <30 nmol/L without signs or symptoms of WE	Interrupt INREBIC treatment. Immediate treatment with parenteral thiamine at therapeutic dosages until thiamine levels are restored to normal range. Consider restarting INREBIC 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.

Concomitant Use of Strong CYP3A4 Inhibitors:

Reduce the INREBIC dose to 200 mg when administering INREBIC with a strong CYP3A4 inhibitor.

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 to 400 mg once daily thereafter as tolerated. Additional dose adjustments should be made as needed based upon frequent monitoring of safety and efficacy.

Special populations

Renal impairment

In patients with severe renal impairment (creatinine clearance [CrCl] 15 mL/min to 29 mL/min), reduce the INREBIC dose to 200 mg. No modification of the starting dose is recommended for patients with mild to moderate renal impairment (CrCl 30 mL/min to 89 mL/min). Due to potential increase of exposure, patients with pre-existing moderate renal impairment may require more intensive safety monitoring and if necessary, dose modifications based on adverse reactions.

Hepatic impairment

No modification of the starting dose is recommended for patients with mild, moderate and severe hepatic impairment.

Paediatric population

The safety and efficacy of INREBIC in paediatric patients less than 18 years of age have not been established.

Elderly population

No dose adjustment based on age is recommended for elderly subjects.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Encephalopathy, including Wernicke's

Serious and fatal encephalopathy, including Wernicke's, was 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.

Assess thiamine levels and nutritional status in all patients prior to starting treatment with INREBIC. Do not start INREBIC in patients with thiamine deficiency; replenish thiamine prior to treatment initiation. While on treatment all patients should receive prophylaxis with oral thiamine and should have thiamine levels assessed as clinically indicated. If encephalopathy is suspected, immediately

discontinue INREBIC and initiate parenteral thiamine treatment while evaluating for all possible causes. Monitor until symptoms resolve or improve and thiamine levels normalise (see Section 4.2 Dose and Method of Administration - Table 3 and Section 4.8 Adverse Effects [Undesirable Effects]).

Anaemia, Thrombocytopenia and Neutropenia

Treatment with INREBIC may cause anaemia, thrombocytopenia and neutropenia. Complete blood counts should be obtained at baseline, periodically during treatment, and as clinically indicated (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.8 Adverse Effects [Undesirable Effects]). Inrebic has not been studied in patients with a baseline platelet count <50 x 10^9/L and absolute neutrophil count <1.0 x 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 as clinically indicated. Patients developing anaemia may require blood transfusions. Consider dose reduction for patients who become red blood cell transfusion dependent (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.8 Adverse Effects [Undesirable Effects]).

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 as clinically indicated. 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. For Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia, dose reduction is recommended (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.8 Adverse Effects [Undesirable Effects]).

Neutropenia

Neutropenia was generally reversible and was managed by temporarily withholding INREBIC (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.8 Adverse Effects [Undesirable Effects]).

Gastrointestinal Toxicity

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

Consider providing appropriate prophylactic anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhoea with anti-diarrhoeal medications promptly at the first onset of symptoms. For Grade 3 or higher nausea, vomiting, or diarrhoea not responsive to supportive measures within 48 hours, interrupt INREBIC until resolved to Grade 1 or less or baseline. Restart dose at 100 mg daily below the last given dose (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.8 Adverse Effects [Undesirable Effects]). Monitor thiamine levels and replenish as needed.

Hepatic Toxicity

Elevations of ALT and AST have been reported with INREBIC treatment.

Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt INREBIC dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC. Grade 3 or 4 ALT and AST elevations were generally reversible with dose modification or permanent

treatment discontinuation (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.8 Adverse Effects [Undesirable Effects]).

Elevated Amylase/Lipase

Elevations of amylase and/or lipase have been reported with INREBIC treatment.

Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher amylase and/or lipase elevations, interrupt INREBIC until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.8 Adverse Effects [Undesirable Effects]).

Uveitis

Uveitis has been observed in post-marketing clinical trials (FREEDOM1, FREEDOM2 and FREEDOM3) (see Section 4.8 Adverse Effects [Undesirable Effects]).

Advise patients on the risks of developing uveitis before starting fedratinib therapy. Certain ethnic groups (such as Asians) may be at higher risk of developing uveitis. Common uveitis symptoms include eye pain, redness, photophobia, floaters, and decreased vision. In case of symptoms, prompt ophthalmologic evaluation is recommended.

