CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215092
Action Date	9/19/2021
OSE RCM #	2020-2456
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	September 15, 2021
Subject	Evaluation of Need for a REMS
Established Name	Omidenepag isopropyl ophthalmic solution, 0.002%
Trade Name	(b) (4)
Name of Applicant	Santen Inc.
Therapeutic Class	Prostaglandin E2 receptor agonist (EP2-receptor agonist)
Formulation	Ophthalmic solution (0.02 mg/mL of omidenepag isopropyl)
Dosing Regimen	One drop in the affected eye(s) once daily in the evening

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, (b) (4) (omidenepag isopropyl) is necessary to ensure the benefits outweigh its risks. P Santen, Inc. submitted a New Drug Application (NDA 215902) for omidenepag isopropyl with the proposed indication for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The Applicant did not submit a proposed REMS or risk management plan with this application. No serious risks related to the use of omidenepag isopropyl were identified during this review. The likely prescribers include ophthalmologists.

Based on the available data, the Division of Risk Management (DRM) and the Division of Ophthalmology (DO) agree that a REMS is not needed to ensure the benefits of omidenepag isopropyl outweigh its risks.

The recommended regulatory action at this time per the clinical review team is a complete response. This recommendation is based on the deficiencies noted at a recent inspection of the (b) (4) manufacturing facility for this application. Additionally, following an inspection performed at the (b) (4) Woodstock Sterile Solutions (FEI 1419377) manufacturing facility, an FDA field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME), (b) (4) (omidenepag isopropyl) is necessary to ensure the benefits outweigh its risks.[a] Santen, Inc. submitted a New Drug Application (NDA 215902) for omidenepag isopropyl with the proposed indication: for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. This application is under review in the Division of Ophthalmology (DO). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

(b) (4) (omidenepag isopropyl), a new molecular entity, is a prostaglandin E2 receptor agonist (EP2-receptor agonist) proposed for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1] Omidenepag isopropyl is proposed as an 0.002% ophthalmic solution (0.02 mg/mL of omidenepag isopropyl). The recommended dose is one drop in the affected eye(s) once daily in the evening and treatment is continued indefinitely.[b] Omidenepag isopropyl is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

The following is a summary of the regulatory history for NDA 215092 relevant to this review:

- 11/19/2020: NDA 215092 submission for omidenepag isopropyl for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.
- 05/10/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that to date, no safety concerns/risk management issues have been identified.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Ocular hypertension is defined as abnormally high intraocular pressure (IOP) (normal range 12-22 mmHg) with no evidence of glaucoma. Among patients who are found to have ocular hypertension, treatment to lower IOP may delay or prevent the onset of open-angle glaucoma. Primary open-angle glaucoma is a progressive, chronic optic neuropathy in adults in which elevated IOP contributes to damage and leads to atrophy of the optic nerve and loss of retinal ganglion cell axons. This manifests as visual field loss and ultimately irreversible blindness if left untreated.[c] Primary open-angle glaucoma is generally bilateral, but often asymmetric.[1] Individuals with open-angle glaucoma rarely experience symptoms. Thus, open-angle glaucoma is generally detected incidentally during comprehensive ophthalmic examination. High elevations of intraocular pressure (IOP), up to 40 mmHg in patients with open-angle glaucoma, generally cause no pain, redness, or visual symptoms. There is no loss of visual acuity as long as central vision is preserved. Central visual field loss is a late manifestation of open-angle glaucoma, usually preceded by ganglion cell loss and optic nerve damage. Some patients are unaware of field loss even when it has progressed to central "tunnel vision" of 10 to 20 degrees. Visual field loss cannot be recovered once it has occurred.

In addition to elevated intraocular pressure (IOP), the major risk factors for developing open-angle glaucoma include age greater than 50, race, and family history. The prevalence of OAG is higher in individuals of West African, Afro-Caribbean, or Latino/Hispanic origin than of other groups. After cataracts, glaucoma is the second leading cause of blindness in the world.[2] It is a leading cause of irreversible blindness and the leading cause of blindness among Black Americans.[3,4] Worldwide in 2015, there were an estimated 57.5 million people with open-angle glaucoma, and this number was projected to increase to 65.5 million by 2020.[d,5] It is estimated that there are 2.8 million people with open-angle glaucoma in the United States in 2010 and that the number increased to approximately 3.4 million in 2020.[6]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS[7]

