Taiwan Food and Drug Administration

Assessment Report

Trade Name：EYBELIS ophthalmic solution 0.002%

Active Ingredient：Omidenepag isopropyl

License Number：MOHW-PI 027906

Applicant：Taiwan Santen Pharmaceutical Co., Ltd.

Approval Date：2020/07/17

Indication：EYBELIS is indicated for the treatment of open-angle glaucoma and ocular hypertension.

1.Background Information

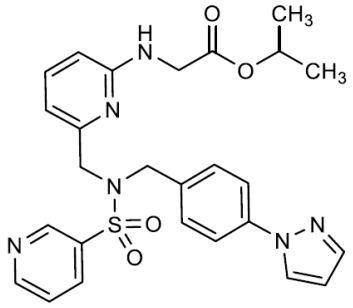
Trade Name	EYBELIS ophthalmic solution 0.002%
Active Ingredient(s)	Omidenepag isopropyl
Applicant	Taiwan Santen Pharmaceutical Co., Ltd
Dosage Form & Strengths	ophthalmic solution 0.002%
Indication	EYBELIS is indicated for the treatment of open-angle glaucoma and ocular hypertension.
Posology	The recommended dose is one drop in the affected eye(s) once daily. If a dose is missed, please take your next dose at its regularly scheduled time. The dose should not exceed one drop per day on each affected eye.
Pharmacological Category ATC Code	S01EX06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, omidenepag isopropyl, is chemically designated as propan-2-yl 2-[[6-[[(4-pyrazol-1-ylphenyl)methyl-pyridin-3-ylsulfonylamino]methyl]pyridin-2-yl]amino] acetate. It has the following structure:



Omidenepag isopropyl is white to light brown crystal or crystalline powder. The molecular formula is $C_{26}H_{28}N_6O_4S$ and the molecular weight is 520.61 g/mol.

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

Adequate specification has been presented for the drug substance.

2.1.2 Drug product

The drug product is a sterile aqueous ophthalmic solution containing 0.002% omidenepag isopropyl and is packaged in a PE bottle. 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. Analytical methods are described well and validated.

Stability studies of the drug product under long-term (2-8℃) and accelerated (25℃/40% RH) condition have been carried out to support the shelf life.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Omidenepag, the active metabolite of omidenepag isopropyl (DE-117), selectively binds to the EP2 receptor with high agonistic activity. *In vitro* pharmacology studies have demonstrated that omidenepag selectively binds to the EP2 receptor with high agonistic activity. *In vivo* pharmacology studies showed that DE-117 ophthalmic solution exerts an IOP-lowering effect in laser-induced ocular hypertensive monkeys.

DE-117 did not inhibit hERG channel at a concentration of 10 μM (4785 ng/mL), which is about 170,000 times the predicted maximum plasma concentration (C_{max}) of 28.3 pg/mL following ocular instillation of 0.002% DE-117 ophthalmic solution in humans. Safety pharmacology was evaluated in general toxicity studies. In the 13-week repeated dose toxicity study in monkeys, no ECG changes were observed at dose 12 μg/kg/day. DE-117 showed no significant adverse effects on the central nervous system and respiratory system function in rats and dogs receiving single doses up to 1.0 mg/kg (subcutaneous) and 2.6 mg/kg (inhalation), respectively.

2.2.2 Toxicological Studies

Repeated-dose toxicity studies were conducted in the rat (subcutaneous) and monkey (ocular) up to 26-week and 39-week, respectively. In the monkey study, no toxic findings attributable to ocular instillation of omidenepag isopropyl were observed. Significant corneal thickness was noted in the left eye of female animals in the 0.01% DE-117 group. However, the finding was also noted in the untreated right eye. There was no change in the density of corneal endothelial cells, and no structural change in the cornea was identified by histopathological examination. Therefore, the finding was not considered to be a toxicologically significant change. The NOAEL of the 39-week monkey study was considered to be 0.01%.

In the rat study, enlargement of the liver, kidney, or thyroid gland and histopathological changes, including increased hepatocyte nuclear chromatin density and accumulation of eosinophilic substances in the proximal tubular epithelium, were observed at dose ≥ 0.04 mg/kg. Besides, loose stools were observed in the 1.0 mg/kg group. Therefore, the NOAEL was considered to be 0.03 mg/kg/day in the 26-week rat study.

