Summary Report of Benefit-Risk Assessment

EYBELIS OPHTHALMIC SOLUTION 0.002%

NEW DRUG APPLICATION

Active Ingredient(s)	Omidenepag Isopropyl
Product Registrant	Santen Pharmaceutical Asia Pte. Ltd.
Product Registration Number	SIN16150P
Application Route	Abridged Evaluation
Date of Approval	07 Apr 2021

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A INTRODUCTION

Eybelis ophthalmic solution is indicated as once-daily treatment for reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

The active substance, omidenepag isopropyl, is a synthetic non-prostanoid agonist of the prostaglandin E2 (PGE2) receptor (subtype 2, EP2). Activation of the EP2 receptor relaxes the ciliary muscle and increasing outflow of aqueous humor through the uveoscleral pathway thereby reducing the intraocular pressure.

Eybelis Ophthalmic Solution 0.002% is available as ophthalmic solution containing 20 µg/mL of omidenepag isopropyl. Other ingredients in the solution are benzalkonium chloride, sodium citrate hydrate, citric acid hydrate, polyoxyl 35 castor oil, disodium edetate hydrate, concentrated glycerine, sodium hydroxide, diluted hydrochloric acid and purified water.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, omidenepag isopropyl, is manufactured at [redacted]. The drug product, Eybelis Ophthalmic Solution 0.002%, is manufactured at Santen Pharmaceutical Co. Ltd., Shiga, Japan.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data were adequate to support the approved storage condition and re-test period. The drug substance is packaged in low-density polyethylene bag in a secondary laminated foil, placed in an appropriate container such as a fibre drum. The polyethylene bag and foil are each goose-necked with a cable tie. The drug substance is approved for storage at room temperature with a re-test period of 36 months.

Drug product:
The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

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The specifications were established in accordance with ICH Q6A and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Adequate information on the reference standards used for identity, assay and impurities testing had been presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored at 2-8ºC, protected from light. The in-use period after opening is one month when store below 30ºC. This was also supported with appropriate data. The container closure system is a low-density polyethylene bottle with a linear low-density polyethylene dropper tip and a polypropylene cap.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of omidenepag isopropyl in the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension was based on data from two pivotal phase III studies (01171503-Stage 2 and 01171505), one phase II dose-ranging study (01171503 – Stage 1) and one supportive phase III long-term study (01171504).

The dose-ranging study (01171503-Stage 1) was a multicentre, randomised, double-blinded, placebo-controlled, parallel group study conducted in subjects with either OAG with elevated IOP or ocular hypertension in both eyes (N=63). Subjects were randomised 1:1:1 to receive 0.002% omidenepag isopropyl one drop once daily (N=22), 0.0025% omidenepag isopropyl one drop once daily (N=22), or placebo ophthalmic solution one drop once daily (N=19), for 4 weeks. The primary endpoint was the change from baseline in mean diurnal IOP at Day 29. The mean diurnal IOP was based on the average of the IOP assessed at 3 time points (9:00 AM, 1:00 PM, and 5:00 PM) to account for diurnal variation in the IOP.

The results showed statistically significant reductions in the baseline mean diurnal IOP compared to placebo (baseline reduction: -2.18 mmHg) for the 0.002% once daily dose (baseline reduction: -5.11 mmHg, p-value: 0.0025) as well as the 0.0025% one-drop once daily dose (baseline reduction: -4.83 mmHg, p-value:0.0031). No formal comparison was made between the two doses of omidenepag isopropyl. It was observed that the magnitude of reduction in the mean diurnal IOP was numerically higher for the 0.002% dose compared to the 0.0025% dose. Similarly, higher responder rates were also observed for 0.002% dose group compared to 0.0025% dose group (47.8%, 31.1 % and 27.3% versus 29.7%, 22.0% and 18.2% for subjects achieving ≥ 20%, ≥ 25% and ≥ 30% reduction in baseline diurnal IOP. The study supported the use of 0.002% dose for the pivotal studies.

The pivotal phase III Studies 01171503-Stage 2 and 01171505 were multicentre, randomised, observer-blind, parallel-group studies conducted in adult subjects with OAG with elevated IOP or ocular hypertension in both eyes. The subjects were randomised in a 1:1 ratio to receive omidenepag isopropyl 0.002% one drop daily or latanoprost 0.05% one drop daily to the eyes. The study duration of 4 weeks in Study 01171503-Stage 2 and 3 months in Study 01171505 was considered acceptable as reduction in IOP generally maximises at around 3-5 weeks.

