Taiwan Food and Drug Administration

Assessment Report

Trade Name：安列庫帕 凍晶靜脈注射劑 / Aliqopa

Active Ingredient：Copanlisib

License Number： MOHW-PI 027745

Applicant：台灣拜耳股份有限公司

Approval Date：108/10/3

Indication：治療曾接受至少兩次全身性治療的復發性濾泡淋巴瘤(FL)成人病人。

ALIQOPA is indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies

1. Background Information

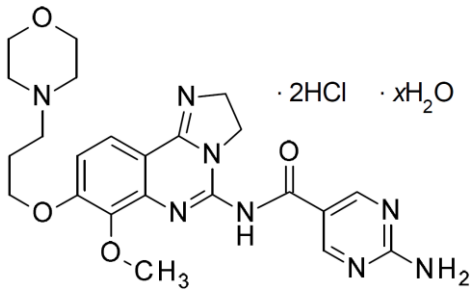
Trade Name	安列庫帕 凍晶靜脈注射劑 / Aliqopa
Active Ingredient(s)	Copanlisib
Applicant	台灣拜耳股份有限公司
Dosage Form & Strengths	凍晶注射劑 60mg
Indication	治療曾接受至少兩次全身性治療的復發性濾泡淋巴瘤(FL)成人病人。 ALIQOPA is indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.
Posology	ALIQOPA 建議劑量為 60 mg，在 28 天的治療週期內，以間歇性療程(三週用藥，一週停藥)，於第 1、8 和 15 天，以 1 小時靜脈輸注之方式給藥。持續接受治療直到病況惡化或發生無法接受的毒性。
Pharmacological Category **ATC Code**	L01XX61

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, copanlisib dihydrochloride, exists as a non-stoichiometric hydrate and has the molecular formula of $C_{23}H_{28}N_8O_4$•2HCl and a molecular weight of 553.45 g/mol. The molecular formula and molecular weight are based on the anhydrous form. The chemical name is 2-amino-N-{7- methoxy-8- [3-(morpholin-4-yl) propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide dihydrochloride. Copanlisib dihydrochloride has the following structure:



It is a white to yellow powder and is not hygroscopic. Adequate information of characterization of the drug substance was provided. The structure of copanlisib dihydrochloride is confirmed by IR spectrum, Raman spectrum, UV spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), mass spectrum, and elemental

analysis. The spectrum assignations are consistent with the declared chemical structure.

The specification of the drug substance includes tests for appearance, identification, appearance of solution, chloride content, elemental impurity, water content, residual solvents, related substances, assay, microbial limit test, and endotoxins.

2.1.2 Drug product

Copanlisib lyophilisate 60 mg for injection (Aliqopa®) is supplied in single-dose vials as a sterile lyophilized solid for reconstitution and further dilution for intravenous infusion. The product is white to slightly yellowish. After reconstitution, the solution is colorless to slightly yellowish. Each vial contains 60 mg copanlisib free base (equivalent to 69.1 mg copanlisib dihydrochloride). After reconstitution, each mL contains 15 mg copanlisib free base (equivalent to 17.3 mg copanlisib dihydrochloride). The quality of all excipients is compliant with the compendial monographs. A robust process is confirmed by adequate process validation.

Adequate release and shelf-life specifications have been presented for the drug product. Test items of release specification include description, color and clarity of reconstituted solution, identification, visible particles, particulate matter, pH value, water content, reconstitution time, uniformity of dosage units, degradation products, assay, endotoxins, and sterility. Analytical methods are described well and validated. Stability studies of drug product under long term (2-8°C) and accelerated (25°C/60% RH) condition have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Copanlisib is a novel, highly selective, pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor with predominant inhibitory activity against both PI3Kα and PI3Kδ isoforms, which are expressed in malignant B cells. The PI3KAKT-mTOR pathway is one of the prominent pathways that promote cellular survival and constitutively activated in many types of cancers. Class I PI3K is the downstream of most cancer associated tyrosine kinase growth factor receptors.

In the *in vitro* and *in vivo* pharmacology studies, copanlisib has demonstrated the efficacy on tumor growth inhibition and tumor regression. Safety pharmacology studies revealed that copanlisib causes vasoconstriction with resulting hypertension, insulin resistance and hyperglycemia, reduced gastrointestinal motility, increased

renal volume and electrolyte excretion, and central nervous system (CNS) depressant effects. This spectrum of effects is similar to that published for other PI3K inhibitors. While hERG potassium currents were unaffected, drug-related systolic and diastolic blood pressures (BP) were increased in anesthetized dogs. No significant effect on respiratory function was observed.

