**EYBELIS-S ophthalmic solution 0.002%w/v**
(Omidenepag isopropyl 0.002%w/v)

## Description
EYBELIS-S ophthalmic solution 0.002%w/v is a clear, colourless and sterile liquid. Each mL of aqueous ophthalmic solution contains 20 micrograms of omidenepag isopropyl. The product has pH 5.5 – 6.1 and osmolar ratio 0.9 - 1.1.

List of excipients: Sodium citrate hydrate, citric acid hydrate, polyoxyl 35 castor oil, disodium edetate hydrate, concentrated glycerin, sodium hydroxide, dilute hydrochloric acid, purified water

## ATC code
S01EX06

## Pharmacodynamic properties
Mechanism of action

The mechanism of intraocular pressure (IOP) lowering effect of omidenepag isopropyl ophthalmic solution is considered to increase aqueous outflow via both trabecular and uveoscleral outflow pathways by stimulating EP2 receptor.

1) Omidenepag (active metabolite) selectively bound to EP2 receptor (Ki=3.6 nM), and showed potent agonistic activity to EP2 receptor ($EC_{50}$=8.3 nM).

2) Aqueous humor dynamics in monkeys with laser-induced ocular hypertension was determined by using a fluorophotometry method when 0.002% omidenepag isopropyl ophthalmic solution was instilled into the monkey eyes once daily for 7 days: No change was observed in aqueous humor production while significant increases were observed in outflow facility (assumed to be via the trabecular outflow pathway) and in uveoscleral outflow.

Clinical efficacy and safety

In the Phase II/III clinical study conducted in 189 patients with primary open angle glaucoma or ocular hypertension in Japan, EYBELIS (once daily administration) was compared to 0.005% latanoprost ophthalmic solution (once daily administration). IOP lowering effect was observed from week 1 at first scheduled visit. Change from baseline diurneal IOP levels (Mean±SD) of this product was -5.96±2.45 mmHg at Week 4, and the reduction in IOP was non-inferior to the comparator.

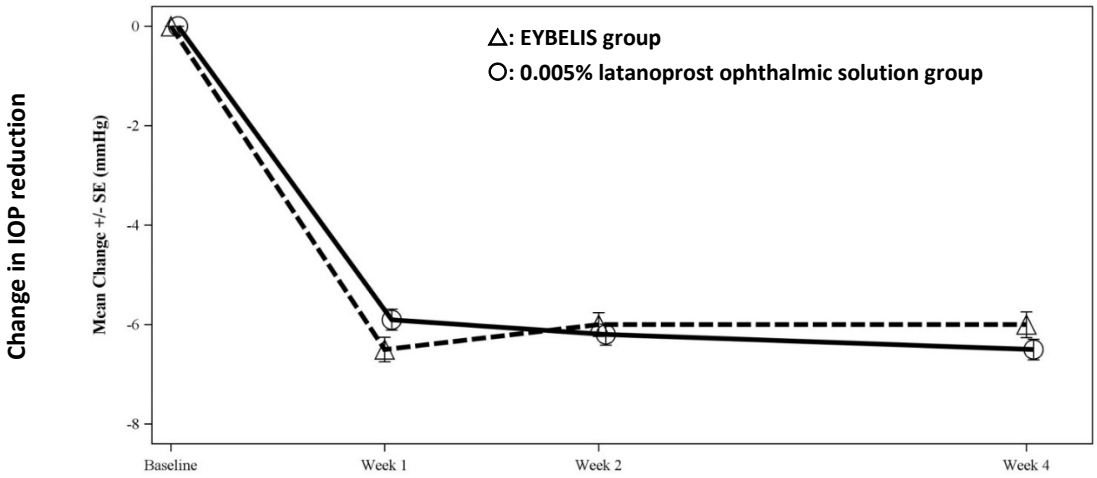


Figure: Change in IOP reduction in Phase II/III study

Table: Comparison of IOP (mmHg) in Phase II/III study

| | EYBELIS (N=94) | Comparator (N=95) |
|---|---|---|
| Mean diurnal baseline IOP | 23.78±1.73 | 23.40±1.51 |
| Mean diurnal IOP at Week 4 | 17.81±2.41 | 16.96±2.24 |
| Variation in the mean diurnal IOP at Week 4 from the baseline IOP | -5.96±2.45 | -6.45±2.01 |
| Difference in the mean diurnal IOP at Week 4 between the administration groups (value of this product minus that of the comparator) | 0.63 | |
| 95% confidence interval between the groups | 0.01-1.26 | |

