Taiwan Food and Drug Administration

Assessment Report

Trade Name：拓舒沃膜衣錠 250 毫克 / TIBSOVO film-coated tablets 250mg

Active Ingredient：Ivosidenib

License Number：MOHW-PI 028815

Applicant：新加坡商施維雅股份有限公司台灣分公司

Approval Date： 113/10/23

Indication：適用於帶有 IDH1 易感變異(susceptible IDH1 mutation)之成人復發性或難治性急性骨髓性白血病 (R/R AML)

Background Information

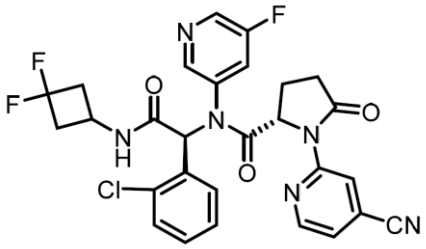
Trade Name	拓舒沃膜衣錠 250 毫克 / TIBSOVO film-coated tablets 250mg
Active Ingredient(s)	Ivosidenib
Applicant	新加坡商施維雅股份有限公司台灣分公司
Dosage Form & Strengths	膜衣錠 250
Indication	適用於帶有 IDH1 易感變異(susceptible IDH1 mutation)之成人復發性或難治性急性骨髓性白血病 (R/R AML)
Posology	詳見仿單 / Please refer to the approved package insert
Pharmacological Category **ATC Code**	L01XX62

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, ivosidenib, is chemically designated as (2S)-*N*-{(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2-oxoethyl}-1-(4-cyano pyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide and has the following structure:



It is a white to light-yellow solid. The molecular formula and the relative molecular mass for ivosidenib are $C_{28}H_{22}ClF_3N_6O_3$ and 583.0, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of ivosidenib has been confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, elemental analysis and high-resolution mass spectrum. Stereochemistry is determined by X-ray diffraction analysis. Adequate specification has been presented for the drug substance and the test items include appearance, identification, assay, related impurities, chiral purity, residual solvents, water content, residue on ignition and elemental impurities. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for oral use as oval and blue film-coated tablet 250 mg ivosidenib. The specifications for excipients used in the film-coated tablet formulation are adequate.

Adequate specification has been presented for the film-coated tablet and the test items include appearance, identification, assay, degradation product, uniformity of dosage units, dissolution and water content. Batch analysis data from representative batches of the tablet are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of the tablet under long term condition (30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 60 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of the tablet can be granted for 60 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Ivosidenib is a first-in-class, oral selective small-molecule inhibitor of mutated IDH1. Inhibition of the mutant IDH1 enzyme R132H or R132C by ivosidenib led to decreased intracellular 2-HG levels and induced myeloid differentiation *in vitro* and *in vivo* in patient-derived xenograft (PDX) mouse models of $IDH1^{R132C}$ or $IDH1^{R132H}$ mutant acute myeloid leukemia (AML). In patient derived IDH1R132C and R132H mutant AML cells ex vivo ivosidenib exhibit ed profound 2-HG lowering and induced myeloblast differentiation, as well as increased percentages of mature myeloid cells. QTc interval prolongation has been observed in nonclinical and clinical safety findings. Electrocardiogram (EKG or ECG) and electrolytes monitoring are recommended for patients.

2.2.2 Toxicological Studies

With repeated administration of ivosidenib in rats and monkeys for up to 3-months, the liver was the main target organ across species. Other noteworthy target organs of ivosidenib-related toxicity included heart (monkey only), and thyroid, bone marrow, spleen, kidney, thymus, as well as glandular and non-glandular stomach (rats only). The NOAEL is not identified in any species. Similar gastrointestinal side effects (diarrhea, nausea, constipation, vomiting, and abdominal pain) was reported in the subjects with R/R AML (74.3%).

