

RETINA TODAY

INJECTION TECHNIQUES

for OZURDEX® (Dexamethasone Intravitreal Implant) 0.7 mg

Covered topics include:

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Indications and Usage

Retinal Vein Occlusion

OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis

OZURDEX® is indicated for the treatment of noninfectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

Contraindications

Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Please see additional Important Safety Information on the following pages.

INJECTION TECHNIQUES

for OZURDEX® (Dexamethasone Intravitreal Implant) 0.7 mg

OZURDEX® (dexamethasone intravitreal implant) 0.7 mg from Allergan, Inc., has been approved since 2009 for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO),¹ and since 2010 for the treatment of noninfectious posterior segment uveitis.¹

More recently, the FDA approved the injection applicator with a needle that is manufactured by TSK Laboratory. Allergan pursued this TSK needle based on feedback from retina specialists relative to the glide factor and penetration of the original needle. The OZURDEX® applicator with TSK needle is 22 gauge and features a coating designed to facilitate glide of the needle through the sclera and into the posterior chamber.

In this insert to *Retina Today*, sponsored by Allergan, Inc., physicians with varying levels of OZURDEX® familiarity discuss their overall injection experiences, highlighting their more recent experiences with the TSK-needle-tipped applicator.



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Dosage and Administration

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

Advanced Glaucoma: OZURDEX® is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

Profiles of the Experienced Injector

Ron P. Gallemore, MD, PhD: I have performed approximately 500 injections of the dexamethasone intravitreal implant. I mostly use this for patients with chronic macular edema secondary to BRVO and CRVO, but I also use it for noninfectious posterior segment uveitis.

Christine R. Gonzales, MD: I have performed about 75 injections of the dexamethasone intravitreal implant, most for BRVO and CRVO, but I have also done a few injections for noninfectious posterior segment uveitis.

Kimberly Drenser, MD, PhD: I have performed approximately 100 injections of the dexamethasone intravitreal implant, mostly for macular edema secondary to CRVO or BRVO. I will use it as first-line treatment for patients with recent vein occlusions, within 1 month of onset, and generally for patients who are older and pseudophakic. OZURDEX® is contraindicated in patients with aphakic eyes and rupture of the posterior lens capsule, and in patients with anterior chamber intraocular lenses and rupture of the posterior lens capsule (due to the risk of implant migration), so I avoid it in such cases. I have also used the dexamethasone intravitreal implant for patients who have undergone previous vitrectomy, although it is not necessarily my first choice in these situations.

Thomas Albini, MD: I have done approximately 100 injections of the dexamethasone intravitreal implant, mostly for noninfectious posterior segment uveitis.

Allen C. Ho, MD: I am a new user of the dexamethasone intravitreal implant, and have done approximately 12 injections, all for CRVO and BRVO.

“I inform patients that the dexamethasone intravitreal implant injection procedure can be brief and that they may feel some pressure.”

-Ron P. Gallemore, MD, PhD

Patient Preparation

Dr. Gallemore: I discuss the injection procedure with the dexamethasone intravitreal implant with my patients in the same way that I would any intravitreal injection. I inform patients that the dexamethasone intravitreal implant injection procedure can be brief and that they may feel some pressure. I advise that they may have a mild stinging sensation immediately afterward because of the iodine-based solution to prevent infection. Patients are also informed that they should leave the gentle pressure patch in place for 4 hours afterward and not to rub or touch the eye for 3 days.

Dr. Gonzales: Most of the patients in whom I use the dexamethasone intravitreal implant have had prior intravitreal injections and so I let them know that this injection will be similar, noting that the pressure sensation might be more than what they feel with other intravitreal injections. I also warn patients of the audible click as the implant is released.

Dr. Drenser: I tell patients that I am using subconjunctival 2% lidocaine to numb the eye and that they will feel some pressure when I perform the injection.

