Taiwan Food and Drug Administration

Assessment Report

Trade Name：適加坦膜衣錠 40 毫克/ Xospata film-coated tablets 40mg

Active Ingredient：Gilteritinib fumarate

License Number：MOHW-PI 027890

Applicant：台灣安斯泰來製藥股份有限公司

Approval Date：2020/08/07

Indication： Xospata is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation.

適用於治療具有 FLT3 突變的復發性或難治性急性骨髓性白血病(R/R AML)成年病人。

Background Information

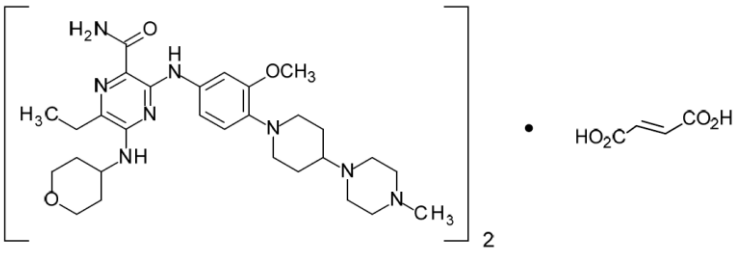
Trade Name	Xospata film-coated tablets 40 mg
Active Ingredient(s)	Gilteritinib fumarate
Applicant	Astellas Pharma Inc.
Dosage Form & Strengths	Film-coated tablets，40 mg
Indication	Xospata is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. 適用於治療具有 FLT3 突變的復發或難治性急性骨髓性白血病(R/R AML)成年病人。
Posology	The recommended starting dose of Xospata is 120 mg (three 40 mg tablets) once daily. Treatment should continue until the patient is no longer clinically benefiting from Xospata or develops intolerable toxicity. Treatment response may be delayed; therefore, continuous treatment at the prescribed dose should be considered for up to 6 months to allow time for a clinical response. In the absence of a response after 4 weeks of treatment (patient does not reach CRc), when the patient can tolerate and clinically necessary, consider increasing the dose to 200 mg (40 mg five tablets). Xospata的建議起始劑量是120 mg（40 mg三錠)每天一次。 應該持續治療直到病人在臨床上不再因Xospata獲益或出現無法耐受的毒性為止。 治療反應可能會延遲；因此，應考慮以處方劑量持續治療達6個月，以便有時間產生臨床反應。 若治療 4 週後沒有出現反應(病人未達到CRc)，當病人可以耐受且臨床上有必要時，可考慮將劑量增加到 200 mg（40 mg五錠)。
Pharmacological Category **ATC Code**	L01XE54

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Gilteritinib fumarate is a light yellow crystal or powder, non-hygroscopic solid.



The chemical structure of the drug substance is confirmed by elemental analysis, ultraviolet spectroscopy, IR, NMR (^{1}H-NMR and ^{13}C-NMR) and mass spectrometry.

The proposed specifications for the drug substance include description, identification, impurities, water content, residue on ignition, and assay. The analytical methods used have been adequately described and appropriately validated.

2.1.2 Drug product

Gilteritinib tablets 40 mg is a film-coated tablet. Each tablet contains 44.2 mg of the drug substance (equivalent to 40 mg of gilteritinib).

All excipients are well known ingredients and suitable for proposed formulation.

The proposed specifications for the drug product include description, identification, related substances, uniformity of dosage units, dissolution, microbial limit, and assay.

Drug product is packaged in a PVC/Alu blister.

Stability studies of drug product under long term condition (25℃/60% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Gilteritinib fumarate inhibited FLT3, LTK, AXL and EML4-ALK variant 1 activities and repressed the proliferation of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y, or FLT3-ITD-D835Y. Phosphorylation of FLT3, STAT5, AKT, and ERK was also inhibited by gilteritinib fumarate in these cells. Gilteritinib fumarate significantly increased the population of MV4-11 cells in the G1 phase and increased the annexin-V-positive population, indicating

that gilteritinib fumarate induced apoptosis.

In *in vivo* pharmacology, high dose gilteritinib fumarate inhibited the growth or induced complete regression in 6 out of 6 mice bearing MV4-11 tumors. The phosphorylation of FLT3 and STAT5 in MV4-11 tumors was also inhibited by oral administration of gilteritinib fumarate. Treatment of 30 mg/kg/day gilteritinib fumarate significantly decreased tumor growth after the inoculation of MV4-11 cells into the tibia. The median survival time of the control group was 61.5 days, whereas no death was observed in the gilteritinib fumarate group until day 168, the final day of observation. Gilteritinib fumarate inhibited the proliferation of 3T3 cells, NCI-H2228 and NSCLC cells expressing EML4-ALK variant 3, and inhibited ALK phosphorylation in NCI-H2228 cells.

In safety pharmacology, gilteritinib fumarate showed no effects on the cardiovascular or respiratory system in dog. Changes as vomiting and a positive fecal occult blood reaction were noted.

