INDICATIONS AND USAGE

Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Retinal Vein Occlusion
OZURDEX® 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.
Contraindications (continued)

**Glaucoma:** OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

**Torn or Ruptured Posterior Lens Capsule:** OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.
Seenu Hariprasad, MD: Each member of the panel participating in this discussion has had extensive experience using the dexamethasone intravitreal implant 0.7 mg (OZURDEX®, Allergan) for each of its FDA-approved indications, which are treatment of noninfectious uveitis affecting the posterior segment of the eye, macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), and diabetic macular edema (DME). Many also participated in the clinical trials that led to the approvals for these indications.

Based on a new understanding that these conditions are multifactorial in that they involve upregulation of vascular endothelial growth factor as well as inflammatory cytokines, our use of OZURDEX® has increased, and the way we use it has evolved. Depending on the patient, we are incorporating the implant to address inflammatory cytokines. Our levels of experience with this treatment option and our injection style have changed, too. In addition, OZURDEX® applicators include a second-generation needle.

The Evolving Use of OZURDEX®

Bruce Saran, MD: In part because of the benefits of its sustained-release formulation, I was an early adopter of OZURDEX®.

If I don't see improvement in visual acuity or adequate response on OCT, I tend to introduce OZURDEX®, Based on my clinical experience, this is the best approach for my patients.

If a retinal vein occlusion or DME patient exhibits prominent macular edema at baseline, I may, after reviewing patient characteristics and contraindications, initiate OZURDEX® as a first-line therapy.

David R.P. Almeida, MD, MBA, PhD: I firmly believe noninfectious posterior segment uveitis, vein occlusion–related macular edema, and DME are multifactorial, and I’ve been treating them as such for quite a while. I find that addressing the inflammatory response early by initiating therapy that addresses multiple inflammatory components is a good approach.

Kimberly Drenser, MD, PhD: Inflammation is an important aspect of managing these diseases, especially diabetic disease. In particular, in DME patients, I’ve seen how using the implant early can make a difference.

Sunir Garg, MD: I, too, have a very low threshold for using the dexamethasone intravitreal implant in a patient’s therapy. I often start with another therapy, and some patients do very well. I don’t like to

IMPORTANT SAFETY INFORMATION (continued)

Hypersensitivity: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, 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.
see only marginal improvement in the patient's vision or OCT over months. For these patients, I can use the dexamethasone intravitreal implant to get them seeing better without having monthly injections by using a sustained-release formulation.¹

Fifteen years ago, no one talked much about cytokines because we didn't have any treatments to target them. Once we learned about the VEGF cytokine and how it plays an important role in retinal vascular disease, we realized that many cytokines are upregulated in these eyes.²³ The more we learn about diabetic eye disease, the more we realize that targeting one cytokine is great, although if we can target multiple cytokines simultaneously, we can focus on the multi-inflammatory component of the disease.⁷

Dr. Hariprasad: I think it's vitally important to practice evidence-based medicine, and your collective statements are based on the data (Table 1). I agree that DME and retinal vein occlusion are multifactorial diseases.¹² I believe my patients are well served when I incorporate the dexamethasone intravitreal implant. This targets different components of the disease,¹² which makes very good sense to me.

Discussions With Patients and Colleagues
Dr. Hariprasad: How do you discuss the dexamethasone intravitreal implant with patients?

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### TABLE 1. OZURDEX® Primary Efficacy Endpoint Results

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Measurement</th>
<th>OZURDEX® (n = 328)</th>
<th>Sham (n = 328)</th>
<th>Estimated Difference (95% confidence interval [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic macular edema</td>
<td>MEAD⁸</td>
<td>Patients gaining ≥ 15 letters (3 lines) in BCVA (n) at month 39</td>
<td>19.5%⁵ (64/328)</td>
<td>10.7% (35/328)</td>
<td>8.8% (3.4%, 14.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients losing ≥ 15 letters in BCVA (n) at month 39</td>
<td>13.7% (45/328)</td>
<td>10.7% (35/328)</td>
<td>3.0% (-2.0%, 8.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean change in BCVA (letters) (standard deviation) at month 39</td>
<td>2.2 (15.88)</td>
<td>0.8 (12.72)</td>
<td>1.3 (-0.9, 3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Measurement</th>
<th>OZURDEX® (n = 427)</th>
<th>Sham (n = 426)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular edema following retinal vein occlusion</td>
<td>GENEVA⁹,¹⁰</td>
<td>Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 30</td>
<td>21.3%⁵ (93/427)</td>
<td>7.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 60</td>
<td>29.3%⁵ (123/427)</td>
<td>11.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 90</td>
<td>21.8%⁵ (93/427)</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 180</td>
<td>21.5%⁵ (93/427)</td>
<td>17.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Measurement</th>
<th>OZURDEX® (n = 77)</th>
<th>Sham (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninfectious posterior segment uveitis</td>
<td>HURON¹¹</td>
<td>Percentage of patients with vitreous haze score of zero at week 8</td>
<td>46.8%⁶ (35/77)</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

¹P = .002 vs sham.  
²P < .001 vs sham.  
³P = Not significant.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)
Steroid-related Effects: Use of corticosteroids including OZURDEX® (dexamethasone intravitreal implant) 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 because of the potential for reactivation of the viral infection.
How do you explain to colleagues why the therapy is important for your patients?

