Taiwan Food and Drug Administration

Assessment Report

Trade Name：恩瑞比膠囊劑 / Inrebic Capsule

Active Ingredient：Fedratinib

License Number：MOHW-PI 028311

Applicant：台灣必治妥施貴寶股份有限公司

Approval Date： 2022.06.21

Indication：

適用於曾接受 ruxolitinib 治療，中度風險或高風險之骨髓纖維化(包括原發性骨髓纖維化、真性紅血球增多症後骨髓纖維化、或血小板增多症後骨髓纖維化)成人病人

For the treatment of adult patients with intermediate or high risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia) who have veen treated with ruxolitinib

Background Information

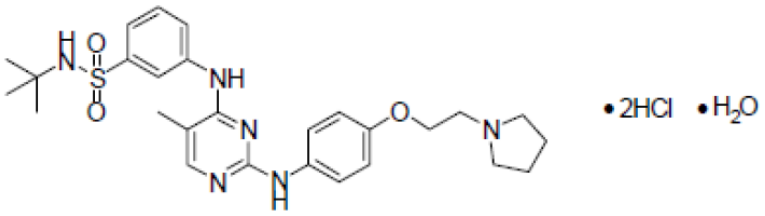
Trade Name	恩瑞比膠囊劑 / Inrebic Capsule
Active Ingredient(s)	Fedratinib
Applicant	台灣必治妥施貴寶股份有限公司
Dosage Form & Strengths	100 mg hard capsule
Indication	適用於曾接受 ruxolitinib 治療，中度風險或高風險之骨髓纖維化(包括原發性骨髓纖維化、真性紅血球增多症後骨髓纖維化、或血小板增多症後骨髓纖維化)成人病人 For the treatment of adult patients with intermediate or high risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia) who have veen treated with ruxolitinib
Posology	詳見仿單/ Please refer to the approved package insert
Pharmacological Category **ATC Code**	Antineoplastic agents L01EJ02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The chemical name of fedratinib is benzenesulfonamide, N-(1,1-dimethylethyl)-3-[[5-methyl-2-[[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]amino]-4-pyrimidinyl]amino]-, hydrochloride, hydrate (1:2:1). Fedratinib is a white to off-white solid. The molecular formula and the molecular weight for fedratinib are $C_{27}H_{36}N_6O_3S{\cdot}2HCl{\cdot}H_2O$ and 615.62 g/mol, respectively. It has the following structure:



The chemical structure of fedratinib is elucidated by elemental analysis, mass spectroscopy, infrared spectroscopy, ultraviolet spectroscopy, ^{1}H-NMR, ^{13}C-NMR and single crystal X-ray crystallography.

The specification for fedratinib includes tests for appearance, identification, chloride content,

assay, related impurities, water content, sulfated ash, residual solvents and particle size distribution.

2.1.2 Drug product

The drug product is an immediate release hard gelatin capsule for oral administration containing 100 mg of fedratinib (eauivalent to 117.3 mg of fedratinib dihydrochloride monohydrate). The specifications for the excipients are adequate.

The specification for the drug product includes tests for appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, water content and microbial limits. Analytical methods are described and well validated.

Stability studies of drug product under long term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In a cell-free enzyme activity assay, fedratinib was shown to be a potent inhibitor of wild-type and mutant (V617F) JAK2, and FLT3. Fedratinib showed higher potency for JAK2 over other family members JAK1, JAK3, and TYK2. Fedratinib inhibited cell proliferation of patient-derived or transgenic mouse $JAK2^{V617F}$ expressing cells, which was caused by reduced STAT3/5 phosphorylation and led to apoptotic cell death. The *in vivo* mouse model studies indicated that fedratinib reduced downstream signaling of STAT3/5 phosphorylation through mutated JAK2 and FLT3, resulting in reduced tumor volume, growth or engraftment, reduced splenomegaly, and increased survival. Regarding safety pharmacology, fedratinib showed no effects on the cardiovascular, CNS, and respiratory functions.