2.2.2 Toxicological Studies

In a rat single-dose toxicity study, the major change was a gastrointestinal disorder. In a rat 13-week repeated-dose toxicity study, decreased body weight and the immune system effects were noted at the low dose and higher dose levels. These changes recovered or tended to recover during the 4-week recovery period.

In a dog 4-week repeated-dose toxicity study, decreased bodyweight, increased aspartate transaminase and increased thymic atrophy in males, lymphocyte necrosis in the mesenteric lymph node in females, and a positive fecal occult blood reaction and increased alkaline phosphatase were observed at the lowest-observed-adverse-effect-level and higher dose levels. In a dog 13-week repeated-dose toxicity study, target organ toxicity was observed at the lowest-observed-adverse-effect-level and higher dose levels in the lungs, epithelial tissues, immune system, liver, and gastrointestinal tract such as positive fecal occult blood reaction, inflammatory cell infiltration, increased neutrophil count, aspartate transaminase, alkaline phosphatase, globulin concentration and total protein, and decreased albumin concentration. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period in both dog studies.

In a rat embryo-fetal development toxicity study, clear fetal toxic changes were observed. High post-implantation loss rate, external abnormalities, visceral abnormalities, and skeletal abnormalities were noted.

In a rat juvenile study, necrosis of the lymphocytes in the thymic cortex was observed in a

moribund sacrificed animal. Furthermore, gilteritinib has the potential to induce *in vivo* chromosomal aberrations, but no phototoxicity was observed.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Gilteritinib exhibited approximate dose proportional pharmacokinetics following once daily administration of gilteritinib over the dose range of 20 to 450 mg in patients with relapsed or refractory AML. Following once daily of gilteritinib 120 mg, $C_{max,ss}$ and $AUC_{0-24,ss}$ were 282.0 ng/mL, and 6180 ng·hr/mL, respectively. Steady-state was achieved within 15 days of once-daily dosing with R_{AC} of 9.04. The $C_{max,ss}$ following 8 doses of 120 mg QD achieved the plateau of inhibition of pFLT3.

Gilteritinib is primarily metabolized via CYP3A4. Though the pharmacological activity of its metabolites were unknown, the three metabolites only stand for <10% of overall parent exposure. The plasma protein binding rate of human plasma is 90% and gilteritinib is primarily bound to albumin.

After a single dose of [14C]-gilteritinib, gilteritinib is maily excreted in feces with 64.5% of the total administered dose recovered in feces. Of the total radiolabeled dose of gilteritinib, 16.4% was recovered in urine as unchanged drug and metabolites. The population estimate of central volume of distribution, $T_{1/2}$, and CL/F were 1092 L, 113 hrs, and 14.85 L/hr, respectively.

Gilteritinib C_{max} and AUC decreased by 26% and <10%, respectively, following co-administration of single dose of 40 mg giltertinib with a high fat meal compared to gilteritinib in fasted condition.

2.3.2 Interaction Studies

Gilteritinib exposure increased less than 2-folds in patients with relapsed or refractory AML when co-administered with a strong CYP3A and/or P-gp inhibitor. Use with caution or considering alternative medicinal products was recommended.

Concomitant use with strong CYP3A/P-gp inducers should be avoided due to significant decrease of gilteritinib plasma concentrations. Avoid concomitant use of $5HT_{2B}$ receptor or sigma nonspecific receptor, and precaution for co-administration of gilteritinib with drugs that might cause QT prolongation were also recommended.

2.3.3 Special Populations

No dose adjustment was recommended for mild to moderate hepatic impaired population and

mild to moderate renal impaired population. The efficacy and safety of gilteritinib have not been studied in patients with severe renal impairment or severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 2215-CL-0301 was reviewed to evaluate the efficacy of gilteritinib in the treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with FMS-like tyrosine kinase-3 (FLT3) mutation. The primary objectives of the study were to determine the clinical benefit of gilteritinib therapy as shown by OS compared to salvage chemotherapy and to determine the efficacy of gilteritinib therapy as assessed by the rate of complete remission and complete remission with partial hematological recovery (CR/CRh). The key secondary objectives of the study were to determine the overall efficacy in event-free survival (EFS) and CR rate.

CR/CRh rate was evaluated at Interim Analysis 1 in the gilteritinib arm only. At Interim Analysis 1, the CR/CRh response rate was 28.2% (95% CI: 20.9%, 36.3%). The predetermined criterion that the lower limit of 95% exact confidence interval (CI) of CR/CRh rate was higher than 12% was met. In addition, the CR/CRh rate for the gilteritinib arm was 34.0% versus 15.3% in the salvage chemotherapy arm in the final analysis. The difference of CR/CRh rate between the 2 treatment arms was 18.6% (95% CI: 9.8%, 27.4%).

