Inrebic

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0020	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update information regarding thiamine levels based on a review of the primary results of the study FEDR-MF-002. This is a Phase 3, multicenter, open-label, randomized study to evaluate the efficacy and safety of fedratinib compared with BAT in subjects with DIPSS intermediate-2 or high-risk primary MF, post-PV MF, or post-ET MF and	30/01/2025	26/02/2025	SmPC and PL	SmPC new text: (…) While on treatment, all patients should receive prophylaxis with daily 100 mg oral thiamine and should have thiamine levels assessed. (…) In a randomised controlled post-marketing study (FEDR-MF-002) of Fedratinib vs. best available therapy (BAT), the incidence of thiamine levels below the lower limit of normal (< 70 nmol/L) was 20.9% for Fedratinib vs

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	previously treated with ruxolitinib. The Package Leaflet has been updated accordingly and also to amend the list of local representatives. The RMP (version 3.1) has also been updated. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				4.5% for BAT. Thiamine levels < 30 nmol/L were not observed in the study. The median time to the first low thiamine level after initiation of Fedratinib was 29.5 days. The frequency of low thiamine levels in participants receiving Fedratinib was 4.8% in those receiving thiamine supplementation 100 mg orally per day vs. 23.9% in those not receiving thiamine supplementation. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10909 /202402	Periodic Safety Update EU Single assessment - fedratinib	05/09/2024	n/a		PRAC Recommendation - maintenance
IA/0024	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/08/2024	n/a		
II/0019	Update of sections 4.2 and 5.2 of the SmPC in order to update posology recommendations in patients with severe hepatic impairment and to update pharmacokinetic information based on final results from study FEDR-CP-001 listed as a category 3 study in the RMP; this is a phase 1, open-label, single-dose study to assess the pharmacokinetics, safety, and tolerability of fedratinib in subjects with moderate and severe hepatic impairment compared with healthy subjects. The RMP version 2.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/05/2024	05/07/2024	SmPC	SmPC new text: Hepatic impairment The safety and pharmacokinetics of a single oral dose of fedratinib were evaluated in subjects with normal hepatic function and with mild to moderate hepatic impairment (Child Pugh class A, B) at 300 mg; in subjects with normal hepatic function and with severe hepatic impairment (Child-Pugh C) at 200 mg. No clinically meaningful effect on the pharmacokinetics of fedratinib was observed in subjects with mild, moderate and severe hepatic impairment compared to that in subjects with normal hepatic function. No modification of the starting dose is required for patients with mild, moderate and severe hepatic impairment, based on the Child-Pugh classification. For more information, please refer to the Summary of

					Product Characteristics.
IA/0022	B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	07/03/2024	n/a		
IA/0021/G	This was an application for a group of variations. B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	07/03/2024	n/a		
PSUSA/10909 /202308	Periodic Safety Update EU Single assessment - fedratinib	07/03/2024	n/a		PRAC Recommendation - maintenance
II/0017	Update of sections 4.4 and 4.5 of the SmPC in order to update drug-drug interaction information with dual inhibitors of CYP3A4 and CYP2C19, based on final results from study FEDR-CP-004; this is a phase 1, open-label study to evaluate the effect of a dual CYP2C19 and CYP3A4 inhibitor, fluconazole, on the pharmacokinetics of fedratinib in healthy adult subjects.	30/11/2023	01/02/2024	SmPC	SmPC new text: The following information regarding Simultaneous inhibition of CYP3A4 and CYP2C19 was added: Co-administration of fluconazole (dual inhibitor of CYP3A4 and CYP2C19, 200 mg once daily) with a single dose of fedratinib (100 mg) increased AUCinf of fedratinib by 1.7-fold. Based on PBPK simulations, co-administration of fluconazole (200 mg once daily) with fedratinib 400 mg

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				once daily is predicted to increase fedratinib AUC at steady state by 1.5-fold. The existing warning on interactions was updated to include that: 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. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10909 /202302	Periodic Safety Update EU Single assessment - fedratinib	28/09/2023	n/a		PRAC Recommendation - maintenance
IB/0015/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/06/2023	n/a		
PSUSA/10909 /202208	Periodic Safety Update EU Single assessment - fedratinib	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0010/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to add new warnings on major adverse cardiac events (MACE), thrombosis and secondary malignancies.	23/02/2023	01/02/2024	SmPC and PL	SmPC new text (section 4.4) Major adverse cardiac events (MACE) In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50

	The updates pertain to three signals, which were identified with another JAK inhibitor (tofacitinib) indicated in rheumatoid arthritis; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				years and older with at least one additional cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, non fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors. Events of MACE have been reported in patients receiving Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older, patients who are current or past long time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors. Thrombosis In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors. Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly in patients with cardiovascular factors (see also section 4.4 “Major adverse cardiovascular events (MACE)”).

					In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, Inrebic should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. Patients should be re-evaluated periodically during Inrebic treatment to assess for changes in VTE risk. Promptly evaluate patients with signs and symptoms of VTE and discontinue Inrebic in patients with suspected VTE, regardless of dose. Secondary malignancies In a large randomised active controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors. Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including Inrebic. Prior to initiating or continuing therapy with Inrebic, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older and patients who are current or past long-time smokers. For more information, please refer to the Summary of

					Product Characteristics.
PSUSA/10909 /202202	Periodic Safety Update EU Single assessment - fedratinib	29/09/2022	n/a		PRAC Recommendation - maintenance
IA/0013	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	23/08/2022	n/a		
IA/0011	A.7 - Administrative change - Deletion of manufacturing sites	23/03/2022	n/a		
PSUSA/10909 /202108	Periodic Safety Update EU Single assessment - fedratinib	10/03/2022	n/a		PRAC Recommendation - maintenance
IB/0008	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/01/2022	n/a		
IAIN/0009	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	07/12/2021	19/12/2022	Annex II and PL	
T/0005	Transfer of Marketing Authorisation	10/09/2021	19/10/2021	SmPC, Labelling and PL	
IA/0006/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/10/2021	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0003/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC in order to update drug-drug interaction information regarding medicinal products renally excreted via organic cation transporter (OCT)2 and multidrug and toxin extrusion (MATE)1/2-K (e.g. metformin) based on data from study FEDR-CP-003 (drug transporter DDI Study) listed as recommendation during initial assessment. The Package Leaflet is updated accordingly. In addition, the MAH is updating the recently revised ATC code in section 5.1 of the SmPC. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/07/2021	19/10/2021	SmPC and PL	SmPC new text: 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 AUCinf 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 AUC0-3h 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. For more information, please refer to the Summary of Product Characteristics.
IB/0004/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.b - Change in the batch size (including batch	02/06/2021	n/a		

	size ranges) of the finished product - Downscaling down to 10-fold B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
IB/0001	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	31/03/2021	n/a		
IB/0002	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	26/03/2021	n/a		