Dr. Garg: I explain to patients that I have treatments that are likely to help. We discuss how we are going to select the appropriate treatment course for their disease and that the effect of the dexamethasone intravitreal implant usually lasts longer. I let them know that I have experience with OZURDEX® (dexamethasone intravitreal implant) 0.7 mg injection.

We also talk about how the injections can potentially cause the pressure inside the eye to increase. If this happens, we can usually lower the pressure by using an eye drop. If, however, the pressure increases too much, a surgical procedure may be necessary. In the 3-year MEAD clinical study, 0.3% (1/324) of OZURDEX® patients required incisional surgery for steroid-induced IOP increase. I also explain to patients that after the procedure, we can continue the injections with good success. And I discuss the possibility of cataract progression,

### TABLE 2. Medical and Surgical Management of IOP in OZURDEX® Clinical Trials

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Patients Receiving IOP Medication at the Final Study Visit</th>
<th>Patients Receiving One IOP Medication at the Final Study Visit</th>
<th>Incisional Surgery for Elevated IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OZURDEX®</td>
<td>Sham</td>
<td>OZURDEX®</td>
</tr>
<tr>
<td>Diabetic macular edema</td>
<td>MEAD®</td>
<td>21.1%     (54/244)²</td>
<td>3.6%   (6/169)³</td>
<td>9.8%     (24/244)³</td>
</tr>
<tr>
<td>Macular edema following retinal vein occlusion</td>
<td>GENEVA®</td>
<td>22.9%     (96/421)⁴</td>
<td>3.8%   (16/423)⁵</td>
<td>16.2%     (68/421)⁶</td>
</tr>
<tr>
<td>Noninfectious posterior segment uveitis</td>
<td>HURON®</td>
<td>16.9%     (13/77)⁹</td>
<td>9.2%   (7/76)¹⁰</td>
<td>13.0%     (10/77)¹⁰</td>
</tr>
</tbody>
</table>

¹Pooled results from 2 multicenter, masked, randomized, sham-controlled, 3-year studies.
²Pooled results from 2 multicenter, randomized, masked, sham-controlled, 6-month studies.
³Multicenter, masked, randomized, 26-week study.

**IMPORTANT SAFETY INFORMATION (continued)**

**Adverse Reactions**

**Diabetic Macular Edema**

Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® (dexamethasone intravitreal implant) for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).
particularly with younger patients. I explain that with the dexamethasone intravitreal implant, cataract surgery may be necessary; but once that’s out of the way, vision should improve, and we can continue with the treatment plan. It is an educational conversation, and I think patients respond well to it.

As far as colleagues in my area, some use the dexamethasone intravitreal implant frequently and some do not.

**Dr. Saran:** I have many patients who come from far away. I seek to reduce the monthly injections for all of my patients, and the OZURDEX® (dexamethasone intravitreal implant) 0.7 mg implant is a significant medication in our treatment arsenal to achieve this goal because it has a sustained-release formulation; in addition, IOP is typically manageable (Tables 2 and 3). Doctors who don’t have experience with the implant may fear the potential side effects, but any of the IOP issues that arise are manageable and patients typically do well. I’ve been able to rely on the safety profile of OZURDEX®.

**Dr. Almeida:** Because I’m a big advocate of therapy that addresses multiple inflammatory components, I usually explain all of the treatment options to the patient right from the beginning.

Rather than cataract progression, I find the biggest obstacle some

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Percentage of Eyes With IOP Increase From Baseline</th>
<th>Percentage of Eyes With IOP ≥ 35 mm Hg</th>
<th>Peak Mean IOP Timing</th>
<th>Generally Returns to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic macular edema</td>
<td>MEAD</td>
<td>28.1% (91/324)</td>
<td>4.0% (13/328)</td>
<td>6.2% (20/324)</td>
<td>45 or 90 days after injection</td>
</tr>
<tr>
<td>Macular edema following retinal vein occlusion</td>
<td>GENEVA</td>
<td>26.6% (112/421)</td>
<td>1.4% (6/423)</td>
<td>5.9% (25/421)</td>
<td>60 days after injection</td>
</tr>
<tr>
<td>Noninfectious posterior segment uveitis</td>
<td>HURON</td>
<td>9.6% (7/73) at week 8</td>
<td>0% (0/71) at week 8</td>
<td>7.9% (6/76)</td>
<td>56 days after injection</td>
</tr>
</tbody>
</table>

TABLE 3. OZURDEX® IOP Across Indications

**IMPORTANT SAFETY INFORMATION (continued)**

**Adverse Reactions (continued)**

**Diabetic Macular Edema (continued)**

**Increased Intraocular Pressure:** IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.
doctors see to using OZURDEX® (dexamethasone intravitreal implant) is the potential for an increase in IOP. The results of the MEAD trial answer that concern. Slightly more than 25% of patients (91/324) showed a ≥ 10 mm Hg IOP increase,⁴,¹² and fewer than half of them required drops (136/324).⁵,¹² My colleagues and I recently published a retrospective case series exploring ocular hypertension in patients with preexisting glaucoma or glaucoma suspects receiving the implant.

