The US Food and Drug Administration (FDA) approval of the dexamethasone intravitreal implant (OZURDEX®, Allergan, Inc.) was the first time that any medical therapy was indicated for macular edema secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Previously, laser was the only approved treatment option for BRVO patients, while the standard of care for CRVO was observation. Thus, this indication opened the door for clinicians to be able to treat these patients and help improve their visual acuity on label.

Additionally, the subsequent approval of the dexamethasone intravitreal implant for the

Indications and Usage
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).

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

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

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.

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Injection Techniques for the Dexamethasone Intravitreal Implant

Indication of noninfectious posterior segment uveitis also widened the field of treatment options for this devastating disease.

The dexamethasone intravitreal implant is delivered via injection using a 22-gauge needle in an office-based procedure. With any intravitreal injection procedure, however, it is important to follow protocols that ensure safety and help increase patient comfort. Retina Today recently had the opportunity to speak with several clinicians who have varying experience with injecting the dexamethasone intravitreal implant for the indications of BRVO, CRVO, and, to a lesser extent, noninfectious posterior segment uveitis. According to all of the doctors with whom we spoke, their learning curve for the injection procedure was shallow. In this insert to Retina Today, sponsored by Allergan, Inc., physicians provide their own experiences with injecting the dexamethasone intravitreal implant and offer pearls on different steps in the procedure and tips on how they advise patients along the way.

Profile of the Experienced Injector
Michael A. Singer, MD: I have performed approximately 200 injections with the dexamethasone intravitreal implant—approximately 95% for retinal vein occlusion (RVO) and 5% for noninfectious posterior segment uveitis. In my experience, it took me three to five injections to become completely comfortable with the procedure. I am constantly modifying my technique, and I have found that over time, I inject with a more fluid motion than in the past. In the past I injected at a 15º-30º angle, but I have gone from this more parallel angle to one that is more perpendicular—

Important Safety Information (continued)
Contraindications (continued)
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Warnings and Precautions
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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 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 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 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)
Adverse Reactions
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Julia A. Haller, MD: I have not found the injection technique for the dexamethasone intravitreal implant to be particularly difficult. Retina surgeons are accustomed to inserting cannulas in eyes that are approximately the same gauge as the injector needle, which is 22 gauge, and the injection itself takes a few seconds. It is, however, a little more involved than performing the intravitreal injections to which we are accustomed.

Gaurav Shah, MD: I have injected the dexamethasone intravitreal implant in approximately 45 to 50 patients, mostly for RVO, but I have also injected the implant for some noninfectious posterior segment uveitis patients since the FDA approval. In my opinion, it takes one or two injections to become fully comfortable with the procedure; in general, it is not a complicated process, particularly for retina surgeons who are accustomed to inserting trocars for surgery. The actual injection takes approximately 30 to 45 seconds.

Pravin U. Dugel, MD: I have been using the dexamethasone intravitreal implant since early in its development. Thus far, I have injected the implant in approximately 50 patients, primarily for RVO. Although it is hard for me to say how difficult the injection procedure is to learn because I have been performing this for so long, I do believe that the learning curve is small for the implant, provided the clinician understands that it requires more effort than a typical intravitreal injection to push the larger gauge

Pearls for Injecting the Dexamethasone Intravitreal Implant

By Michael Singer, MD

Following are some important points regarding injecting the dexamethasone intravitreal implant:

- Do not inject the dexamethasone intravitreal implant in a patient who cannot lie back (ie, patients with breathing problems).
- Use subconjunctival anesthetic and wait for it to take effect. See two or three patients in between to ensure the patient is numb when you return to do the injection.
- Explain to the patient that he or she will feel pressure.
- Tell the patient that he or she will hear a click when the implant releases from the injector so there is no surprise, making the patient flinch.
- If you encounter resistance from a tough sclera, increase your angle.
- Do not make your first implant injection in a patient who has undergone vitrectomy.

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Needle into the eye. This means that patients feel more pressure during the injection. It is also important that doctors counsel their patients about what to expect. For instance, when the medicine is going in, patients will hear a click. Some patients may find this to be disconcerting, so it is wise to inform them ahead of time.

David S. Boyer, MD: I have implanted approximately 50 dexamethasone intravitreal implants, mostly for RVO but a few for noninfectious posterior segment uveitis since its approval for that indication.

Jeffrey S. Heier, MD: I have performed approximately 20 injections of the dexamethasone intravitreal implant thus far for a variety of situations in patients with macular edema due to RVO or in noninfectious posterior segment uveitis. In general, I do not counsel patients any differently for the implant injection than I do for any intravitreal injection.

