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Understanding the safety & efficacy of DURYSTA (bimatoprost implant)

MODERATOR

ARSHAM SHEYBANI, MD

- Assistant Professor, Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri
- sheybaniar@wustl.edu
- Financial disclosure: None

PANEL

TOSIN SMITH, MD

- Attending Clinician and Surgeon, Glaucoma Associates of Texas, Dallas
- Associate Professor, University of Texas Southwestern Medical School, Dallas
- tsmith@glaucomaassociates.com
- Financial disclosure: Consultant (Aerie Pharmaceuticals, Allergan, Glaukos, New World Medical); Research (Allergan); Speaker's bureau (Aerie Pharmaceuticals, Allergan, Bausch + Lomb)

JASON BACHARACH, MD

- Founding Partner and Medical Director, North Bay Eye Associates, Sonoma County, California
- Director of Glaucoma Services, California Pacific Medical Center, San Francisco
- jb@northbayeye.com
- Financial disclosure: Investigator and/or consultant (Aerie, Allergan, Bausch + Lomb, EyePoint, Injectsense, Insite, Ocular Therapeutix)

RANDY CRAVEN, MD

- Chief, Associate Professor of Ophthalmology, Johns Hopkins Wilmer Eye Institute, Bethesda, Maryland
- erandycraven@gmail.com
- Financial disclosure: Consultant (Allergan, Gore, Santen, Sight Sciences); Research (Allergan)

FRANCIS MAH, MD

- Director, Cornea Service, Scripps Clinic, La Jolla, California
- mah.francis@scrippshealth.org
- Financial disclosure: Aerie, Alcon, Bausch + Lomb, Eyenovia, Fluent Ophthalmics, Glaukos, Ivantis, Novartis, Ocular Sciences, PolyActiva, Sight Sciences, Sun Pharma

AN OVERVIEW OF DURYSTA (BIMATOPROST IMPLANT)

DURYSTA (Allergan, an AbbVie company) is a first-in-class, biodegradable, intracameral implant for the lowering of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).[1] DURYSTA was approved by the FDA in March 2020.[2] The DURYSTA implant is inserted into the anterior chamber and comes to rest in the iridocorneal angle, where it provides a sustained release of bimatoprost for several months.[1] Arsham Sheybani, MD; Francis Mah, MD; Randy Craven, MD; Jason Bacharach, MD; and Tosin Smith, MD, participated in the first of a 3-part series of roundtable discussions about DURYSTA. This first piece is focused on understanding the safety and efficacy of DURYSTA, as well as which patients might be best served by this novel treatment.

STUDY OUTCOMES

Arsham Sheybani, MD: The FDA approval of the first biodegradable, intracameral, sustained-release implant to reduce IOP in patients with OAG or OHT[1] is a milestone in glaucoma management. Our goal here is to understand the efficacy and safety data and discuss how we will use this treatment with our patients. The phase 3 studies, ARTEMIS 1 and 2,

INDICATIONS AND USAGE

DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DURYSTA™ (bimatoprost implant) is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

WARNINGS AND PRECAUTIONS

The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

Please see additional Important Safety Information on the following pages.

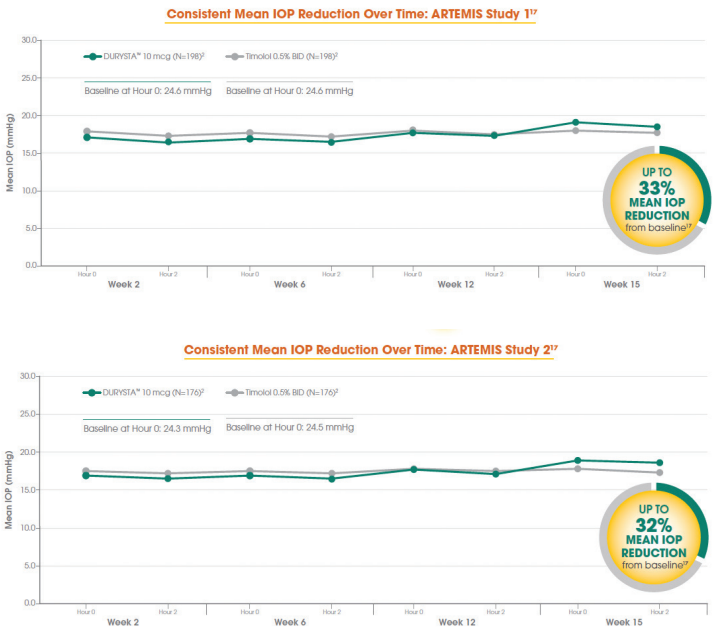


Figure 1. Data from the ARTEMIS 1 Trial (top) and the ARTEMIS 2 Trial (bottom).