Major Adverse Cardiac Events (MACE)

Another Janus Kinase (JAK)-inhibitor has increased risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which INREBIC is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with INREBIC, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which INREBIC is not indicated. In patients with MF treated with INREBIC in clinical trials, the rates of thromboembolic events were similar in INREBIC and placebo-treated patients.

Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Secondary Malignancies

Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding non-melanoma skin cancer (NMSC) (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which INREBIC is not indicated. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with INREBIC, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Use in the elderly

Of patients with myelofibrosis who received a INREBIC dose of 400 mg in the clinical studies, 47.3% were greater than 65 years of age and 12.3% were greater than 75 years of age. No overall differences in safety or effectiveness of INREBIC were observed between these patients and patients ≤65 years of age and ≤75 years of age.

Paediatric use

The safety and efficacy of INREBIC in paediatric patients less than 18 years of age have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on fedratinib

Strong and Moderate CYP3A4 Inhibitors

Concomitant administration of INREBIC with a strong CYP3A4 inhibitor increases fedratinib exposure. Increased exposure of fedratinib 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, reduce the dose of INREBIC when administering with strong (CYP3A4 inhibitors [e.g., ketoconazole, ritonavir], see Section 4.2 Dose and Method of Administration).

Co-administration of ketoconazole (strong CYP3A4 inhibitor: 200 mg twice daily) with a single dose of fedratinib (300 mg) increased the fedratinib AUC by approximately 3-fold. Based on physiologically based pharmacokinetic (PBPK) simulations, co-administration of a strong CYP3A4 inhibitor such as ketoconazole (400 mg once daily) with INREBIC 400 mg once daily is predicted to increase fedratinib AUC at steady state by 2-fold (see Section 4.2 Dose and Method of Administration).

Based on PBPK simulations, coadministration of moderate CYP3A4 inhibitors, erythromycin (500 mg three times daily) or diltiazem (120 mg twice daily), with INREBIC 400 mg once daily is predicted to increase fedratinib AUC at steady state by 1.2-, and 1.1-fold, respectively.

Simultaneous inhibition of CYP3A4 and CYP2C19

Concomitant administration of INREBIC with a dual CYP3A4 and CYP2C19 inhibitor increases fedratinib exposure. Increased exposure of fedratinib may increase the risk of adverse reactions.

Co-administration of fluconazole (dual inhibitor of CYP3A4 and CYP2C19, 200 mg once daily) with a single dose of fedratinib (100 mg) increased AUC of fedratinib by 1.7-fold. Based on PBPK simulations, co-administration of a dual inhibitor of CYP3A4 and CYP2C19 such a fluconazole (200 mg once daily) with INREBIC 400 mg once daily is predicted to increase fedratinib AUC at steady state by approximately 1.5-fold.

Due to potential increase of exposure of INREBIC, 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 Dose and Method of Administration).

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. The PBPK simulations suggest that repeated doses of a strong and moderate CYP3A4 inducer, rifampicin or efavirenz, respectively, decrease the AUC of a single 400 mg dose of fedratinib by approximately 85 or 60%, respectively. Agents that strongly or moderately induce CYP3A4 (e.g., phenytoin, rifampicin, efavirenz), may decrease fedratinib plasma concentrations and should be avoided in patients receiving INREBIC.

Proton Pump Inhibitor (PPI)

Co-administration of an oral proton pump inhibitor, pantoprazole (40 mg once daily on days 1-7) and INREBIC (500 mg orally once on day 7) increased fedratinib AUC by approximately 1.15-fold, indicating that the INREBIC dose does not need to be adjusted when taken with drugs that increase gastric pH (such as antacids, histamine-2 blockers, and PPIs).

P-gp Inhibitors

Fedratinib is a substrate of P-gp in vitro. However, fedratinib showed rapid absorption in both preclinical and clinical studies, and available data indicate that permeability and efflux is not limiting its absorption. In the clinically relevant dose range of 300 to 500 mg, fedratinib exposure was roughly dose proportional in MF patients, indicating no non-linearity due to any efflux. There was no impact of genotype variations of transporters including P-gp on fedratinib exposure in healthy subjects and patients. Taken together, significant interaction with P-gp inhibitors is not expected to occur with fedratinib.