The primary endpoint was the change from baseline mean diurnal IOP at Day 29 in Study 01171503-Stage 2 and mean diurnal IOP at day 91 in Study 01171505. Omidenepag isopropyl was considered non-inferior to latanoprost 0.05 % if the upper limit of the confidence interval

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of the difference between the test and control was at or below the non-inferiority margin of 1.5 mmHg.

Study 01171505 also included two additional key secondary endpoints. IOP at the specified time points of 09:00, 13:00, and 17:00 hr at Day 8, Day 43 days, and Day 91 days was the first key secondary endpoint and non-inferiority was considered demonstrated if the upper limit of the 95% CIs for the difference between omidenepag isopropyl and latanoprost was ≤ 1.5 mmHg at all time points (9 out of 9 time points) and ≤ 1.0 mmHg at the majority of the time points (5 out of 9 time points). Mean diurnal IOP at Day 8 days was set as the second key secondary endpoint, and superiority of omidenepag isopropyl over latanoprost was considered demonstrated if the upper limit of the 95% CIs for the difference in the mean diurnal IOP at Week 1 was < 0 mmHg. The non-inferiority margin of 1.5 mmHg was considered acceptable.

Other secondary endpoints included the proportion of responders with ≥ 20%, ≥ 25% and ≥ 30% reduction from baseline diurnal IOP in both studies, as well as the mean diurnal IOP < 18 mmHg in Study 01171505.

In the Study 01171503-Stage 2, a total of 189 subjects were included in the efficacy analysis. The subjects were randomised in a 1:1 ratio to receive either omidenepag isopropyl (N=94) or latanoprost (N=95). The patient demographics and baseline characteristics were well balanced between the treatment arms. The mean age was 63.6 years and mean diurnal IOP was 23.59 mmHg. 41.8% of the subjects had primary open angle glaucoma and 58.2% had ocular hypertension. 31.2% did not have any prior use of IOP-lowering medications.

The primary analysis demonstrated that omidenepag isopropyl 0.002% was non-inferior to latanoprost 0.05% after 4 weeks of treatment, as the upper limit of 95%CI was below the 1.5 mmHg non-inferiority margin (Difference: 0.63 mmHg, 95% CI 0.01; 1.26). The proportion of subjects with ≥ 20%, ≥ 25% or ≥ 30% reduction from baseline in diurnal IOP at Week 4 was numerically greater with latanoprost 0.05% compared to omidenepag isopropyl 0.002% (IOP ≥ 20%: 81.1% vs 76.6%, p-value = 0.48; IOP ≥ 25%: 66.3% vs 56.4%, p-value = 0.18; IOP ≥ 30%: 40.0% vs 26.6%, p-value = 0.06).

In Study 01171505, a total of 369 subjects were included in the efficacy analysis. The subjects were randomised in a 1:1 ratio to receive either omidenepag isopropyl (N=184) or latanoprost (N=185). The patient demographics and baseline characteristics were well balanced between the treatment arms. The mean age was 53.6 years and 75.9% of the subjects were under the age of 65. Mean diurnal IOP was 24.54 mmHg. 66.9% of the subjects had open angle glaucoma and 33.1% had ocular hypertension. 46.9% did not have any prior use of IOP-lowering medications.

The primary analysis demonstrated omidenepag isopropyl 0.002% was non-inferior to latanoprost 0.05% after 3 months of treatment as the upper limit of 95%CI was below the 1.5 mmHg non-inferiority margin (Difference: 0.64 mmHg, 95% CI 0.04; 1.24). Non-inferiority and superiority were not demonstrated for the first and second key secondary endpoints, respectively. Nevertheless, the difference between the two treatments were marginal and was not considered clinically significant as the differences were less than 1.5 mmHg for 9 out of 10 time-points assessed. For the responder rates, the proportions of subjects with reduction from baseline in diurnal IOP ≥ 20%, ≥ 25% or ≥ 30% and IOP <18mmHg at Month 3 were numerically greater with latanoprost 0.05% compared to omidenepag isopropyl 0.002% (IOP ≥ 20%: 86.4% vs 78.2%; IOP ≥ 25%: 72.7% vs 61.8%; IOP ≥ 30%: 61.4% vs 45.3%; IOP<18 mmHg: 66.5% vs 58.2%).