2.2.2 Toxicological Studies

Copanlisib was assessed in single-dose and repeat-dose toxicity studies up to 3 or 4 cycles in rats and dogs. The major toxicity target organs were the lymphoid and hematopoietic system, liver, kidneys, teeth, bone/femorotibial growth plates, heart, and male and female genital systems in the rat. Dogs showed adverse effects in the lymphoid and hematopoietic system, stomach (gastric mucosa), and male genital system. Copanlisib was negative in the standard battery of genotoxicity studies and in the *in vitro* phototoxicity study. No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer.

No nonclinical studies of male and female fertility were conducted. The rat and dog repeated-dose studies suggested that copanlisib may impair the fertility in humans. Daily intravenous injection of copanlisib resulted in clear-cut embryo-fetal developmental toxicity at dose ≥ 0.75 mg/kg. Severe post implantation loss, and developmental toxicity, including embryofetal toxicity and teratogenicity were observed in the rat pilot embryo-fetal developmental toxicity study. Females of reproductive potential should use effective contraception during the treatment with copanlisib.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The AUC and C_{max} of copanlisib following iv administration increase in a dose proportional manner over a dose range of 0.1~1.2 mg/kg (5-93 mg). Minimal accumulation with weekly dosing was observed. The C_{max} and $AUC_{0\text{-}25h}$ after achieving steady state at 0.8 mg/kg are 463 (CV 64.4%) ng/mL and 1570 (CV 38.4%) ng*hr/mL, respectively. The *in vitro* protein binding rate is 84.2% which mainly binds to human albumin. Copanlisib distributes extensively into peripheral tissues with the geometric mean volume of distribution of 871 L.

Approximately >90% of copanlisib is metabolized by CYP3A and <10% by CYP1A1. The M-1 metabolite possess similar pharmacological potency as the parent

compound but only stands for 5% of total radioactivity AUC. Copanlisib is excreted approximately 50% as unchanged form and 50% as metabolites in human. The terminal elimination $T_{1/2}$ is 39.1 hours. The geometric mean clearance is 17.9 L/hr.

2.3.2 Interaction Studies

Copanlisib is a substrate of P-gp and BCRP. As co-administration strong CYP3A and P-gp inducer, rifampin, and iv single dose of 60 mg copanlisib in cancer patients, it resulted in a 63% decrease in AUC and 15 decrease in C_{max} of copanlisib. Avoid concomitant use of copanlisib with strong CYP3A4 inducers.

As co-administration with strong inhibitor of CYP3A and P-gp, itraconazole, and iv single dose of 60 mg copanlisib in cancer patients, it has resulted in a 53% increase in AUC and no effect on C_{max}. If concomitant use with strong CYP3A inhibitors cannot be avoided, reduce the copanlisib dose to 45 mg.

Based on various *in vitro* DDI studies on transporters, CYP, and non-CYP enzymes, copanlisib was only identified as an inhibitor of MATE2-K under the therapeutic plasma concentration. The DDI study between copanlisib and MATE2-K substrate, metformin, is still ongoing.

2.3.3 Special Populations

According to population PK analysis, mild hepatic impairment [total bilirubin (TB) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or TB < 1-1.5 x ULN and any AST], and mild to moderate renal impairment (CLcr ≥ 30 mL/min) had no clinically significant effect on the pharmacokinetics of copanlisib. The dedicated hepatic and renal impairment study (Study 18041) are still ongoing.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 16349 Part B was reviewed to evaluate the efficacy of copanlisib for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

Study 16349 Part B was an open-label, single arm Phase II study to evaluate efficacy and safety of copanlisib as a single agent in patients with relapsed or refractory indolent B-cell NHL. The patients were to be relapsed or refractory after ≥ 2 prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen), and must have had received rituximab and alkylating agent(s).

The primary efficacy variable was the objective response rate (ORR), defined as the proportion of patients who had a best response rating of complete response (CR) or partial response (PR) according to the Revised Response Criteria for Malignant Lymphoma. The null hypothesis of ORR lower or equal to 40% was tested using an exact one-sided binominal test. The primary analysis set was the FAS, which included all patients assigned to study treatment.

Of the 142 patients, 130 patients received copanlisib fixed dose 60 mg and 12 patients received 0.8 mg/kg. The most common indolent NHL histological subtype was FL reported in 104 patients (73.2%) by the investigator (local pathology).