David Callanan, MD: I have performed over 100 injections with the dexamethasone intravitreal implant, mostly for patients with RVO, but a few for patients with noninfectious posterior segment uveitis. I have found that the difficulty of the injection varies depending on the thickness of the sclera. In patients who have a really thick sclera, it takes longer and requires more pressure to get through it. I have injected the implant in patients with a normal

Other Considerations With the Dexamethasone Intravitreal Implant

By Pravin U. Dugel, MD

Anti-infectives. For those physicians who have not yet implanted the dexamethasone intravitreal implant, I would suggest that they use povidone-iodine prior to the injection. Regarding the use of antibiotics, I would also advise skepticism toward small studies that show any kind of reduction or increase in rates of endophthalmitis as a result of the use of a particular antibiotic.

Reinjections. In my practice, the greatest number of reinjections with the dexamethasone intravitreal implant was three (not including the initial implant). This patient had a central retinal vein occlusion with severe edema, and the first injection of the implant elicited minimal response. The patient continued to progress with each subsequent injection of the dexamethasone implant. This case demonstrates that there is a lack of information regarding the effects of the implant injected sequentially for an extended period of time. Additionally, this case shows that retinal vein occlusion is a diverse disease with a variable response to treatment. Outcomes with the dexamethasone intravitreal implant are, in my opinion, patient-dependent.

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.

Adverse Reactions

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to less thick sclera, and the 22-gauge needle goes through easily.

Preparing the Patient for the Injection

Dr. Singer: Before administering the injection of the implant, I tell my patients to expect a feeling of pressure. I advise them to be still and that the procedure is very quick—I have found that if I divert a patient’s attention, he or she does not even realize that they are receiving an injection until it is over. The injection itself takes me approximately 5 seconds.

My protocol for anesthesia includes instilling povidone-iodine and then using two cotton-tip applicators that are soaked in proparacaine to rub the conjunctiva for approximately 30 seconds. I then use a subconjunctival lidocaine 2% and epinephrine injection because I have found that it helps to decrease the incidence of subconjunctival hemorrhage. After I give the anesthetic, I will see two or three patients (5-10 minutes) and then return to administer the injection of the dexamethasone intravitreal implant.

I employ calipers, both to mark the spot where I will inject, but also to test the eye for sensation. I then apply povidone-iodine again, wait 20 to 30 seconds to allow for bacterial eradication, and then I prepare the injection. When I take the applicator from the carton and the foil, I carefully pull off the cap of the needle and then pull out the safety to ensure that the implant is still in the applicator.

Dr. Haller: Prior to the injection, I numb the eye further with a subconjunctival injection of lidocaine and wait for it to take effect for approximately 1 to 2 minutes. I use povidone-iodine prior to the injection to disinfect the ocular surface.

Dr. Shah: When I see a patient and I decide that he or she fits the criteria for the dexamethasone implant, I instill a drop of a fourth-generation fluoroquinolone and then one drop of tetracaine hydrochloride 0.5%. The patient then fills out the appropriate paperwork (consent, insurance forms), allowing the drop to penetrate for approximately 10 to 15 minutes. At the time of prep, I will instill another drop of tetracaine and have that sit for approximately another 5 minutes. I find that the tetracaine helps to minimize postinjection subconjunctival hemorrhage. The 22-gauge needle for the implant is larger than the needles I use for other intravitreal injections, so I want to do as much as I can to prevent blood being drawn into the eye during the procedure.

I use a speculum along with a cotton-tip applicator to stabilize the eye for injection. I tell patients to expect a sensation of pressure on their eye as I make the injection and that they will hear an audible click as the medicine is released.

Dr. Dugel: My preinjection anesthesia protocol is no different than it is for any other intravitreal injection I perform. After we know a patient is going to have an injection, one of the technicians will dip one or two cotton-tip applicators in 4% lidocaine and place it inferotemporally to numb that part of the eye. I then inject subconjunctival lidocaine in the area where I will do the injection and step out of the room to see another patient. During that time, the technician instills povidone-iodine to clean the eye, lids, and lashes, after which another drop of lidocaine is applied. This routine has been effective and my patients have not reported any pain during the injection.

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I would not recommend using topical drops or gels because this procedure requires a larger needle and increased pressure for injection. Patients do feel the injection pressure required for this injection, and if it hurts, it is never a good experience.

Dr. Boyer: When a patient comes in to have the implant injected, I tell them that they will feel a good amount of pressure. If he or she has had a previous intravitreal injection, I explain that the sensation of pressure will be greater with the dexamethasone implant.

