CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	211911
PDUFA Goal Date	March 6, 2020
OSE RCM #	2019-1167
Reviewer Name	Mona Patel, PharmD, RAC
Team Leader	Laura Zendel, PharmD
Deputy Director	Jamie Wilkins, PharmD
Review Completion Date	March 3, 2020
Subject	Evaluation of Need for a REMS
Established Name	bimatoprost (b) (4) implant
Trade Name	Durysta
Name of Applicant	Allergan Incorporated
Therapeutic Class	prostaglandin analog
Formulation	intracameral implant
Dosing Regimen	10 mcg in NOVADUR drug delivery system (b) (4)

Table of Contents

Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Durysta (bimatoprost implant) for intracameral administration is necessary to ensure the benefits outweigh its risks. Allergan, Inc. submitted a New Drug Application (NDA 211911) for Durysta with the proposed indication to reduce intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT). The risks associated with the use of Durysta include conjunctival hyperemia, corneal endothelial cell loss, and corneal edema. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of Durysta outweigh its risks. Durysta has proven to reduce intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. In general, ophthalmologists should be familiar with the risks associated with Durysta, due to the similar adverse event profile to other marketed topical prostaglandin analogues with the exception of an increased risk of corneal endothelial cell loss. (b) (4) .

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Durysta (bimatoprost (b) (4) implant) is necessary to ensure the benefits outweigh its risks. Allergan, Inc submitted a New Drug Application (NDA 211911) for Durysta with the proposed indication to reduce intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT). This application is under review in the Division of Transplant and Ophthalmology Products (DTOP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Durysta, classified as a 505(b)(1) due to new dosage form, is a prostaglandin analog that acts as an ocular anti-hypertensive agent. Durysta is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

Durysta is proposed to be available as a 10 mcg implant in the single-use Novadur® sustained-release drug delivery system (DDS) to be administered via intracameral injection in patients (b) (4) . Durysta is implanted by an ophthalmologist who has had adequate training and has been approved by Allergan to perform the procedure.

[a] FDAAA factor (D): The expected or actual duration of treatment with the drug

Durysta was approved in the United States as an ophthalmic solution under the tradename Latisse 0.03% to treat hypotrichosis of the eyelashes and Lumigan 0.03%, 0.01% and PF in 2001 for the reduction of intraocular pressure in patients with OAG or OHT. Lumigan is currently licensed and marketed in more than 80 countries.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211911 relevant to this review:

- 12/6/2018: A preliminary discussion on the need for a REMS was held at the pre-NDA meeting. The Agency informed the Applicant a REMS is not required to be submitted with the original NDA filing for this product. However, a determination on the need for a REMS would occur during the review of the application.
- 5/6/2019: NDA 211911 submission for Durysta to reduce IOP in patients with OAG or OHT.
- 7/16/2019: FDA sent information request to Allergan to provide the Protocol Procedure Manuals for Studies 192024-091 and 192024-092 to ascertain information regarding prescriber training for drug administration.
- 7/26/2019: FDA received an amendment containing a response to the July 16, 2019 information request.
- 8/28/2019: FDA received an amendment containing the 120 Day Safety Update Report and an updated US Package Insert to include additional safety data that does not introduce any new or unexpected safety concerns.
- 2/4/2020: FDA sent information request to Allergan on information related to patients treated with bimatoprost implant who subsequently had one or more corneal endothelial surgeries.
- 2/10/2020: Amendment received providing a response to 2/4/2020 information request
- 3/2/2020: FDA received an amendment containing the final labeling for Durysta

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Elevated IOP is a major risk factor for the development and progression of glaucoma, and it is the only existing factor that ophthalmic intervention can affect. Lowering IOP will slow or delay appearance or progression of glaucomatous damage and loss of visual field. Glaucoma is characterized by progressive optic neuropathy with associated visual field defects, and it is the leading cause of irreversible blindness in the world.[b] Glaucoma is classified by Becker-Shaffer into 3 broad types: developmental glaucoma, angle-closure glaucoma, and open angle glaucoma (OAG). Worldwide, over 60 million people are estimated to be affected by glaucoma with a majority of people having OAG). Open-angle glaucoma is a multifactorial optic neuropathy with a characteristic acquired atrophy of the optic nerve and loss of