Dr. Albini: I tell patients that the needle for the dexamethasone intravitreal implant is larger than what I would use for injecting bolus steroids or anti-VEGF,

IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Please see additional Important Safety Information on the following pages.

and so they might feel more pressure when I am injecting.

Dr. Ho: If a patient has had prior intravitreal injections, I will tell them that the injection of the dexamethasone intravitreal implant will be different in that they will have a speculum placed in the eye to help the eyelids, that there is more pressure, and that the process takes slightly longer.

The Injection Procedure

Dr. Gallemore: When I perform the injection, per protocol, I check the lids first for any blepharitis and when possible have patients perform lid hygiene before the procedure. I prep the eye with Betadine and administer a subconjunctival injection of anesthetic 3 mm posterior to the limbus and wait 3-5 minutes before I perform the injection. I add another drop of Betadine just prior to the injection.

I always displace the conjunctiva first with a cotton-tipped swab, then I inject the dexamethasone intravitreal implant at a fairly steep angle, between 15° and 30°, and I bury the bevel only into the sclera. I then move toward the optic nerve at a 75°-90° angle to the sclera, after which I push the needle in and release the implant by pressing the plunger.

As soon as I remove the needle, I raise the lower lid with my gloved finger and press it over the injection site for about 30 seconds. I then check the site for any bleeding, and if some exists, I continue compression intermittently, on and off for ten second intervals until the bleeding stops, most commonly required for patients on anticoagulants. I make an effort to avoid large conjunctival vessels at the injection site.

I modify my injection technique for post-vitrectomy patients by maintaining a continuous 30° angle to the vitreous base area while inserting the needle from the bevel to the hub, where I release the implant. In my

The Injection Technique: OZURDEX® Prescribing Information²



Figure 1. The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).



Figure 2. Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.



Figure 3. 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. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Potential Steroid-related Effects: Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

The most common ocular adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%),



Figure 4. The long axis of the applicator should be held parallel to the limbus, and the sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path.



Figure 6. Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface.



Figure 5. The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.



Figure 7. Remove the needle in the same direction as used to enter the vitreous. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay. Each applicator can only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new applicator must be used, and the sterile field, syringe, gloves, drapes, and eyelid speculum should be changed before OZURDEX® is administered to the other eye.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Adverse Reactions (continued)

ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Please see additional Important Safety Information on the following pages.

experience, post-vitrectomized eyes can have a leakier incision port and maintaining a steeper angle may reduce the risk of leakage. The conjunctival displacement can help with this in that the eye will form a little bleb, and there will not be direct leakage to the surface.

Dr. Gonzales: I use subconjunctival lidocaine in all patients and prep the eye with povidone-iodine prior to the injection.

“I insert the needle into the sclera the same way as I would trocars in 23- and 25-gauge surgery.”
-Christine R. Gonzales, MD

I insert the needle into the sclera the same way as I would trocars in 23- and 25-gauge surgery. I enter at approximately a 25° angle and then rotate the needle so that it is perpendicular to the sclera. I insert the needle into the posterior segment to the point where the sleeve reaches the sclera and then depress the plunger, releasing the implant. I then withdraw the needle at the same 25° angle that I used for insertion.

Afterward, I use an indirect ophthalmoscope to check the placement of the implant in the posterior chamber and check the intraocular pressure (IOP).

Dr. Drenser: Preinjection, I use a subconjunctival injection of 2% lidocaine. I prep the eye with povidone-iodine, and use gloves and a speculum.

I perform the actual injection in a similar manner to

how I insert 23- or 25-gauge trocar systems for vitreo-retinal surgery. I enter at approximately a 25° angle, tangential to the iris plane, at about 3-3.5mm back, and go extremely flat with the needle, about 10°, until I break through the first layer of sclera. I then rotate the needle to be directly perpendicular to the sclera and insert it into the posterior chamber before releasing the implant from the injector. Releasing the implant from the injector using the plunger is very easy. I press closer to the distal end of the plunger so that it slowly pushes in and you do not feel a “trigger” effect.

