

Intraocular Pressure Elevations Are Not Necessarily Glaucoma:

Perspectives on OZURDEX (dexamethasone intravitreal implant) 0.7 mg Treatment

A discussion on the differences between elevated intraocular pressure (IOP) and glaucoma, and how to assess each in patients with diabetic macular edema.

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.

Intraocular Pressure Elevations Are Not Necessarily Glaucoma: Perspectives on OZURDEX Treatment

A discussion on the differences between elevated IOP and glaucoma, and how to assess each in patients with diabetic macular edema.

OZURDEX (Allergan) is approved for the treatment of diabetic macular edema (DME), macular edema following branch or central retinal vein occlusion (BRVO or CRVO), and noninfectious posterior segment uveitis.¹ Elevated IOP is a known adverse reaction associated with ophthalmic steroids, including OZURDEX.¹ All patients treated with OZURDEX are monitored for elevated IOP and managed with eye drops, and, rarely, with surgery.¹ In clinical practice, concerns about elevated IOP remain.² We gathered a group of retina specialists and a glaucoma specialist to discuss the differences between elevated IOP and glaucoma, and how to assess each in patients with DME. The content of this supplement reflects the perspectives and experiences of the participants.

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IMPORTANT SAFETY INFORMATION (continued)

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.

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

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WHAT IS GLAUCOMA?

Jason Bacharach, MD: The term *glaucoma* usually brings with it a presumption that we are talking about intraocular pressure (IOP). But if we look to the American Academy of Ophthalmology's Preferred Practice Patterns on primary open-angle glaucoma (POAG) and POAG suspects,³ glaucoma is defined as a primary open-angle disease that's chronic, progressive, optic neuropathy in adults in which there is characteristic acquired atrophy of the optic nerve, and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy.³

Michael A. Singer, MD: I always believed IOP was the *sine qua non* of glaucoma. As a retina specialist, it surprised me when mention of IOP was removed from the 2015 AAO Preferred Practice Patterns in glaucoma.^{3,4}

Jeremy D. Wolfe, MD: I was also unaware IOP was not part of the 2015 definition before I read the latest guidelines.

DIFFERENCES BETWEEN ELEVATED IOP AND GLAUCOMA

Dr. Singer: In your practices, what do you use to assess glaucoma? I have always used IOP—do others use that as a standard benchmark as well?

Jorge A. Fortun, MD: I was trained that glaucoma was a particular phenotype of optic neuropathy. I have always thought of the disorder as glaucomatous optic neuropathy.³ Not just *glaucoma*. As frustrated as retina specialists are with some of our disease processes and not fully understanding them, Dr. Bacharach can certainly attest to the frustration on the part of glaucoma specialists trying to fully understand the multifactorial aspects of glaucoma. Most retina specialists I know believe high IOP equates to glaucoma. We are only now realizing that is not necessarily the case.

HOW TO ASSESS FOR ELEVATED IOP

Dr. Singer: In clinical trials, for elevated IOP in the study eye up to 30 mm Hg, the need for treatment was at the discretion of the investigator based on the patient's risk factors for optic nerve damage. For IOP > 30 mm Hg, consultation with a glaucoma specialist was recommended.⁵ When someone presents with an elevated pressure, what are your thought processes? How do you evaluate the cause of the elevated pressure?

Dr. Wolfe: There are a few concerns with these patients—including why the pressure is elevated. A steroid treatment may account for the elevated IOP. We need to evaluate more than just the pressure, though—if someone has an IOP of 25 to 28 mm Hg, but the optic nerve is healthy, I will watch him or her and recheck the pressure in a month. If that same patient has an IOP of 25 to 28 mm Hg and the nerve looks like it has glaucomatous damage, that would change my management strategy.^{2,6} I am in a retina-only practice, so in the latter example I would refer the patient to a glaucoma colleague.

Dr. Singer: Is there a trigger? How high does the IOP have to be for you to take a step back and decide you need to intervene rather than monitor?

Dr. Wolfe: Presuming there is a healthy optic nerve, I get uncomfortable with pressures around 30 mm Hg or higher. I am a lot more flexible if the nerve is healthy. If the nerve is not normal, however, I consider referrals to a glaucoma colleague if the IOP is around 22 mm Hg or above.^{2,6}

In our clinic, our technicians check pressures with a handheld tonometer and also check visual acuity with an autorefractor. If the pressure readings are different between the two eyes or above normal, I will applanate the patient myself and verify the technician's reading.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX® (dexamethasone intravitreal implant), have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® 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 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.