DE-117 was negative for genotoxicity in the bacterial reverse mutation test and rat micronucleus test. In the mouse lymphoma TK test, the positive and equivocal results were considered to be due to increased T-MF resulting from an increase in small-colony mutant frequency. The maximum concentrations at which there was no significant increase in T-MF were 20 to 55 times higher than the proposed concentration of 0.002%. Besides, since it was presumed that neither omidenepag isopropyl nor omidenepag accumulates in the eyes, the results from this mouse lymphoma TK test were not considered to cause concerns about genotoxicity in the eyes during treatment with DE-117 ophthalmic solution.

No significant effect on fertility and early embryonic development was observed in rats. In the study on embryo-fetal development in rats, no changes considered to be due to omidenepag isopropyl were observed. However, in rabbits, hyperemia of the iris was observed in the dams. Besides, the number of dead embryos and fetuses and post-implantation loss were higher, and the number of live fetuses and fetal viability index were lower in this group than in the control group. Based on these findings, the NOAEL was considered to be 0.08 mg/kg/day. Omidenepag isopropyl had no significant effect on pre- and postnatal development in rats.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Omidenepag isopropyl is an ester prodrug and is rapidly hydrolyzed to its active form, omidenepag, after ocular instillation. Due to the extremely low exposure, plasma concentration of omidenepag isopropyl was not determined in most PK studies. Following repeated ocular instillation of 0.0025% DE-117 ophthalmic solution (one drop instilled in both eyes once daily for 7 days) in healthy subjects, omidenepag was rapidly absorbed into the systemic circulation with mean C_{max} peaked at about 10~15 minutes. Plasma omidenepag concentrations were below 1 pg/mL after 4 hours post-instillation. Mean terminal half-life of omidenepag was approximately 30 minutes. The plasma PK of omidenepag did not change after repeated ocular instillation of DE-117 ophthalmic solution. The plasma protein binding ratio of omidenepag in human plasma was 97.8%, not depending on omidenepag concentration. In humans, omidenepag isopropyl is metabolized to omidenepag by CES1, and omidenepag is metabolized by CYP3A4. By 48 hours after single ocular instillation,

3.11%, 19.8%, and 50.4% of the administered radioactivity dose were excreted in the urine, feces, and bile, respectively in bile duct-cannulated male SD rats.

2.3.2 Interaction Studies

Based on the results from *in vitro* studies, significant inhibition or induction on tested CYP450 isozymes are unlikely at clinically relevant concentration of omidenepag. Omidenepag may be a substrate for OAT3, OATP1B1, OATP1B3, and P-gp. No formal *in vivo* drug interactions were performed for omidenepag isopropyl and omidenepag.

2.3.3 Special Populations

No dedicated PK studies were conducted to evaluate the impact of intrinsic factors on omidenepag PK. Given the systemic exposures of omidenepag were extremely low, the impacts of hepatic impairment, renal impairment and other intrinsic factors are considered to be minor.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two studies, Study 01171503 and study 01171505, were used to evaluate the efficacy of omidenepag isopropyl for treating open-angle glaucoma (OAG)or ocular hypertension (OHT). These two studies enrolled adult patients who had POAG or OHT whose IOP was≧ 22mmHg and≦34mmHg after washout period. Subjects must not have eye surgery within 90 days.

Study 01171503 was a randomized, double-blinded, phase II/III study to assess the efficacy and safety of omidenepag isopropyl in Japanese adult patients with OAG or OHT. In stage 1 (dose-selection stage) of this study,63 subjects were enrolled and randomized to receive 0.002% omidenepag isopropyl, 0.0025% omidenepag isopropyl, or placebo treatment for 4 weeks. The change in mean diurnal IOP from baseline at week 4 was -2.30mmHg, -5.16mmHg, and -4.93mmHg in placebo group, 0.002% omidenepag isopropyl group, and 0.0025% omidenepag isopropyl. There was no obvious dose-response relationship. To select 0.002% omidenepag isopropyl as the target dose is reasonable.