Effect of fedratinib on other medicinal products

Effects on enzymes: CYP3A4, CYP2C19, or CYP2D6 Substrate Drugs

Concomitant administration of INREBIC with the CYP3A4 substrate, midazolam, the CYP2C19 substrate, omeprazole, and the CYP2D6 substrate, metoprolol, increased midazolam, omeprazole, and metoprolol AUC by 4-, 3-, and 2-fold, respectively. Therefore, dose modifications of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates should be made as needed with close monitoring of safety and efficacy.

Effects on transporters

In vitro, fedratinib inhibits P-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and OCT2 at clinically relevant concentrations, but not BSEP, MRP2, OAT1, or OAT3.

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 exposure of digoxin, rosuvastatin, and metformin.

Renal clearance of metformin was decreased by 36% in the presence of fedratinib. Caution should be exercised, and dose modifications should be made as needed for agents that are renally excreted via OCT2 and MATE1/2-K such as metformin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effect of fedratinib on fertility. Fedratinib had no effect on fertility in male or female rats at oral doses up to 30 mg/kg/day. The exposure (plasma AUC) at the dose of 30 mg/kg/day is approximately 0.10 to 0.13 times the clinical exposure at the maximum recommended dose of 400 mg once daily. There are no data on effects on fertility in animals at clinically relevant exposures.

Use in pregnancy - Category D

There are no studies with the use of INREBIC in pregnant women to inform drug-associated risks. Fedratinib was shown to cause embryofetal lethality in animals at exposure levels well below that of patients. If fedratinib is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

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

Administration of fedratinib to pregnant rats during organogenesis caused increased post-implantation loss, lower fetal body weight and altered fetal skeletal development (seen as an increased incidence of

additional ossification centres of the cervical vertebral neural arches, a skeletal variation) at an oral dose of 30 mg/kg/day. This dose yielded exposure in animals 0.11 times that of patients at the maximum recommended human dose. Maternal administration to rats at this dose level during gestation and lactation resulted in reduced body weight of the offspring (at birth and pre- and post-weaning). No adverse effects on embryofetal development were observed with fedratinib in pregnant rabbits, but the highest tested dose (30 mg/kg/day) yielded only very limited exposure (0.08 times that of patients at the maximum recommended human dose).

Use in lactation

There are no data on the presence of fedratinib or its metabolites in milk, the effects of INREBIC on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with INREBIC and for at least 1 month after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

INREBIC has no sedating effect but may cause dizziness in some people. Patients should be advised not to drive or operate machinery if they experience dizziness after taking fedratinib.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety information of INREBIC was assessed in 484 patients who received INREBIC 400 mg for the first 6 cycles in studies JAKARTA, JAKARTA2, ARD11936, FREEDOM1, FREEDOM2 and FREEDOM3. This safety information, which includes crossover population, is summarised below and described in Tables 4 and 5.

A separate assessment was conducted in 608 patients who received continuous doses of INREBIC in nine Phase 1, 2 and 3 clinical studies (JAKARTA, JAKARTA2, ARD11936, TED12037, TED12015, ARD12042, ARD12888, INT12497 and TES13519). This safety information is described under Description of Selected Adverse Drug Reactions.

Primary or Secondary Myelofibrosis (JAKARTA, JAKARTA2, ARD11936, FREEDOM1, FREEDOM2 and FREEDOM3)

In clinical studies of patients with primary myelofibrosis (MF), post polycythemia vera (post-PV MF), or post essential thrombocythemia myelofibrosis (post-ET MF), treated with INREBIC 400 mg (N=484), including patients previously exposed to ruxolitinib.

Among the 484 patients with MF treated with a 400 mg dose of INREBIC in the clinical studies up to 6 cycles, the most frequent non-haematologic adverse events were diarrhoea, nausea, and vomiting. The most frequent haematologic adverse events were anaemia and thrombocytopenia (Table 4). Serious adverse events, regardless of causality occurring in ≥2% of patients receiving INREBIC 400 mg daily included anaemia (2.7%) and pneumonia (2.5%). Fatal adverse events, regardless of causality occurred in 3.7% of patients receiving INREBIC 400 mg daily.

Permanent discontinuation due to adverse event regardless of causality occurred in 11.8% of patients receiving 400 mg of INREBIC. Most frequent reasons for permanent discontinuation in ≥1% of patients receiving 400 mg of INREBIC included thrombocytopenia (1.9%), diarrhoea (1%) and nausea (1%).