Of the available IOP-lowering interventions, topical pharmaceutical agents are most often chosen as initial therapy. Topical medications work either by increasing aqueous outflow (prostaglandins, alpha adrenergic agonists, cholinergic agonists, rho kinase inhibitor) or by decreasing aqueous production (alpha adrenergic agonists, beta blockers, topical and systemic carbonic anhydrase inhibitors). Netarsudil, a rho kinase inhibitor, is the most recently FDA approved agent for topical use for open-angle glaucoma or ocular hypertension. It is believed to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork. Combining drops from different classes can cause a greater reduction in the IOP than monotherapy and several drugs are available as fixed combination products. Appendix A contains a table of FDA approved drug products used for lowering elevated IOP.

Among the current treatment options, prostaglandin agonists are standard-of-care as first line agents because of better efficacy, once-a-day dosing, and a tolerable safety profile. Ocular side effects of prostaglandins include hyperemia, eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter two are more easily noticed if only one eye is treated.

Topical beta blockers are contraindicated in some patients with pulmonary or cardiac disease. In these patients, side effects are similar to those associated with systemic beta-blocker therapy including worsening of heart failure, bradycardia, heart block, and increased airway resistance.

Alpha adrenergic agonists are similarly effective to beta blockers in lowering IOP in open-angle glaucoma, but they are associated with a number of ocular side effects including allergic conjunctivitis, hyperemia, and ocular pruritus.

Cholinergic agonists have fewer systemic adverse effects than beta blockers, but ocular side effects include fixed, small pupils, myopia, and increased visual disturbance related to coexistent cataracts.

Laser therapy (trabeculoplasty) is a non-pharmacologic treatment to increase aqueous outflow by improving drainage of aqueous humor. The procedure is performed as an outpatient in the ophthalmologist's office or hospital outpatient clinic. Trabeculoplasty is a first-line approach only for patients with severe visual field loss at baseline, and as a second-line approach for those patients with advanced open-angle glaucoma who have not responded to medications or laser therapy.

4 Benefit Assessment

Omidenepag was evaluated in three Phase 3 randomized, double-masked, active-controlled clinical trials 01171505 (n = 370) National Clinical Trial (NCT) 02981446, 011709IN (n = 426) National Clinical Trial (NCT) 03691649, and 011710IN (n = 409) National Clinical Trial (NCT) 03691662 in subjects with open-angle glaucoma or ocular hypertension with average baseline IOP of 24-26 mmHg. Patients were randomized in all three studies in a 1:1 ratio to receive either the active control or omidenepag daily. The active control in study 01171505 was latanoprost 0.005% daily, while the active control in studies 011709IN and 011710IN was timolol 0.5% twice daily. The treatment duration was 3 months in all 3 studies. In addition, Study 011709IN included a 9-month open-label safety extension period during

which all subjects received omidenepag.

For studies 011710IN and 011709IN, the primary efficacy endpoint was IOP in the study eye measured at three scheduled times of the day (08:00, 10:00, and 16:00hrs) on each of the three follow-up visits, Week 1, Week 6, and Month 3 (for a total of 9 measurement timepoints). For Study 01171505, the primary efficacy endpoint was the mean diurnal IOP (average of IOP at 3 time points: 09:00, 13:00, and 17:00hrs) at Month 3. This study also evaluated IOP at three scheduled timepoints (09:00, 13:00, and 17:00hrs) at Week 1, Week 6, and Month 3 (i.e., IOP at 9 measurement timepoints). This endpoint is consistent with primary endpoints considered for this indication where latanoprost is used as an active comparator. In the three studies, IOP reductions were observed for all treatment arms. [e]

In the omidenepag arm across all three studies, the reduction in IOP ranged from 5.3-7.3 mmHg. The corresponding reductions for the timolol and latanoprost arms were 5.4-7.0 mm Hg and 6.1-7.9mm Hg, demonstrating non-inferiority of omidenepag relative to the active comparators.[8]

5 Risk Assessment & Safe-Use Conditions

The safety database for omidenepag is compiled from 12 clinical trials (Phases 1 through 3), with a total of 1454 subjects having received omidenepag.[9] Across the clinical development program, the most common adverse reactions with incidence ≥ 1% are conjunctival hyperemia (9%), photophobia (5%), vision blurred (4%), dry eye (3%), instillation site pain (3%), eye pain (2%), ocular hyperemia (2%), corneal staining with instillation of fluorescein (aka vital dye staining of cornea present) (2%), headache (2%), eye irritation (1%), and visual impairment (1%).

