Taiwan Food and Drug Administration

Assessment Report

Trade Name： PIQRAY 50, 150, 200 mg Film-Coated Tablets

Active Ingredient：Alpelisib

License Number：MOHW-PI 027994, 027995, 027996

Applicant：台灣諾華股份有限公司

Approval Date：2020/12/23

Indication：與 fulvestrant 併用可治療患有荷爾蒙受體(HR)陽性、第二型人類表皮生長因子受體(HER2)陰性及 PIK3CA 突變的局部晚期或轉移性乳癌，且曾接受內分泌治療但疾病惡化的停經後女性及男性病人。

PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

Background Information

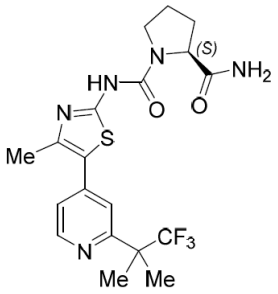
Trade Name	PIQRAY 50, 150, 200 mg Film-Coated Tablets
Active Ingredient(s)	Alpelisib
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	Film-Coated Tablets 50, 150, 200mg
Indication	與 fulvestrant 併用可治療患有荷爾蒙受體(HR)陽性、第二型人類表皮生長因子受體(HER2)陰性及 PIK3CA 突變的局部晚期或轉移性乳癌，且曾接受內分泌治療但疾病惡化的停經後女性及男性病人。 PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.
Posology	• Piqray 的建議劑量為連續每日一次隨餐口服 300 毫克。持續治療直到疾病惡化或無法耐受的毒性。 • -與 Piqray 併用時，fulvestrant 的建議劑量為在第 1 日、第 15 日、第 29 日注射 500 毫克，之後每個月注射一次。 • The recommended dose of PIQRAY is 300 mg taken orally, once daily, with food. Continue treatment until disease progression or unacceptable toxicity occurs. • When given with PIQRAY, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, and 29, and once monthly thereafter.
Pharmacological Category ATC Code	L01XX65

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

Drug Substance

The drug substance, alpelisib, is chemically designated as (2*S*)-*N*-{4-methyl-5-[2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl}pyrrolidine-1,2-dicarboxamide. The chemical structure of alpelisib is shown below:



It is a white to almost white powder. The molecular formula and the molecular weight are $C_{19}H_{22}F_3N_5O_2S$ and 441.47 g/mol, respectively. It is slightly hygroscopic.

Adequate information of characterization of the drug substance has been provided. The specification of the drug substance includes tests for appearance, particle size, identity, related substances, enantiomer, water content, residual solvents, sulfated ash, assay and microbial enumeration tests.

Drug Product

PIQRAY Film-Coated Tablets are supplied for oral administration with three strengths that contain 50 mg, 150 mg and 200 mg of alpelisib.

The excipients used in the drug product formulation comply with the compendial monographs.

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

Stability studies of PIQRAY Film-Coated Tablets under long term condition (25℃/60% RH and 30℃/75% RH) and accelerated condition (40℃/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Alpelisib (BYL719) is an α specific class I phosphatidylinositol 3-kinase (PI3Kα) inhibitor.

In vitro pharmacology studies demonstrated that alpelisib treatment could effectively inhibit the phosphorylation of PI3K downstream targets Akt in breast cancer cells. Moreover, alpelisib showed markedly selective efficacy in *PIK3CA* mutant cell lines when compared to wild-type cell lines and when compared to pan-PI3K inhibitors. *In vivo*, alpelisib treatment shows dose-and time-dependent inhibition of the PI3K/Akt pathway in relevant tumor xenograft models.

Xenograft models exposed to combinations of alpelisib with other small molecule inhibitors (such as letrozole, ribociclib, fulvestrant) or the HER2 inhibitor, trastuzumab, demonstrated greater tumor regression than those without alpelisib.

Alpelisib showed no effect on neuronal, ECG, or respiratory function. Alpelisib inhibited hERG with IC_{50} of 9.4 μM (4.3 μg/ml). In a single dose invasive telemetry study in dogs, an increase in systolic and diastolic blood pressure was seen at exposure levels below clinical levels, in the absence of any electrophysiological abnormality. In mouse, rat, and dog, alpelisib interfered with glucose/insulin homeostasis, evidenced as hyperglycemia and increased blood insulin serum due to the induction of insulin resistance/insensitivity.