**Dr. Drenser:** When discussing the dexamethasone intravitreal implant with colleagues, I focus on the fact that the multifactorial nature of the disease makes it necessary in order to address both inflammation and other factors.¹,²

Also, I think many have concerns about IOP increase, so I can tell them from experience it’s manageable. I also mention the second-generation applicator needle, which features a coating designed to facilitate glide of the needle through the sclera and into the posterior.¹⁶,¹⁷

We’re able to see patients less frequently for the purpose of giving them an injection.⁴

**OZURDEX® Injection: Patient Experience**

**Dr. Hariprasad:** Do you discuss with patients the clicking sound that occurs as you administer the dexamethasone intravitreal implant?

**Dr. Garg:** As long as I tell patients ahead of time that they’re going to hear a click, they are totally fine with it. I say, “In a second, you’re going to hear a click, and that’s normal.”¹²

**Dr. Drenser:** As long as we talk them through it, patients handle the implant injection well.

**Preparing the Patient and Delivering the Injection**

*Please see the Administration instructions from the U.S. Prescribing Information Section 2.2 included at the end of this supplement.*

**Dr. Hariprasad:** How do you prepare the patient for the OZURDEX® injection, and how do you handle the components of the injection procedure?

**Dr. Garg:** Except for very select circumstances, our technicians handle all of the preparation. We have a well-established protocol for all of our injections. I don’t use a lid speculum; the assistant uses both thumbs to retract the eyelids. I refrain from talking during the injection.

For anesthesia, I use approximately 0.25 mL of subconjunctival lidocaine injection, 0.2 mL or 0.3 mL, which I let sit for about 5 minutes.¹²,¹⁸ It makes the procedure virtually pain free for the patient. In the past, I used a pledget, but my patients prefer the subconjunctival lidocaine. Research that our group¹⁹ and others have published suggests that routine use of topical antibiotics after intravitreal injection may increase bacterial...

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"I find that addressing the inflammatory response early by initiating therapy that addresses multiple inflammatory components is a good approach."

— DAVID R.P. ALMEIDA, MD, MBA, PHD
resistance, so we use copious povidone iodine.12,20

Once I uncap the needle, I want to perform the injection immediately. I remove the cap quickly, but I’m cognizant to pull it along the plane of the needle to make sure I’m not hitting the tip. I feel as if I have better control pulling off the cap quickly rather than trying to slowly separate it. I don’t use calipers to measure 3 mm to 4 mm from the limbus. I do shift the conjunctiva peripherally with a cotton-tipped swab, which I think helps to stabilize the eye.

Because of the Bell’s response, I inject inferotemporally. I put the needle into the eye, similar to the way I place a trocar for microincision vitrectomy. I enter at an approximately 20-degree angle, and when the needle is inserted about 1 mm, I rotate the injector and continue perpendicular to the eye. It’s a smooth motion, not a deliberate reposition. Rather than hold the OZURDEX® (dexamethasone intravitreal implant) applicator like a pencil, which is how I hold other injection needles for intravitreal injections, I lay it across my fingers with my thumb perpendicular to the button. That gives me better control and I can simply rotate my wrist to get the implant into the eye. The angle works well for me because the applicator is larger than a traditional syringe. After the injection, I don’t look into the back of the eye to visualize the implant.

Dr. Drenser: My protocol is similar to Dr. Garg’s. Most of the time, I prepare the patient myself, but we have some very experienced technicians who were surgical techs and are very good with aseptic technique. If they’re working with me on a given day, they handle the patient prep.

I use subconjunctival lidocaine to numb the eye for most patients. Some dislike it, so for them, I use topical tetracaine HCl 0.5% (TetraVisc Forte, Accutome), and patients do surprisingly well. I ask patients to look to the side for the injection because I find the eye moves less and I don’t have to manipulate it as much. Because it’s a slightly larger needle, I tend to look at the injection like a 23-gauge implant, but we require them to pass a preparation test first. We prep with povidone iodine but not antibiotics, and we’ve moved away from subconjunctival lidocaine. I have found that subconjunctival injections increase the chance of subconjunctival hemorrhage and this adds to postinjection discomfort and increased patient calls. For all but approximately 5% of our patients, we instill topical tetracaine — we no longer use TetraVisc. When the decision is made to treat, we place the first anesthetic drop in the eye.