2.2.2 Toxicological Studies

In repeated dose studies in rats and dogs, target organs of fedratinib included bone marrow (hypoplasia) and liver (bile duct hypertrophy and necrosis, hepatocellular necrosis and degeneration, Kupffer cell hyperplasia, and cholestasis). Effects were also observed in the lymphoid tissues (atrophy of thymus, spleen, mesenteric lymph nodes; histiocytic infiltrates in mesenteric lymph nodes), lungs (histiocytic infiltration), skeletal muscle (necrosis), non-glandular stomach (edema and squamous cell hyperplasia), intestines (glandular atrophy), heart (increased incidence of cardiomyopathy), and male reproductive organs (aspermia, seminiferous tubule degeneration). More exaggerated liver toxicity effects were also observed in moribund dogs. Comparing animal and human exposures revealed that exposures achieved in patients exceeded the highest exposures achieved in rats and dogs.

Fedratinib was neither genotoxic in the standard battery of genotoxicity studies nor carcinogenic in the 6-month Tg.rasH2 transgenic mouse model. In a rat fertility study, there were no fedratinib-related effects on fertility or reproductive performance in males and females. Fedratinib produced evidence of embryo-fetal toxicity in the rat, including increased post-implantation loss, lower fetal body weights, and skeletal effects at dosages of 30 mg/kg/day (equivalent to 0.1-fold the human exposure at the recommended dose). The malformations of forelimbs, hind limbs, pectoral and pelvic girdle were observed in few rats at the dosages of 10 mg/kg/day (equivalent to 0.02-fold the human exposure at the recommended dose). However, fedratinib produced no evidence of embryo-fetal toxicity in the rabbit at very low dosages up to 30 mg/kg/day (equivalent to 0.08-fold the human exposure at the recommended dose). In a rat pre- and post-natal development study, there was no effect on any developmental landmark or behavioral assessments.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Fedratinib was absorbed rapidly with a median T_{max} at 2 hours (range: 1 to 4 hours). Over the range of 300 mg ~ 500mg following orally once daily, the C_{max} and AUC of fedratinib increased dose proportional following multiple doses. The accumulation ratio was about 3 ~ 4, and steady state was achieved at 15 days following 400 mg or 500 mg daily dosing. High-fat or low-fat meal did not affect the C_{max} of fedratinib, but increased AUC by 19% and 22%, respectively. Thus, fedratinib can be taken with or without food. However, due to GI TEAEs (e.g. nausea and vomiting) were occurred more frequent in the fasted state; thus, fedratinib was advised to be taken with a meal.

Following oral administration, the apparent volume of distribution of fedratinib at steady-state was approximately 1770 L in patients with myelofibrosis at 400 mg once daily. The human plasma protein binding ratio was > 92%. Fedratinib was metabolized by CYP3A4 (major), CYP2C19, and flavin-containing monooxygenase (FMOs). Fedratinib was the predominant circulating compound in plasma (79.8% of total circulating drug), and none of the metabolites contributed greater than 10% of total drug related exposure in plasma. Following a single oral dose of radiolabeled fedratinib, elimination was primarily through metabolism with approximately 77% (23% unchanged) of radioactivity excreted in feces and approximately 5% (3% unchanged) excreted in urine.

2.3.2 Interaction Studies

Coadministration of fedratinib with a strong CYP3A4 inhibitor increases fedratinib exposure; thus, reduce the dose of fedratinib to 200 mg once daily. Based on PBPK simulation data, strong and moderate CYP3A4 inducers decreased the exposure (AUC) of fedratinib by 71% and 27%, respectively. And, a strong CYP2C19 and moderate CYP3A4 inhibitor increased

the exposure (AUC) of fedratinib by 3.2-fold. Thus, avoid combination aforementioned drugs with fedratinib. Besides, it is not necessary to adjust fedratinib dose when combined with drugs that increase gastric pH (such as antacids, histamine-2 blockers, and proton pump inhibitors). Coadministration of fedratinib with drugs that are CYP3A4 substrates, CYP2C19 substrates, or CYP2D6 substrates increases the concentrations of these drugs. So, fedratinib should be used with caution with these drugs.

2.3.3 Special Populations

No dose adjustment was required based on age (20 years to 95 years), gender, and body weight (40 kg to 135 kg). The fedratinib dose should be reduced from 400 mg QD to 200 mg QD in severe renal impairment patients, but it is not necessary to adjust dose in mild to moderate RI patients. No modification of the starting dose is required for patients with mild to moderate hepatic impairment. Avoid use of fedratinib in patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The two key clinical studies to support the efficacy of fedratinib in subjects with intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post- essential thrombocythemia myelofibrosis with splenomegaly are Study ADR12181 (also known as JAKARTA2) and Study EFC12153 (also known as JAKARTA).