2.2.2 Toxicological Studies

Repeated-dose toxicity studies were conducted in rats and dogs up to 13-weeks. The major target organs included gastrointestinal tract and mucosal tissues, hematopoietic and lymphopoietic organs, skin, hyperglycemia with increased blood insulin serum, and reproductive organs. The other alpelisib-related toxicities were atrophy in the mammary gland and lacrimal glands, odontoblast degeneration with dentin thinning and pulpa necrosis, thickening and decreased metaphyseal trabecular bone density, and ocular toxicity. Most toxicities were generally reversible after a 4- or 8- week recovery period. The toxicity profiles in animals were similar to those in patients treated with alpelisib. The most observed toxicities can be associated primarily with the expected pharmacologic activities of alpelisib.

Alpelisib is not genotoxic *in vitro* and *in vivo*. In the rat embryo-fetal development study, maternal toxicities, decreased mean fetal weights, and increased numbers of litters with fetal malformations and fetal variations started from 10 mg/kg/day, with exposure about 0.8-fold the human exposure at the recommended dose 300 mg/day. No viable fetuses due to increased pre-implantation and post-implantation losses were observed at 30 mg/kg/day, equivalent to about the 3-fold the human exposure at 300 mg/day. In the non-GLP rabbit study, increased embryo-fetal deaths and major fetus malformation were observed at ≥15 mg/kg/day, at exposure levels about 5-fold above human therapeutic exposure. Based on animal data and its mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential and male patients with female partners

of reproductive potential should use effective contraception during treatment with alpelisib and for 1 week after the last dose (at least 5 half-lives for alpelisib, $T_{1/2}$= 8-9h).

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Alpelisib was quickly absorbed following oral administration with a median T_{max} of 2-4 hours. Alpelisib showed dose-proportional increase in both C_{max} and AUC across the dose range of 30~450 mg following a single dose and multiple doses. The mean accumulation ratios following 90~450 mg were between 1.3- and 1.5-fold. Compared to the fasted state, a high-fat, high-calorie meal increased AUC_{inf} by 73% and C_{max} by 84%, and a low-fat low-calorie meal increased AUC_{inf} by 77% and C_{max} by 145% following a single dose of alpelisib. In the presence of a LFLC meal, AUC was decreased by 21% and C_{max} by 36% with ranitidine.

The apparent V_d at steady-state is predicted to be 114 L. *In vitro*, protein binding of alpelisib is 89% and is independent of concentration. The population derived terminal half-life is 8 to 9 hours. *In vitro*, alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4. In the systemic circulation, the relative abundance of BZG791 was between 20%~30% of alpelisib. Following a single oral dose of 400 mg radiolabeled alpelisib, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine.

2.3.2 Interaction Studies

Based on *in vitro* studies, alpelisib is a strong time-dependent inhibitor of CYP3A4 and also identified to be a strong inducer of CYP3A4. *In vitro*, alpelisib induces activity of CYP2B6 and CYP2C9. At clinically relevant concentration ranges, alpelisib inhibits P-gp. No clinically significant differences in the PK of everolimus (a substrate of CYP3A4 and P-gp) were observed when coadministered with alpelisib. BZG791 will not cause any metabolic or transporter-mediated DDIs with concomitant medications based on its systemic exposure and low free fraction.

2.3.3 Special Populations

The population PK analysis showed that there are no clinically relevant effects of age, body weight, or gender on the systemic exposure of alpelisib. The results of the hepatic impairment study showed that there is no clinically meaningful impact of moderate or severe hepatic impairment on the PK of alpelisib. Based on the results of population PK analysis, mild (CLcr 60 to <90 mL/min) and moderate (CLcr 30 to <60 mL/min) renal impairment had no effect on the exposure of alpelisib. The effect of severe renal impairment (CLcr < 30 mL/min) on the PK of alpelisib is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

This applicant provided one Phase III study (Study C2301) for this submission. It was an ongoing, multinational, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of treatment with alpelisib plus fulvestrant versus placebo plus fulvestrant in men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer which progressed on or after aromatase inhibitor (AI) treatment.

A tumor sample (either archived tissue or new biopsy) was collected to establish the *PIK3CA* mutation status prior to randomization and subjects were classified according to *PIK3CA* mutation status (*PIK3CA* mutant and *PIK3CA* non-mutant cohort). Within each cohort, subjects were randomized in a 1:1 ratio to the:

- Alpelisib arm: alpelisib 300 mg orally every day (QD) + fulvestrant 500 mg administered intramuscularly on Day 1 and Day 15 of Cycle 1 and on Day 1 ± 3 days on a 28-day cycle thereafter, or
- Placebo arm: placebo orally QD + fulvestrant 500 mg administered intramuscularly on Day 1 and Day 15 of Cycle 1 and on Day 1 ± 3 days on a 28-day cycle thereafter

Randomization was stratified by lung and/or liver metastases (yes versus no) and previous treatment with any CDK 4/6 inhibitor (yes versus no). Subjects received study treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

In Study C2301, progression free survival (PFS) by investigator assessment in the *PIK3CA* mutant cohort was the primary endpoint, and overall survival (OS) in the *PIK3CA* mutant cohort was the key secondary endpoint.