Other Considerations With the Dexamethasone Intravitreal Implant

By David S. Boyer, MD

Needle gauge. It is important to note that injecting the dexamethasone intravitreal implant with a 22-gauge needle is different from the intravitreal injections with which we are accustomed. The injection process for the implant has similarities to trocar insertion for vitrectomy. Many doctors have difficulty when the globe becomes retroplaced from the needle being pressed posteriorly. Pushing the needle in quickly helps to avoid this. When I first began injecting the dexamethasone intravitreal implant, I was concerned that the size of the needle would lead to wound leaks, but this has not been a factor for me.

Insertion angle. I use a two-plane 10°-20°-angle incision because I believe that it seals better than a more perpendicular angle. Stanislao Rizzo, MD, published a paper that demonstrated better wound sealing using a more parallel oblique incision vs a straight incision.1 All of my incisions with the implant injector have sealed well using this technique.

Depressing the actuator button. Once the OZURDEX® applicator needle has been inserted into the eye, you need to press the actuator button to eject the OZURDEX® implant into the vitreous. It is important to note that the speed at which the implant is ejected is directly proportional to the speed at which the button is depressed. There also will be an audible click when the button is depressed.

I have now started pushing the back portion of the actuator button for two reasons. First, it seems to allow greater control of the speed at which the implant is ejected. By pushing the back of the actuator button, the travel of the internal mechanism may be longer, making the speed easier to control. The second reason is that the audible click is much softer. I still warn patients that they may hear the click, as some people can be alarmed; however, it is much less pronounced since I started pushing the back part of the button.


IMPORTANT SAFETY INFORMATION (continued)
Warnings and Precautions (continued)

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intravitreal implant. I advise patients of the side effect of IOP elevation, which is usually controlled well with glaucoma drops.

Prior to the injection, all patients receive a topical drop of tetracaine and then I give a subconjunctival injection of lidocaine, ballooning the area, which not only anesthetizes, but also offers space to reduce the risk of vitreous prolapse. I then let the patient sit for approximately 10 to 12 minutes. After that time, I flush the eye with povidone-iodine, place the lid speculum, and proceed with the injection.

Dr. Heier, MD: Prior to the injection, I administer povidone-iodine and a subconjunctival injection of lidocaine and wait 5 minutes for the anesthetic to take effect. When taking the tip off the injector to expose the needle, it is important not to have the needle touch the tip as the needle can be blunted, making entry more difficult.

Dr. Callanan: Before I inject the implant, I soak a cotton-tip applicator in proparacaine and hold it to the site. I put a drop of povidone-iodine in the cul-de-sac and administer a subconjunctival lidocaine 2% and epinephrine injection. I wait approximately 5-10 minutes, during which time I will see one or two patients. By that time, the povidone-iodine is dry and I put the lid speculum in, after which I take another cotton-tip applicator that has been soaked in povidone-iodine and I roll it over the quadrant where I will inject. I do not use preinjection antibiotics.

**Injection Procedure**

Dr. Singer: For the actual injection, I have the patient lie back in the chair and, stabilizing the eye with a cotton-tip applicator to prevent rotation, I upwardly displace the conjunctiva and inject, needle bevel-up, at approximately a 60° angle. If the needle enters the sclera at too shallow an angle, it is not going to have enough torque to reach far enough posteriorly. When I come across this problem, I pull back, lift my hand up, and increase the angle by about 15°. The maximum angle that I will employ is 75°, keeping the needle bevel-up.

Once the safety stop touches the sclera, I rotate to a perpendicular 90° and, aiming toward the posterior pole, push down the actuator button on the handpiece slowly until I hear the click. I wait 5 seconds to ensure that there is no recoil of medicine and then I take a cotton-tip applicator, roll it back over the insertion point, rotate my hand down, and pull the needle out.

Dr. Haller: I perform the injection inferotemporally and so I ask the patient to look up, which also helps to stabilize the eye. I use an oblique angle, approximately 30°-45°, which is similar to my incision for vitrectomy. I will occasionally use a cotton-tip applicator to displace the conjunctiva and to stabilize the eye.

When making the injection, I use the same amount of pressure that I would when inserting cannulas. If I encounter a sclera that is particularly tough, I will apply slightly more pressure.

When injecting the dexamethasone intravitreal implant in vitrectomized eyes or eyes with filtering blebs, I do not necessarily change my technique—I might push a bit harder, but I am prepared for that. I use a cotton-tip applicator as I withdraw the injector and rub it over the incision to ensure that it is sealed.

