Taiwan Food and Drug Administration

Assessment Report

Trade Name：盼樂膜衣錠 3 毫克 / 4 毫克 / 5 毫克
Balversa film-coated tablets 3mg / 4mg / 5mg

Active Ingredient：Erdafitinib

License Number：MOHW-PI 027912 / MOHW-PI 027913 / MOHW-PI 027914

Applicant：嬌生股份有限公司

Approval Date：2020/07/10

Indication：

治療局部晚期或轉移性泌尿道上皮癌的成人病人，並且：
・帶有具感受性 FGFR3 或 FGFR2 基因變異，以及
・先前曾於使用至少一種含鉑化學療法治療期間或治療後[包括接受前導性(neoadjuvant)或輔助性(adjuvant)含鉑化學療法治療的 12 個月內]出現惡化現象。

本適應症係依據腫瘤整體反應率加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

Balversa is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma , that has:
- susceptible FGFR3 or FGFR2 genetic alterations, and
- progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Background Information

Trade Name	盼樂膜衣錠 3 毫克 / 4 毫克 / 5 毫克 Balversa film-coated tablets 3mg / 4mg / 5mg
Active Ingredient(s)	Erdafitinib
Applicant	嬌生股份有限公司
Dosage Form & Strengths	膜衣錠 3 毫克/ 4 毫克 / 5 毫克
Indication	治療局部晚期或轉移性泌尿道上皮癌的成人病人，並且： •帶有具感受性 FGFR3 或 FGFR2 基因變異，以及 •先前曾於使用至少一種含鉑化學療法治療期間或治療後[包括接受前導性(neoadjuvant)或輔助性(adjuvant)含鉑化學療法治療的 12 個月內]出現惡化現象。 本適應症係依據腫瘤整體反應率加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 Balversa is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma , that has: • susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Posology	建議起始劑量為每日一次口服 8 毫克(2 顆 4 毫克錠劑)，並可依據第 14 至 21 天的血清磷酸鹽(PO4)濃度與耐受性將劑量提高至每日一次 9 毫克(3 顆 3 毫克錠劑)。 The recommended starting dose of Balversa

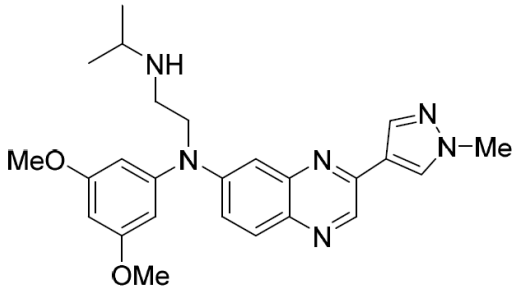
	is 8 mg (two 4 mg tablets) orally once daily, with a dose increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate (PO4) levels and tolerability at 14 to 21 days.
Pharmacological Category **ATC Code**	L01EX16

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, erdafitinib, is chemically designated as *N*-(3,5-dimethoxyphenyl)-*N*'-(1-methylethyl)-*N*-[3-(1-methyl-1*H*-pyrazol-4-yl) quinoxalin-6-yl]ethane-1,2-diamine. It has the following structure:



Erdafitinib is a yellow powder. The molecular formula is $C_{25}H_{30}N_6O_2$ and the molecular weight is 446.56 g/mol.

Adequate information of characterization of the drug substance has been provided. The spectral data are consistent with the structural assignment using high resolution mass spectrometry (MS), CHN analysis, infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy.

The specification of the drug substance includes tests for appearance, identification, chromatographic purity, residual solvents, and assay.

2.1.2 Drug product

The drug product is presented as a film-coated tablet containing 3 mg, 4 mg, or 5 mg of erdafitinib. All excipients used in the drug product formulation are well known ingredients. A robust process is confirmed by adequate process validation.

Adequate specification has been presented for the drug product and the test items include appearance, identification, assay, chromatographic purity, uniformity of dosage units, dissolution, and microbiological purity. Analytical methods are described well and validated.

Stability studies of the drug product under long-term (25°C/60% RH and 30°C/75% RH) and accelerated (40°C/75% RH) condition have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Erdafitinib is a drug for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma which has susceptible FGFR3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. The *in vitro* pharmacology studies showed that erdafitinib inhibited FGFR1, FGFR2, FGFR3, and FGFR4 kinase. Erdafitinib inhibited FGFR pathway signaling and FGFR-dependent proliferation of cancer cell lines with FGFR alterations.