(Mean±SD)

Clinical efficacy and safety in Asia countries/regions (Singapore, India, Taiwan, and Korea)

In the Phase III clinical study conducted in 369 patients with open-angle glaucoma or ocular hypertension in Singapore, India, Taiwan, and Korea, EYBELIS (once daily administration) was compared to 0.005% latanoprost ophthalmic solution (once daily administration). Baseline mean diurnal IOP was 24.57 and 24.50 mmHg in EYBELIS and control group, respectively. The results demonstrated that change in arithmetic mean diurnal IOP levels (Mean±SD) from baseline at Month 3 was -7.28±3.13 mmHg. The least squares mean diurnal IOP reduction at Month 3 for EYBELIS calculated from the MMRM* analysis was non-inferior to comparator.

*: mixed-effects model for repeated measures

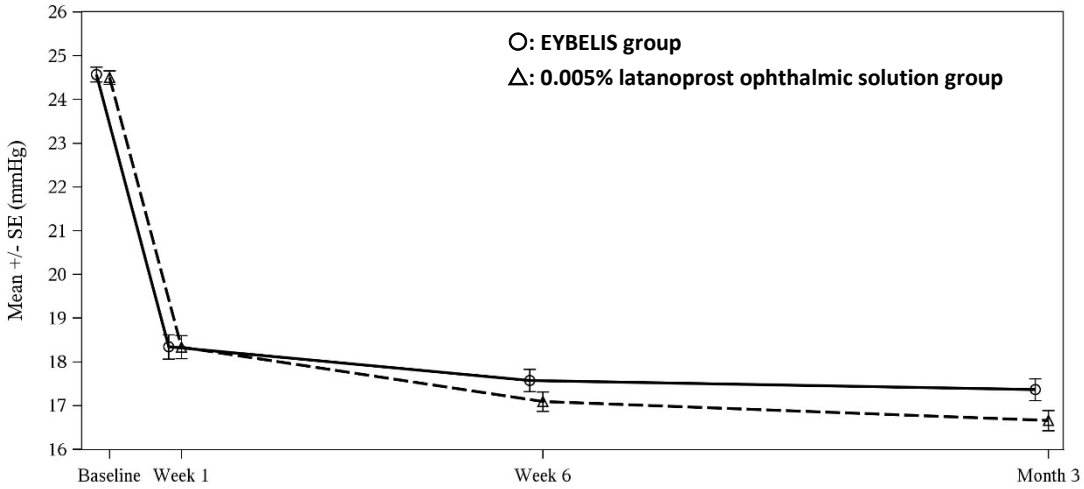


Figure: Mean Diurnal IOP (Arithmetic Mean of Score)

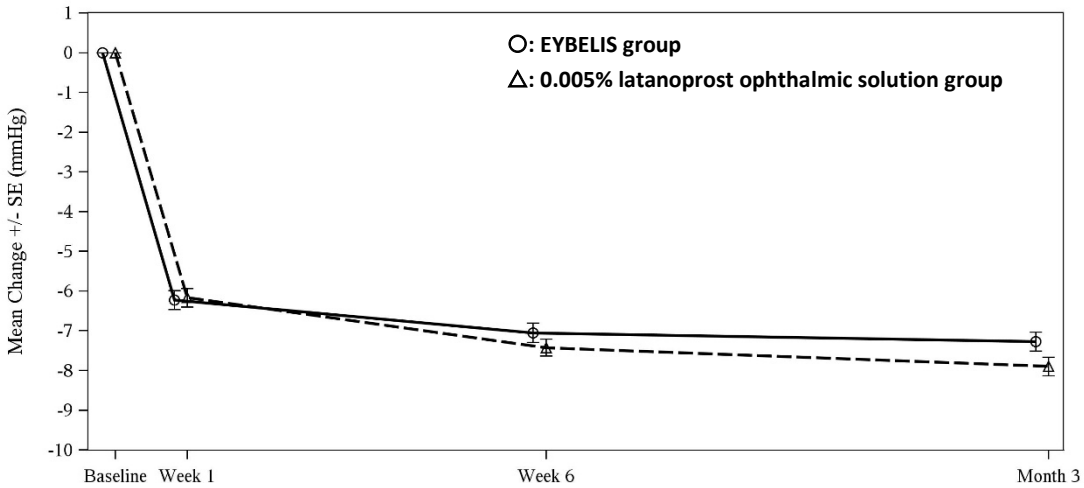


Figure: Change in IOP reduction (Arithmetic Mean of Score)