Dr. Albini: I approach the injection very much the same way that I would a standard 32-gauge intravitreal injection. I place a lidocaine pledget on the surface of the eye for a few minutes and then I place the lid speculum and instill povidone-iodine. I then perform a subconjunctival lidocaine injection with a 32-gauge needle, put in another drop of povidone-iodine. I displace the conjunctiva with a cotton-tipped swab and approach the eye with the injector needle at a fairly low angle—10°-30°—and perform a 2-step beveled incision through the conjunctiva and the sclera. I usually have the patient look in a superonasal direction and administer the injection inferotemporally. I roll the cotton-tipped swab over the wound as I withdraw the injector to help it to seal. Finally, I use an indirect ophthalmoscope to check to be sure the implant is in the eye. I then remove the lid speculum, rinse the eye, and have my technician check the IOP to be sure it rises above 8 mm Hg.

Dr. Ho: In my experience, I would compare doing this injection to trocar placement in small-gauge surgery.

Prior to the injection, I use topical proparacaine and a liberal amount of topical povidone-iodine, letting it

IMPORTANT SAFETY INFORMATION

Contraindications

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Advanced Glaucoma: OZURDEX® is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

“In my opinion, the OZURDEX® applicator design makes the penetration into the sclera smooth. It goes in with little resistance and little pressure on the globe into the orbit.”
-Thomas Albini, MD

sit in the eye for several minutes. I then put in some subconjunctival lidocaine and let it work for about 5 minutes, after which I will put in more povidone-iodine. I use a speculum, which I do not normally use for other in-office injections, and once the speculum is in the eye, I displace the conjunctiva upward centrally with a cotton-tipped swab to provide counter pressure. I make a beveled incision through the sclera at about a 30° angle. Once in the eye, I rotate the needle perpendicular to the sclera, and then press down on the plunger to release the implant.

I remove the needle at the same 30° angle and I use the cotton-tipped swab to compress the wound as the needle exits the eye.

I like to confirm that the pellet is placed in the eye with indirect ophthalmoscopy. Usually I will see it somewhere outside of the visual axis anteriorly because I inject into the anterior quadrant.

OZURDEX® Applicator Design

Dr. Gallemore: The OZURDEX® applicator with TSK needle penetrates the sclera easily.

Dr. Gonzales: I have not had any issues inserting the

implant since the OZURDEX® applicator with TSK needle was introduced.

The pressure with which I perform the injection of the dexamethasone intravitreal implant is similar to that which I use for 23- and 25-gauge trocars.

Dr. Drenser: The approved OZURDEX® applicator for injecting the dexamethasone intravitreal implant, in my experience, glides through the sclera.

The pressure that is applied for this injection is more than what I would apply for an intravitreal injection because of the larger needle gauge, but it is similar to what is used for inserting trocars for surgery, so anyone who is used to performing vitreoretinal surgery will be comfortable doing this.

Dr. Albini: In my opinion, the OZURDEX® applicator design makes the penetration into the sclera smooth. It goes in with little resistance and little pressure on the globe into the orbit. Additionally with this needle, I have had very infrequent incidence of postinjection hypotony.

Dr. Ho: I have found that the coating on the OZURDEX® applicator allows for a nice pass into and withdrawal from the scleral tissue. The needle tip is sharp and helps make the incision and injection smooth.

There is more pressure with this injection than with other intravitreal injections simply because the gauge of needle is larger, but it is similar to inserting trocars. The pressure applied should be steady and deliberate to allow the needle to pass easily through the sclera. It is important not to be hesitant when performing this

IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Potential Steroid-related Effects: Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Please see additional Important Safety Information on the following pages.

Other Considerations With the Dexamethasone Intravitreal Implant

By Ron P. Gallemore, MD, PhD

Steroid response. My experience with the implant is similar to the clinical trials, where during the initial treatment period, 1% of patients who received the implant required surgical intervention for management of elevated IOP.² Any rises in IOP that are not as dramatic are usually well controlled with medication, but if a patient has to go on 3 or more glaucoma drops, I will most likely discontinue use of the dexamethasone implant.