Please see additional Important Safety Information on the following pages.

Andrew Moshfeghi, MD: It is very similar for us at University of Southern California. Most of us use handheld tonometers, but some technicians prefer using traditional tonometry. I personally do not have a preference.

Dr. Bacharach: If you are using a handheld tonometry device, make sure there is a minimal 95% confidence interval on the readout.

Dr. Fortun: We also need to have a low threshold for bringing in our glaucoma colleagues for consultation. I make it a point to look at the optic nerve, and I am quick to tell the patient that I might be suspicious they are developing glaucoma, and that because I'm suspicious I am going to refer them to a specialist.

Dr. Singer: So for you, it is the optic nerve that serves as your trigger for a referral?

Dr. Fortun: We know from the Ocular Hypertension Treatment Study (OHTS)⁷ that we can decrease the risk of developing glaucoma if we lower IOP, so I have a very low threshold for referral to glaucoma.

Dr. Moshfeghi: IOP gets our attention because it is one of the key pieces of an ophthalmic examination. But what really catches my attention more than anything else is the optic nerve appearance. If I am seeing asymmetry and some notching or if I am seeing parapapillary internal hemorrhage, that gets my attention and warrants a referral.³

Dr. Bacharach: Exactly. We cannot look at IOP in isolation. For one thing, most patients who develop elevated IOP do not develop glaucoma.³ Those patients who have structural change in their nerve may already have glaucoma.⁸

TABLE 1. KEY RISK FACTORS FOR DEVELOPING OPEN-ANGLE GLAUCOMA³

Higher IOP	Older age	Family history of glaucoma
Thinner central cornea	Lower ocular perfusion pressure	Type 2 diabetes mellitus
Myopia	Lower systolic and diastolic blood pressure	Disc hemorrhage
Larger cup-to-disc ratio	Higher pattern standard deviation on threshold visual field testing	African race or Latino/Hispanic ethnicity

RISK FACTORS IN GLAUCOMA

Dr. Singer: In our multispecialty practice, we share technicians with the other specialties. Perhaps because of that, when our technicians see something unusual during our retina workups, they are able to bring it to our attention more quickly.

Dr. Moshfeghi: Where I practice, we also receive a lot of referrals, presumably from other ophthalmologists who have already recommended or suggested additional expertise.

Dr. Bacharach: When a family history suggests a higher risk for glaucoma, it makes sense to have your technician discuss some of the key points with the patient. Table 1 lists some of the key risk factors as determined from multiple cohort studies.³

Dr. Singer: How do you measure ocular perfusion?

Dr. Bacharach: A simple way to measure ocular perfusion is to push gently on the globe and look at the central

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%).



“Most patients who develop elevated IOP do not develop glaucoma.”³

—Jason Bacharach, MD

retinal artery perfusion. This will allow you to identify if that patient may be at risk for having poor perfusion pressure. And if ocular ischemic syndrome is present, there may be a few blot and dot hemorrhages in the periphery.^{9,10}

Dr. Fortun: That is not something we usually think about in clinic; we typically see it in the operating room. But it is widespread in our patient population and especially in people with vasculopathy and type 2 diabetes.⁸

Dr. Bacharach: Interestingly enough, in my opinion, the connection between type 2 diabetes and glaucoma, from an evidence-based medicine standpoint, is inconclusive.^{11,12} There are those of us in the glaucoma world who think there may be an association.

Disc hemorrhage may be something you will see more often in your practices—some are related to diabetes and hypertension, but they also serve as an important risk factor in glaucoma. A similar argument can be made for cup-to-disc ratios.⁸

Another risk factor to consider is family history. Do you ask about a family history of glaucoma when you are screening your retina patients?

Dr. Fortun: Yes, I ask everyone about family history, as it may also put the patient at a higher risk for developing or having glaucoma.⁸

Dr. Singer: I ask patients about family history, and that sometimes determines whether I will start patients on medication. I have started to consider family history as being just as much a risk factor as the others. From your perspective, though, is there an order to the weight of the risk factors we should be following?

Dr. Bacharach: Race is a very strong risk factor. In fact, the prevalence rates of glaucoma are significantly higher in black and Latino populations than in whites.^{13,14} Those races tend to be underserved in the United States and the Western world for these diseases and, for that reason, that should be taken very seriously.