were 2 identical, multicenter, randomized, parallel-group, controlled, 20-month studies, including an 8-month extended follow-up.[1] In these studies, the efficacy of DURYSTA was compared to twice-daily topical timolol 0.5% drops in patients with OAG or OHT. DURYSTA is for single administration only and should not be re-administered to an eye that received a prior DURYSTA.[1]

When you look at the phase 3 data (Figure 1), the average baseline IOP was in the mid 20s, and treatment with DURYSTA provided up to 33% reduction (≈ 5-8 mm Hg) in pressure over the 12-week primary efficacy period. In your minds, which aspects of DURYSTA are most compelling to you, and how do you plan to use it within your practice?

Tosin Smith, MD: As clinicians, we're looking at how many points of pressure reduction we need, and what can get us there. Looking at the numbers, up to 8 mm Hg of pressure reduction is effective in reducing eye pressure for my patients, and a single administration of DURYSTA provides us the ability to lower their IOP for several months.[1]

Jason Bacharach, MD: Dr. Sheybani and colleagues published data showing that a lot of IOP fluctuations occur outside of office hours and may not be detected.[3] It will be interesting to see how our patients benefit from 24/7 delivery of medication for several months.[1] I am looking forward to following my patients who've received DURYSTA to lower their IOP and monitoring their response to this sustained-release therapy.[1]

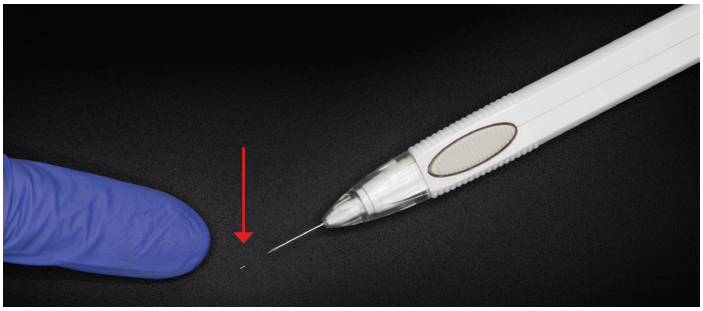


Figure 2. The DURYSTA implant (red arrow) and applicator.

BENEFITS OF DURYSTA

Dr. Sheybani: I'd like to discuss some of the potential benefits of DURYSTA, in particular, physician-guided administration and targeted delivery to diseased tissues. The intracameral administration of DURYSTA allows the preservative-free implant to bypass the ocular surface and be placed within the anterior chamber angle, delivering drug to targeted tissues (Figure 2).[1] What are the potential benefits of sustained-release therapies for lowering IOP in patients with primary OAG (POAG)?

Dr. Smith: With DURYSTA, the clinician administers the medicine and knows that the patient is receiving therapy for several months without having to administer the medication on their own.[1]

Dr. Bacharach: There are some very important benefits to extended-release medications. In many other subspecialties of medicine, there are now options for sustained-release therapy. In ophthalmology, cataract surgeons can now inject sustained-release medicines postoperatively; in retina, we see sustained-release treatments being utilized regularly. The physician-guided administration of DURYSTA allows us to deliver medication in a way that bypasses the ocular surface, a physical barrier through which the medication must pass.[1,4] In addition, with the current pandemic, while patients are still coming into my office for their regular follow-up visits, they are looking to make fewer trips outside of their home—specifically, fewer trips to the pharmacy.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Please see additional Important Safety Information on the following pages.

Randy Craven, MD: Sustained-release drugs have many benefits. As Dr. Bacharach mentioned, there are benefits to different methods of delivering the drug to the tissue. The intracameral delivery of this sustained-release implant and its bypassing of the ocular surface allow for targeted delivery to the diseased tissues. Targeted delivery to the diseased tissues of the anterior chamber angle allows for just 10mcg of bimatoprost to provide sustained IOP control over the course of several months.[1]

Dr. Sheybani: From a cornea perspective, what is the clinical value of a sustained-release implant to lower IOP for your glaucoma patients?