Table: Mean Diurnal IOP: Analysis on Score using MMRM

| Effect/Visit | Score (mmHg) | EYBELIS | Comparator |
|---|---|---|---|
| Month 3 | LS Mean (SE) | 17.45 (0.25) | 16.81 (0.25) |
| | Difference (SE) [1] | 0.64 (0.31) | |
| | 95% CI of Difference | 0.04, 1.24 | |
| | P-Value | 0.0366 | |

The model includes treatment, visit, diagnosis, country and treatment-by-visit interaction as fixed effects, baseline IOP as a covariate, and subject as a random effect.

**Pharmacokinetic properties**

1. Plasma concentrations

Plasma concentrations of omidenepag (active metabolite) were determined when 0.0025% omidenepag isopropyl ophthalmic solution was instilled into both eyes of 14 healthy adult volunteers (7 Japanese and 7 Caucasian subjects) one drop a time, once daily for 7 days. The concentrations reached the peak of about 34 pg/mL at 10 minutes after the instillation (Day 1), and that of about 35 pg/mL at 15 minutes after instillation (Day 7), respectively. The half-life was about 30 minutes (Days 1 and 7). (Note: The concentration of EYBELIS is 0.002%)

2. Ocular tissue distribution in animals

(Monkeys)

Concentrations in the ocular tissues reached the maximum between 15 minutes to 4 hours after a single ocular instillation of 0.03% $^{14}$C-omidenepag isopropyl ophthalmic solution into monkey eyes. High concentrations were observed especially in the cornea, conjunctiva and trabecular meshwork. In these tissues, the concentrations reached the peak level at 15 minutes after instillation, and $^{14}$C-omidenepag isopropyl was eliminated thereafter.

**Preclinical safety data**

Single dose toxicity:

Single dose ocular irritation was evaluated with 0.1% omidenepag isopropyl ophthalmic solution in cynomolgus monkeys. There were no mortalities and no test article-related changes in clinical signs. Slight conjunctival hyperemia was observed just after the instillation and recovered until 6 hours after the instillation.

Single dose toxicity was evaluated with 0.4, 1.3, 4 mg/kg omidenepag isopropyl in Sprague Dawley rats by SC route. Rats received once SC doses of omidenepag isopropyl solution. There were no mortalities in any group. Loose stool was transiently observed from 1 to 5 hours after the dosing in all groups.

Repeated dose toxicity:

The ocular and systemic toxicity of omidenepag isopropyl ophthalmic solution (0.003%–0.03%) administered by ocular route once or twice daily (equivalent to 0.0009–0.036 mg/body/day) were investigated in male and female cynomolgus monkeys for 13 weeks. There were no mortalities or any test article-related changes in body weight, food consumption, ophthalmology (except for corneal thickness and miosis), electrocardiogram (ECG), blood pressure, urinalysis, hematology, serum biochemistry, necropsy, organ weight, or histopathology in any group. Clinical signs of anisocoria were seen in all animals after twice daily (BID) administration of 0.03% omidenepag isopropyl. It is postulated that this effect was the result of miosis in the treated eye due to the pharmacological action of omidenepag isopropyl. The miosis is considered not to be toxicologically significant because it was reversible after a 4-week recovery period and function of light reflex was normal. A mild increase in corneal thickness was observed at all doses of omidenepag isopropyl ophthalmic solution at week 4 and appeared to be dose-dependent. The degree of the increase in corneal thickness at omidenepag isopropyl doses of 0.003% QD, 0.01% QD, 0.03% QD, and two drops of 0.03% BID was 3.4%, 3.1%, 3.9%, 8.1% for males, and 4.4%, 5.7%, 5.1%, and 8.4% for females, respectively, compared with the pre-dosing baseline. The effect on corneal thickness was reversible after a 4-week recovery period and there was no

additional deterioration of corneal thickness from 4 weeks to 13 weeks. In addition, no corneal endothelial cell loss was observed in specular microscopy and no structural change of cornea was observed in histopathology. Therefore, the mild increase in corneal thickness is also considered not to be toxicologically significant. In this study, the no-systemic-toxicity dose level and the no-local-irritation dose level was more than 0.03% BID (0.036 mg/body/day).

