Fedratinib (Inrebic®) for the treatment of primary and secondary myelofibrosis

General information [1]

Drug description	Indication
Fedratinib is a protein kinase inhibitor. Its antineoplastic activity is linked to the selective inhibition of the Janus associated kinases (JAKs) involved in the signaling mediation of a number of cytokines and growth factors that are important for haematopoiesis and immune function.	Fedratinib is indicated for the treatment of primary myelofibrosis and of myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.

Current treatment [2]

- Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, however, it is only suitable for people who are fit enough to undergo treatment.
- Other treatment options aim to relieve symptoms and improve QoL, including hydroxycarbamide, other chemotherapies, androgens, splenectomy, radiation therapy, erythropoietin and red blood cell transfusion.
- NICE guidelines recommend ruxolitinib as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, only in people with intermediate-2 or high-risk disease.
- There are no approved treatments options post ruxolitinib. Therefore, the treatment pathway for patients post-ruxolitinib is unclear.

Regulatory status

EMA [1]	FDA [3, 4]
Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Inrebic®. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 08/02/2021 <u>The full indication is:</u> ❖ 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 JAK inhibitor naïve or who have been treated with ruxolitinib. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 16 August 2019, the FDA approved fedratinib (Inrebic®) for adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythaemia) myelofibrosis. **Other indications**: none ✓ **Priority review** ✓ **Orphan drug designation**

Costs

120 Inrebic® hard capsules 100 mg = € 4,575.00 [5]

Posology [6]

- 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 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. Initiating treatment with Inrebic® is not recommended in patients with a baseline platelet count below 50 x 109/L and ANC < 1.0 x 109/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. 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. 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.

Warning [6]

- **<u>Encephalopathy, including Wernicke's encephalopathy:</u>**

- 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.
- 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.

❖ **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. Inrebic® has not been studied in patients with a baseline platelet count < 50 x 109/L and ANC < 1.0 x 109/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.
- Thrombocytopenia:
    - Thrombocytopenia generally occurs within the first 3 months of treatment. Patients with low platelet counts (< 100 x 109/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). 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®.

❖ **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.

❖ **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.

❖ **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.

❖ **Elevated creatinine**

- Elevations of creatinine have been reported with Inrebic® treatment. 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.

❖ **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.

- 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®.
- Agents that strongly or moderately induce CYP3A4 (e.g. phenytoin, rifampicin, efavirenz) can decrease Inrebic® exposure and should be avoided in patients receiving Inrebic®. 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.
- The concomitant use of haematopoietic growth factors with Inrebic® has not been studied. The safety and efficacy of these co-administrations are not known.

❖ **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'.

Study characteristics [7]

Trial name	*n*	Intervention (I)	Intervention (I2)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
JAKARTA NCT01437787	289	Oral fedratinib 400 mg/day for at least 6 consecutive 4-week cycles, n=96	Oral fedratinib 500 mg/day for at least 6 consecutive 4-week cycles, n=97	Matching placebo, n=96	spleen response (≥35% reduction in spleen volume from baseline as determined by magnetic resonance imaging or computed tomography) at week 24 and confirmed 4 weeks later	randomized, double-blind, placebo-controlled phase 3 trial	JAK2	Sanofi	Link

Efficacy (I vs. I2 vs. C)

Proportion of patients with at least a 35% reduction in spleen volume (spleen response) at 24 weeks, and confirmed 4 weeks later, was significantly higher (p< .001 for the comparison of each dose with placebo): 36% vs. 40% vs. 1%

Response rates at week 24 (without confirmation): 47% vs. 49% vs.1%; (p< 0.001)

Among patients with available data, all except 3 patients in I and 2 patients in I2 experienced **some degree of spleen volume reduction at 24 weeks** of up to 70%, whereas a majority of patients (75%) in the C had an increase in spleen volume at this point.

Spleen response rates were higher in I and I2 compared with C regardless of baseline platelet count, disease subtype, risk status, or JAK2 mutational status.

Proportions of patients (in patients with available baseline TSS) **with a reduction of at least 50% in the TSS from baseline to week 24**: 36% (95% CI, 26%-46%) vs. 34% (95% CI, 24%-44%) vs. 7% (95% CI, 2%-12%); p<0.001

In fedratinib-treated patients with baseline TSS greater than 0, **median TSS** decreased from baseline at 4 weeks, with the benefit continuing to 24 weeks.

26 patients in C vs. 14 patients in I vs. 9 patients in I2 showed **no improvement** in TSS.

JAK2 Allele Burden: no meaningful changes were observed in allele burden during treatment (median [range] changes at 24 weeks: +0.4% (−99% to 196%) vs. +0.8% (−77% to 115%) vs. +2% (−74% to 96%).

Safety (I vs. I2 vs. C)

Any TEAE grade 3 or 4: n=52/96 (54%) vs. n=68/97 (70%) vs. n=30/95 (32%)

Serious TEAE grade 3 or 4: n=17/96 (18%) vs. n=23/97 (24%) vs. n=14/95 (15%)

Deaths[1]: n=1/96 (1%) vs. n=4/97 (4%) vs. n=4/95 (4%)

Discontinuation[2]: n=13/96 (14%) vs. n=24/97 (25%) vs. n=8/95 (8%)

One case of **Wernicke encephalopathy (WE)** and 1 case of encephalopathy of unknown origin were reported before data cutoff. Following database lock and notification of investigators of the 2 prior cases, 2 additional cases of WE were reported in patients during the study, 1 of which was reported after fedratinib trials had been halted. All 4 cases were in women who received fedratinib 500 mg. [3]

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	yes	yes[4]	Low risk

[1] Deaths attributed to AEs

[2] discontinuation due to AE(s) at any time during the first 24 weeks

[3] 3 of these cases were confirmed by an independent expert safety panel, which included a neurooncologist and a neuroradiologist, as WE on the basis of both clinical features and MRI. Diagnosis of WE in the fourth case was confirmed by the panel on the basis of clinical symptoms alone in the absence of specific MRI findings.

[4] The study sponsor participated with the academic authors in the design and conduct of the study. Data were collected by the investigators and analyzed by the study sponsor with oversight, feedback, and approval from the investigators and a data-monitoring committee. The manuscript was written by the authors with medical writing assistance funded by the study sponsor. The manuscript was reviewed by the study sponsor, but the authors had the final decision to submit the manuscript for publication.

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLcr=creatinine clearance, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, JAK=Janus associated kinases, n=number, NICE=National Institute for Health and Care Excellence, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TSS=total symptom score, WE=Wernicke encephalopathy

References:

1. European Medicines Agency (EMA). Medicines. Inrebic [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/inrebic.
2. National Institute for Health Research (NIHR). Fedratinib for myelofibrosis [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2018/07/23927-Fedratinib-for-myelofibrosis-V1.0-JUN2018-NON-CONF.pdf.
3. U.S. Food and Drug Administration (FDA). Inrebic. Label Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212327s000lbl.pdf.
4. U.S. Food and Drug Administration (FDA). FDA approves fedratinib for myelofibrosis [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fedratinib-myelofibrosis.
5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/.
6. European Medicines Agency (EMA). Inrebic: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/inrebic-epar-product-information_en.pdf.
7. Pardanani A, Harrison , Cortes JE, Cervantes F, Mesa RE, et al. Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis. A Randomized Clinical Trial. JAMA Oncol 2015;1(5):643-651 Published online June 18, 2015.