In stage 2 of study 01171503, 190 subjectswere randomly assigned to 0.002% omidenepag isopropyl or latanoprost treatment for 4 weeks. The study demonstrated that omidenepag isopropyl ophthalmic solution 0.002% was non-inferior to 0.005% latanoprost ophthalmic solution in that the upper limit of the 95% confidence interval of the difference (omidenepag isopropyl - latanoprost) in mean diurnal IOP change from baseline to Week 4 not over the 1.5 mmHg non-inferiority margin {LS mean change (SE): -5.93 (0.23) vs -6.56 (0.22); LS mean difference (95% CI): 0.63 (0.01, 1.26); descriptive statistics [mean (SD)]: 17.81(2.41)

vs 16.96 (2.24)}

Study 01171505 was a randomized, observer-masked, active-controlled study. Eligible subjects (n370), Asian adult patients with open angle glaucoma or ocular hypertension, were randomly assigned to 0.002% omidenepag isopropyl or latanoprost treatment for 3 months. The study demonstrated that omidenepag isopropyl ophthalmic solution 0.002% was non-inferior to 0.005% latanoprost ophthalmic solution in that the upper limit of the 95% confidence interval of the difference (omidenepag isopropyl - latanoprost) in mean diurnal intraocular pressure (IOP) at Month 3 not over the 1.5 mmHg non-inferiority margin [LS mean (SE): 17.45 (0.25) vs 16.81 (0.25); LS mean difference (95% CI): 0.64 (0.04, 1.24); descriptive statistics (mean (SD)):17.36 (3.24) vs 16.66 (3.03)]

2.4.2 Safety Results

The safety data of omidenepag isopropyl were mainly came from two efficacy studies (study 01171503 and study 01171505) alone with one long term 52-week open-label study 01171504 and one phase III open-label switching from latanoprost study 01171506. In clinical studies, total 412 subjects received omidenepag isopropyl. Ocular AEs occurred more frequently among omidenepag isopropyl treated patients than latanoprost treated patient, Ocular AEs occurred more often in patients with combination treatment of omidenepag isopropyl and timolol compared to those with omidenepag isopropyl alone in study 01171504.
The most common AEs in the omidenepag isopropyl treatment arm were conjunctival hyperemia, corneal thickening, and photophobia. Most AEs were mild in severity. Few cases of iritis and uveitis were noted in the omidenepag isopropyl treatment arm and some of these cases (2 of 6) discontinued study treatment.

In all clinical trials, there were 16 cases of macular edema. Most cases of macular edema occurred in long term 52-week study 01171504. Macular edema occurred in several months (ranged from 2 months to 12 months) after start of study treatment. All subjects except one who developed macular edema were pseudophakic patients. Considering relative high risk for developing macular edema in pseudophakic patients, omidenepag isopropyl treatment is contraindicated for pseudophakic patients.Omidenepag isopropyl treatment is contraindicated for subjects with implanted intraocular lens.

2.5 Bridging Study Evaluation

A phase I study (Study 01171502) was conducted in Japanese and Caucasian healthy subjects to assess the impact of ethnic factor on omidenepag PK. Following repeated ocular instillation of 0.0025% DE-117 ophthalmic solution (one drop instilled in both eyes once daily for 7 days), the plasma omidenepag exposures (C_{max} and AUC_{inf}) were approximately

12%~22% higher in Japanese compared to Caucasian on Day 7. The difference in systemic exposures between the Japanese and Caucasian subjects was not considered clinically relevant. Furthermore, the absorption, distribution, metabolism, and excretion properties of omidenepag ophthalmic solution made it less likely to be sensitive to ethnic factors. Overall, race is not a sensitive factor on omidenepag PK.

The efficacy and safety of Omidenepag isopropyl for treating open-angle glaucoma (OAG) or ocular hypertension (OHT) mainly came from Study 01171503, Study 01171504, Study 01171506, and Study 01171505. All these studies were conducted in East Asian, including 101 Taiwanese. The data was sufficient to evaluate the use of omidenepag isopropyl in Asian. Further bridging study is not needed.

In summary, the bridging study of omidenepag isopropyl could be waived.

2.6 Conclusion

The risk/benefit profile was favorable for omidenepag isopropyl. This NDA is suggested to be approved.

The approved indication is “treatment of open-angle glaucoma and ocular hypertension”.

3. Post-Marketing Requirements

There is no post-marketing requirement other than routine pharmacovigilance.