The ocular and systemic toxicity of omidenepag isopropyl ophthalmic solution (0.003%, 0.01%) administered by ocular route once daily (equivalent to 0.0009, 0.003 mg/body/day) were investigated in male and female cynomolgus monkeys for 39 weeks. There were no mortalities or any test article-related changes in body weight, food consumption, ophthalmology, electrocardiogram (ECG), blood pressure, urinalysis, hematology, serum biochemistry, necropsy, organ weight, or histopathology in any group. Clinical signs of anisocoria were seen in all omidenepag isopropyl groups. They are considered not to be toxicologically significant same as the 13-week study. A mild increase in corneal thickness was observed in 0.01% omidenepag isopropyl group but the increase of corneal thickness was also observed in non-treated eyes. In addition, no corneal endothelial cell loss was observed in specular microscopy and no structural change of cornea was observed in histopathology. Therefore, the mild increase in corneal thickness is considered to be incidental and not to be toxicologically significant. In this study, the no-systemic-toxicity dose level and the no-local-irritation dose level was more than 0.01% QD (0.003 mg/body/day).

Carcinogenesis:
Carcinogenicity studies have not been conducted with omidenepag isopropyl.

Mutagenesis:
There was no genotoxicity associated with omidenepag isopropyl in clinical dose.

Reproductive and developmental toxicity:

Fertility:
Omidenepag isopropyl have not been found to have any effect on fertility and early embryonic development in rats at doses approximately 50,000 times the indicated dose in human.

Pregnancy:
Reproduction studies have been performed in rats and rabbits. In rats, omidenepag isopropyl have not been found to have any effect on embryo-fetal development at doses approximately 50,000 times the indicated dose in human. In rabbits, it has not been found to have any effect on embryo-fetal development at doses approximately 4,000 times the indicated dose in human, but a high number of embryo-fetal deaths, percentage post implantation loss, and a low number of live fetuses and percentage fetal viability were noted at doses approximately 40,000 times the indicated dose in humans.

## Therapeutic indications
Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension

## Posology and method of administration
Posology
The recommended dose is one drop in the affected eye(s) once daily in the evening.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

*Paediatric population*

The safety and efficacy of omidenepag isopropyl in children and adolescents have not yet been established. No data are available.

Method of administration
For ocular use.

Be careful not to touch the tip of the container to the eye directly in order to avoid the contamination of the drug.

If more than one topical ophthalmic product is being used, each one should be administered at least 5 minutes apart.

**Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in 'Description'.

Patients with aphakic eyes or intraocular lens (IOL) inserted eyes (see 'Undesirable effects').

Concomitant use with tafluprost (see 'Interactions').

**Special warning and precautions for use**
Mild, reversible ocular inflammation has been reported during clinical trials. EYBELIS should be used with caution in patients with active ocular inflammation, including iritis/uveitis (see 'Undesirable effects').

Macular edema including cystoid macular edema as well as iritis may occur. Patients should be instructed to immediately consult with medical professionals if they experience abnormalities such as worsening vision (see 'Undesirable effects').

There is no clinical experience in patients with angle-closure glaucoma. It is advisable to use with caution in patients with angle-closure glaucoma.

**Interactions**
Tafluprost
Moderate to severe photophobia and ocular inflammation such as iritis were frequently seen in a clinical trial with concomitant administration of tafluprost and omidenepag isopropyl at dose of 0.003% to 0.03%. Although concomitant use of EYBELIS with tafluprost has not been studied, concomitant use may increase the risk of ocular inflammation because tafluprost is known to be associated with ocular inflammation. Therefore, EYBELIS must not be used concomitantly with tafluprost (see 'Contraindications').

Glaucoma/ocular hypertension medications (such as timolol maleate) excluding tafluprost
Frequency of ocular inflammatory adverse reactions including conjunctival hyperemia was elevated in a clinical trial with concomitant administration of EYBELIS and timolol maleate. There is no experience of concomitant use with other drugs. Therefore, concomitant use of EYBELIS with other glaucoma/ocular hypertension medications should be done with caution.