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The clinical efficacy of omidenepag isopropyl 0.002% for the long-term maintenance therapy was assessed in Study 01171504. Study 01171504 was a 52-week, open-label, uncontrolled study in which a cohort of 37 subjects with OAG and baseline diurnal IOP ≥ 22 mmHg to ≤ 34 mmHg were treated with omidenepag isopropyl 0.002% one drop once-daily alone. The reduction in baseline IOP was -5.82 mmHg (95%CI: -6.78; -4.86), -5.17 mm Hg (95% CI -6.29; -4.06) and -5.64 mmHg (95%CI: -6.63; -4.65) at Week 4, Week 12 and Week 52, respectively, demonstrating maintenance of treatment effect up to 52 weeks. The magnitude of the reduction in IOP in this study was similar to that observed in the short-term pivotal studies 01171503-Stage 2 (Difference from baseline at Week 4: -5.93 mmHg) and 01171505 (Difference from baseline at Month 3: -7.28 mmHg).

Overall, the studies demonstrated efficacy in reduction in IOP with omidenepag isopropyl 0.002% one drop once-daily in patients with either OAG with elevated IOP or ocular hypertension, although when compared with latanoprost the magnitude of IOP reduction numerically favoured latanoprost 0.05%.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of omidenepag isopropyl 0.002% was based on safety data derived from the two pivotal Phase III studies (Study 01171503-stage 2 and Study 01171505) and the supportive dose-ranging (Study 01171503-stage 1), as well as the long-term study (Study 01171504). The safety analysis set comprised a total of 686 patients who received at least one dose of study treatment: 386 subjects in the omidenepag isopropyl 0.002% arm, 281 subjects in the latanoprost 0.05% arm and 19 subjects in the placebo arm.

Overview of safety profile

	***Study* 01171503 – Stage 1 and 2**			**Study 01171505**		**Study 01171504**
AE	**ODP 0.002% (N=116)**	**LTP 0.05% (N=96)**	**Placebo (N=19)**	**ODP 0.002% (N=185)**	**LTP 0.05% (N=185)**	**ODP 0.002% (N=85)**
Any AE, n (%)	55 (47.4)	26 (27.1)	2 (10.5)	74 (40.0)	55 (29.7)	65 (76.5)
Ocular AE	51 (44.0)	21 (21.9)	1 (5.3)	68 (36.8)	39 (21.1)	42 (49.4)
SAE	0	0	0	2 (1.1)	2 (1.1)	4 (4.7)
Ocular SAE	0	0	0	0	0	0
Discontinuations due to AE	2 (1.7)	2 (2.1)	0	4 (2.2)	2 (1.1)	9 (10.6)
Discontinuations due to ocular AE	2 (2.1)	1 (1.0)	0	4 (2.2)	1 (0.5)	9 (10.6)
Deaths due to AE	0	0	0	0	0	0

ODP = Omidenepag isopropyl; LTP = Latanoprost

The incidences of any AEs and ocular AEs were higher with omidenepag isopropyl 0.002% arm compared to latanoprost 0.05 % and placebo. Conjunctival hyperaemia, dry eye, eye pain, photophobia and corneal thickening were the most frequently reported ocular AEs in the Omidenepag isopropyl 0.002% arm. Most of the events were mild in severity.

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The long-term AE profiles of omidenepag isopropyl 0.002% monotherapy up to week 52 was generally consistent with AE profiles observed in the short-term studies. Other ocular AEs of concern observed with long-term treatment were macula oedema, iritis and anterior chamber cell. For macula oedema, the events were mild to moderate in intensity and occurred in subjects with pseudophakic/phakic eyes. The incidence of macular oedema was similar to the incidences (1.6% - 27%) observed with other Prostaglandin F receptor (FP receptor) agonists. For the ocular inflammation – iritis, all the events were mild and were resolved.

Appearance-altering local adverse reactions, such as iris and eyelid pigmentation, eyelash growth, and deepening of upper eyelid sulcus known to be associated with FP receptor agonists were not observed during the long-term treatment omidenepag isopropyl in Study 01171504.