Tabulated Summary of Adverse Events

Table 4: Treatment-emergent Adverse Events Reported in ≥5% of Patients in Any Treatment Group - First 6 Cycles (Safety and Crossover Population)

Preferred Term	INREBIC 400 mg[1] N=484		Placebo[2] N=95		BAT[2,3] N=67	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Gastrointestional disorders						
Diarrhoea	235 (48.6)	13 (2.7)	15 (15.8)	0	2 (3.0)	0
Nausea	216 (44.6)	2 (0.4)	14 (14.7)	0	10 (14.9)	0
Vomiting	133 (27.5)	5 (1.0)	5 (5.3)	0	3 (4.5)	0
Constipation	93 (19.2)	2 (0.4)	7 (7.4)	0	6 (9.0)	0
Abdominal pain	39 (8.1)	2 (0.4)	8 (8.4)	0	5 (7.5)	0
Abdominal pain upper	32 (6.6)	4 (0.8)	12 (12.6)	1 (1.1)	8 (11.9)	0
Blood and lymphatic system disorders						
Anaemia	211 (43.6)	155 (32.0)	13 (13.7)	7 (7.4)	23 (34.3)	13 (19.4)
Thrombocytopenia	106 (21.9)	79 (16.3)	8 (8.4)	6 (6.3)	11 (16.4)	4 (6.0)
Neutropenia	27 (5.6)	17 (3.5)	0	0	2 (3.0)	1 (1.5)
Leucocytosis	8 (1.7)	6 (1.2)	1 (1.1)	1 (1.1)	4 (6.0)	3 (4.5)
General disorders and administration site conditions						
Fatigue	53 (11.0)	7 (1.4)	9 (9.5)	0	8 (11.9)	1 (1.5)
Asthenia	50 (10.3)	9 (1.9)	6 (6.3)	1 (1.1)	15 (22.4)	1 (1.5)
Oedema peripheral	50 (10.3)	0	8 (8.4)	0	7 (10.4)	0
Pyrexia	29 (6.0)	0	3 (3.2)	1 (1.1)	7 (10.4)	1 (1.5)
Investigations						
Blood creatinine increased	50 (10.3)	2 (0.4)	1 (1.1)	0	1 (1.5)	0
Alanine aminotransferase increased	31 (6.4)	8 (1.7)	1 (1.1)	0	1 (1.5)	0
Weight decreased	28 (5.8)	1 (0.2)	5 (5.3)	0	0	0
Vitamin B1 decreased	24 (5.0)	0	0	0	1 (1.5)	0
Infections and infestations						
Urinary tract infection	28 (5.8)	2 (0.4)	1 (1.1)	0	4 (6.0)	0
COVID-19	17 (3.5)	3 (0.6)	0	0	5 (7.5)	2 (3.0)
Skin and subcutaneous tissue disorders						
Pruritis	54 (11.2)	1 (0.2)	7 (7.4)	0	7 (10.4)	1 (1.5)
Night sweats	20 (4.1)	0	2 (2.1)	0	7 (10.4)	2 (3.0)
Metabolism and nutrition disorders						
Hyperkalaemia	31 (6.4)	16 (3.3)	2 (2.1)	2 (2.1)	0	0
Decreased appetite	29 (6.0)	3 (0.6)	3 (3.2)	1 (1.1)	8 (11.9)	0
Hyperuricaemia	24 (5.0)	2 (0.4)	4 (4.2)	1 (1.1)	1 (1.5)	1 (1.5)
Musculoskeletal and connective tissue disorders						
Muscle spasms	32 (6.6)	0	1 (1.1)	0	4 (6.0)	0
Pain in extremity	28 (5.8)	0	4 (4.2)	0	0	0
Arthralgia	24 (5.0)	0	6 (6.3)	1 (1.1)	3 (4.5)	1 (1.5)
Bone pain	24 (5.0)	1 (0.2)	2 (2.1)	0	4 (6.0)	0
Nervous system disorders						
Headache	36 (7.4)	2 (0.4)	1 (1.1)	0	4 (6.0)	0
Dizziness	33 (6.8)	0	3 (3.2)	0	1 (1.5)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	42 (8.7)	4 (0.8)	6 (6.3)	2 (2.1)	3 (4.5)	0
Cough	39 (8.1)	1 (0.2)	6 (6.3)	0	2 (3.0)	0
Epistaxis	22 (4.5)	1 (0.2)	5 (5.3)	0	0	0

[1] AEs after crossover include the AEs with the onset date on/after the crossover first fedratinib dosing date.
[2] AEs for placebo/BAT subjects with crossover are not included if AEs occurred on/after the crossover first fedratinib dosing date.
[3] BAT: best available therapy

Tabulated List of Adverse Drug Reactions (ADRs)

These reactions are presented by MedDRA System Organ Class and by frequency. 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).