“I use a cotton-tipped swab to displace the conjunctiva, and I enter the eye in a beveled manner.”
— KIMBERLY DRENSER, MD, PHD

**IMPORTANT SAFETY INFORMATION (continued)**

**Adverse Reactions (continued)**

**Diabetic Macular Edema (continued)**

**Cataracts and Cataract Surgery:** The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® (dexamethasone intravitreal implant) group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group.
After the informed consent process is complete, we instill another drop. In a period of about 5 minutes, patients receive 3 to 4 drops. Once in a while, if a patient mentions he or she was uncomfortable during the procedure, we make a note in the chart and suggest subconjunctival lidocaine the next time. I like to use a speculum because it protects the lid margin from getting near the injection site. The patient is instructed not to talk. I find it beneficial to give the patient something to focus on during the injection by having technicians wiggle their fingers where I want the patient to look. I perform the injection at a 20-degree angle, typically in the inferior temporal quadrant. This allows the implant to enter away from the macula and float in the inferior quadrants outside central vision. Also, any subconjunctival hemorrhage is masked by the lower lid.

**Dr. Almeida:** According to our standardized practice pattern, a technician prepares the patient for the injection using povidone iodine. We ask patients not to talk. I don't use calipers and I don't shift the conjunctiva. I don't use a cotton-tipped swab either, because I think the fewer items in the eye, the better. I make sure I'm not touching the needle at any point during the injection process. I inject superotemporally or inferotemporally. After the injection, I don't visualize the implant in the eye.

**Dr. Hariprasad:** Either I or one of our retina fellows prepares the patient and the applicator. To numb the eye, we dip two cotton-tipped swabs in 4% lidocaine, place them under the superior temporal and superior nasal fornices, and leave them there for a minute. We do this 3 times. We use povidone iodine swabs 3 times to prep the eye. For the injection, I use clean gloves and a lid speculum with a lash guard. I ask everyone in the room to keep the talking to a minimum. Although I know I am in the minority, I use a drop of a fourth-generation fluoroquinolone right after the injection procedure is completed. I’m very careful about how I remove the cap from the applicator design and second-generation needle.

**Applicator Design and Second-Generation Needle**

**Dr. Hariprasad:** The second-generation applicator has a needle manufactured by TSK Laboratory. Allergan pursued this TSK needle based on feedback from Retina Specialists relative to the glide.

“I’m delighted to have this treatment to offer my patients. It expands how well I can treat them. The more we learn about it, the more we find that it’s a great option to have.”

— SUNIR GARG, MD

IMPORTANT SAFETY INFORMATION (continued)

**Adverse Reactions (continued)**

**Diabetic Macular Edema (continued):** Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.
factor and penetration of the original needle. The OZURDEX® (dexamethasone intravitreal implant) 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.\textsuperscript{16,17}

In my opinion, the OZURDEX® applicator is cleverly and elegantly designed. The actuator button squeezes an accordion-like piece below it. The accordion flattens and pushes the implant inside the eye via the needle. I’ve always found the design to be intelligent because a trained surgeon controls the pressure that is applied to the button.\textsuperscript{12}

What has been your experience with the second-generation applicator needle versus the previous needle? Studies have evaluated the second-generation needle with favorable performance in glide and penetration.\textsuperscript{16,17}

\textbf{Dr. Drenser:} I was impressed right away by the ease with which it goes into the eye.

\textbf{Dr. Saran:} Using the second-generation needle is smooth. There’s very little resistance entering the eye.

\textbf{Dr. Almeida:} I agree that the second-generation needle penetrates the sclera easily.

\textbf{Dr. Garg:} The second-generation needle is great. It is smooth and goes in nicely.

\textbf{Dr. Hariprasad:} I’ve done many, many dexamethasone intravitreal implants, in clinical trials and post approval, and in patients with different sclera. I’ve had success in performing the procedure at the intended site of injection. It’s a minimal concern at most. As long as the doctor performs the injection with confidence and is well trained, it is unlikely he or she would be unable to complete the procedure.

**Injection Tips and Techniques**

\textbf{Dr. Almeida:} One tip I’ve given to new OZURDEX® users — and received positive feedback on — is to use subconjunctival lidocaine for the first series of injections. That way, the patient isn’t feeling pressure while the doctor is reaching his or her comfort level.

\textbf{Dr. Garg:} In my opinion, the most helpful advice for doctors new to OZURDEX® is to take advantage of the wet labs that Allergan offers. The company will bring a pig eye or model eye to you and you can perform as many sample injections

> “The actuator button squeezes an accordion-like piece below it. The accordion flattens and pushes the implant inside the eye via the needle. I’ve always found the design to be intelligent because a trained surgeon controls the pressure that is applied to the button.”

— \textsc{Seenu Hariprasad, MD}

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**Figure 1: OZURDEX® applicator**

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**IMPORTANT SAFETY INFORMATION (continued)**

**Adverse Reactions (continued)**

**Retinal Vein Occlusion and Posterior Segment Uveitis**

Adverse reactions reported by greater than 2% of patients in the first 6 months following injection of OZURDEX® (dexamethasone intravitreal implant) 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%).

*Study was conducted in porcine eyes.*
as you want so you can practice. For experienced vitreoretinal surgeons, the learning curve is really very short. To me, it’s actually more simple to inject an OZURDEX® (dexamethasone intravitreal implant) implant than it is to insert a cannula with a trocar during surgery.

As Dr. Hariprasad mentioned, I advise doctors to “own the injection.” When you execute with confidence, you have an ease and rapidity of motion that makes for a good experience for the patient and for yourself.