Dr. Shah: I make my incision at a 30° angle and, as the safety stop meets the eye, I rotate the injector to

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“When making the injection, I use the same amount of pressure that I would when inserting cannulas. If I encounter a sclera that is particularly tough, I will apply slightly more pressure.”

— Julia A. Haller, MD

Because this location ensures that the implant will not be sitting in the line of patients’ vision. I angle the incision as much as possible—20º—without having it flat. I do not change my approach for a tough sclera.

When I have completed the injection and am taking the needle out of the eye, I angle the incision back to 20º, just as I would for trocar removal in surgery, and remove the needle with my right hand, using my left hand to slide a cotton-tip applicator over the incision to provide counter pressure and minimize vitreous incarceration.

In regard to vitrectomized eyes, I do not change any aspect of my injection technique. If, however, a patient has undergone multiple surgeries with large incisions and there are areas of scleral thinning, I would avoid such areas.

Dr. Boyer: Displacing the conjunctiva with a cotton-tip applicator, I enter the sclera at a fairly straight 10º-20º angle. Once I feel that the needle is in, I turn it to approximately 90º and aim posteriorly, and I push it in very quickly. If you push the needle slowly, it will not go into the eye. An analogy would be trying to push a straw into an orange. If the straw is pushed hard with a quick motion, it might get into the orange, but if pushed slowly, the straw will bend. The needle should not be advanced past the Teflon safety sleeve. I then press the actuator button very slowly to release the implant.

After the implant is in the eye, I withdraw the needle exactly as I insert it—I turn the handpiece from 90º to an almost flat, 10º angle and pull the needle out of the wound. I use a cotton-tip applicator to go over the wound to ensure that there is no leaking vitreous or any other sign of fluid, and then I check the placement of the implant postinjection. It can be hard to see because it may be anterior in the vitreous space, but 90% of the time, I can actually see the implant as it goes in.

Dr. Dugel: I perform the injection inferotemporally a 90º angle and slowly depress the actuator button to release the implant. If I encounter a tough sclera, I will make the injection more slowly—I try to twist the handpiece as I inject so that it slides in without more pressure.

Although I do inject the dexamethasone intravitreal implant in vitrectomized eyes, I would be more hesitant for someone to start his or her first injection on such a patient. This particular type of patient may be more likely to have some hypotony after the injection, so one needs to be more vigilant in terms of proper technique. The only thing that I change about my injection technique is to increase the bevel in my incision, entering at a flatter angle so that I achieve a wound that seals well. I would also be cautious with patients who have deep-set orbits, because these eyes tend to be pushed back into the globe, making the injection difficult.

I always check the placement of the implant postinjection. It can be hard to see because it may be anterior in the vitreous space, but 90% of the time, I can actually see the implant as it goes in.

IMPORTANT SAFETY INFORMATION (continued)
Warnings and Precautions (continued)

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wound internally to ensure that there is no bleeding and the entire implant is in the proper place.

Dr. Heier: I enter the sclera at a 30º transverse angle. Once the needle has entered the eye, I turn the handpiece perpendicularly and aim toward the posterior segment. I find that a more transverse entry makes it easier. If I find that the sclera is tough, I will often twist the injector as I am moving in at the perpendicular angle.

I use counter-pressure with a cotton-tip applicator on the equator of the globe to stabilize the eye if I have to press and twist the injector fairly hard.

For vitrectomized eyes, I am concerned about wound leaks, so when I am withdrawing the injector from the eye, I use a cotton-tip applicator and massage the area lightly for approximately 30 seconds and then have the patient stay in the office for a bit longer so I can assess for any leakage.

Dr. Callanan: I inject at a 20º-30º angle. For a tough sclera, I rotate the handpiece slightly while advancing the needle. It is helpful to use nontooth forceps or a cotton-tip applicator to apply counter pressure and stabilize the globe during the injection. I also roll a cotton-tip applicator over the injection site immediately after withdrawing the needle.

Postinjection Protocol

Dr. Singer: After the injection, I always double-check that the implant is where I want it in the eye—sometimes it is easy to see, and other times it is not, but usually when I have the patient look in the direction that I have injected, inevitably I’ll see the implant somewhere near the vitreous base. When injecting in patients who have had vitrectomies, wound leaks are of greater concern. For these patients, I carefully check the incision postinjection to ensure that I have made a good biplanar incision.

I send the patient home with a topical antibiotic and instructions to use it every 2 hours on the first day and then four times a day for 2 days following. We tell patients that if they notice any changes, such as acute pain, they should call.