Table 5 : List of Adverse Drug Reactions[a]

System Organ Class	ADRs	Frequency
Infections and infestations	Urinary tract infection	Uncommon
Blood and lymphatic system disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Neutropenia	Common
Metabolism and nutrition disorders	Amylase increased	Common
	Lipase increased	Common
	Vitamin B1 deficiency	Common
Nervous system disorders	Headache	Common
	Dizziness	Common
	Wernicke's encephalopathy[b, c]	Common
Eye disorders	Uveitis[d]	Common
Vascular disorders	Hypertension	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Dyspepsia	Common
Hepatobiliary disorders	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common
Musculoskeletal and connective tissue disorders	Muscle spasms	Common
	Bone pain	Uncommon
	Pain in extremity	Common
Renal and urinary disorders	Blood creatinine increased	Common
	Dysuria	Uncommon
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common
Investigations	Weight increased	Common

[a] N=484 includes studies JAKARTA, JAKARTA2, ARD11936, FREEDOM1, FREEDOM2 and FREEDOM3 taking 400 mg for up to 6 cycles (safety and crossover population). Frequency includes all grades.
[b] Frequency is based on all patients who received continuous doses of fedratinib in clinical studies (N=608).
[c] Patients reported as having Wernicke's Encephalopathy were all taking a dose of 500 mg at the time of symptoms.
[d] Frequency is based on studies FREEDOM1, FREEDOM2 and FREEDOM3 in patients who took at least 1 dose of fedratinib regardless of dose.

Description of Selected Adverse Drug Reactions

The following safety information is from nine Phase 1, 2 and 3 clinical studies (N=608), unless otherwise specified.

Encephalopathy, including Wernicke's

Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC in clinical trials and 0.16% (1/608) of cases were fatal. Seven out of the 8 subjects 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 subject

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. In a solid tumour study, one patient with head and neck cancer, brain metastasis, difficulty eating and weight loss had a fatal outcome (see Section 4.2 Dose and Method of Administration - Table 3 and Section 4.4 Special Warnings and Precautions for Use).

In FEDR-MF-002, a randomised controlled post-marketing study 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 1.5% in those receiving thiamine supplementation 100 mg orally per day vs. 39.1% in those not receiving thiamine supplementation.

Anaemia

In patients with primary or secondary myelofibrosis treated with 400 mg of INREBIC, 43% of patients developed Grade 3 anaemia; no patients developed Grade 4 anaemia. The median time to first onset of Grade 3 anaemia event was approximately 45 days, with 75% of cases occurring within 3 months. Red blood cell transfusions were received by 51% of 400 mg INREBIC-treated patients and permanent discontinuation of 400 mg INREBIC occurred due to anaemia in 1% of patients (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.4 Special Warnings and Precautions for Use).

Thrombocytopenia

In patients with primary or secondary myelofibrosis treated with 400 mg of INREBIC, 13% and 4% of patients developed Grade 3 and Grade 4 thrombocytopenia, respectively. The median time to first onset of Grade 3 or 4 thrombocytopenia was approximately 43 days, with 75% of cases occurring within 3 months. Platelet transfusions were received by 4% of 400 mg INREBIC-treated patients. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention occurred in 2% and 6%, respectively of 400 mg INREBIC-treated patients (see Section 4.2 Dose and Method of Administration - Table 1 and Section 4.4 Special Warnings and Precautions for Use).

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 63% of patients, nausea in 59% of patients, and vomiting in 39% 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 1 day, with 75% of cases occurring within 2 weeks of starting treatment (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.4 Special Warnings and Precautions for Use).

Hepatic Toxicity

Elevations of ALT and AST (all grades) occurred in 43% and 52%, 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 2-3 months. Grade 3 or 4 ALT and AST elevations were generally reversible with dose modification or permanent treatment discontinuation (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.4 Special Warnings and Precautions for Use).

Elevated Amylase/Lipase

Elevations of amylase and/or lipase (all grades) occurred in 20% and 32%, respectively, with Grade 3/4 in 1.5% and 9%, respectively, of INREBIC-treated MF patients. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation (see Section 4.2 Dose and Method of Administration - Table 2 and Section 4.4 Special Warnings and Precautions for Use).