Dr. Drenser: It’s helpful for residents or fellows to gain experience injecting OZURDEX® in the wet lab setting to increase comfort level when subsequently injecting OZURDEX® into an anesthetized eye.

Dr. Saran: The key is to think of the OZURDEX® injection technique as one fluid motion rather than several isolated steps. You have to commit, choose your site, do the entry, and then press the applicator button in one swift motion. That limits the amount of contact time with the eye and increases patient cooperation. I gently squeeze the trigger, which allows for a controlled injection. Patients can perceive your confidence, and the procedure is smooth and seamless.

Dr. Almeida: I’ve seen beginners who aren’t accustomed to using trocars get hung up on trying to bevel the incision.

Dr. Hariprasad: It is sensible for inexperienced injectors, or even experienced surgeons who want to try delivering the implant before performing the procedure on a patient, to take advantage of the opportunity to practice with an Allergan OZURDEX® (dexamethasone intravitreal implant) 0.7 mg wet lab. Also, it’s worth reiterating the importance of approaching the injection with confidence and using a fluid motion. With proper training and experience, it’s a simple procedure, and it’s not necessary to overcomplicate it.

Meeting an Important Need in Patient Care

Dr. Hariprasad: Let’s close with thoughts on the dexamethasone intravitreal implant and its importance in the treatment algorithms for DME and macular edema following BRVO or CRVO.

Dr. Garg: I’m delighted to have this treatment to offer my patients. It expands how well I can treat them. The more we learn about it, the more we find that it’s a great option to have.

“Using the second-generation needle is smooth. There’s very little resistance entering the eye.”

— BRUCE SARAN, MD

Dr. Drenser: I’ve found that OZURDEX® can be effective for many patients. I have a growing number of OZURDEX® patients who have their visual acuity managed effectively without the need for monthly injections. I’ve steadily increased my use of OZURDEX®. Its use is straightforward. Also, it is helpful to have the second-generation needle and all of the support from Allergan regarding patient assistance.

Dr. Saran: My primary impression of the dexamethasone intravitreal implant is that it fills an important need. OZURDEX® helps treat the inflammatory component of DME without the need for monthly injections.

Dr. Almeida: OZURDEX® produces good visual improvements,
and it can be efficiently incorporated into a busy practice flow. In vivo, the matrix dissolves completely into its components, lactic acid and glycolic acid. In turn, these are converted to carbon dioxide and water. 12,21

**OZURDEX® Progress**

**Dr. Hariprasad:** In conclusion, I would like to give a special thanks to Drs. Drenser, Garg, Saran, and Almeida for taking time out of their busy schedules to share with us their extensive experience in utilizing steroids in the management of vitreoretinal diseases. It is clear from this discussion that the utilization of OZURDEX® (dexamethasone intravitreal implant) has progressed over the past few years. Their generosity in openly sharing their expertise on this topic will be valued by our clinician colleagues and their patients. •

**References**

12. OZURDEX® Prescribing Information.

**Dosage and Administration**

FOR OPHTHALMIC INTRAVITREAL INJECTION. 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.

**Please see full Prescribing information at the end of this article.**
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)
- The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
- The treatment of diabetic macular edema (1.3)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection. (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)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by 20–70% of patients were cataract, 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: 9/2014
**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.

1.3 Diabetic Macular Edema

**OZURDEX**® is indicated for the treatment of diabetic macular edema.

2 **DOSAGE AND ADMINISTRATION**

2.1 General Dosing Information

For ophthalmic intravitreal injection.

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 periorcular 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 Glaucoma

**OZURDEX**® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

4.3 Torn or Ruptured Posterior Lens Capsule

**OZURDEX**® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for **OZURDEX**® use.

4.4 Hypersensitivity

**OZURDEX**® is contraindicated in patients with known hypersensitivity to any components of this product [see Adverse Reactions (6)].

5 **WARNINGS AND PRECAUTIONS**

5.1 Intravitreal Injection-related Effects

Intravitreal injections, including those with **OZURDEX**®, 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 Steroid-related Effects

Use of corticosteroids including **OZURDEX**® may produce posterior subcapsular cataracts, increased intraocular pressure, and
Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see Adverse Reactions (6.1)].

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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 including OZURDEX® 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.

Retinal Vein Occlusion and Posterior Segment Uveitis
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):

Table 1: Adverse Reactions Reported by Greater than 2% of Patients

<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.