In the final analysis, median OS for patients in the gilteritinib 120 mg arm was significantly longer compared with the patients in the salvage chemotherapy arm (median OS: 9.3 months versus 5.6 months; HR: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value: 0.0004). The primary study objective of OS was achieved (adjusted 1-sided efficacy boundary for OS of < 0.0238). The key secondary study objective of EFS was not achieved (HR: 0.793; 95% CI: 0.577, 1.089; 1-sided P-value: 0.0415). The median EFS duration was 2.8 months in the gilteritinib arm versus 0.7 months in the salvage chemotherapy arm. EFS showed a favorable trend in the gilteritinib arm. Due to the preplanned hierarchical testing method, the test procedure will be stopped at this step. The CR rate for the gilteritinib arm was 21.1% (52/247) versus 10.5% (13/124) in the salvage chemotherapy arm, for a difference of 10.6% (95% CI: 2.8%, 18.4%).

In summary, Study 2215-CL-0301 demonstrated the efficacy of gilteritinib in the treatment of patients with R/R AML with FLT3 mutation.

2.4.2 Safety Results

The safety profile of gilteritinib was similar to other kinase inhibitors. The major safety issues includes differentiation syndrome (rare), posterior reversible encephalopathy syndrome (rare), prolonged QT interval (1.3% had a QTc interval greater than 500 msec and

6.6% had an increase from baseline QTc greater than 60 msec) and potential embryo-fetal toxicity. The labeling had proposed strategies of dosage modifications and risk monitoring suggestions for aforementioned drug-related toxicities. The applicant had proposed a Risk Management Plan by request for further mitigation of risks. Moreover, additional risk minimization procedures like Communication Plan with health-care providers to ensure proper risk monitoring in clinical practice should also be implemented.

2.5 Bridging Study Evaluation

The applicant provided one global phase 3 Study 2215-CL-0301, one global phase I/II Study 2215-CL-0101 and one Japan phase I Study 2215-CL-0102 to support the overall efficacy and safety of gilteritinib, and also for evaluation of any potential ethnic difference.

Pharmacokinetics and Pharmacodynamics

The absorption extent of Japanese population following 120mg QD was similar to those of western population with advanced solid tumor in mass balance study. The median C_{trough} between Asians (including Taiwan, Japan and Korea) and non-Asians were similar in the pivotal study (2215-CL-0301).

Gilteritinib exhibits a linear PK with a narrow therapeutic window. The proposed therapeutic dose has achieved the maximum inhibition of FLT3 phosphorylation but was associated with prolonged QT intervals. Though the metabolism extent was unknown due to lack of absolute availability, the enzyme responsible for metabolism (CYP3A4) was not considered to be ethnicity sensitive. In addition, gilteritinib possess large inter-subject variation in the target population.

Overall, sponsor has provided sufficient PK data from Japanese target patients following multiple dose. None to minimally ethnic sensitivity was demonstrated in median C_{trough} in pivotal study and mass balance study.

Clinical

Among the 371 subjects in Study 2215-CL-0301, 94 (25.3%) subjects were East Asian population, including subjects from Taiwan, Japan and Korea. The primary efficacy endpoint of overall survival showed comparable result between East Asian and non-East Asian population (gilteritinib vs C/T；Overall ITT：median OS 9.3m vs 5.6m，HR 0.637 [95% CI 0.490，0.830]，1-sided P=0.0004；East Asian：10.8m vs 5.6m，HR 0.378 [95% CI 0.206，0.693], P=0.0011; non-East Asian：8.6m vs 5.8m，HR 0.717 [95% CI 0.538，0.956], P=0.0229).

In Study 2215-CL-0301, the exposure-adjusted incidence of each category in overview of TEAEs was similar between East Asian and non-East Asian population. Some TEAEs

happened more frequently in East Asian population, but most of those were not serious AEs or AEs leading to treatment discontinuation. The overall safety profile in East Asian and non-East Asian population were comparable and acceptable.

In summary, sufficient comparative data between East Asian and non-East Asian population had been provided and showed no clinically significant ethic difference. The Bridging Study Evaluation is suggested to be waved.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of gilteritinib was demonstrated by a significantly prolonged overall survival for patients treated by gilteritinib monotherapy as compared with the patients treated by salvage chemotherapy (median OS: 9.3 months versus 5.6 months ; HR: 0.637; 95% CI: 0.490, 0.830) in randomized controlled Study 2215-CL-0301. The safety issues of gilteritinib include differentiation syndrome, posterior reversible encephalopathy syndrome, prolonged QT interval and potential embryo-fetal toxicity.

Implement of Risk Management Plan (RMP) that includes Communication Plan with health care providers after approval is mandatory for adequate risk management. The overall benefit/risk ratio is favorable to support the approval of Xospata, for the treatment of treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation.

3. Post-Marketing Requirements

None