Elevated Creatinine

Elevations of creatinine (all grades) occurred in 68% of myelofibrosis patients taking 400 mg of INREBIC, and were generally asymptomatic Grade 1 or 2 events, with Grade 3 or 4 occurring in 1.5% and 0%, respectively. The median time to onset of any grade creatinine elevation was 17 days, with 75% of cases occurring within 2 months.

Uveitis

Uveitis has been observed in post-marketing clinical trials (FREEDOM1, FREEDOM2 and FREEDOM3) with an overall incidence of 4.4%. The incidence is highest among Japanese patients (19.4%), suggesting variability in risk by ethnicity/race. 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. Among the patients developing uveitis, most (55%) had more than one episode of uveitis. The uveitis episodes varied in grade, with Grade 1/2 in 60% of episodes, and Grade 3/4 in 40% of episodes. Topical steroids were sufficient for treatment in 75% of episodes, and systemic steroids were required in 25% of episodes. Fedratinib was discontinued due to uveitis in 27% of patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience with overdose of fedratinib is limited. During clinical studies of fedratinib 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 fedratinib should be administered; the individual should be monitored clinically and supportive measures should be undertaken as clinically indicated.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fedratinib is an oral 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. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms (MPNs), including myelofibrosis and polycythemia vera. In cell models expressing mutationally active $JAK2^{V617F}$ or $FLT3^{ITD}$, fedratinib reduced phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of $JAK2^{V617F}$-driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT3/5, and improved survival, white blood cell counts, haematocrit, splenomegaly, and fibrosis.

Pharmacodynamic Effects

Fedratinib inhibits cytokine induced STAT3 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.

Cardiac Electrophysiology

The potential for QTc prolongation with fedratinib was evaluated in 31 patients with solid tumours receiving fedratinib 500 mg doses every day (QD) for 14 days. The largest time-matched mean QTcF difference for fedratinib vs. placebo observed at 4-hour post-dose was 4.32 msec (90% confidence interval [CI]: 1.16, 7.49). Overall, no large mean increase in the QTc interval (>20 msec) was detected with daily dosing of fedratinib 500 mg (1.25 times the recommended dose of 400 mg QD) for 14 days.

Clinical trials

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-polycythemia 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 fedratinib 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. The median age was 65 years (range 27 to 86 years) with 40% of patients between 65 and 74 year and 11% of patients at least 75 years, and 59% were male. Sixty-four percent (64%) of patients had primary MF, 26% had post-polycythemia 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 at baseline was 213.5 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 at baseline and a median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) of 2568 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 a ≥35% reduction from baseline in spleen volume at Week 24 (End of Cycle 6, EOC6) 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 EOC6 as measured by the modified Myelofibrosis Symptoms Assessment Form (MFSAF) v2.0 diary.

Analyses of reduction in spleen volume are presented in Table 6.

Table 6: Percentage of Patients Achieving Spleen Volume Reduction and Spleen Size Reduction from Baseline to the End of Cycles 6 (ITT Population)

Spleen Volume and Spleen Size at the End of Cycles 6	INREBIC 400 mg N=96 n (%)	Placebo N=96 n (%)
Spleen Volume		
Number (%) of Patients with Spleen Volume Reduction by ≥35% at EOC6	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% at EOC6 (confirmed 4 weeks later)	35 (36.5)	1 (1.0)
95% confidence interval	26.8, 46.1	0.0, 3.1

Spleen Volume and Spleen Size at the End of Cycles 6	INREBIC 400 mg N=96 n (%)	Placebo N=96 n (%)
p-value	p<0.0001	

A higher proportion of patients in the INREBIC 400 mg group achieved a ≥35% reduction from baseline in spleen volume regardless of the presence or absence of the $JAK2^{V617F}$ 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 with a ≥50% reduction in TSS at the EOC6 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.