Francis Mah, MD: As Dr. Bacharach mentioned, to reach the intended tissues, medication must permeate the hydrophilic and hydrophobic layers of the cornea.[4] With DURYSTA, we have the ability to administer a medication that bypasses the ocular surface and put the medication directly within the anterior chamber angle.[1]

ADAPTING THE TREATMENT PARADIGM

Dr. Sheybani: Whenever you have a novel therapeutic modality, there needs to be discussion surrounding when and how to use it. Can you each summarize how you will use DURYSTA within your practice?

Dr. Bacharach: We're really talking about putting a novel treatment into a paradigm that's been around for a very long time. Minimally invasive glaucoma surgery (MIGS) treatments really opened up the treatment paradigm and found surgeons mixing and matching and getting excellent results. To start with, I wouldn't pigeonhole it. The efficacy is good, and there are times when I may use DURYSTA prior to selective laser trabeculoplasty (SLT) and times I would use it afterward. Drop application can be challenging for patients with mental or physical comorbidities. I may consider DURYSTA early on in a patient who does not want drops, or for whom drops are not suitable (eg, inability to instill drops, forgetfulness). Bimatoprost is thought to lower IOP by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral (unconventional) pathways,[1] making me very interested to see how it will work on my patients with whom I've used other interventions such as SLT. That is really intriguing to me as a physician.

Dr. Craven: Within my practice, DURYSTA is a sound treatment option for patients with mild to moderate glaucoma who need IOP lowering and require an alternative to topical therapy. That could be because they have difficulty remembering to take drops or applying drops. I think it is useful in pseudophakic patients as well. Initially, this is where I've found utility with this product. As I continue to gain experience with DURYSTA, I'll likely move on to other indicated patient groups.

Dr. Smith: I would say that you can consider using DURYSTA before or after SLT, depending on what you are trying to achieve. Now I can offer DURYSTA or SLT to the patient who needs IOP lowering and either does not want or is not a good candidate for topical drops, as they may prefer the option to not need to take medication daily. We have patients with moderate disease and patients who are early in their treatment who are taking topical drops to lower their IOP but are looking for an alternative option. DURYSTA could be a great option for these patients. DURYSTA can also be an option for patients who could benefit from a preservative-free treatment, are between interventions, or are post SLT and have not yet received MIGS and need IOP lowering for their glaucoma.

Dr. Mah: From the perspective of a cornea specialist, an intracameral implant that does not sit on the ocular surface can be useful (Figure 3).[5,6] I have always felt that options like MIGS and SLT should be more widely adopted, or at least considered along with drops, especially for patients who may be sensitive (or experience sensitivity) to preservatives.[5,6] I would want people to be considering SLT, MIGS, and DURYSTA early in the treatment in addition to drops, where appropriate, and I think comprehensive ophthalmologists and cataract surgeons have also adopted this view. A significant percentage of glaucoma patients needing IOP lowering may experience some sensitivity to preservatives.[7] I believe this should be considered when weighing treatment options.

Dr. Sheybani: In the phase 3 studies, following washout ranging 4 to 42 days depending on the treatment, a single administration of DURYSTA was able to control patients' IOP for several months. What are the potential benefits of sustained IOP control?

Dr. Smith: More and more, I am consciously trying to monitor my patients' treatment journey and make decisions on the appropriate time

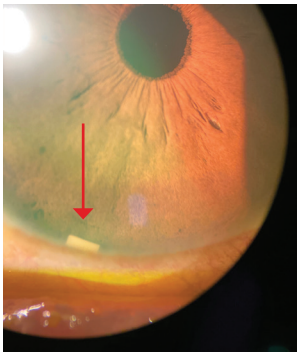


Figure 3. DURYSTA implant (red arrow).

IMPORTANT SAFETY INFORMATION FOR DURYSTA (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Please see additional Important Safety Information on the following pages.

to take the next step. DURYSTA allows me to control a patient's IOP for several months and gives me time before deciding which intervention to use next.

Dr. Mah: Several months of IOP control is an important consideration for patients who may be sensitive to preservatives. This will buy us time, as we consider what intervention comes next in the patient's treatment process.