I see patients back in 4 to 6 weeks, and it is at that time that we check IOP. Almost all IOP rises with the dexamethasone intravitreal implant can be addressed with glaucoma drops. For vitrectomized eyes, I make a more biplanar incision and take great care to check for wound leaks. Before I send these patients home, I check to ensure that the IOP is at a normal level.

Dr. Haller: After the injection, I instill povidone-iodine because it has a detergent effect on the cilia. I instill an antibiotic ointment to protect against punctate keratitis and irritation.

I counsel all of my patients who receive an intravitreal injection that the most significant risk is endophthalmitis. I instruct patients to call the office immediately if

“I typically see patients for follow-up 3-4 weeks after the injection, telling them to call the office if they experience any redness or pain that seems to worsen over time.”

— Gaurav Shah, MD

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they notice an increase in floaters, pain, or increased redness. Unless there is a problem, I typically see patients back at approximately 60 days postinjection.

Dr. Shah: After the injection I instill a drop of fourth-generation fluoroquinolone. If there is none on hand, I will give the patient a bottle of Polytroin to instill for a few days after the injection. I typically see patients for follow-up 3-4 weeks after the injection, telling them to call the office if they experience any increased redness or pain that seems to worsen over time. If a patient has had a subconjunctival hemorrhage, however, there will be more redness, so I am careful to explain this to him or her.

Dr. Dugel: I will usually see patients 1 month after the injection, but will have them come into the office 1 to 2 weeks after the injection for an interim pressure check. In my experience, any subsequent rises in IOP can usually be managed with topical glaucoma drops.

Our patient counseling prior to discharge is the same as with any intravitreal injection: We instruct patients to call the office if they notice any loss of vision or discomfort. Although the eye will be red after an injection, we tell patients to maintain a low threshold for any other structural or functional changes. We send patients home with antibiotic drops that they take for 3 days postinjection.

Dr. Boyer: Although I am not convinced postinjection antibiotics are necessary, I do use them. If no vitreous is leaking and everything appears normal, I do not check IOP postinjection. I see patients 4 weeks later.

I send patients home with instructions to call if they have any difficulties with their vision such as haze, or if they have any pain. The eye will certainly be red after an injection, but if there is unusual discomfort or any discharge, the patient must be examined.

For most of my patients, the greatest amount of discomfort comes from the povidone-iodine, so I apply ointment and use a patch for all of my patients at the end of the procedure.

I do not change my technique for vitrectomized eyes; however, I do maintain a higher level of concern regarding hemorrhages due to neovascularization, particularly in patients with diabetes. If I observe any leakage due to a soft globe, I will patch the patient as usual and see him or her back the next day. This has not, however, been a problem in my practice.

Dr. Heier: After a routine dexamethasone implant injection, I see patients back in 1 month. If I have any concerns about a wound leak, I may see a patient back the next day, although this scenario is highly unusual. With the dexamethasone implant, IOP is usually not an issue. I do have patients’ IOPs checked before they leave the office postinjection, but it is rarely an issue, partly because of the force that is used to inject the implant. Before patients leave the office, we instruct them to call us if they notice significant pain or decrease of vision that is different from what they experienced immediately after the injection of the implant.

Dr. Callanan: After the injection, I instill a single drop of a fourth-generation fluoroquinolone in all eyes postinjection. Patients with thin sclerae or with a history of diabetes or vitrectomy receive a bottle of antibiotics with instructions to use them for 2-3 days afterward.

This insert to Retina Today is sponsored by Allergan, Inc.
Injection Techniques for the Dexamethasone Intravitreal Implant

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.

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

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 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.

Please see full OZURDEX® prescribing information at the end of this article.

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**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. 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)

**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)

**ADVERSE REACTIONS**

In controlled studies, the most common adverse reactions reported by ≥ 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

Revised: 09/2010
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 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 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 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.

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

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

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.

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 μg) 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:

![Chemical structure of dexamethasone](image)

MW 392.47; molecular formula: C_{22}H_{29}FO_{5}.

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):

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DEX 700 N=201</td>
<td>Sham N=202</td>
</tr>
<tr>
<td>Day 30</td>
<td>40 (20%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Day 60</td>
<td>58 (29%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Day 90</td>
<td>45 (22%)</td>
<td>25 (12%)</td>
</tr>
<tr>
<td>Day 180</td>
<td>39 (19%)</td>
<td>37 (18%)</td>
</tr>
</tbody>
</table>

*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% vs. 12%). The percent of patients achieving a 3-line improvement from baseline BCVA was 43% for patients receiving OZURDEX® vs. 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 15º-30ºC (59º-86ºF).

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 patients 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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