Reinjections. Approximately 80% of my patients have received a second injection of the dexamethasone intravitreal implant. [Note: OZURDEX® pivotal trials had an initial treatment phase of 180 days with an open-label extension of 180 days following a second injection of OZURDEX® in cases where a second injection was needed.]

“I have found that the coating on the OZURDEX® applicator allows for a nice pass into and withdrawal from the scleral tissue. The needle tip is sharp and helps make the incision and injection smooth.”

-Allen C. Ho, MD

Tips for Tough Sclera

Dr. Gallemore: When performing any injection into tough sclera it is important to proceed with confidence. If you feel resistance meet this with equal resistance. Remain precise and committed and the procedure will go smoothly. In some elderly patients, there are areas of calcification near the rectus muscle insertions that may appear as an area of grey discoloration and I make an effort to avoid these (Figure 1).

Dr. Gonzales: I do not change my angle of entry for tough sclera, but I do find that more pressure is necessary to penetrate the sclera.

Dr. Drenser: If I encounter a very thickened sclera, I will not enter at such a flat angle as I would other-

injection because that will cause difficulties with the injection and for the patient.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Potential Steroid-related Effects (continued): Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

The most common ocular adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

wise—I will steepen the angle of my injection.

Dr. Ho: For tough sclera, I do not change the angle of entry. If you use a sterile cotton-tipped swab to displace conjunctiva as I do, you can also use it to press inward on the globe, which raises the pressure of the eye, making all tissue, including the sclera, more rigid, allowing for easier entry into the eye. The OZURDEX® applicator design makes the penetration into the sclera smooth. It goes in with little resistance and little pressure on the globe into the orbit. An analogy could be made to a soft balloon—it is harder to puncture a soft balloon than one that is firm.

Postinjection Protocols

Dr. Gallemore: Postinjection, I will have the patient use a topical antibiotic for 5-7 days. Using postoperative antibiotics and the above injection technique, we have an infection rate under 1/20,000 in our practice.

Dr. Gonzales: I have the patient use a topical antibiotic for 3 days after the injection.

Dr. Drenser: Postinjection, I irrigate the eye with saline solution and apply a topical antibiotic. I have the patient use a topical antibiotic for 4 days following the injection.

Dr. Albini: I usually give patients a topical antibiotic for 3 days.

Injection Pearls

Dr. Gallemore: The dexamethasone intravitreal implant should be injected as you do any other intravitreal injection—with confidence and precision. The larger needle and the pathway through the sclera are

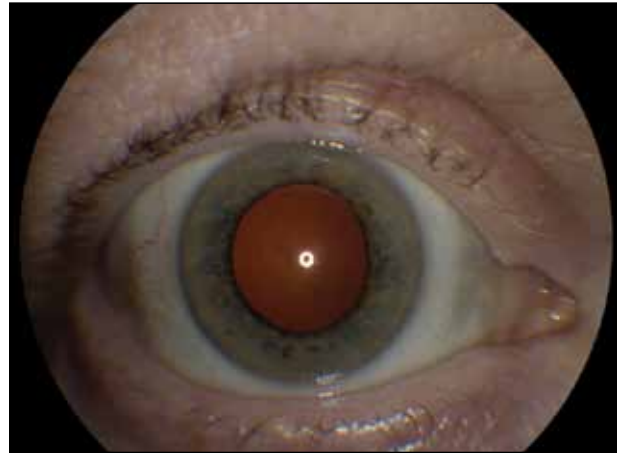


Figure 1. Subtle grey discoloration from calcification may be found adjacent to rectus muscle insertions and signify a region of tough sclera to be avoided during intravitreal injection. (Photo courtesy of Calvin Chou, BS, CRA.)

very much like inserting the trocar-cannula during vitrectomy surgery. The key to the technique is to perform the injection with confidence. Once you commit, perform the injection in a smooth fashion and it will proceed quickly and easily.