The *in vivo* pharmacology studies showed that erdafitinib inhibited the growth of tumor expressing FGFR with genetic alterations (*i.e.*, mutation, fusion, or amplification). The IC_{50} of hERG assay was 182.19 ng/mL and was lower than the C_{max} in humans receiving therapeutic dose. The pro-arrhythmic risk of erdafitinib was evaluated in the medical section.

2.2.2 Toxicological Studies

The major toxicity of erdafitinib in repeated-dose toxicity studies in rats and dogs included atrophy in multiple organs/tissues and optic changes (ocular discharge, corneal opacification, and blepharospasm). Like other pan-FGFR tyrosine kinase inhibitors, hyperphosphatemia was also noted after erdafitinib administration. Hyperphosphatemia is attributed to the inhibition of phosphate excretion and leads to the soft tissue mineralization and cartilage dysplasia.

Erdafitinib showed teratogenic potential in rats, and the NOAEL in the fetus was lower than the dam. The teratogenic potential has been mentioned in the label of erdafitinib. Males and females with reproductive potential should use effective contraception during treatment and for 1 month after the last dose (approximate 5 half-lives); this is acceptable. The genotoxicity study presented negative results. Erdafitinib caused skin sensitization and eye irritation but not caused vascular irritation in the nonclinical studies. The safety of impurities was evaluated and could support the safety of the final product of erdafitinib.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following administration of 8 mg erdafitinib once daily, median time to achieve peak plasma concentration (T_{max}) was 2.5 hours, the mean (coefficient of variation [CV%]) erdafitinib $C_{max,ss}$, $AUC_{tau,ss}$, and $C_{min,ss}$ were 1,399 ng/mL (51%), 29,268 ng•h/mL (60%), and 936 ng/mL (65%), respectively.

Following single and repeat once daily dosing, erdafitinib exposure increased proportionally across the dose range of 0.5 to 12 mg. Steady state was achieved after 2 weeks with once daily dosing and the mean accumulation ratio was 4-fold.

No clinically meaningful differences with erdafitinib pharmacokinetics (14% lower in C_{max} and 6.4% lower in AUC_{inf} compared with the fasted state) were observed following administration of a high-fat and high-calorie meal in healthy subjects.

The mean apparent volume of distribution of erdafitinib was 29 L in patients. *In vitro*, protein binding of erdafitinib is > 99%, primarily to alpha-1-acid glycoprotein. The mean total apparent clearance (CL/F) of erdafitinib was 0.362 L/h and mean effective half-life of erdafitinib was 59 hours in patients.

Erdafitinib is primarily metabolized by CYP2C9 and CYP3A4. The contribution of CYP2C9 and CYP3A4 in the total clearance of erdafitinib is estimated to be 39% and 20% respectively. Unchanged erdafitinib was the major drug-related moiety in plasma, there were no circulating metabolites.

Following a single oral dose of radiolabeled erdafitinib, approximately 68.7% of the dose was recovered in feces (19% as unchanged) and 18.7% in urine (13% as unchanged).

2.3.2 Interaction Studies

In vitro study demonstrated that erdafitinib is a substrate of CYP2C9, CYP3A4 and P-gp.
Co-administration of erdafitinib with moderate inhibitors of CYP2C9 or strong inhibitors of CYP3A4 increased erdafitinib plasma concentrations; therefore consider alternative therapies that are not moderate inhibitors of CYP2C9 or strong inhibitors of CYP3A4 during treatment with erdafitinib. Avoid co-administration of strong inducers of CYP2C9 or CYP3A4 with erdafitinib Due to co-administration of erdafitinib with moderate inducers of CYP2C9 or CYP3A4 may decrease erdafitinib plasma concentrations, the dose modification is required based on serum phosphate levels and tolerability. Avoid concomitant use with agents that can alter serum phosphate levels before the initial dose modification period and sensitive CYP3A4 substrates with narrow therapeutic indices.

Consider alternative agents or consider reducing the dose of OCT2 substrates based on tolerability because co-administration of erdafitinib with OCT2 substrates may increase the plasma concentrations of OCT2 substrates.