A total of 341 subjects were enrolled and randomized in the *PIK3CA* mutant cohort: 169 subjects in the alpelisib arm and 172 subjects in the placebo arm. The baseline demographic and disease characteristics were generally comparable between the two arms. Except one male subject in the alpelisib arm, the remaining subjects were female. The majority of subjects were White and 21.7% subjects were Asian. The majority of subjects had Stage IV disease at study entry, and 56.6% subjects had visceral involvement. All subjects had HR-positive and HER2-negative disease. The majority of subjects had prior surgery and 72.1% subjects had prior radiotherapy. All subjects had received prior hormone therapy, and the most commonly used agents were AIs. Primary endocrine resistance was observed in 13.2% of subjects and secondary endocrine resistance in 72.4% of subjects. Nine (5.3%)

subjects in the alpelisib arm and 11 (6.4%) subjects in the placebo arm had received prior treatment with CDK 4/6 inhibitor.

Study C2301 met its primary objective. Median PFS in *PIK3CA* mutant cohort was prolonged by 5.3 months (from 5.7 to 11.0; stratified log-rank test p = 0.00065, one-sided) for the alpelisib arm versus the placebo arm (HR = 0.65; 95% CI 0.50, 0.85).

Given that the PFS primary endpoint was met, the remained alpha was allocated to test OS. The first interim analysis for OS was not statistically significant. The second interim analysis for OS data was submitted with data cut-off of 30-Sep-2019. Percentage of events are 40.8% in alpelisib arm and 48.8% in placebo arm; median OS was reached for alpelisib (40.6 months) and placebo (31.2 months) arms. The pre-specified interim O'Brien-Fleming stopping boundary (one-sided $p \leq 0.0117$) was not crossed (HR = 0.77; 95% CI: 0.56, 1.06; p = 0.06).

Only one male subject was enrolled and treated with alpelisib plus fulvestrant in Study C2301. Breast cancer is rare in men and the treatment guidelines generally extrapolate the results from female subjects to male subjects. Besides, male subjects with solid tumors had been enrolled in the Phase I study and the pharmacokinetic analysis demonstrated no clinical meaningful difference between male and female subjects. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner and its effect is not altered with the level of estrogen. Based on the above considerations, an extrapolation of the efficacy results mainly from female subjects to male subjects is considered justified.

Only 5.9% subjects enrolled in the mutant cohort of Study C2301 had received prior CDK 4/6 inhibitors. The efficacy analysis for PFS in this small subgroup still demonstrated a positive result, favoring alpelisib. Alpelisib targets on different molecules other than CDK 4/6. Besides, activation of the PI3K/AKT/mTOR pathway is known to be a crucial factor in resistance to endocrine therapy, and correlation of this pathway with resistance to CDK 4/6 inhibitors has also been reported. Based on the above consideration and clinical practice, it is justified to accept the proposed indication.

In conclusion, the results of PFS demonstrated the benefit of the combination of alpelisib plus fulvestrant in postmenopausal women, and men, with HR-positive, HER2-negative, advanced breast cancer with a *PIK3CA* mutation after disease progression following an endocrine-based regimen.

2.4.2 Safety Results

The safety review is based on the combined data from the *PIK3CA* mutant cohort and the

PIK3CA non-mutant cohort in Study C2301, including 283 subjects who were exposed to alpelisib plus fulvestrant, and 286 subjects exposed to placebo plus fulvestrant.

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The duration of exposure to alpelisib was comparable to the duration of exposure to the placebo. However, dose interruptions and/or dose reductions were more frequent in the alpelisib arm compared to the placebo arm and the majority of these dose interruptions and reductions were due to adverse events (AEs).

Overall, the proportion of subjects with treatment-related AEs, Grade 3-4 AEs, serious AEs (SAEs), AEs leading to treatment discontinuation, AEs leading to dose adjustment/ interruption was higher in the alpelisib arm compared to the placebo arm.

The most common (≥ 20%) AEs reported in the alpelisib arm, with a difference ≥ 10% relative to the placebo arm, included hyperglycemia, diarrhea, nausea, decreased appetite, rash, vomiting, weight decreased, and stomatitis.

