INREBIC®

100mg hard-capsules

Swiss Summary of the Risk Management Plan (RMP) for INREBIC® (Fedratinib)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of INREBIC is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of INREBIC in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic.

Celgene GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of INREBIC.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR INREBIC (FEDRATINIB)

This is a summary of the risk management plan (RMP) for INREBIC. The RMP details important risks of INREBIC, how these risks can be minimised, and how more information will be obtained about INREBIC's risks and uncertainties (missing information).

INREBIC's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how INREBIC should be used.

This summary of the RMP for INREBIC should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of INREBIC's RMP.

I. The Medicine and what it is Used for

INREBIC is authorised for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF), post polycythaemia vera myelofibrosis (post-PV MF) or post essential thrombocythaemia myelofibrosis who are Janus Associated Kinase (JAK) inhibitor naïve, or have been treated with ruxolitinib.

See SmPC for the full indication. It contains fedratinib as the active substance and it is given by the oral route.

Further information about the evaluation of INREBIC's benefits can be found in INREBIC's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of INREBIC, together with measures to minimise such risks and the proposed studies for learning more about INREBIC's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of INREBIC is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of INREBIC are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INREBIC. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Important identified and potential risks, together with missing information, are summarised in Table 1.

Table 1: List of Important Risks and Missing Information

Important Identified Risks:	• Anaemia • Thrombocytopenia/bleeding • Encephalopathy, including Wernicke's • Gastrointestinal toxicities (diarrhoea, nausea, vomiting)
Important Potential Risks:	• Pancreatitis • Severe hepatotoxicity • Severe infections including viral reactivation
Missing Information:	• Use in patients with severe hepatic impairment • Long-term safety, including secondary malignancies

II.B. Summary of Important Risks

Table 2: Anaemia

Important Identified Risk: Anaemia	
Evidence for linking the risk to the medicine	Grade 3 or 4 anaemia frequently leads to the need for red blood cell (RBC) transfusions including RBC transfusion dependence. In PMF, anaemia and the need for RBC transfusions is associated with a shorter overall survival and shorter leukaemia-free survival (Pardanani and Tefferi, 2011). Given the prognostic implications and the observation of Grade 3 anaemia as a very common adverse reaction in patients treated with fedratinib, this risk is considered an important identified risk.

Table 2: Anaemia (Continued)

Important Identified Risk: Anaemia	
Risk factors and risk groups	Patients with baseline haemoglobin < 10 g/dL are more likely to develop severe anaemia. The median time to first onset of Grade 3 anaemia event was approximately 45 days with 75% of cases occurring within 3 months of starting treatment. Patients with underlying renal disease may be at an increased risk of anaemia. In patients with myelofibrosis (MF), anaemia may occur as part of the primary disease and patients may be transfusion dependent at the start of the study.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of anaemia discussed. SmPC Section 4.8 and PL Section 4 – details of events and anaemia listed as a very common adverse drug reaction (ADR). **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 3: Thrombocytopenia/Bleeding

Important Identified Risk: Thrombocytopenia/Bleeding	
Evidence for linking the risk to the medicine	While Grade 3 or 4 thrombocytopenia was similar in fedratinib-treated patients and patients receiving placebo in the randomised controlled Phase 3 study in the JAK inhibitor naïve setting, the rate of Grade 3 or 4 thrombocytopenia was higher in MF patients previously treated with ruxolitinib. These previously exposed patients fulfil an area of high unmet medical need and it is expected that fedratinib will be primarily utilised in this setting. As thrombocytopenia may lead to bleeding events, thrombocytopenia is considered an important identified risk of fedratinib.
Risk factors and risk groups	Patients with baseline platelets < 100×10^9/L are more likely to develop severe thrombocytopenia. Thrombocytopenia generally occurs within the first 3 months of treatment, then stabilises. Previous chemotherapies including ruxolitinib and severity of the underlying disease are also an important contributor to thrombocytopenia and subsequent bleeding risks.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4 and PL Section 2 – warnings, advice and management of thrombocytopenia discussed. SmPC Section 4.8 and PL Section 4 – details of events and thrombocytopenia listed as a very common ADR. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.

Table 3: Thrombocytopenia/Bleeding (Continued)

Important Identified Risk: Thrombocytopenia/Bleeding	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 4: Encephalopathy, Including Wernicke's