Ivosidenib was negative in the standard battery of genotoxicity studies. Ivosidenib did not demonstrate phototoxic potential. Uterus atrophy was observed in repeated-dose toxicity studies in females at non-tolerated dose levels. Lower fetal body weight and skeletal variations (reduced ossification of the rib and unossified sternebrae) were observed in rats at approx. 2 times the human exposure at the recommended daily dose of 500 mg. Treatment with pregnant rabbits resulted in maternal toxicity. It contributed spontaneous abortions as well as fetal developmental findings (including decreased fetal weights, skeletal variations, and visceral variations) at doses of 180 mg/kg/day (approx. 3.9-times the human exposure at the recommended daily dose of 500 mg). The NOAEL identified for rats and rabbits were only approx. 0.4- and 1.4-times, respectively, the human exposure at the recommended daily dose of 500 mg. Therefore, the patients should be advised about potential risks to a fetus.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

A high-fat meal didn’t change the absorption rate but increase ivosidenib bioavailability (↑25% of AUC and↑98% of C_{max}). Therefore, to minimize the effects of a high-fat meal on ivosidenib Cmax, subjects should avoid consuming a high-fat meal when ivosidenib is

administered with food in case increasing the risk of QTc prolongation.

The AUC and C_{max} of ivosidenib increase in a less than dose-proportional manner from 200 mg to 1,200 mg daily. After 14 days of multiple dosing, ivosidenib achieved steady state with accumulation factor of 1.9 for AUC and 1.5 for C_{max}. The $C_{max,ss}$ and $AUC_{0-24,ss}$ of patients with advanced AML were 6551 ng/mL and 117348 ng*hr/mL, respectively, following therapeutic dosage regimen of 500 mg QD.

The protein binding rate ranged 92~96%. It was mainly metabolized via CYP3A4, followed by CYP2B6, and 2C8. Fecal excretion appeared to be the predominant route of elimination with a mean recovery of total radioactivity in urine, and feces of 16.9% and 77.4%, respectively.

2.3.2 Interaction Studies

Ivosidenib is an inducer of human CYP3A4/5, substrate of P-gp, but may be an inducer of CYP2B6, CYP2C8, CYP2C9, and a weak inhibitor of OATP1B1 and OATP1B3.

Concomitant treatment with moderate/strong CYP3A4 inhibitors is expected to increase steady-state ivosidenib AUC or Cmax by ≤100%, it was recommended to avoid concomitant use, or reduce ivosidenib to 250 mg QD. When ivosidenib is co-administered with systemic moderate or strong CYP3A4 inhibitors, careful monitoring of QTc prolongation should be considered.

No dose adjustment is considered necessary for co-administration with weak or moderate CYP3A4 inducers. Co-administration of ivosidenib with strong CYP3A4 inducers (such as rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort) should be avoided.

Avoid concomitant use with sensitive CYP3A4 substrate, itraconazole or ketoconazole, was recommended due to expected loss of antifungal efficacy. For CYP2C9, use althernative therapies that are not sensitive CYP2C9 substrate. Co-administration of ivosidenib may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving ivosidenib.

2.3.3 Special Populations

Age, body weight, BMI and sex did not possess apparent effect on ivosidenib PK. No dose adjustment is necessary in subject with mild, moderate renal impairment, and mild or moderate hepatic impairment. The PK and safety of ivosidenib in subjects with severe renal impairment or severe hepatic impairment are unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A multicenter, open-label, single-arm Phase 1study (AG120-C-001) was reviewed to evaluate the efficacy of TIBSOVO (ivosidenib) for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (R/R AML) with a susceptible IDH1 mutation.

The primary evidence of efficacy for the proposed indication was based on data from IDH1 mutation-positive R/R AML Arm 1-eligible (Arm 1+) subjects in Study AG120-C-001. The primary endpoint was the rate of complete remission (CR) plus complete remission with only partial hematologic recovery (CRh).

In Study AG120-C-001, a total of 179 subjects had R/R AML whose starting dose was 500 mg QD ivosidenib. Of these, 159 subjects were included in the Arm 1+ subset (R/R AML). Among the Arm 1+ subjects, 125 subjects (33 subjects were from the dose escalation portion and 92 were from the expansion portion) received their first dose of ivosidenib at least 6 months prior to the data cutoff date of 12 May 2017 and therefore comprise the primary efficacy analysis set (Arm 1+ FAS1).