[b] 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.*

ganglion cells and their axons. Open angle glaucoma is categorized into primary OAG (POAG) and secondary OAG (which includes both pigmentary and pseudoexfoliation glaucoma), with the former being the predominant form of OAG. It is estimated that 2.25 million people in the United States over the age of 40 years have POAG.[c] Three to 6 million people in the US are at increased risk for developing POAG because of elevated IOP (≥21 mm Hg) or ocular hypertension. Approximately 10% of eyes with elevated IOP will convert to OAG over the course of a decade.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently available approaches to lowering IOP include topical pharmacologic therapy, laser trabeculoplasty, incisional surgery, and cyclodestructive procedures. FDA approved medications that are commonly used to treat glaucoma include β-blockers, prostaglandin analogs, α-agonists, carbonic anhydrase inhibitors, and cholinergic agonists. A table summarizing the types of topical treatment options that are FDA-approved and used to treat patients with elevated IOP is below:

Table 1: Summary of classes of pharmacologic therapy used to lower intraocular pressure

Class of Drugs	Example	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Prostaglandin analogues (prostamide)	Latanoprost, travoprost, bimatoprost	1 drop at bedtime	Conjunctival hyperemia, darkening of eyelashes, discoloration of iris, macular edema, uveitis	None
β -adrenergic blockers	Timolol, levobunolol, betaxolol	1-2 drops twice daily	Ocular irritation/ stinging, tachyphylaxis (long-term); CI in asthma patients, COPD, and bradycardia	None
α -adrenergic agonists	Brimonidine, apraclonidine	1-2 drops three times daily	Ocular irritation, dry eyes, ocular allergy; CNS effects & respiratory arrest	None

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

			in children; caution in patients with cerebral or coronary insufficiency, postural hypotension, and renal or hepatic failure	
Carbonic anhydrase inhibitors (CAIs)	Dorzolamide, brinzolamide, acetazolamide (oral)	1 drop (tablet) 2-3 times daily	Ocular irritation, blurred vision/tearing, burning sensation; oral associated with paresthesia, nausea, diarrhea, loss of appetite/taste	None
Cholinergic agonists	Pilocarpine, carbachol	1-2 drops 3-4 times daily	Ocular irritation, increased myopia, decreased vision due to ciliary spasm; cholinergic systemic effects	None

β -blockers and prostaglandin analogues are currently the most frequently used topical agents. Prostaglandin analogues are generally selected as first-line options in treatment due to their once-daily dosing and effectiveness. Other agents such as α -agonists and topical CAIs are suitable first-line or adjunct therapies to β -blockers or prostaglandin analogues. The α-agonists should be used with caution in patients with cardiovascular, cerebrovascular, and renal disease. The topical CAIs, such as dorzolamide and brinzolamide, should be used before acetazolamide as the latter is often used in patients failing to respond to or tolerate topical therapy. The carbonic anhydrase inhibitors should be avoided in patients with sulfa allergies, sickle cell disease, and hepatic and renal disease patients. The cholinergic agents are generally reserved as third line agents due to multiple daily dosing and adverse effects as listed in the above table.

Laser trabeculoplasty procedures are often used for patients who are nonadherent with topical ophthalmic medications. It is not effective in all patients, but in patients for whom it is effective, IOP reduction is typically less than that achieved by topical therapies and lasts only 1 to 2 years. Additional laser trabeculoplasty may be required. More invasive incisional surgeries are indicated when medication

or laser trabeculoplasty are insufficient to control a patient's disease. Incisional procedures carry risk of post-surgical complications, including infection, inflammation, bleeding, corneal problems, poor postoperative IOP control, and consequent progression of disease. Cyclodestructive procedures are the last resort in surgical treatment and not frequently used.