Dr. Sheybani: In the clinical trials for DURYSTA, the most common ocular adverse reaction was conjunctival hyperemia, which occurred in 27% of patients. Other common ocular adverse reactions reported in 5% to 10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, IOP increased, corneal endothelial cell loss, vision blurred, and iritis.[1]

Ocular adverse reactions occurring in 1% to 5% of patients were anterior chamber cell, lacrimation increased, corneal edema, aqueous humor leakage, iris adhesions, ocular discomfort, corneal touch, iris hyperpigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema.[1]

The most common nonocular adverse event was headache, which was observed in 5% of patients.[1]

While there were no cases of endophthalmitis in the clinical trials,[1] we know these types of intraocular, surgical procedures and injections have been associated with endophthalmitis, so proper aseptic technique must always be used when administering DURYSTA, and patients should be monitored following the administration.[1] When you look at this, what stands out in your mind as truly significant and how will this impact your patient selection?

Dr. Smith: Patient selection will play a role in this procedure. Physicians will have to perform gonioscopy and make sure the angle is deep enough to receive the implant without touching the corneal endothelium.

Dr. Bacharach: As my colleagues have stated, you must look at the angle, and pick the right patients. DURYSTA should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (eg, scarring) that may prohibit settling in the inferior angle.[1]

THE PATIENT CONVERSATION

Dr. Sheybani: Whenever you have a novel treatment like this intracameral implant, you must also consider the patient conversation. We are the ones who first discuss this treatment option with our patients, so we need to be able to convey the risks and benefits and our treatment goals in a way that overcomes any natural reticence to injections. How do you talk to your patients about DURYSTA?

Dr. Craven: I think this is very easy to explain to patients. I tell them that we have an implantable medication to use, I explain why this is the option I've chosen for them, and I give the reasons why I recommend it. I explain that injections are frequently used in other types of ophthalmic conditions and are commonplace.

Dr. Bacharach: When I have a patient who is challenged by drop instillation and is looking for a different option, I tell them about DURYSTA. I explain that it is a sustained-release implant approved by the FDA to lower eye pressure in patients with OAG, and since I will be administering it, they don't need to remember to take it every day.

Dr. Smith: I focus on discussing the benefits of the treatment. I explain that it is a different treatment that allows me to place their medication in the front part of their eye, where it is slowly released for several months, and without them having to administer their medication on their own. I explain that this is done in the office and why it may be beneficial to them, and with that, they are usually more receptive. If they ask specifically about the injection process, then I add more information. After the procedure, I counsel them that if their eye becomes red, sensitive to light, painful, or develops a change in vision, they should immediately call the office.[1]

Dr. Sheybani: DURYSTA represents a novel way to treat our patients—one that takes into account patients who are looking for a preservative-free option as well as those who may have difficulties administering medication on their own. This intracameral, biodegradable implant provides 24/7 drug delivery for several months targeted directly to the diseased tissue.[1] Thank you for an excellent discussion on the outcomes of the clinical trials and how you are each translating that information into your individual practices. ■

1. DURYSTA™ Prescribing Information.
2. US Department of Health and Human Services. Supplemental approval. NDA 211911. Drugs @ FDA website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/211911Orig1s000ltr.pdf. Published March 4, 2020. Accessed September 14, 2020.
3. Sheybani A, Scott R, Samuelson TW, et al. Open-angle glaucoma: Burden of illness, current therapies, and the management of nocturnal IOP variation. ***Ophthalmol Ther***. 2020;9(1):1-14.
4. Bachu RD, Chowdhury P, Al-Saedi ZHF, et al. Ocular drug delivery barriers-role of nanocarriers in the treatment of anterior segment ocular diseases. ***Pharmaceutics***. 2018;10(1):28.
5. Zhang X, Vadoothker S, Munir WM, et al. Ocular surface disease and glaucoma medications: A clinical approach. ***Eye Contact Lens***. 2019;45(1):11-18.
6. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. ***Br J Ophthalmol***. 2002;86(4):418-423.
7. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. ***J Glaucoma***. 2008;17(5):350-355.

IMPORTANT SAFETY INFORMATION FOR DURYSTA (CONTINUED)

ADVERSE REACTIONS

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

Please see the full Prescribing Information on the following pages.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DURYSTA™ safely and effectively. See full prescribing information for DURYSTA™.