As of 12 May 2017, the CR+CRh rate in Arm 1+ FAS1 (125 subjects) was 30.4% (95% CI: 22.5%, 39.3%). For patients who achieved a CR or CRh, the median duration of CR+CRh was 8.2 months (95% CI: 5.5, 12.0) and the median time to CR+CRh was 2.7 months (range: 0.9, 5.6).

Further, at data cutoff date of 2 November 2018, all 159 Arm 1+ subjects have had the opportunity to be followed for a minimum of 6 months or discontinued earlier (Arm 1+ FAS). The CR+CRh rate in Arm 1+ FAS was 29.6% (95% CI: 22.6%, 37.3%). For patients who achieved a CR or CRh, the median duration of CR+CRh was 8.2 months (95% CI: 5.6, 12.9) and the median time to CR+CRh was 2.7 months (range: 0.9, 5.6).

2.4.2 Safety Results

Common TEAEs include diarrhea, leukocytosis, febrile neutropenia, nausea, fatigue, dyspnea, QTc prolongation, peripheral edema, pyrexia, cough, constipation, decreased appetite, vomiting, hypokalemia, pneumonia, arthralgia, epistaxis, thrombocytopenia, dizziness, asthenia, back pain, headache, pleural effusion, hypomagnesemia, hypotension, IDH differentiation syndrome, abdominal pain, tumor lysis syndrome, polyneuropathy and rash.

In the clinical trial, 11.2% of patients with relapsed or refractory AML treated with ivosidenib experienced IDH differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or

fatal if not treated. Symptoms of differentiation syndrome consisted of dyspnea, unexplained fever, weight gain, unexplained hypotension, acute kidney injury, and pulmonary infiltrates or pleuropericardial effusion. Recommended treatments are corticosteroids and hemodynamic monitoring.

2.5 Bridging Study Evaluation

From PK perspective, the bridging data of Asian population in ivosidenib were from Japanese healthy volunteers. Though the PK difference following single dose of 500 mg were not much significant in a cross-study comparison between Asian and non-Asian healthy population, higher absorption in Japanese healthy volunteers was observed than that in Caucasians in head-to-head PK study. The number of Asian target patients was too small to be representative. The PK characteristic of ivosidenib included non-linear, undetermined steep PK-PD curve, and narrow TI, it is difficult to extrapolate the PK data from healthy population to target patients and exclude the concern of ethnic sensitivity.

From clinical perspective, the sponsor provided East Asian subgroup analysis of Study AG120-C-001 as bridging data. However, few East Asian subjects (6) were enrolled. Adequate comparison of efficacy and safety between Asian and non-Asian group could not be made.

Considering the unmedical need of the claimed indication, the feasibility and the limitation of provided bridging, conditional waiver of bridging study was granted. The sponsor should submit the complete study report (CSR) of ongoing Studies AG120-C-009 (combination therapy with azacitidine), AG-221-AML-005 (combination therapy with azacitidine) and CS3010-10. East Asian subgroup analyses should be included along with CSR of Studies AG120-C-009 and AG-221-AML-005. PK/PD data should also be included in CSR of Study CS3010-101.

2.6 Conclusion

Overall, the submitted NDA package of ivosidenib for CMC, PT, PK and Clinical section were considered adequate and acceptable. The benefit/risk ratio is positive in the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation. Important risks are IDH differentiation syndrome and QTc prolongation, which could be fatal and should be closely monitored through label warning.

3. Post-Marketing Requirements

- The sponsor should submit the complete study report (CSR) of Studies AG120-C-009 (combination therapy with azacitidine), AG-221-AML-005 (combination therapy with azacitidine) and CS3010-101. East Asian subgroup analysis should be included along with CSR of Studies AG120-C-009 and AG-221-AML-005. PK/PD data should also be included in CSR of Study CS3010-101.

- The sponsor should also provide the overall survival data of patients who receive HSCT based on the following database once available.
  - Pooled results of Studies AG120-C-001, AG120-C-009 and AG-221-AML-005.