While topical drug therapy is a mainstay for lowering IOP, the high level of adherence and persistence to topical therapy required to maintain IOP control is not frequently met. Laser trabeculoplasty and incisional therapy are alternative therapies that do not require strict patient adherence; however, retreatment value is limited with both of these options. A long-term, repeatable therapeutic option that provides improvement of treatment adherence with favorable benefit-risk profile will satisfy unmet medical need in patients that require IOP-lowering therapy.

4 Benefit Assessment

The efficacy and safety of bimatoprost implant to reduce intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) was derived primarily from two ongoing Phase 3 studies (192024-091 and 192024-092) comparing bimatoprost implant versus topical timolol twice daily. Safety findings from completed Phase 1/2 Study 192024-041D as well as data from ongoing Phase 3 studies 192024-093 and 192024-095 are also available as supportive safety evidence. The two primary studies were similar in design: multicenter, randomized, parallel-group, patient- and efficacy evaluator-masked, 20-month evaluation (52-week active treatment period with 8 months extended follow-up). Both studies had the same primary and secondary efficacy endpoints: the study eye IOP at each hour evaluated (Hours 0 and 2) at Weeks 2, 6 and 12. The secondary endpoints are exploratory. Noninferiority compared to timolol reflects clinical significance.

In study 192024-091, 594 subjects were randomized and included in the intent to treat population, of which 7 subjects were randomized but not treated and discontinued from the study. Five hundred eighty-seven subjects were treated to receive bimatoprost 15 mcg (n=193), bimatoprost 10 mcg (n=197), or timolol 0.5% (n=197). For patients in the bimatoprost 10 mcg and 15 mcg groups, the study eye was to receive an initial administration of bimatoprost on treatment day 1, a second administration at 16 weeks, and a third administration 16 weeks following the second administration. Overall, this study demonstrated an IOP reduction of up to 8 mmHg in patients with a mean baseline IOP of 24.5 mm Hg. According to clinical reviewer, both bimatoprost 15 mcg and 10 mcg dose strengths were noninferior to timolol (upper limit of 95% CI≤ 1.5 mm Hg) for each of the 6 primary timepoints [Hour 0 and 2 at Week 2, 6, and 12 of Cycle 1]). Mean IOP in the study eye was lower for the bimatoprost 15 mcg and 10 mcg treatment group compared with timolol group for all measured timepoints (Hour 0 and Hour 2) at Weeks 2, 6, and 12 of both Cycle 2 and Cycle 3.

In study 192024-092, 528 subjects were randomized and included in the intent to treat population, of which 4 subjects were randomized but not treated and discontinued from the study. Five hundred twenty-four subjects were treated to receive bimatoprost 15 mcg (n=176), bimatoprost 10 mcg (n=175), and timolol 0.5% (n=173). The study eye was to receive an initial administration of bimatoprost on treatment day 1, a second administration at 16 weeks, and a third administration at 16 weeks following the second administration. According to the clinical reviewer, both bimatoprost 15 mcg and 10 mcg dose

strengths were noninferior to timolol (upper limit of 95% CI≤ 1.5 mm Hg) for each of the 6 primary timepoints [Hour 0 and 2 at Week 2,6, and 12 of Cycle 1]). (b) (4) . Overall, this study demonstrated the same reduction in IOP as the above study.

5 Risk Assessment & Safe-Use Conditions

Across the ongoing, pooled Phase 3 studies (192024-091 and 192024-092), a total of 1111 patients (369 in bimatoprost 15 mcg group, 372 in bimatoprost 10 mcg group, and 370 in timolol group) received study treatment and were included in safety population.

Ocular serious TEAEs were reported in 4.9% of study eyes in the bimatoprost 15 mcg group and 3% in the bimatoprost 10 mcg group. No ocular serious TEAEs were reported in study eyes treated with timolol. The most common ocular serious TEAES were corneal endothelial cell loss and corneal edema which was reported at a higher incidence in study eyes in bimatoprost 15 mcg group (3.8% and 1.1% respectively) versus the bimatoprost 10 mcg group (1.3% and 0.5% respectively). Nonocular treatment-related serious TEAEs were reported in 9.5% of patients in the bimatoprost 15 mcg group, 6.5% in the bimatoprost 10 mcg group, and 7.0% in the timolol group. The most common nonocular treatment-related serious TEAES were gastrointestinal and immune system disorders. Gastrointestinal disorders were reported at a higher incidence in study eyes in bimatoprost 15 mcg group (8.9%) versus the bimatoprost 10 mcg group (5.9%) and timolol group (7.3%). Immune system disorders were reported at a higher incidence in study eyes in bimatoprost 10 mcg group (2.7%) versus bimatoprost 15 mcg group (1.4%) and timolol group (1.1%).