Separate erdafitinib administration by at least 6 hours before or after administration of P-gp

substrates with narrow therapeutic indices.

2.3.3 Special Populations

No clinically meaningful trends in the PK of erdafitinib were observed based on age (21 to 88 years), sex, body weight (36-132 kg), mild or moderate renal impairment or mild hepatic impairment.

The pharmacokinetics of erdafitinib in patients with severe renal impairment, renal impairment requiring dialysis, moderate or severe hepatic impairment is unknown.

Monitor for increased adverse reactions in patients who are known or suspected to have CYP2C9*3/*3 genotype because patients with CYP2C9*3/*3 genotype may have a higher erdafitinib plasma concentrations due to reduced metabolic clearance.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study BLC2001 was reviewed to evaluate the efficacy of erdafitinib in subjects with locally advanced or metastatic urothelial carcinoma and whose tumors had certain FGFR genetic alterations. Study BLC2001 was a Phase 2, multicenter, and open-label study. At the start of the study, subjects were randomly assigned to receive 10 mg intermittent (regimen 1) or erdafitinib 6-mg daily (regimen 2). After an interim analysis of data from regimen 1 and regimen 2 and further PK/PD modeling, regimen 3 (8 mg once daily with pharmacodynamically guided uptitration to 9 mg once daily) was selected for further development. Furthermore, the proposed indication is limited to chemotherapy relapsed/refractory subjects.

The primary hypothesis was that erdafitinib at 8-mg daily had an ORR > 25%. Response assessment was first performed by investigators. If the lower bound of the 95% CI for response rate was more than 25%, then assessment of response by independent radiologic review committee (IRRC) was performed and the IRRC assessment of response was to be used as primary endpoint. The confirmed ORR for chemotherapy relapsed/refractory subjects was 40.2% (95% CI: 29.9%, 50.5%) as assessed by the investigator and 32.2% (95% CI: 22.4%, 42%) as assessed by IRRC. Investigator assessed ORR met the primary objective with the lower bound of the 95% CI above 25%. IRRC assessed ORR did not meet the primary objective while the lower bound of the 95% CI was less than 25%.

2.4.2 Safety Results

Major TEAEs include stomatitis, dry mouth/skin, diarrhea, constipation, nausea, vomiting, hyperphophataemia, decreased appetite, asthenia, fatigue, pyrexia, alopecia, infections, dysgeusia, blurred vision, nail toxicities, palmar-plantar erythrodysaesthesia, QTc

prolongation, renal impairment and anemia.

2.5 Bridging Study Evaluation

At the single dose-normalized to 8 mg, the difference of total and free erdafitinib exposure (C_{max} or AUC_{0-24h}) was less than 20% between Japanese cancer patients and non-Asian patients. After multiple dosing (dose-normalized to 8 mg QD), the total erdafitinib exposure in Japanese patients was 1.3-fold higher than non-Asian patients and the free erdafitinib exposure in Japanese patients was 2-fold higher than non-Asian patients.

In population PK analysis (10% Asian population involved), the total AUC_{0-24h} and free AUC_{0-24h} of erdafitinib in Asian population is 1.02-fold and 1.22-fold higher than that in Non-Asian population.

Since the inter-subject variation of erdafitinib was about 30%, erdafitinib is considered none to minimal ethnically sensitive between Asian and non-Asian from PK aspect.

There were limited Asian subjects (only five in 8 mg QD regimen) in efficacy analysis. Fifty-nine East Asian subjects were included in safety dataset pooling data from other cancer trials. Some TEAEs rates were higher in East Asians: hyperphosphatemia (93.2% v.s. 75.5%)、increased AST (39.0% v.s. 8.5%) and increased ALT (32.2% v.s. 16.0%). Due to unmet medical need, bridging study was waived under the condition of submission of East Asian subgroup analysis of confirmatory trial BLC3001.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy was demonstrated by ORR 32% in patents with locally advanced or metastatic urothelical carcinoma in a multicenter, open-label, single-arm study.
For locally advanced or metastatic urothelical carcinoma, 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 that 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 Requirement

Submit the following CSRs while available：
Results of confirmatory trial BLC3001 which is an MRCT comparing the efficacy (OS) and

safety between erdafitinib and standard of care (chemotherapy or pembrolizumab) should be submitted.