Diabetic Macular Edema
The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in Table 2 were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are shown in Tables 2 and 3:

Table 2: Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract1</td>
<td>166/243 ² (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>15 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>14 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous opacities</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Retinal aneurysm</td>
<td>10 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>7 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>7 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Table 2: Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients (continued)

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX&lt;sup&gt;®&lt;/sup&gt; (N=324 (%))</th>
<th>Sham (N=328 (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal tear</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Non-ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (13%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (5%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

1 Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX<sup>®</sup> subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

2 243 of the 324 OZURDEX<sup>®</sup> subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

**Increased Intraocular Pressure**

Table 3: Summary of Elevated Intraocular Pressure (IOP) Related Adverse Reactions

<table>
<thead>
<tr>
<th>IOP</th>
<th>Treatment: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥10 mm Hg from Baseline at any visit</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
<td>50 (15%)</td>
</tr>
<tr>
<td>Any IOP lowering medication</td>
<td>136 (42%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4 (1.2%)</td>
</tr>
</tbody>
</table>

<sup>+</sup> OZURDEX<sup>®</sup>: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy

Sham: 1 laser iridotomy

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period) shown below:

![Figure 1: Mean IOP during the study](image)

**Cataracts and Cataract Surgery**

At baseline, 243 of the 324 OZURDEX<sup>®</sup> subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX<sup>®</sup> group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX<sup>®</sup> group and 12 months in the Sham group. Among these patients, 61% of OZURDEX<sup>®</sup> subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX<sup>®</sup> group and 20 for Sham) of the studies.

6.2 Postmarketing Experience

The following reactions have been identified during post-marketing use of OZURDEX<sup>®</sup> 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<sup>®</sup>, or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema, endophthalmitis, hypotony of the eye (associated with vitreous leakage due to injection), and retinal detachment.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis.

8.3 Nursing Mothers
Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with OZURDEX® is low [see Clinical Pharmacology (12.3)]. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is 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 sustained-release drug delivery system. OZURDEX® is preloaded into a single-use, 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:

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 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 with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantification (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. 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. Adequate fertility studies have not been conducted in animals.
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 4: Number (Percent) of Patients with ≥ 15 Letters Improvement from Baseline in BCVA

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OZURDEX®</td>
<td>Sham</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 ≥ 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.

### Diabetic Macular Edema

The efficacy of OZURDEX® for the treatment of diabetic macular edema was assessed in two, multicenter, masked, randomized, sham-controlled studies. Subjects were to be evaluated for retreatment eligibility every three months starting from Month 6 but could only receive successive treatments at least 6 months apart. Retreatment was based on physician’s discretion after examination including Optical Coherence Tomography. Patients in the OZURDEX® arm received an average of 4 treatments during the 36 months.

The primary endpoint was the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 39 or final visit for subjects who exited the study at or prior to Month 36. The Month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received re-treatment at Month 36. Only fourteen percent of the study patients completed the Month 39 visit (16.8% from OZURDEX® and 12.2% from Sham).

### Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCFc)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>OZURDEX®</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>56 (10)</td>
<td>57 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>59 (34-95)</td>
<td>58 (34-74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>34 (21%)</td>
<td>19 (12%)</td>
<td>9.3% (1.4%, 17.3%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>15 (9%)</td>
<td>17 (10%)</td>
<td>-1.1% (-7.5%, 5.3%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>4.1 (13.9)</td>
<td>0.9 (11.9)</td>
<td>3.2 (0.4, 5.9)</td>
</tr>
<tr>
<td>2*</td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>55 (10)</td>
<td>56 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>58 (34-72)</td>
<td>58 (36-82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>30 (18%)</td>
<td>16 (10%)</td>
<td>8.4% (0.9%, 15.8%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>30 (18%)</td>
<td>18 (11%)</td>
<td>7.1% (-0.5%, 14.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>0.4 (17.5)</td>
<td>0.8 (13.6)</td>
<td>-0.7 (-4.1, 2.6)</td>
</tr>
</tbody>
</table>

*Study 1: OZURDEX®, N=163; Sham, N=165

*Study 2: OZURDEX®, N=165; Sham, N=163

*14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. The visual acuity improvement from baseline increases during a treatment cycle, peaks at approximately 3 Months posttreatment and diminishes thereafter. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the final study visit.
Figure 2: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye

Figure 3: Mean BCVA Change from Baseline
The best corrected visual acuity outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 39 are presented in Table 6.

Table 6: Visual Acuity outcomes at Month 39 (Subgroup for pooled data with LOCFc)

<table>
<thead>
<tr>
<th>Subgroup (Pooled)</th>
<th>Outcomes</th>
<th>OZURDEX®</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPseudophakic</td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>16 (20%)</td>
<td>11 (11%)</td>
<td>8.4% (-2.2%, 19.0%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>4 (5%)</td>
<td>7 (7%)</td>
<td>-2.2% (-9.1%, 4.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>5.8 (11.6)</td>
<td>1.4 (12.3)</td>
<td>4.2 (0.8, 7.6)</td>
</tr>
<tr>
<td>aPhakic</td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>48 (20%)</td>
<td>24 (11%)</td>
<td>9.0% (2.7%, 15.4%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>41 (17%)</td>
<td>28 (12%)</td>
<td>4.4% (-1.9%, 10.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>1.0 (16.9)</td>
<td>0.6 (12.9)</td>
<td>0.3 (-2.4, 3.0)</td>
</tr>
</tbody>
</table>

*Pseudophakic: OZURDEX®, N=82; Sham, N=99
*Phakic: OZURDEX®, N=246; Sham, N=229
*14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients the data at Month 36 or earlier was used in the analysis.