Dr. Gonzales: For those who have not injected the dexamethasone intravitreal implant, I would offer that this procedure can be performed efficiently. If a physician is performing injections and/or vitreoretinal surgery, the learning curve is short.

After pushing the actuator button to release the implant, I would suggest that physicians wait for just a few seconds to be sure that the pellet has dislodged from the injector. Also, I think it is important to warn

IMPORTANT SAFETY INFORMATION

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Advanced Glaucoma: OZURDEX® is contraindicated in patients with advanced glaucoma.

Aphakic Eyes with Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

ACIOL and Rupture of the Posterior Lens Capsule: OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

Please see additional Important Safety Information on the following pages.

Setting Treatment Goals

Each patient must be treated as an individual because the underlying causes for the edema may be different from patient to patient. Physicians should have treatment goals that help them establish individualized plans. For example, what is considered a good response? Is visual acuity more important than anatomical response or vice versa, or are they equally important?

Some patients may respond well to 1 initial agent, while others may require a multipronged approach, utilizing treatments from multiple classes. Thus, it is critical for physicians to accurately measure response and to know the available treatment options should the patient require a different approach.

“If you are used to small-gauge surgery and are comfortable with trocar placement, you will find this to be the same sort of procedure.”
-Kimberly Drenser, MD, PhD

patients about the audible click so that they don't flinch or jump when they hear it. The bevel of the incision is also important so that the wound seals well and hypotony is avoided.

Dr. Drenser: I think that the two main pieces of advice I would offer someone new to injecting the dexamethasone intravitreal implant would be (1) to practice the injection in a wet lab setting first, if pos-

sible, so that the comfort level is high when injecting the first patient; and (2) if you are used to small-gauge surgery and are comfortable with trocar placement, you will find this to be the same sort of procedure.

Dr. Albini: My advice for those who are new to injecting the dexamethasone intravitreal implant would be to approach it much like your standard intravitreal injections. If a physician does not have experience with small-gauge surgery, I would definitely recommend a wet lab so that he or she can practice the injection. For a vitreoretinal surgeon, however, the injection is pretty straightforward.

I recommend using a smaller gauge needle for the subconjunctival lidocaine. I believe a lot of physicians are accustomed to using 27- or 30-gauge needles for lidocaine, but using a 32-gauge needle ensures that the patient does not feel that initial injection as much and allows for a smoother procedure overall.

IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Potential Steroid-related Effects: Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Dr. Ho: It is important for physicians to not be shy when injecting into the sclera—the injection is similar to inserting microincisional trocars. Additionally, creating counter pressure with the cotton-tipped swab helps for an easier pass of the needle through the sclera and into the vitreous cavity. ■

Ron P. Gallemore, MD, PhD, is Director of the Retina Macula Institute and Research Center in Los Angeles and is an Assistant Clinical Professor at the Jules Stein Eye Institute, University of California, Los Angeles. He states that he is a consultant for Bausch + Lomb and receives clinical trial support from Alcon Laboratories, Inc., Allergan, Inc., Genentech, Novartis, and Sirion. Dr. Gallemore may be reached at rongallemoremd@gmail.com.

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Allen C. Ho, MD, is a Partner with Mid Atlantic Retina and is a Professor of Ophthalmology at Thomas Jefferson University Retina Service and Wills Eye Hospital in Philadelphia. He states that he is a consultant for Alcon Laboratories, Inc., Genentech, Janssen, Merck, Ophthotech, PRN, Regeneron, and Thrombogenics. He receives lecture fees for Alcon Laboratories, Inc., Genentech, Janssen, Regeneron, and Thrombogenics and grant support from Alcon Laboratories, Genentech, the NEI/NIH, Ophthotech, PRN, Regeneron, and Second Sight. He is an equity owner in PRN. Dr. Ho is the Chief Medical Editor of Retina Today. Dr. Ho may be reached at acho@att.net.