Study ADR12181 was a phase 2, multinational, multicenter, single-arm, open-label study in subjects previously exposed to ruxolitinib. The spleen response rate (RR), defined as the proportion of subjects with ≥ 35% spleen volume reduction (SVR), at the End of Cycle (EOC) 6 was 22.7%.

Study EFC12153 was a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study in ruxolitinib-naïve subjects. The study met the primary endpoint of spleen RR, defined as the proportion of subjects with ≥ 35% SVR, at the EOC6 confirmed 4 weeks later. For the ITT Population, the spleen RR at the EOC6 confirmed 4 weeks later was 36.5% in the 400 mg arm and 40.2% in the 500 mg arm compared with 1.0% in the placebo arm. Both active treatment arms showed statistically significant differences compared with placebo ($p < 0.0001$, 2-sided at a significance level = 0.025 for each comparison)

2.4.2 Safety Results

The most common reported adverse events (AEs) with fedratinib were gastrointestinal toxicities (diarrhea, nausea and vomiting), and hematological toxicities (anemia and thrombocytopenia). The most frequently reported Grade 3 or 4 AEs with fedratinib were

anemia and thrombocytopenia.

The most common cause of death in clinical studies was disease progression. The most frequently reported serious AEs (SAEs) with fedratinib 400 mg were pneumonia (4.4%), cardiac failure (3.0%), and anemia (2.5%).

The most frequently reported AEs leading to treatment discontinuation or modification (dose reduction or dose interruption) were also primarily gastrointestinal and hematological AEs.

Seven (1.2%) cases were identified as possible Wernicke's encephalopathy or cases that cannot be ruled out. All cases occurred in subjects receiving fedratinib 500 mg at the time of experiencing neurological symptoms. All had pre-existing malnutrition, weight loss, significant gastrointestinal AEs that were not adequately controlled, or other risk factors that may have contributed to thiamine deficiency. All subjects had received thiamine supplementation. The majority of subjects recovered or recovered with sequela with the exception of 1 fatal case.

The frequencies of subjects with laboratory abnormalities in aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, creatinine increased, serum amylase increased, lipase increased, hyperglycemia, hypercalcemia, hypophosphatemia, hypokalemia, hyperkalemia, hyponatremia, hypomagnesemia, and hypermagnesemia were higher in the fedratinib 400 mg group comparing to the placebo group. Most of these laboratory abnormalities were Grade 1 or Grade 2. One subject treated with fedratinib 300 mg had a SAE of hepatic failure and met Hy's Law. Fedratinib was withdrawn, and the laboratory abnormalities returned to normal range.

2.5 Bridging Study Evaluation

Based on population PK analysis, the Cl/F between Asian population (n=43) and non-Asian population (n=364) was similar. Also, there was no significant intrinsic factors to affect the PK of fedratinib, and the doses can be adjusted according clinical efficacy and adverse effects. Thus, the ethnic difference was recognized minor from PK point of view. However, the number of East Asian population was still limited, and lack of direct PK parameter comparison data between East Asian population and non-East Asian population, it was advised the applicant can continue to collect the data from East Asian population.

The prevalence of primary MF, post-ET MF and post-VT MF was less than 5/10,000 in East Asia region. It is therefore difficult to enroll adequate number of East Asian subjects in clinical studies. In Study EFC12153, 3/96 (3.1%), 8/96 (8.3%), and 13/97 (13.4%) East Asian subjects were enrolled in the placebo, fedratinib 400 mg, and fedratinib 500 mg arm, respectively. These subjects were from Korea, Singapore, and Taiwan. The clinical efficacy

and safety of fedratinib 400 mg were generally consistent between the East Asian and overall populations.

The bridging study of fedratinib for the proposed indication was recommended to be waived. However, the number of East Asian population was limited, it was advised the applicant can continue to collect the PK and clinical data from East Asian population.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of fedratinib.

1. Recommended Indication：For the treatment of adult patients with intermediate or high risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia) who have veen treated with ruxolitinib.
2. Recommended dose：400 mg, once daily.

3. Post-Marketing Requirements

Submit the clinical study reports (CSRs) of the following trials once available:

1. Trial FEDR-CP-001 and FEDR-CP-004.
2. Trial FEDR-MF-01, FEDR-MF-02, and FEDR-MF-03.