**Pregnancy and lactation**

Pregnancy

There are no adequate data from the use of omidenpag isopropyl in pregnant women. A study in rabbits has shown reproductive toxicity (see 'Preclinical safety data'). Therefore, EYBELIS should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits are judged to outweigh the possible risks associated with the treatment.

Breast-Feeding

It is unknown whether omidenepag isopropyl or its metabolites are excreted in human milk. A study in rats has shown omidenepag isopropyl was not detected in their milk after a single subcutaneous administration. When EYBELIS is used in breast-feeding women, breast feeding should be weighed, taking into consideration benefits of the therapy and breast-feeding.

Fertility

It is unknown whether omidenepag isopropyl or its metabolites affect fertility in humans. In rats, no treatment-related changes were noted in the parameters on fertility and early embryonic development (see 'Preclinical safety data'). Risk benefit should be weighed when considering to use EYBELIS while trying to conceive.

**Effects on ability to drive and use machine**

Because temporary blurred vision or photophobia may develop after instilling this product, patients should be instructed not to drive or to operate machines until the symptom disappears.

**Undesirable effects**

a) Summary of the safety profile

In clinical studies conducted in Japan, 267 patients were treated with EYBELIS for up to 52 weeks. The most frequently reported adverse reaction was ocular hyperemia including conjunctival hyperemia (22.8%). It was mild in most cases and did not lead to discontinuation of treatment.

b) Tabulated list of adverse reaction

The following adverse reactions have been reported with EYBELIS during clinical trials in Japan:

| System organ class | Frequency | Adverse reaction |
|---|---|---|

| | | |
|---|---|---|
| Eye disorders | Very common (≥1/10) | Conjunctival hyperemia |
| | Common (≥1/100 to <1/10) | Corneal thickening, macular edema (including cystoid macular edema)*, iritis (anterior chamber cells, anterior chamber flare)*, eye pain, photophobia, ocular discomfort (such as irritation), corneal epithelial disorders |
| | Not known | Dry eye sensation |
| Nervous system disorders | Not known | Headache |

*see section c)

c) Description of selected adverse reactions

Macular edema (including cystoid macular edema):
There were 14 cases (5.2%) with macular edema including cystoid macular edema. Events were mild to moderate in severity and vision returned to baseline with local treatment of corticosteroids or Nonsteroidal anti-inflammatory drugs (NSAIDs) and discontinuation of EYBELIS. All of the events were found in patients with IOL inserted eye and the only currently identified risk factor for developing macular edema is pseudophakia (see 'Contraindications').

If symptoms such as worsening vision or visual impairment are found, vision should be checked and detailed ophthalmoscopy should be performed immediately. Additional testing such as optical coherence tomography (OCT) or fluorescence fundus angiography may be considered if available. If macular edema is present, appropriate measures such as discontinuation of this product should be taken (see 'Special warning and precautions for use').

Iritis:
There were 4 cases (1.5%) with iritis and 5 cases (1.9%) with anterior chamber cells. Inflammation was generally mild in severity and resolved with local treatment with corticosteroids or NSAIDs, or discontinuation of EYBELIS. No significant impact to IOP or vision was reported (see 'Special warning and precautions for use').

d) Summary of the safety profile in Asia countries/regions (Singapore, India, Taiwan, and Korea)
In clinical studies conducted in Asia countries/regions (Singapore, India, Taiwan, and Korea), 185 patients were treated with EYBELIS for up to 3 months. The most frequently reported adverse reaction was conjunctival hyperemia (9.7%). It was mild in most cases and did not lead to discontinuation of treatment

**Overdose**
Overdose is unlikely to occur after ocular administration.

If overdose occurs, treatment should be symptomatic.

**Special precautions for storage**
Protect from light. Store unopened pouches under refrigeration at 2°C to 8°C. After opening of pouch, store below 30°C and use within one month.

**Shelf life**
36 months

**Nature and contents of container**
Translucent polyethylene single dose containers. Each container has a fill volume of 0.3 mL. Box of 3 aluminum foil pouches. Each aluminum foil pouch has 10 single dose containers of 0.3 mL.

**Manufactured by**
Santen Pharmaceutical Co., Ltd.
Noto plant: 2-14, Shikinami, Hodatsushimizu-cho, Hakui-gun, Ishikawa, Japan

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