The OHTS study compared treated and untreated patients with ocular hypertension; the 5-year results showed that treatment reduced the development of open-angle glaucoma by 50%, bringing down the cumulative probability from 9.5% to 4.4%.⁷ Another way to interpret this is that fewer than 10% of people with elevated IOP develop open-angle glaucoma, which is why the other risk factors are equally important. If patients are on the higher side of pressure readings, especially if the corneal pachymetry measurements are thin or even in the normal range, that should heighten your concern and may warrant a referral.⁸

Dr. Wolfe: I probably have a lower threshold for giving a consultation simply because I do not have a lot of the ancillary information. If I see a disc hemorrhage, I bring in their primary eye care physician so there are others who are also monitoring the health of the patient's eye.

Dr. Moshfeghi: I am not thinking about glaucoma for all my patients, but I do want an evaluation if I am considering using a corticosteroid or some other procedure that might be influenced by IOP or glaucoma.

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.

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).

Please see additional Important Safety Information on the following pages.

Dr. Wolfe: For those of us in retina-only practices who do not have the ancillary information, what do you think should concern us and make us refer?

Dr. Bacharach: When glaucoma specialists see patients who are referred by retina colleagues, we know it is because of an underlying pathology that looks suspicious or it is because someone has developed an elevated pressure and needs confirmation that it is not glaucoma. Once that patient is in our offices, we are going to manage that pathology. Most of my colleagues would agree that a long discussion is not necessary—just a copy of the electronic medical records and we can take it from there.

EVALUATING RISK FACTORS IN DME PATIENTS

Dr. Bacharach: Figure 1 illustrates some of the classic identifying characteristics of glaucoma as characterized by the Focusing Ophthalmology on Reframing Glaucoma Evaluation, known as FORGE, a systematic approach for the evaluation of the optic disc and retinal nerve fiber layer for glaucoma. FORGE was developed by glaucoma specialists and is commonly used in clinical practice.¹⁵

First, look at the scleral ring to the border of the nerve to determine the size. Then look at the rim itself. Follow the ISNT rule—where inferior thickness is usually the widest, followed by superior followed by nasal followed by temporal.¹⁵ As clinicians, we know that rule is not perfect, but it is an excellent clinical tool. You might be able to see dropout, particularly with red-free light, but if not, you truly can see that on an optical coherence topography (OCT).

If the nerve fiber layer is thin, you will easily see the blood vessel. In my opinion, β -parapapillary atrophy is probably an underutilized tool in assessing glaucoma. The African Descent in Glaucoma Evaluation Study (ADAGES) demonstrated that in African-Americans in particular, β -parapapillary atrophy is a very good prognostic sign of a potential for glaucoma damage

in that area of the nerve.^{16,17} Interestingly enough, whites were more at risk to have associations with optic nerve hemorrhages.¹⁶ In Figure 1, both of those pathologies are noted.