DURYSTA™ (bimatoprost implant), for intracameral administration
Initial U.S. Approval: 2001

INDICATIONS AND USAGE

DURYSTA™ is a prostaglandin analog indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT). (1)

DOSAGE AND ADMINISTRATION

- For ophthalmic intracameral administration. (2.1)
- The intracameral administration should be carried out under standard aseptic conditions. (2.2)

DOSAGE FORMS AND STRENGTHS

Intracameral implant containing bimatoprost 10 mcg, in the drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Corneal endothelial cell dystrophy (4.2)
- Prior corneal transplantation (4.3)
- Absent or ruptured posterior lens capsule (4.4)
- Hypersensitivity (4.5)

WARNINGS AND PRECAUTIONS

- Endothelial cell loss: Due to possible corneal endothelial cell loss, administration of DURYSTA™ should be limited to a single implant per eye without retreatment. (5.1)
- Corneal Adverse Reactions: DURYSTA™ has been associated with corneal adverse reactions and risks are increased with multiple implants. Use caution in patients with limited corneal endothelial cell reserve. (5.1)
- Iridocorneal Angle: DURYSTA™ should be used with caution in patients with narrow angles or anatomical angle obstruction. (5.2)

ADVERSE REACTIONS

In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

2 DOSAGE AND ADMINISTRATION

2.1 General Information

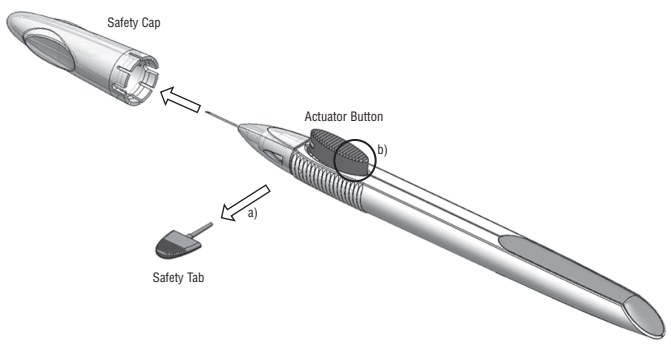
DURYSTA™ is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant. DURYSTA™ should not be readministered to an eye that received a prior DURYSTA™.

2.2 Administration

The intracameral injection procedure must be performed under magnification that allows clear visualization of the anterior chamber structures and should be carried out using standard aseptic conditions for intracameral procedures, with the patient's head in a stabilized position. The eye should not be dilated prior to the procedure.

Remove the foil pouch from the carton and examine for damage. Then, open the foil pouch over a sterile field and gently drop the applicator on a sterile tray. Once the foil pouch is opened, use promptly.

Figure 1



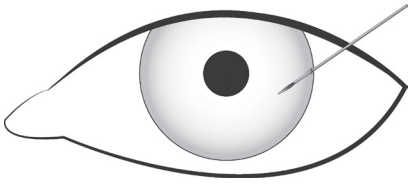
Perform a detailed visual inspection of the applicator, including ensuring that the actuator button has not been depressed, and the safety tab is in place. Carefully remove the plastic safety cap taking care to avoid contacting the needle tip. Inspect the needle tip for damage under magnification prior to use; the implant retention plug may be visible in the bevel and should not be removed.

Prior to use, remove the safety tab by pulling it out perpendicular to the long axis of the applicator (refer to Figure 1a above). Do not twist or bend the tab.

Stabilize the eye as the needle is advanced through the cornea. Enter the anterior chamber with the needle bevel visible through clear cornea. Enter parallel to the iris plane, adjacent to the limbus through clear cornea in the superotemporal quadrant.

The needle should be inserted approximately 2 bevel lengths with the bevel completely within the anterior chamber; avoid positioning the needle bevel directly over the pupil. Ensure the needle is not bent before depressing the actuator button. See Figure 2.

Figure 2



Depress the back half of the actuator button (refer to Figure 1b above) firmly until an audible and/or palpable click is noted.

Following the release of the implant, remove the needle via the same track in which it was inserted and tamponade the opening. The implant should not be left in the corneal injection track.

Check the injection site for leaks; make sure that it is self-sealing and the anterior chamber is formed.

After injection, **do not** recap the needle. Dispose of the used applicator in a sharps disposal container and in accordance with local requirements.

Instruct the patient to remain upright for at least 1 hour after the procedure so the implant can settle.

Some degree of eye redness and discomfort is expected following administration. However, it is recommended to instruct patients that if the eye becomes progressively red, sensitive to light, painful, or develops a change in vision, they should immediately contact the physician.

3 DOSAGE FORMS AND STRENGTHS

Intracameral implant containing 10 mcg of bimatoprost in a drug delivery system.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections.

4.2 Corneal Endothelial Cell Dystrophy

DURYSTA™ is contraindicated in patients with corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy) *[see Warnings and Precautions (5.1)]*.