Important Identified Risk: Encephalopathy, Including Wernicke's	
Evidence for linking the risk to the medicine	Due to the limited understanding of the causal association of fedratinib with this risk based on the fact that fedratinib does not interfere with thiamine receptors and that Wernicke's encephalopathy (WE) can be fatal if not recognised and treated properly, the risk of encephalopathy, including Wernicke's is considered an important identified risk. To evaluate any possible association between concerns of encephalopathy, including Wernicke's in fedratinib-treated patients, the fedratinib clinical database of 608 patients receiving continuous daily doses of fedratinib for MPNs or solid tumours was searched for reports of encephalopathy of any type, including Wernicke's, and any signs or symptoms (eg, mental status changes, ophthalmoplegia (eg, nystagmus, diplopia) and cerebellar findings) that could be suggestive of thiamine deficiency or encephalopathy, including Wernicke's. Eight fedratinib-treated patients with neurological signs or symptoms suggesting the potential diagnosis of encephalopathy, including Wernicke's, were identified. Only one patient had thiamine levels evaluated at the time of symptoms and it was normal. These patients' case histories and neuro-imaging data were reviewed by five independent experts. Based on the experts' reviews, all agreed that one patient was identified as having WE. One patient was identified as not having WE, but rather hepatic encephalopathy. For the remaining six patients, there was no consensus among the experts. Therefore, taken conservatively, at most seven cases of WE occurred in over 600 fedratinib-treated patients.
Risk factors and risk groups	Four common and distinct (but overlapping) presentations of encephalopathies the physician is likely to encounter in clinical practice are: encephalopathy from metabolic disorder or deficiency, encephalopathy due to a severe systemic illness or organ failure, encephalopathy due to medication-related toxicity, and encephalopathies diagnosed primarily by findings on brain imaging. For WE, specifically, conditions associated with thiamine deficiency and subsequent development of WE include chronic alcoholism, hyperemesis, malabsorption, poor dietary intake, increased loss of thiamine by the kidneys (eg, in diabetes or renal disease), or an increased metabolic requirement of thiamine (Isenberg-Grzeda, 2016). Myelofibrosis patients may be malnourished due to splenomegaly causing a feeling of fullness or loss of appetite. In addition, fedratinib is very commonly associated with gastrointestinal (GI) adverse events (AEs) including nausea, vomiting and diarrhoea. Inadequate treatment of these GI AEs, especially in the thiamine setting of underlying malnutrition, may predispose to thiamine deficiency and thus WE.

Table 4: Encephalopathy, Including Wernicke's (Continued)

Important Identified Risk: Encephalopathy, Including Wernicke's	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 – includes guidance on thiamine replenishment if levels are low and dose recommendations. SmPC Section 4.4 – advice on monitoring of thiamine levels and nutritional status, warnings regarding WE and GI toxicity and recommendations for prophylaxis and supportive treatment of encephalopathy, including Wernicke's. SmPC Section 4.8 – details of encephalopathy, including Wernicke's, ADRs and WE listed as a common ADR. PL Sections 2 and 4 – warnings regarding encephalopathy, including Wernicke's, details of encephalopathy, including Wernicke's, side effects, signs of encephalopathy, including Wernicke's. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 5: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)

Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)	
Evidence for linking the risk to the medicine	Diarrhoea (62.6%), nausea (58.6%) and vomiting (39.4%) were the most common nonhaematologic TEAEs (all grades) in MF patients who received 400 mg fedratinib. Most of the GI events were Grade 1 or 2. Grade 3 and 4 AEs of diarrhoea, nausea and vomiting were reported for 5.4%, 0.5% and 2.0% patients with MF who received 400 mg fedratinib, respectively. Despite the high rate of GI TEAEs, these events were not a common reason for permanent treatment discontinuation.
Risk factors and risk groups	In the clinical development program, GI toxicities were observed across all indications including patients with MF, with solid tumours and in heathy volunteers.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 –recommendations regarding prophylactic anti-emetics and administration with a high fat meal. SmPC Section 4.4 –advice regarding prophylactic treatment, treatment that should be given on the onset of symptoms, and monitoring and replenishment of thiamine levels. SmPC Section 4.8 – diarrhoea, vomiting and nausea listed as very common ADRs. PL Sections 2 and 4 – warning to talk to a doctor or pharmacist if symptoms including nausea, vomiting or diarrhoea, are present before and during fedratinib treatment. Diarrhoea, vomiting and nausea listed as very common side effects. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.

Table 5: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting) (Continued)

Important Identified Risk: Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 6: Pancreatitis

Important Potential Risk: Pancreatitis	
Evidence for linking the risk to the medicine	Grade 3 and 4 elevations of lipase were a dose-limiting toxicity in the Phase 1 dose finding study at high dose (up to 800 mg). Elevations of amylase (20%) and lipase (32%), all grades, were reported with fedratinib in patients with MF. Most of these events were Grade 1 or 2 and the more severe elevations responded to dose modification. During the clinical development programme, only one case of pancreatitis was observed in a patient in the Phase 3 study who presented with acute onset of abdominal pain and Grade 4 lipase increased by laboratory evaluation. The event occurred at the beginning of Cycle 7, and no elevations of lipase or amylase were detected by laboratory assessment before this event, including at the End-of-Cycle 6 visit. The event resolved with treatment discontinuation. Given the above, the risk of pancreatitis is considered an important potential risk.
Risk factors and risk groups	Higher doses of fedratinib were associated with more severe elevations of amylase and lipase. Risk factors for pancreatitis include gallstones, prolonged alcohol use, high triglycerides and pancreatitis is commonly associated with diabetes, obesity and smoking (Forsmark, 2016).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 – includes dose recommendations for other ≥ Grade 3 non-haematologic toxicities. SmPC Section 4.4 – advice on monitoring of amylase and lipase. SmPC Section 4.8 – details of events of pancreatitis and elevated amylase/lipase. Amylase increased and lipase increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding history of problems with the pancreas (and the liver) and history of kidney problems, details of side effects of increased lipase and amylase. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 7: Severe Hepatotoxicity