Patients who have been treated with ruxolitinib

FREEDOM2 is an ongoing Phase 3, multicentre, open-label, randomised study in patients with DIPSS-intermediate or high-risk primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib. Patients had splenomegaly, platelet count $\geq 50 \times 10^9$/L and were relapsed or refractory to prior ruxolitinib treatment or intolerant to ruxolitinib. A total of 201 patients were randomised to receive either fedratinib 400 mg (n=134) or investigator-selected best available therapy (BAT, n=67), including ruxolitinib or other approved JAK inhibitors, in repeated 28-day treatment cycles. The most frequent BAT was ruxolitinib which was reported for 77.6% subjects of the BAT group. The median age was 70 years (range 38 to 91 years), 70% of patients were older than 65 years, and 52% were male. The median (Q1, Q3) treatment duration until the cut-off date was 43.0 (19.0, 75.1) weeks in the fedratinib group and 24.7 weeks (22.6, 26.7) in the BAT group. Fifty-five percent (55%) of patients had primary MF, 27% had post-polycythaemia vera MF, and 18% had post-essential thrombocythemia MF. Seventy-six percent (76%) of patients had intermediate-2 risk and 23% had high-risk disease. Twenty percent (20%) of patients were RBC transfusion dependent. The median haemoglobin count at baseline was 9.3 g/dL (range 5.7 to 14.4 g/dL). The median platelet count was 120 x 10^9/L (range 29 to 1715 x 10^9/L); 34.3% of patients had a platelet count < 100 x 10^9/L and 61.7% of patients had a platelet count ≥ 100 x 10^9/L. Patients had a median palpable spleen length of 16 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 2678.97 mL (range of 383.1 to 8909.4 mL) at baseline. (The median normal spleen volume is approximately 215 mL).

The primary efficacy endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at EOC6. Spleen volume was assessed by MRI/CT scan at screening, end of cycles 3, 6, 12, 18, 24, and at the end of treatment.

The key secondary endpoint was the proportion of patients achieving a ≥50% reduction from baseline in total symptom score (TSS) on the Myelofibrosis Symptom Assessment Form (MFSAF) at EOC6.

Table 7: Spleen Volume Response Rate at End of Cycle 6 (≥35% Spleen Volume Reduction) by MRI or CT (ITT Population in study FREEDOM2)

Response	INREBIC 400 mg N=134 n (%)	BAT N=67 n (%)
Subjects with ≥35% reduction in spleen volume at EOC6[a]	48 (35.8)	4 (6.0)
95% confidence interval[b]	27.7, 44.6	1.7, 14.6

Response	INREBIC 400 mg N=134 n (%)	BAT N=67 n (%)
Stratified analysis, based on eCRF[c]		
Difference in proportion	29.6	
95% CI[d]	19.9, 39.4	
p-value	p<0.0001	
Stratified analysis, based on IRT[c]		
Difference in proportion	29.6	
95% CI[d]	19.9, 39.3	
p-value	p<0.0001	
Unstratified analysis[e]		
Difference in proportion	29.9	
95% CI[d]	19.9, 39.8	
p-value	p<0.0001	

[a] Subjects with missing assessment at the EOC6, including those who met the criteria for progression of splenomegaly before the EOC6, were considered non-responders. They were included in the denominator.

[b] The two-sided 95% CI was based on the exact Clopper-Pearson method.

[c] The stratified p-value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to small cell count issue.

[d] The 95% CI of the difference was based on Greenland and Robins method.

[e] The unstratified p-value was one-sided based on the z-test with an un-pooled estimate of variance.

Table 8: Symptom Response Rate at End of Cycle 6 (ITT Population with non-zero baseline TSS)

Response	INREBIC 400 mg N=126 n (%)	BAT N=65 n (%)
Subjects with ≥50% reduction in TSS at EOC6[a]	43 (34.1)	11 (16.9)
95% confidence interval[b]	25.9, 43.1	8.8, 28.3
Stratified analysis, based on eCRF[c]		
Difference in proportion	17.1	
95% CI[d]	4.8, 29.4	
p-value	0.0033	
Stratified analysis, based on IRT[c]		
Difference in proportion	17.2	
95% CI[d]	4.9, 29.5	
p-value	0.0030	
Unstratified analysis[e]		
Difference in proportion	17.2	
95% CI[d]	4.9, 29.5	
p-value	0.0031	

[a] Subjects with missing assessment at the EOC6, including those who met the criteria for progression of splenomegaly before the EOC6, were considered non-responders. They were included in the denominator.

[b] The two-sided 95% CI was based on the exact Clopper-Pearson method.

[c] The stratified p-value was one-sided based on CMH test using the Greenland and Robins method to adjust for stratification factors: spleen size by palpation and platelet counts. The third stratification factor 'refractory/relapsed or intolerance to ruxolitinib treatment' was dropped due to small cell count issue.

[d] The 95% CI of the difference was based on Greenland and Robins method.

[e] The unstratified p-value was one-sided based on the z-test with an un-pooled estimate of variance.