The most common (≥ 5%) Grade 3-4 AEs reported in the alpelisib arm, with a difference ≥ 5% relative to the placebo arm, included hyperglycemia, rash, rash maculo-papular, and diarrhea.

The most commonly (≥ 2%) reported SAEs in the alpelisib arm were hyperglycemia, diarrhea, and abdominal pain. The majority of SAEs were resolved or resolving.

A total of 78 subjects in the alpelisib arm died in Study C2301, and the majority (74 subjects) were due to progression of underlying disease. One death due to thrombotic microangiopathy was suspected to be related to study treatment by the investigator. The thrombotic microangiopathy event was reported with onset date within the on-treatment period, and the patient died more than 30 days after last dose of study drug.

The most commonly (≥ 2%) reported AEs leading to treatment discontinuation in the alpelisib arm included hyperglycemia, rash, diarrhea, and fatigue. The most commonly (≥ 10%) reported AEs leading to dose adjustment/interruption in the alpelisib arm included hyperglycemia, diarrhea, rash, and rash maculo-papular.

AEs of special interest (AESIs) included gastrointestinal (GI) toxicity (nausea, vomiting, and diarrhea), hyperglycemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis, pneumonitis and severe cutaneous reactions. Generally, these events were able to be managed with concomitant medication and alpelisib dosing modifications, including discontinuation,

interruption or dose reduction.

Two cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome were reported from a compassionate use program and another clinical study, respectively. A causal role of alpelisib in DRESS syndrome is considered suspected or cannot be ruled out.

Osteonecrosis of the jaw (ONJ) were more frequently reported in the alpelisib arm compared to the placebo arm. An increased risk of development of ONJ cannot be excluded.

Laboratory abnormalities in the alpelisib arm with a difference ≥ 10% relative to the placebo arm included decreased hemoglobin, decreased lymphocyte, increased blood glucose, increased creatinine, increased lipase, and decreased potassium. Except increased blood glucose, most of the laboratory abnormalities were Grade 1-2. No subject met the Hy's Law criteria.

2.5 Bridging Study Evaluation

The pharmacokinetic (PK) impact of ethnicity was assessed by population means in the Phase I pool and Phase III data. The Phase I dataset included 25 subjects (10%) of Japanese patients with advanced solid malignancies. The model estimated that Japanese subjects had a lower C_{min} by 35% and higher C_{max} by 19% at steady state compared to non-Japanese subjects following a daily dose of 300 mg. Compare the differences observed in exposure parameters with inter-patient variability, the differences was not considered clinically relevant.

The impact of ethnicity was also evaluated in the Phase III population PK model [n=271 subjects, 54 (19.9%) East Asian and 192 (70.8%) Caucasian] and was found not significant. Overall, the race is not an ethnic sensitive factor on alpelisib PK.

The clinical impact of ethnicity was assessed in the Phase III Study C2301. A total of 65 subjects were enrolled at Asian centers in the *PIK3CA* mutant cohort, including 6 subjects enrolled in Taiwan.

Generally, no clinically significant ethnic difference for efficacy and safety of alpelisib was identified. There were 4 cases of severe cutaneous reactions (erythema multiforme in 3 subjects and Stevens-Johnson syndrome in 1 subject) reported in Study C2301. All 4 subjects were Japanese. However, severe cutaneous reactions were also reported in Caucasian subjects from other studies, and no severe cutaneous reactions were reported in the other Japanese study. The possible ethnic difference in the severe cutaneous reactions should be followed in future Periodic Safety Update Reports.

2.6 Conclusion

Based on the above multidiscipline review, review team recommends approval of alpelisib.

1. The recommended indication for approval is: “PIQRAY is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)¬positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, locally advanced or metastatic breast cancer following progression on or after an endocrine-based regimen”.
2. The recommended dose of PIQRAY is 300 mg taken orally, once daily, with food. Continue treatment until disease progression or unacceptable toxicity occurs. When given with PIQRAY, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29, and once monthly thereafter.
3. Under the storage temperature lower than 30℃, the shelf-life is 2 years.

3. Post-Marketing Requirements

1. Submit the final clinical study report of Study C2301 after completion of the study.
2. Submit the final complete study reports of drug-drug interaction (US FDA postmarketing commitments No. 3573-2 and 3573-3).
3. Provide the education material to inform the risk of severe cutaneous reactions with drug to patients and medical providers since the possibility of higher risk in Asian patients has not been excluded. Evaluate the incidence and characteristics of severe cutaneous reaction in post-marketing surveillance and provide the results in the Periodic Safety Update Reports (PSURs).