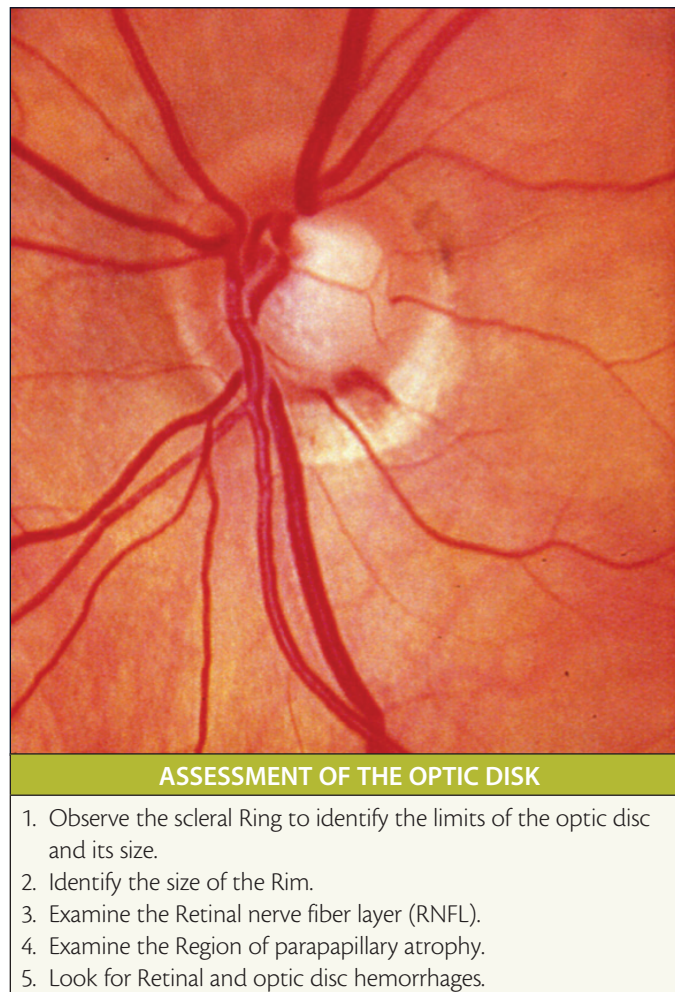


Figure 1. Image of optic disc and the use of 5 Rs for its assessment.¹⁵

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. 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.

Dr. Singer: Does the size matter, or how many quadrants the β -parapapillary atrophy involves?

Dr. Bacharach: Not necessarily. You can see β -parapapillary atrophy as a potential risk without cupping.⁸

Dr. Fortun: I agree with Dr. Wolfe that for retina specialists, the optic nerve's health is more of a trigger point than whatever the IOP may be. On every single patient in our practice, we get a macular OCT, so we are looking at the optic nerve on everyone. If the infrared image indicates slight cupping, I will pay closer attention to the optic nerve.

Dr. Bacharach: Another quick pearl—if you are using a 78, 60, or 90 diopter lens with a stereoscopic view of the macula, take a second or two to slide it over to look at the optic nerve in 3D. You might get a very different assessment of the optic nerve *live* than you would in a 2D representation.

You can see a big cup, or you might see a notch. The negative of just looking at an image is that it is 2D. If you are concerned about a patient's IOP, do you start them on IOP-lowering therapy?

Dr. Singer: I would. My rationale is that sometimes there is a disconnect and this way I know they have got medication in case they fall through the cracks. The glaucoma specialist may adjust what I have done, but at least the patient has received treatment on the day I see them.

Dr. Wolfe: If this patient's pressure was 30 mm Hg, I would start them on a medicine. If this patient's pressure was 22 mm Hg, I would still send them to a glaucoma specialist, but I may not start the medicine.^{2,6}

Dr. Bacharach: How do your treatment strategies change from the patient with diabetes to the patient with an inflamed eye or uveitis?

Dr. Moshfeghi: I would not use a prostaglandin analog in an inflammatory situation.³ I think if the pressure is approaching 30 mm Hg, I would probably start the patient on a drop.^{5,6}

Dr. Bacharach: A non-prostaglandin?

Dr. Moshfeghi: I would use a non-prostaglandin and then emphasize the importance of follow-up.^{2,5,6}

Dr. Fortun: I tend not to initiate treatment because a pressure of 30 mm Hg did not just happen. If I believe the patient has the ability to follow through on referrals, I will let the glaucoma specialist determine the proper treatment.

Dr. Bacharach: A fixed combination product may help patients with their treatment and bring down the pressure quite a bit.³

Dr. Wolfe: I will not prescribe a prostaglandin in inflammatory cases,⁶ and I use caution in patients with macular edema.

Dr. Bacharach: There is some controversy here. I use prostaglandins with caution in patients who have macular edema, but other options may be effective as well.^{5,18} The structural identification of nerve damage is more important than visual field analysis, which I would not expect retina specialists to perform. OCT, on the other hand, is a tool that has made it much easier for us to diagnose abnormalities. When you are obtaining OCTs, do you also obtain optic nerve scans?

Dr. Fortun: I do not, but should retina specialists be performing these tests on a semi-regular basis?

Dr. Moshfeghi: I do not, because I would then be responsible for appropriately managing the results of that test as well as the retinal pathology—and that is best left to a glaucoma specialist who can interpret the results better than I.

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%).

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

Please see additional Important Safety Information on the following pages.