Conjunctival hyperemia, corneal endothelial cell loss, and corneal edema were the TEAEs most frequently reported as severe, and of these severe events, most occurred in bimatoprost 15 ug group. In the bimatoprost 15 mcg group, 4.9% of study eyes experienced severe conjunctival hyperemia, as compared to 3.0% of study eyes in the bimatoprost 10 mcg and 0.8% in the timolol group. Severe corneal endothelial cell loss also occurred more frequently in the bimatoprost 15 mcg study eyes (2.7%) as compared with 1.1% in the bimatoprost 10 mcg study eyes and 0 in the timolol study eyes.

Because of the endothelial cell loss observed with repeat implantations, Durysta 10 mcg will be the only strength of the implant approved for a single implantation and will be contraindicated in patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss. Durysta should also be used with caution in patients with limited corneal endothelial cell reserve.

6 Expected Postmarket Use

The likely prescribers will be trained ophthalmalogists who should be familiar with the risk associated with Durysta due to the similar adverse event profile to other marketed topical prostaglandin analogues with the exception of an increased risk of corneal endothelial cell loss. (b) (4) . Due to possible corneal endothelial cell loss, Durysta will be

limited to a single implant per eye without re-treatment. Durysta may be implanted by an ophthalmologist in the inpatient or outpatient setting after adequate training has been provided by Allergan to perform the intracameral injection technique.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Durysta beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Office of New Drugs recommends approval of Durysta based on the data in the submission, the seriousness of reducing IOP in patients with OAG or OHT, and an adequately favorable benefit/risk profile.

Glaucoma is characterized by progressive optic neuropathy with associated visual field defects, and it is the leading cause of irreversible blindness in the world. Elevated IOP is a major risk factor for the development and progression of glaucoma, and it is the only existing factor that ophthalmic intervention can affect. Lowering IOP will slow or delay appearance or progression of glaucomatous damage and loss of visual field.

Two ongoing, parallel group, trials demonstrate effectiveness of bimatoprost intracameral implant for reducing IOP in patients with open angle glaucoma or ocular hypertension. Studies 192024-091 and study 192024-092, which evaluated patients on bimatoprost implant 10 mcg and 15 mcg compared to timolol 0.5%, showed noninferiority to timolol. Both studies also demonstrated an IOP reduction of up to 8 mmHg in patients with a mean baseline IOP of 24.5 mm Hg for both bimatoprost treated groups.

The most serious risks associated with Durysta include conjunctival hyperemia, corneal endothelial cell loss, and corneal edema. Because of the outcomes observed with these risks in the trials, Durysta 10 mcg will be the only strength of the implant approved, and the Warnings & Precautions section of the proposed labeling will recommend Durysta be limited to a single implant per eye without re-treatment and contraindicated in patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy) given its increased risk of corneal endothelial cell loss. Durysta should also be used with caution in patients with limited corneal endothelial cell reserve.

Therefore, based on the data available, prescribing community's likely familiarity with the risks associated with Durysta due to the similar adverse event profile to other marketed topical prostaglandin analogues (with the exception of an increased risk of corneal endothelial cell loss), and (b) (4) , DRISK is not recommending a REMS for the management of the risks of Durysta at this time.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with Durysta will be addressed in labeling, and in general, ophthalmologists

who prescribe Durysta should be familiar with the risk associated with the implant, due to the similar adverse event profile to other marketed topical prostaglandin analogues (with the exception of an increased risk of corneal endothelial cell loss), and (b) (4) . As there is an increased risk of corneal endothelial cell loss, Durysta will be limited to a single implant per eye without re-treatment and contraindicated in patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy). Should DTOP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 REFERENCES

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