4.3 Prior Corneal Transplantation

DURYSTA™ is contraindicated in patients with prior corneal transplantation, or endothelial cell transplants [e.g., Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK)].

4.4 Absent or Ruptured Posterior Lens Capsule

DURYSTA™ is contraindicated in patients whose posterior lens capsule is absent or ruptured, due to the risk of implant migration into the posterior segment. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for DURYSTA™ use if the intraocular lens fully covers the opening in the posterior capsule.

4.5 Hypersensitivity

DURYSTA™ is contraindicated in patients with hypersensitivity to bimatoprost or to any other components of the product *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Corneal Adverse Reactions

The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

5.2 Iridocorneal Angle

Following administration with DURYSTA™, the intracameral implant is intended to settle within the inferior angle. DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

5.3 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.4 Intraocular Inflammation

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.5 Pigmentation

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

5.6 Endophthalmitis
Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Implant migration *[see Contraindications (4.4)]*
- Hypersensitivity *[see Contraindications (4.5)]*
- Corneal adverse reactions *[see Warnings and Precautions (5.1)]*
- Macular edema *[see Warnings and Precautions (5.3)]*
- Intraocular inflammation *[see Warnings and Precautions (5.4)]*
- Pigmentation *[see Warnings and Precautions (5.5)]*
- Endophthalmitis *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with DURYSTA™ in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis. Ocular adverse reactions occurring in 1-5% of patients were anterior chamber cell, lacrimation increased, corneal edema, aqueous humor leakage, iris adhesions, ocular discomfort, corneal touch, iris hyperpigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema. The following additional adverse drug reactions occurred in less than 1% of patients: hyphema, iridocyclitis, uveitis, corneal opacity, product administered at inappropriate site, corneal decompensation, cystoid macular edema, and drug hypersensitivity.

The most common nonocular adverse reaction was headache, which was observed in 5% of patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary

There are no adequate and well-controlled studies of DURYSTA™ (bimatoprost implant) administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures *[see Animal Data]*.

Data

Animal Data

In an embryofetal development rat study, oral administration of bimatoprost to pregnant rats during organogenesis produced abortion at 0.6 mg/kg/day (1770-times the human systemic exposure to bimatoprost from DURYSTA™, based on C_{max} and a blood-to plasma partition ratio of 0.858). The No Observed Adverse Effect Level (NOAEL) for abortion was 0.3 mg/kg/day (estimated at 470-times the human systemic exposure to bimatoprost from DURYSTA™, based on C_{max}). No fetal abnormalities were observed at doses up to 0.6 mg/kg/day.

In an embryofetal development mouse study, oral administration of bimatoprost to pregnant mice during organogenesis produced abortion and early delivery at 0.3 mg/kg/day (2240-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max} level; blood-to plasma partition ratio of 0.858). The NOAEL for abortion and early delivery was 0.1 mg/kg/day (400-times the human systemic exposure to bimatoprost from DURYSTA™, based on C_{max}). No fetal abnormalities were observed at doses up to 0.6 mg/kg/day (5200-times the human systemic exposure to bimatoprost from DURYSTA™, based on C_{max}).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max}).

8.2 Lactation
Risk Summary

There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing woman.

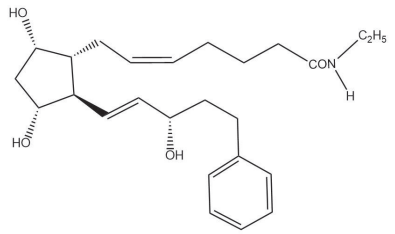
The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DURYSTA™ and any potential adverse effects on the breastfed child from DURYSTA™.

8.4 Pediatric Use
Safety and effectiveness of DURYSTA™ in pediatric patients have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

DURYSTA™ is a sterile intracameral implant containing 10 mcg of bimatoprost, a prostaglandin analog, in a solid polymer sustained-release drug delivery system (DDS). The drug delivery system consists of poly (D,L-lactide), poly (D,L-lactide-co-glycolide), poly (D,L-lactide) acid end, and polyethylene glycol 3350. DURYSTA™ is preloaded into a single-use, DDS applicator to facilitate injection of the rod-shaped implant directly into the anterior chamber of the eye. The chemical name for bimatoprost is (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenyl-1-pentenyl] cyclopentyl]-*N*-ethyl-5-heptenamide, and its molecular weight is 415.57. Its molecular formula is $C_{25}H_{37}NO_4$. Its structural formula is:



Bimatoprost is a white to off-white powder, soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. The polymer matrix slowly degrades to lactic acid and glycolic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. Bimatoprost is believed to lower IOP in humans by increasing outflow of aqueous humor through both the trabecular meshwork (conventional) and uveoscleral routes (unconventional). Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

12.3 Pharmacokinetics

After a single administration of DURYSTA™, bimatoprost concentrations were below the lower limit of quantitation (0.001 ng/mL) in the majority (approximately 92%) of patients. The maximum bimatoprost concentration observed in any patient was 0.00224 ng/mL. Bimatoprost acid concentrations were also below the lower limit of quantitation (0.01 ng/mL) in almost all (approximately 99%) of patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

Mutagenesis

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

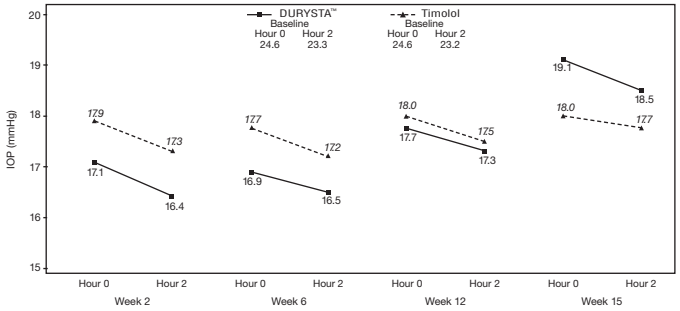
Impairment of Fertility

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max}; blood-to-plasma partition ratio of 0.858).

14 CLINICAL STUDIES

Efficacy was evaluated in two multicenter, randomized, parallel-group, controlled 20-month (including 8-month extended follow-up) studies of DURYSTA™ compared to twice daily topical timolol 0.5% drops, in patients with OAG or OHT. DURYSTA™ demonstrated an IOP reduction of approximately 5-8 mmHg in patients with a mean baseline IOP of 24.5 mmHg (see Figures 3 and 4).

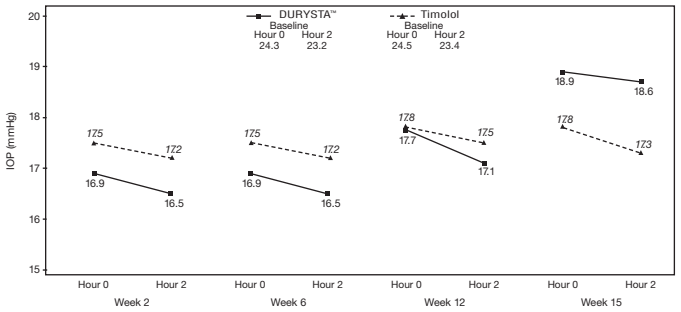
Figure 3: Study 1 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP



DURYSTA™ vs. Timolol (95% CI)

	Week 2	Week 6	Week 12	Week 15
Hour 0	-0.8 (-1.47, -0.14)	-0.8 (-1.47, -0.21)	-0.3 (-1.09, 0.43)	1.1 (0.22, 1.89)
Hour 2	-0.9 (-1.50, -0.31)	-0.7 (-1.27, -0.04)	-0.2 (-0.90, 0.46)	0.9 (0.10, 1.64)

Figure 4: Study 2 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP



DURYSTA™ vs. Timolol (95% CI)

	Week 2	Week 6	Week 12	Week 15
Hour 0	-0.6 (-1.30, 0.13)	-0.6 (-1.35, 0.17)	-0.1 (-0.88, 0.72)	1.0 (0.15, 1.94)
Hour 2	-0.7 (-1.38, -0.05)	-0.6 (-1.36, 0.06)	-0.3 (-1.11, 0.42)	1.2 (0.35, 2.06)

16 HOW SUPPLIED/STORAGE AND HANDLING

DURYSTA™ contains a 10 mcg bimatoprost intracameral implant in a single-use applicator that is packaged in a sealed foil pouch containing desiccant, NDC 0023-9652-01.

Storage

Store refrigerated at 2°C to 8°C (36°F to 46°F).

17 PATIENT COUNSELING INFORMATION

Treatment-related Effects

Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis *[see Warnings and Precautions (5.1, 5.4, 5.6)]*.

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent *[see Warnings and Precautions (5.5)]*.

When to Seek Physician Advice

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.6)]*.

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