Important Potential Risk: Severe Hepatotoxicity	
Evidence for linking the risk to the medicine	Elevations of alanine aminotransferase (ALT) (43%) and aspartate aminotransferase (AST) (52%), all grades, were reported with 400 mg fedratinib in MF patients. Most of these elevations were Grade 1 or 2; however, Grade 3 and 4 ALT, AST and total bilirubin (TBL) elevations in the Phase 1 study (TED12037/TED12015) at higher fedratinib doses (patients received up to 800 mg) were observed and in a Phase 2 dose-range finding study, one patient at 300 mg developed hepatic failure with Grade 4 elevations of ALT, AST and bilirubin. Fedratinib was withdrawn, and the patient recovered. Grade 3 or 4 elevations of ALT and AST were generally reversible with dose modification and permanent treatment discontinuation. Recommendations for dose modifications (including dose reductions) for severe hepatic enzyme elevations in order to prevent the potential risk of severe hepatotoxicity are included in Section 4.2 of the SmPC.
Risk factors and risk groups	Risk factors may include higher doses of fedratinib. In the Phase 1 study (TED12037/TED12015), Grade 3 and 4 ALT, AST and TBL elevations were observed at higher fedratinib doses (patients received up to 800 mg). Risk factors for severe hepatotoxicity from drugs include medication dose, drug lipophilicity and extent of hepatic metabolism (Leise, 2014). Pre-existing liver disease/extramedullary haematopoiesis is also commonly observed in the liver in MF patients, and may increase the risk of severe hepatotoxicity. Host-related risk factors include the patient's age, sex, genetics, previous episodes of drug-induced liver injury, and underlying chronic liver disease. Environmental risk factors include the patient's metabolic features (eg, obesity), diet type, alcohol, coffee and tobacco consumption, multidrug therapy, immune state (eg, immunocompromised), and nutritional status (Licata, 2016).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 – dose recommendations are provided. SmPC Section 4.4 – advice on monitoring of hepatic function. SmPC Section 4.8 – details of events of ALT increased and AST increased. ALT increased and AST increased listed as very common ADRs. PL Sections 2 and 4 – warnings regarding liver problems, details of side effects of ALT increased and AST increased. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 8: Severe Infections Including Viral Reactivation

Important Potential Risk: Severe Infections Including Viral Reactivation	
Evidence for linking the risk to the medicine	Infections including tuberculosis, urinary tract infections (UTI) and herpes zoster are an important identified risk of treatment with ruxolitinib, a JAK1/JAK2 inhibitor. In Study EFC12153, the frequencies of patients with infection treatment-emergent adverse events was similar between placebo and treatment arms (clinical study report EFC12153, Section 12.3.1.3.4.2) however there was an increased frequency of UTI in fedratinib-treated patients compared to placebo but these were Grade 1 or 2 events. Therefore, the risk of severe infections including viral reactivation is considered an important potential risk for fedratinib.
Risk factors and risk groups	Risk factors include underlying neutropenia, immunosuppressive disease or taking immunosuppressive agents. Prolonged hospitalisation may also increase the risk of serious infections.
Risk minimisation measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 9: Use in Patients with Severe Hepatic Impairment

Important Missing Information: Use in Patients with Severe Hepatic Impairment	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 5.2 – statement that fedratinib PK have not been studied in patients with severe HI and warning to avoid use of fedratinib in patients with severe HI (Child-Pugh class C or TBL > 3 times upper limit of normal (ULN) and any AST increase). **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-CP-001 See Section II.C of this summary for an overview of the postauthorisation development plan.

Table 10: Long-term Safety, Including Secondary Malignancies

Important Missing Information: Long-term Safety, Including Secondary Malignancies	
Risk minimisation measures	**Routine risk minimisation measures:** None proposed. **Additional risk minimisation measures:** None proposed. **Legal status:** Fedratinib is subject to restricted medical prescription.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** FEDR-MF-002 See Section II.C of this summary for an overview of the postauthorisation development plan.

II.C. Postauthorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of INREBIC.

II.C.2. Other Studies in Postauthorisation Development Plan

FEDR-MF-002

Purpose of the study: the primary objective of the study is to evaluate the efficacy of INREBIC (the proportion of subjects who have a ≥ 35% reduction in spleen volume) as compared to BAT and to further evaluate the safety of INREBIC. The secondary objectives of the study include to evaluate the safety of INREBIC and to assess the effectiveness of the risk mitigation strategy for GI events and encephalopathy, including Wernicke's.

FEDR-CP-001

Purpose of the study: to characterise the effects of moderate and severe HI on the PK of INREBIC to provide guidance on the use of INREBIC in patients with HI.