TABLE 2. OZURDEX ACROSS INDICATIONS ^{5,22-24}							
Indication	Study	Percentage of Eyes with ≥10 mm Hg IOP Increase from Baseline		Percentage of Eyes with ≥35 mm Hg IOP Increase from Baseline		Peak Mean IOP Timing	Generally Returns to Baseline
		OZURDEX	Sham	OZURDEX	Sham	OZURDEX	
Diabetic macular edema	MEAD—Pooled results from 2 multicenter, masked, randomized, sham-controlled, 3-year studies ²²	28.1% (91/324) at any visit ⁵	4.0% (13/328) at any visit ⁵	6.2% (20/324) at any visit ⁵	0.9% (3/328) at any visit ⁵	45 or 90 days after injection ¹⁸	180 days after injection ¹⁸
Macular edema following retinal vein occlusion	GENEVA—Pooled results from 2 multicenter, randomized, masked, sham-controlled, 6-month studies ²³	26.6% (112/421) at any visit ⁵	1.4% (6/423) at any visit ⁵	5.9% (25/421) at any visit ⁵	0% (0/423) at any visit ⁵	60 days after injection ⁵	180 days after injection ⁵
Noninfectious posterior segment uveitis	HURON—Multicenter, masked, randomized, 26-week study ²⁴	9.6% (7/73) at week 8 ⁵	0% (0/71) at week 8 ⁵	7.9% (6/76) overall ⁵	1.3% (1/75) overall ⁵	56 days after injection ⁵	182 days after injection ⁵
IOP=intraocular pressure							

Dr. Singer: I will do some management of basic ocular hypertension for patients whom I suspect have glaucoma. Having said this, it is interesting how few OCTs of the optic nerve I have performed in comparison to OCT of the macula in patients who have developed ocular hypertension on steroid intravitreal therapy. But if I am concerned about the optic nerve deterioration in a patient, I will send the patient to a glaucoma specialist.

Dr. Bacharach: For patients whom you are planning to refer, the real-world consensus is that the glaucoma specialist can

handle the optic nerve side of things. But I would recommend an OCT in your glaucoma suspects. The AAO Preferred Practice Pattern notes that a glaucoma suspect is an individual with clinical findings and/or a constellation of risk factors that indicate an increased likelihood of developing primary open-angle glaucoma.⁸ Based on that definition, what percentage of patients in your clinics are glaucoma suspects?

Dr. Fortun: In my practice, the number is around 30%.

Dr. Wolfe: It is around 25% in my practice.

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.



“It is important to distinguish between a temporary IOP elevation and one that is longer term and can cause damage.”

—Jason Bacharach, MD

Dr. Singer: For me, the number of patients in my practice who are suspected to have glaucoma falls between 20% and 25%.

DIFFERENTIATING IOP ELEVATIONS

Dr. Bacharach: It is important to distinguish between a temporary IOP elevation and one that is longer term and can cause damage. Steroid-induced glaucoma is IOP that is elevated primarily due to increased outflow resistance.¹⁹ Elevated IOP is facilitated by an upregulation of glucocorticoid receptors on the trabecular meshwork, altering the rate of protein synthesis and inhibiting degradation of the extracellular matrix.^{6,19} It is these glycans that interfere with the normal processes in the trabecular meshwork and cause a reduced resistance to outflow.

Do you then take into consideration the route of administration, or type of steroid that you are utilizing, and its potential ramifications of IOP?

Dr. Moshfeghi: I use the dexamethasone intravitreal implant 0.7 mg (OZURDEX; Allergan).

Dr. Fortun: I also use OZURDEX.

Dr. Bacharach: In general, we do not use a topical steroid challenge before initiation of an intravitreal steroid injection treatment.^{2,20,21}

Dr. Moshfeghi: I also do not perform a topical steroid challenge, but I do take it into consideration if someone has a history of steroid response.^{2,20,21}

Dr. Fortun: I do not perform a topical steroid challenge either, because if I put them on a steroid and they do not have a steroid response, it does not really do anything to alleviate my concerns that they are not going to have a steroid response with an intravitreal steroid.

MONITORING FOR POTENTIAL IOP ELEVATIONS WITH OZURDEX

Dr. Singer: Table 2 shows us OZURDEX across indications and the IOP increases. MEAD and GENEVA found 28% of patients had a 10 mm Hg or more increase from baseline, and much smaller percentages, around 6%, in patients who had IOPs of 35 mm Hg or higher.^{5,22-24} But when we look at HURON, only 9.6% of patients had a 10 mm Hg or more increase.⁵ In clinical trials, elevations in IOP were assessed at each study visit. It is recommended that patients should be monitored for elevations in IOP regularly following the injection. How often do you see patients after you have injected them with OZURDEX the first time and then subsequently?