1. Data on file, Allergan, Inc.
2. OZURDEX® Prescribing Information.

This insert to *Retina Today* is sponsored and edited by Allergan, Inc.

IMPORTANT SAFETY INFORMATION (continued)

Warning and Precautions (continued)

Adverse Reactions

The most common ocular adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® for retinal vein occlusion and posterior segment uveitis include: intraocular pressure increased (25%), conjunctival hemorrhage (22%), eye pain (8%), conjunctival hyperemia (7%), ocular hypertension (5%), cataract (5%), vitreous detachment (2%), and headache (4%).

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Please see OZURDEX® full Prescribing Information at the end of this article.

OZURDEX[®]

(dexamethasone intravitreal implant) 0.7 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OZURDEX[®] safely and effectively. See full prescribing information for OZURDEX[®].

OZURDEX[®] (dexamethasone intravitreal implant)

Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

- Contraindications, Aphakic Eyes with Rupture of the Posterior Lens Capsule (4.3) 09/2012
- Contraindications, ACIOL and Rupture of the Posterior Lens Capsule (4.4) 09/2012
- Warnings and Precautions, Risk of Implant Migration (5.3) 02/2012

INDICATIONS AND USAGE

OZURDEX[®] is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1) and for the treatment of non-infectious uveitis affecting the posterior segment of the eye. (1.2)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the NOVADUR[®] solid polymer drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Advanced glaucoma (4.2)
- Aphakic eyes with rupture of the posterior lens capsule (4.3)
- ACIOL and rupture of the posterior lens capsule (4.4)
- Hypersensitivity (4.5)

WARNINGS AND PRECAUTIONS

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)
- The implant may migrate to the anterior chamber if the posterior lens capsule is not intact. (5.3)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by $\geq 20\%$ of patients were increased intraocular pressure and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis

OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only.

2.2 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

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. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. **Do not twist or flex the tab.** The long axis of the applicator should be held parallel to the limbus, and the sclera should be engaged at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path. The tip of the needle is advanced within the sclera for about 1 mm (parallel to the limbus), then re-directed toward the center of the eye and advanced until penetration of the sclera is completed and the vitreous cavity is entered. The needle should not be advanced past the point where the sleeve touches the conjunctiva.

Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each applicator can only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new applicator must be used, and the sterile field, syringe, gloves, drapes, and eyelid speculum should be changed before **OZURDEX**® is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR**® solid polymer drug delivery system.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

4.2 Advanced Glaucoma

OZURDEX® is contraindicated in patients with advanced glaucoma.

4.3 Aphakic Eyes with Rupture of the Posterior Lens Capsule

OZURDEX® is contraindicated in patients who have aphakic eyes with rupture of the posterior lens capsule.

4.4 ACIOL and Rupture of the Posterior Lens Capsule

OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

4.5 Hypersensitivity

OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [see *Patient Counseling Information* (17)].

5.2 Potential Steroid-related Effects

Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

5.3 Risk of Implant Migration

Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients in the First Six Months

MedDRA Term	OZURDEX® N=497 (%)	Sham N=498 (%)
Intraocular pressure increased	125 (25%)	10 (2%)
Conjunctival hemorrhage	108 (22%)	79 (16%)
Eye pain	40 (8%)	26 (5%)
Conjunctival hyperemia	33 (7%)	27 (5%)
Ocular hypertension	23 (5%)	3 (1%)
Cataract	24 (5%)	10 (2%)
Vitreous detachment	12 (2%)	8 (2%)
Headache	19 (4%)	12 (2%)

Increased IOP with **OZURDEX®** peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received **OZURDEX®** required surgical procedures for management of elevated IOP.

Following a second injection of **OZURDEX®** in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

6.2 Postmarketing Experience

The following reactions have been identified during post-marketing use of **OZURDEX®** in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **OZURDEX®**, or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema, endophthalmitis, and hypotony of the eye (associated with vitreous leakage due to injection).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

Topical dexamethasone has been shown to be teratogenic in mice producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day at 3 or 5 days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant

rhesus monkeys would be approximately 85 times higher than an **OZURDEX®** injection in humans (assuming 60 kg body weight).