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

Steroid-related Effects
Advertise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advertise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advertise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

Intravitreal Injection-related Effects
Advertise patients that in the days following intravitreal injection of OZURDEX®, patients are at risk for potential complications including particularly, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

When to Seek Physician Advice
Advertise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines
Advertise patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

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Made in Ireland.
Based on 72212US18
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)
For Intravitreal Injection
Initial U.S. Approval: 1958

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)
• The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
• The treatment of diabetic macular edema (1.3)

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)
• Glaucoma (4.2)
• Torn or ruptured posterior lens capsule (4.3)
• Hypersensitivity (4.4)

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 20–70% of patients were cataract, increased intraocular pressure and conjunctival hemorrhage. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION.
Revised: 05/2018

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  1.2 Posterior Segment Uveitis
  1.3 Diabetic Macular Edema

2 DOSAGE AND ADMINISTRATION
  2.1 General Dosing Information
  2.2 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS
  4.1 Ocular or Periocular Infections
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  4.3 Torn or Ruptured Posterior Lens Capsule
  4.4 Hypersensitivity

5 WARNINGS AND PRECAUTIONS
  5.1 Intravitreal Injection-related Effects
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6 ADVERSE REACTIONS
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8 USE IN SPECIFIC POPULATIONS
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14 CLINICAL STUDIES

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

1.3 Diabetic Macular Edema
OZURDEX® is indicated for the treatment of diabetic macular edema.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
For ophthalmic intravitreal injection.

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 periorcular 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 Glaucoma
OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

4.3 Torn or Ruptured Posterior Lens Capsule
OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

4.4 Hypersensitivity
OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product [see Adverse Reactions (6)].

5 WARNINGS AND PRECAUTIONS
5.1 Intravitreal Injection-related Effects
Intravitreal injections, including those with OZURDEX®, 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 Steroid-related Effects
Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see Adverse Reactions (6.1)].

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
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 including OZURDEX® 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.

Retinal Vein Occlusion and Posterior Segment Uveitis

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):

Table 1: Adverse Reactions Reported by Greater than 2% of Patients

<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.

In a 2-year observational study, among patients who received >2 injections, the most frequent adverse reaction was cataract 54% (n= 96 out of 178 phakic eyes at baseline). Other frequent adverse reactions from the 283 treated eyes, regardless of lens status at baseline, were increased IOP 24% (n=68) and vitreous hemorrhage 6.0% (n=17).

Diabetic Macular Edema

The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in Table 2 were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are shown in Tables 2 and 3:

Table 2: Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>166/243* (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>15 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>14 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous opacities</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Retinal aneurysm</td>
<td>10 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>7 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>7 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>
Table 2: Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients (continued)

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (13%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (5%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

1 Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

2 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

**Increased Intraocular Pressure**

Table 3: Summary of Elevated Intraocular Pressure (IOP) Related Adverse Reactions

<table>
<thead>
<tr>
<th>IOP</th>
<th>Treatment: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OZURDEX® N=324</td>
</tr>
<tr>
<td>IOP elevation ≥10 mm Hg from Baseline at any visit</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
<td>50 (15%)</td>
</tr>
<tr>
<td>Any IOP lowering medication</td>
<td>136 (42%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP*</td>
<td>4 (1.2%)</td>
</tr>
</tbody>
</table>

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy
Sham: 1 laser iridotomy

The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period) shown below:

**Figure 1: Mean IOP during the study**

Cataracts and Cataract Surgery
At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

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, hypotony of the eye (associated with vitreous leakage due to injection), and retinal detachment.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice, and malformations of the abdominal wall/intestines and kidneys in rabbits at doses 5 and 4 times higher than the recommended human ophthalmic dose (RHOD) of OZURDEX® (0.7 milligrams dexamethasone), respectively.
In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

**Data**

**Animal Data**

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.75 mg/kg/day in the mouse is approximately 5 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.20 mg/kg/day, on gestational day 6 followed by 0.13 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis. A no-observed-adverse-effect-level (NOAEL) was not identified in the mouse or rabbit studies.

**8.2 Lactation**

**Risk Summary**

Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production or cause other unwanted effects. There is no information regarding the presence of dexamethasone in human milk, the effects on the breastfed infants, or the effects on milk production to inform risk of OZURDEX® to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for OZURDEX® and any potential adverse effects on the breastfed child from OZURDEX®.

**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 sustained-release drug delivery system. OZURDEX® is preloaded into a single-use, 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](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 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 with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. 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**

Animal studies have not been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis or mutagenesis. Fertility studies have not been conducted in animals.
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 4: Number (Percent) of Patients with ≥ 15 Letters Improvement from Baseline in BCVA

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OZURDEX®</td>
<td>Sham</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% 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.

Diabetic Macular Edema

The efficacy of OZURDEX® for the treatment of diabetic macular edema was assessed in two, multicenter, masked, randomized, sham-controlled studies. Subjects were to be evaluated for retreatment eligibility every three months starting from Month 6 but could only receive successive treatments at least 6 months apart. Retreatment was based on physician's discretion after examination including Optical Coherence Tomography. Patients in the OZURDEX® arm received an average of 4 treatments during the 36 months.