	Study 01171503 – Stage 1 and 2			**Study 01171505**		**Study 01171504**
Adverse Event Severity	**ODP 0.002% (N=116)**	**LTP 0.05 % (N=96)**	**Placebo (N=19)**	**ODP 0.002% (N=185)**	**LTP 0.05 % (N=185)**	**ODP 0.002% (N=85)**
Conjunctival hyperaemia	28 (24.1)	10 (10.4)	0	22(11.9)	10 (5.4)	16 (18.8)
Mild	27 (23.3)	9 (9.4)	0	14 (7.6)	8 (4.3)	16 (18.8)
Moderate	1 (0.9)	1 (1.0)	0	8 (4.3)	2 (1.1)	0
Corneal thickening	13 (11.2)	1 (1.0)	0	7 (3.8)	2 (1.1)	2 (2.4)
Mild	13 (11.2)	1 (1.0)	0	6 (3.2)	2 (1.1)	2 (2.4)
Moderate	0	0	0	1 (0.5)	0	0
Eye Pain	5 (4.3)	1 (1.0)	0	5 (2.7)	6 (3.2)	2 (2.4)
Mild	5 (4.3)	1 (1.0)	0	4 (2.2)	5 (2.7)	2 (2.4)
Moderate	0	0	0	1 (0.5)	1 (0.5)	0
Photophobia	4 (3.4)	0	0	10 (5.4)	1 (0.5)	2 (2.4)
Mild	4 (3.4)	0	0	10 (5.4)	1 (0.5)	2 (2.4)
Dry eye	0	0	0	9 (4.9)	4 (2.2)	0
Mild	0	0	0	8 (4.3)	4 (2.2)	0
Moderate	0	0	0	1 (0.5)	0	0
Macular oedema (incl. cystoid macular oedema)	0	0	0	0	0	10 (11.7)
Mild	0	0	0	0	0	5 (5.9)
Moderate	0	0	0	0	0	5 (5.9)
Iritis	0	0	0	0	0	2 (2.4)

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Mild	0	0	0	0	0	2 (2.4)
Anterior chamber cell	0	0	0	0	0	2 (2.4)
Mild	0	0	0	0	0	2 (2.4)

ODP = Omidenepag isopropyl; LTP = Latanoprost

Overall, omidenepag isopropyl 0.002% was well tolerated. While the incidences of ocular AEs were higher with omidenepag isopropyl 0.002%, most of the events were mild in severity and were resolved or resolving without additional treatment either during the study period or after study completion.

Corneal thickening was a frequent AE observed with omidenepag isopropyl but the change in corneal thickness was not clinically significant in view that the change was not associated with cornea edema or visual acuity change. Furthermore, no clinically significant changes in central corneal endothelial cell count or corneal curvature were observed with long-term treatment.

Macular oedema is known to occur in patients with aphakic eyes or implanted intraocular lenses treated with latanoprost, and similar occurrence was observed with omidenepag isopropyl. While the events were mild to moderate in severity, the use is contraindicated in patients with aphakic eyes or implanted intraocular lenses as most of the cases were accompanied by reduction in visual acuity or visual impairment.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The studies demonstrated non-inferiority of omidenepag isopropyl 0.002% to latanoprost 0.05% for reduction of IOP from baseline and the benefit was sustained over long-term in the maintenance study. The magnitude of the improvement in IOP of -5.93 mmHg at week 4- and -7.28-mmHg at Month 3 with omidenepag isopropyl was clinically meaningful even though it was numerically less compared to latanoprost. Furthermore, ocular AEs like abnormal eyelash growth, pigmentation of iris and eye lid, and deepening of upper eyelid associated with FP agonists were not observed with omidenepag isopropyl 0.002% treatment in the studies. This may present a potential advantage to patients whose compliance may be impacted by these appearance-altering side effects with FP agonists.

Conjunctival hyperaemia, dry eye, eye pain, photophobia and corneal thickening were the most frequently reported ocular AE with omidenepag isopropyl 0.002% compared to latanoprost. Nevertheless, these events were mostly mild in severity, self-limiting or were recovering without additional treatment and rarely resulted in treatment discontinuation. Macular oedema accompanied with visual loss had been observed with long-term treatment but this risk was mitigated as subset of patients who may be at risk could be identified and the use was contraindicated in the predisposed subjects.

Overall, the benefit-risk profile of omidenepag isopropyl 0.002% in reduction of intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension was considered favourable.

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F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of omidenepag isopropyl 0.002% in reduction of intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension was considered favourable. Approval was granted on 07 Apr 2021.

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