There are no adequate and well-controlled studies in pregnant women. **OZURDEX®** (dexamethasone intravitreal implant) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

8.4 Pediatric Use

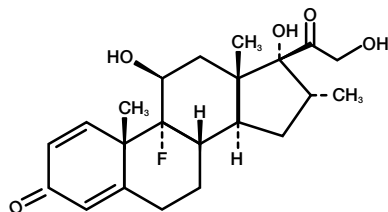
Safety and effectiveness of **OZURDEX®** in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

OZURDEX® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR®** solid polymer drug delivery system. **OZURDEX®** is preloaded into a single-use, specially designed **DDS®** applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR®** system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The chemical name for dexamethasone is Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α)-. Its structural formula is:



MW 392.47; molecular formula: C₂₂H₂₉FO₅

Dexamethasone occurs as a white to cream-colored crystalline powder having not more than a slight odor, and is practically insoluble in water and very soluble in alcohol.

The PLGA matrix slowly degrades to lactic acid and glycolic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

12.3 Pharmacokinetics

Plasma concentrations were obtained from 21 patients in two 6 month studies prior to dosing and on Days 7, 30, 60, and 90 following the intravitreal implant containing 0.35 mg or 0.7 mg dexamethasone. In both studies, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 10 of 73 samples in the 0.7 mg dose group and from 2 of 42 samples in the 0.35 mg dose group were above the LLOQ, ranging from 52 pg/mL to 94 pg/mL. The highest plasma concentration value of 94 pg/mL was observed in one subject from the 0.7 mg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In an in vitro metabolism study, following the incubation of [¹⁴C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether **OZURDEX**[®] (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of **OZURDEX**[®], dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells in vitro or in the in vivo mouse micronucleus test.

14 CLINICAL STUDIES

Retinal Vein Occlusion

The efficacy of **OZURDEX**[®] for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, **OZURDEX**[®] demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

Number (Percent) of Patients with ≥ 15 Letters Improvement from Baseline in BCVA

Study Day	Study 1			Study 2		
	DEX 700 N=201	Sham N=202	p-value*	DEX 700 N=226	Sham N=224	p-value*
Day 30	40 (20%)	15 (7%)	< 0.01	51 (23%)	17 (8%)	< 0.01
Day 60	58 (29%)	21 (10%)	< 0.01	67 (30%)	27 (12%)	< 0.01
Day 90	45 (22%)	25 (12%)	< 0.01	48 (21%)	31 (14%)	0.039
Day 180	39 (19%)	37 (18%)	0.780	53 (24%)	38 (17%)	0.087

*P-values were based on the Pearson's chi-square test.

In each individual study and in a pooled analysis, time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with **OZURDEX**[®] compared to sham ($p < 0.01$), with **OZURDEX**[®] treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a ≥ 15 letter (3-line) improvement in BCVA with **OZURDEX**[®] occurs within the first two months after implantation in approximately 20-30% of subjects. The duration of effect persists approximately one to three months after onset of this effect.

Posterior Segment Uveitis

The efficacy of **OZURDEX**[®] was assessed in a single, multicenter, masked, randomized study of 153 patients with non-infectious uveitis affecting the posterior segment of the eye.

After a single injection, the percent of patients reaching a vitreous haze score of 0 (where a score of 0 represents no inflammation) was statistically significantly greater for patients receiving **OZURDEX**[®] versus sham at week 8 (primary time point) (47% versus 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving **OZURDEX**[®] versus 7% for sham at week 8.

16 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX[®] (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator, NDC 0023-3348-07.

Storage: Store at 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

In the days following intravitreal injection of **OZURDEX**[®], patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist.

Patients may experience temporary visual blurring after receiving an intravitreal injection. They should not drive or use machines until this has resolved.

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