The primary endpoint was the proportion of patients with 15 or more letters improvement in BCVA from baseline at Month 39 or final visit for subjects who exited the study at or prior to Month 36. The Month 39 extension was included to accommodate the evaluation of safety and efficacy outcomes for subjects who received re-treatment at Month 36. Only fourteen percent of the study patients completed the Month 39 visit (16.8% from OZURDEX® and 12.2% from Sham).

Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>OZURDEX®</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>56 (10)</td>
<td>57 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>59 (34-95)</td>
<td>58 (34-74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of ≥15 letters in BCVA (n(%) )</td>
<td>34 (21%)</td>
<td>19 (12%)</td>
<td>9.3% (1.4%, 17.3%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%) )</td>
<td>15 (9%)</td>
<td>17 (10%)</td>
<td>-1.1% (-7.5%, 5.3%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>4.1 (13.9)</td>
<td>0.9 (11.9)</td>
<td>3.2 (0.4, 5.9)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) Baseline BCVA (Letters)</td>
<td>55 (10)</td>
<td>56 (9)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>Median (range) Baseline BCVA (Letters)</td>
<td>58 (34-72)</td>
<td>58 (36-82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain of ≥15 letters in BCVA (n(%) )</td>
<td>30 (18%)</td>
<td>16 (10%)</td>
<td>8.4% (0.9%, 15.8%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%) )</td>
<td>30 (18%)</td>
<td>18 (11%)</td>
<td>7.1% (-0.5%, 14.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>0.4 (17.5)</td>
<td>0.8 (13.6)</td>
<td>-0.7 (-4.1, 2.6)</td>
</tr>
</tbody>
</table>

*aStudy 1: OZURDEX®, N=163; Sham, N=165
*bStudy 2: OZURDEX®, N=165; Sham, N=163
*c14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. The visual acuity improvement from baseline increases during a treatment cycle, peaks at approximately 3 Months posttreatment and diminishes thereafter. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the final study visit.
Figure 2: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye

Study 1: Phakic Subjects
Proportion of Subjects Gaining >=15 Letters (ITT LOCF)

Study 2: Phakic Subjects
Proportion of Subjects Gaining >=15 Letters (ITT LOCF)

Study 1: Pseudophakic Subjects
Proportion of Subjects Gaining >=15 Letters (ITT LOCF)

Study 2: Pseudophakic Subjects
Proportion of Subjects Gaining >=15 Letters (ITT LOCF)

Figure 3: Mean BCVA Change from Baseline

Study 1: Phakic Subjects
Mean Change from Baseline in BCVA (Letter) (ITT LOCF)

Study 2: Phakic Subjects
Mean Change from Baseline in BCVA (Letter) (ITT LOCF)

Study 1: Pseudophakic Subjects
Mean Change from Baseline in BCVA (Letter) (ITT LOCF)

Study 2: Pseudophakic Subjects
Mean Change from Baseline in BCVA (Letter) (ITT LOCF)
The best corrected visual acuity outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 39 are presented in Table 6.

**Table 6: Visual Acuity outcomes at Month 39 (Subgroup for pooled data with LOCF)**

<table>
<thead>
<tr>
<th>Subgroup (Pooled)</th>
<th>Outcomes</th>
<th>OZURDEX(^a)</th>
<th>Sham</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudophakic</td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>16 (20%)</td>
<td>11 (11%)</td>
<td>8.4% (-2.2%, 19.0%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>4 (5%)</td>
<td>7 (7%)</td>
<td>-2.2% (-9.1%, 4.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>5.8 (11.6)</td>
<td>1.4 (12.3)</td>
<td>4.2 (0.8, 7.6)</td>
</tr>
<tr>
<td>Phakic</td>
<td>Gain of ≥15 letters in BCVA (n(%))</td>
<td>48 (20%)</td>
<td>24 (11%)</td>
<td>9.0% (2.7%, 15.4%)</td>
</tr>
<tr>
<td></td>
<td>Loss of ≥15 letters in BCVA (n(%))</td>
<td>41 (17%)</td>
<td>28 (12%)</td>
<td>4.4% (-1.9%, 10.7%)</td>
</tr>
<tr>
<td></td>
<td>Mean change in BCVA (SD)</td>
<td>1.0 (16.9)</td>
<td>0.6 (12.9)</td>
<td>0.3 (-2.4, 3.0)</td>
</tr>
</tbody>
</table>

\(^a\)Pseudophakic: OZURDEX\(^\circ\), N=82; Sham, N=99

\(^b\)Phakic: OZURDEX\(^\circ\), N=246; Sham, N=229

\(^c\)14% (16.8% from OZURDEX\(^\circ\) and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients the data at Month 36 or earlier was used in the analysis.

16  **HOW SUPPLIED/STORAGE AND HANDLING**

OZURDEX\(^\circ\) (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**

**Steroid-related Effects**

Advise patients that a cataract may occur after repeated treatment with OZURDEX\(^\circ\). If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX\(^\circ\) treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

**Intravitreal Injection-related Effects**

Advise patients that in the days following intravitreal injection of OZURDEX\(^\circ\), patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

**When to Seek Physician Advice**

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

**Driving and Using Machines**

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

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