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 peak concentrations (C_{max}) and the area under the plasma concentration time curve over the dosing interval (AUC_{tau}). The mean steady state levels are achieved within 15 days of daily dosing. The mean accumulation ratio ranged between 3- to 4-fold.

At the dose of 400 mg once daily, the geometric mean (coefficient of variation, %CV) fedratinib C_{max} is 1804 ng/mL (49%) and AUC_{tau} is 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 77%.

Food Effect

A low-fat, low-calorie (total 162 calories: 6% from fat, 78% from carbohydrate and 16% from protein) or a high-fat, high-calorie (total 815 calories: 52% from fat, 33% from carbohydrate and 15% from protein) meal increased area under the curve over time to infinity (AUC_{inf}) up to 24% and C_{max} up to 14% of a single 500 mg dose of fedratinib. 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 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 92%, mostly to α_1-acid glycoprotein.

Metabolism

Fedratinib is chiefly metabolised by CYP3A4, with a lesser contribution from CYP2C19 and flavin-containing monooxygenases 3 (FMO3).

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 drug related exposure in plasma.

Excretion

Following a single oral dose of radiolabeled-fedratinib, elimination was primarily through metabolism with approximately 77% of radioactivity excreted in faeces and only approximately 5% of the excreted in urine. Unchanged drug 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

Renal Impairment

Following a single 300 mg dose of fedratinib, the AUC_{inf} of fedratinib increased by 1.5-fold in subjects with moderate (CrCl 30 mL/min to 59 mL/min) renal impairment and 1.9-fold in subjects with severe (CrCl 15 mL/min to 29 mL/min) renal impairment, compared to that in subjects with normal renal function (CrCl ≥90 mL/min) (see Section 4.2 Dose and Method of Administration).

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 A, B) at 300 mg; in subjects with normal hepatic function and with severe hepatic impairment [Child-Pugh C] at 200 mg. The geometric mean ratios (90% confidence interval) of AUCinf were 1.07 (0.74, 1.54), 1.14 (0.77, 1.67) and 0.66 (0.37, 1.19) in subjects with mild (n=8), moderate (n=8), and severe hepatic impairment (n=6), respectively, to subjects with normal hepatic function. 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 Dose and Method of Administration).

Paediatric and adolescent

The safety and efficacy of fedratinib in paediatric patients less than 18 years of age have not been established.

Elderly

In a population pharmacokinetics analysis of cumulative data from patients, age was not a significant covariate influencing AUC.

No clinically meaningful effect on the pharmacokinetics of fedratinib was observed with regard to age (20 years to 95 years). Therefore, no dose adjustment based on age is recommended for elderly subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Fedratinib was not carcinogenic in a 6-month study in transgenic (Tg.rasH2) mice with oral administration up to the highest dose tested (30 mg/kg/day). This dose yields exposure in male and female animals 0.44 and 0.76 times, respectively, that of patients at the maximum recommended human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content: Silicified microcrystalline cellulose, sodium stearylfumarate

Capsule shell: Gelatin, titanium dioxide, iron oxide red

Printing ink: OPACODE monogramming ink S-1-18086 White (TGA Proprietary Ingredient ID 107579)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in the original package.

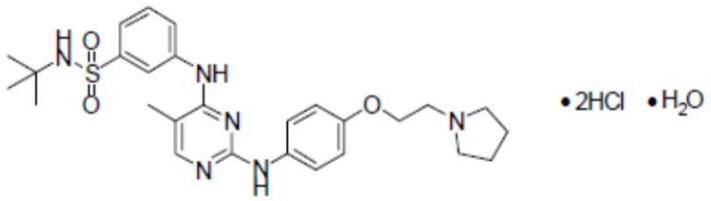
6.5 NATURE AND CONTENTS OF CONTAINER

High-density Polyethylene (HDPE) bottles with polypropylene child resistant closure and induction seal. Pack size: 120 capsules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Molecular formula	$C_{27}H_{36}N_6O_3S$, 2HCl, H_2O
Molecular weight	615.62
Chemical name	*N-tert*-butyl-3-[(5-methyl-2-{ [4-(2-pyrrolidin-1-ylethoxy)phenyl]amino}pyrimidin-4-yl)amino]benzenesulfonamide dihydrochloride monohydrate
Chemical Abstract Service (CAS) registry number	1374744-69-0
Chemical structure	

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
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9 DATE OF FIRST APPROVAL (ARTG ENTRY)

13 February 2025

10 DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	Initial version

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