Of the 142 patients in the FAS, 84 patients achieved objective tumor response (CR or PR) based on independent review resulting in ORR of 59.15% (95% CI: [50.60%, 67.32%]). For the FAS, the lower limit of 95% CI of ORR exceeded the pre-defined threshold of 40%, as the p-value for the one-sample exact binomial test was < 0.0001. Of the 104 FL patients in the FAS, 61 achieved objective tumor response based on the independent review resulting in ORR of 58.65% (95% CI: [48.58%, 68.23%]). The lower limit of 95% CI of ORR in the FL subgroup was also greater than the pre-defined threshold of 40%.

2.4.2 Safety Results

The integrated safety analyses were conducted in several sets. The indolent non-hodgkin's lymphoma (iNHL) pool included all iNHL patients (N=168) treated with copanlisib monotherpay. The FL pool included FL patients (N=126) treated with copanlisib monotherpay. The demographic and baseline characteristics were similar in the FL and iNHL pools. In the iNHL Pool, the median overall time under treatment (including dose interruptions/delays and drug holidays) was 22.00 weeks. The extent of exposure to copanlisib was similar in the FL and iNHL pools.

In the iNHL pool, 18.5% of treated patients terminated treatment due to adverse events not associated with clinical disease progression. The majority of patients (98.8%) had at least 1 TEAE during the treatment. The majority of TEAEs were Grade 3 or 4 in severity. The incidences of TESAEs (26%) and TEAEs leading to discontinuation of study drug were high. The most commonly reported (≧20%) TEAEs were hyperglycemia, diarrhea, hypertension, fatigue, nausea, neutropenia, and pyrexia. Serious adverse reactions were reported in 44 (26%) patients. The most frequent serious adverse reactions that occurred were pneumonia (8%), pneumonitis (5%) and hyperglycemia (5%). The most common reasons for dose reduction were

hyperglycemia, neutropenia and hypertension. The most common reasons for drug discontinuation were pneumonitis and hyperglycemia. The AE profiles of FL pool were similar to the iNHL Pool.

The adverse reactions which need close monitor and proper management at use are infection (the incidence of serious cases: 19%, the same below), hyperglycemia (2.8%), hypertension (0.9%), non-infection pneumonitis, neutropenia (1.3%) and severe cutaneous reactions (0.9%).

2.5 Bridging Study Evaluation

PK/PD Perspective:

There were two Japanese Phase I studies, one Phase II study and two population PK analyses for bridging study evaluation. Whether subjects were dosing by body weight or fixed dosing regimen, there were no significant differences between Japanese patient and Western patient populations.

Copanlisib possess linear characteristic and steep PK-PD curve. After intravenous administration, it was metabolized extensively by CYP3A4 in liver. After enterohepatic circulation, 64% and 22% of radioactive dose was excreted in feces and urine, respectively. And the excretion form was equal between unchanged compound and metabolites (50:50).

According to the provided information above, it is adequate to support the non-ethnic sensitivity of copanlisib.

Clinical Perspective:

Clinical bridging data was from the Asian subjects in Study 16349 Part B and the Japanese Phase Ib/II Study 17792. A total of 14 Asian patients with FL were enrolled in Study 16349 Part B. There were 25 Japanese patients with indolent B-cell NHLs relapsed after or refractory to standard therapy in Study 17792.The IRRC-assessed ORRs were similar between Asian/ non-Asian subjects in Study 16349 Part B and Japanese subjects in Study 17792. The interpretation of these differences on safety was limited due to small sample sizes of Asian patients.

Based on current available data, no ethnic difference with clinical impact was observed. Meanwhile, it is not feasible to obtain a clinically and statistically meaningful Asian trial due to the small patient population of refractory/resistant iNHL.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of copanlisib as a single agent was demonstrated by an objective response rate (ORR) 58.65% (95% CI: [48.58%, 68.23%]) in a subgroup of patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies in an open label, single arm Phase II study. For indolent NHL, ORR is considered a potential surrogate endpoint which is reasonably likely to predict a clinical benefit. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure the benefits of the drug outweigh the risks.

In conclusion, the overall benefit/risk ratio is favorable to support accelerated approval of the claimed indications.

3. Post-Marketing Requirements

- Routine pharmacovigilance should be conducted.
- Submit the following CSRs while available：

1. Submit the complete final clinical report of Study 16349 Part B (CHRONOS-1).
2. Submit the complete final clinical report from a randomized, double-blind, placebo-controlled trial of Aliqopa in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-hodgkin’s lymphoma (CHRONOS-4).