The rates of adverse events known to be caused by prostaglandin analogs, such as iris pigmentation, blepharal pigmentation, growth of eyelashes, eyelash thickening, and DUES (deepening of upper eyelid sulcus) in studies 011709IN and 011710IN were lower in the omidenepag group compared to the timolol group.[f] In study 01171505, which compared omidenepag to latanoprost, cosmetic change adverse events were only reported in the latanoprost group.

Adverse events leading to study discontinuation accounted for 5.0% of the subjects treated with omidenepag, compared to 1.9% of the subjects treated with timolol and 1.1% treated with latanoprost. The corresponding numbers in the timolol arm were 3.8% for conjunctival hyperemia and 0.5% for photophobia.[8]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

No serious risks related to the use of omidenepag isopropyl that would warrant a REMS were identified during this review.

Deaths

Three subject deaths were reported across the clinical development program for omidenepag. One subject receiving omidenepag in study 011710IN, another during the open-label period in study 011709IN, and 1 subject receiving timolol in the double-masked period in 011709IN; all deaths were due to non-ocular adverse events that were not related to study drug.[9]

6 Expected Postmarket Use

Omidenepag isopropyl will be prescribed and administered primarily in the outpatient setting. The likely prescribers include ophthalmology specialists. These prescribers should be familiar with managing the adverse effects associated with ophthalmic agents, including the class of prostaglandin analogs, used to lower intraocular pressure in ocular hypertension and open-angle glaucoma.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance and labeling.[10]

8 Discussion of Need for a REMS

Glaucoma is a life-long progressive disease that may lead to irreversible optic nerve damage and, eventually, vision loss. It is not uncommon for a patient with glaucoma to require more than one class of IOP-lowering products to control elevated IOP. If drug therapy fails or is not tolerated, patients may require laser or surgical treatment.

The benefits of treatment with omidenepag were demonstrated by meeting the primary endpoints of the clinical trials. Based on these results, omidenepag was found to be efficacious with an acceptable safety profile for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Omidenepag is generally well tolerated with no serious risks associated with its use. If approved, omidenepag would provide an option for patients who have failed available therapies or experience adverse events with other therapies. At the time of this review, labeling is on-going.

This application will receive a complete response based on the deficiencies noted at a recent inspection of the (b) (4) manufacturing facility for this application.

Based on the available data, the Division of Risk Management (DRM) and the Division of Ophthalmology (DO) agree that a REMS is not needed to ensure the benefits of omidenepag isopropyl outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for omidenepag isopropyl to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was on-going and the recommended regulatory action is a complete response due to deficiencies found at manufacturing facilities. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

Appendix A

FDA approved drug products used for lowering elevated IOP

Pharmacologic Class	Trade Name	Established Name
Alpha-2 Agonists		
	Alphagan / Alphagan-P	Brimonidine tartrate
	Iopidine	Apraclonidine
Beta-adrenergic antagonists		
	Betoptic / Betoptic S	betaxolol hydrochloride
	Ocupress	carteolol hydrochloride
	Betagan	levobutanol hydrochloride
	Optipranolol	Metipranolol
	Betimol	timolol hemihydrate
	Timoptic / Istalol / Timoptic XE	Timolol maleate
Carbonic Anhydrase Inhibitors		
	Diamox	acetazolamide
	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
	Azopt	Brinzolamide
	Trusopt	dorzolamide hydrochloride
Cholinergic Agonist		
	Pilopine HS / Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
	Lumigan	bimatoprost
	Xalatan	latanoprost
	Travatan / Travatan Z / Izba	travoprost
	Zioptan	tafluprost
	Vyzulta	latanoprostene bunod
Sympathomimetics		
	Propine	dipivefrin hydrochloride
Combination Products		
	Cosopt / Cosopt PF	dorzolamide hydrochloride/timolol maleate

	Combigan	brimonidine tartrate/timolol maleate
	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Other		
	Rescula	unoprostone isopropyl

11 References

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10. Santen, Inc. (b) (4) (omidenepag isopropyl opthalmic solution, 0.002%). NDA 215902. Module 1.16 - Risk Management Plan. November 19, 2020.

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