Dr. Fortun: Tonometry is recommended following the injection. I will see them 6 to 8 weeks, or more frequently as required by the patient's condition, after the first injection to check for elevated pressure (but I do not necessarily treat that). I will see them back at their 3-month visit, or sooner depending on the patient.¹

Dr. Wolfe: I request that patients return one month after their first injection so I can assess how the drug is working and watch the pressure. After that, I follow up with them every 6 to 8 weeks, or more frequently as required by the patient's condition. For me, it is more of the change in IOP than a set number.

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.

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

Please see additional Important Safety Information on the following pages.

A patient with a baseline pressure of 12 mm Hg that increases to 25 mm Hg will cause concern. But a patient with a baseline of 22 mm Hg that increases to 25 mm Hg is not as disconcerting.

Dr. Moshfeghi: I see patients 6 weeks after an OZURDEX intravitreal implant, or more frequently as required by the patient's condition. I also do not have a number per se. The IOP is just one part of the overall determination about whether to treat the escalation.

Dr. Singer: When does your follow-up change in terms of bringing them back for IOP monitoring, presuming there is no IOP rise after the first injection?

Dr. Fortun: I will monitor them for the first 2 or 3 cycles, then I extend to every 6 to 8 weeks until the fifth cycle. Then, if everything looks good, I will spread out the visits to every 3 to 4 months, depending on the patient's condition.²²

Dr. Moshfeghi: I bring them back every 6 weeks, or sooner depending on the patient's condition. If they have not had an IOP elevation after the first 2 injections, I am comfortable extending the time period for follow-up.

Dr. Fortun: Dr. Bacharach, should we be treating those IOP elevations? Let us say the patient has an IOP elevation but as the drug wears off, the IOP returns to baseline. Is that elevation predictive for developing long-term steroid-induced glaucoma? Is that elevation enough—even for the short amount of time it occurs—over the life span of treating the patient to cause glaucoma?

Dr. Bacharach: More than likely, no. If you look at the data of steroid-related IOP rise, it tends to be weeks to months and then it comes back down to the baseline level.^{5,18}

If we look at the MEAD study, for DME, where injections were given every 6 months, 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). Those who had an escalation in IOP had generally returned to baseline by the next injection delivery.^{18,22}

Dr. Singer: If we look at the MEAD study for DME, 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). In GENEVA, which evaluated OZURDEX in patients with retinal vein occlusion, at 6 months, only 1.2% of people had an IOP rise of 10 mm Hg or more.⁵ The HURON trials showed the same thing—after week 26, 1.4% of patients had an IOP rise of 10 mm Hg or more from baseline.⁵ What are your thoughts about OZURDEX from an ocular hypertensive standpoint?

Dr. Fortun: Based on my experience, I know what will happen with IOP with OZURDEX.

Dr. Wolfe: With the OZURDEX intravitreal implant, patients who have pressure elevations generally return to baseline before the next injection.¹

Dr. Singer: Do you check pressures before an injection?

Dr. Fortun: Yes. I check pressures before and after an injection.

Dr. Wolfe: Patients in my office are checked at every visit.

Dr. Singer: We have touched on this a bit, but after you have given an OZURDEX intravitreal implant, is there a certain IOP level that makes you want to refer?

IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

Torn or Ruptured Posterior Lens Capsule: OZURDEX® (dexamethasone intravitreal implant) 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.

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

Dr. Fortun: There is not an absolute IOP number because you have to take into account what the baseline was. For one person, a pressure of 20 mm Hg may be good, but may be a substantial increase from baseline in someone else. Typically, if it is more than a 10-point rise from baseline I will initiate IOP-lowering treatment.^{2,6} If it is elevated less than that, I will watch them if there is sustained elevated pressure at a later follow-up date. At that point, if there is sustained elevation, I will get the referral to have a glaucoma specialist's blessing to continue.

IMPORTANCE OF IOP COMANAGEMENT IN DME

Dr. Singer: Once a glaucoma specialist has given the green light to proceed, let us presume the patient is on a combination topical therapy and when you reinject there is a pressure elevation to 25 mm Hg or 28 mm Hg. What is the thought process?

Dr. Wolfe: I will communicate with the glaucoma specialist since it is his call to change the medication.

Dr. Moshfeghi: I also stay in constant contact with my glaucoma colleague.

Dr. Bacharach: We cannot overemphasize how important it is to work collaboratively with your glaucoma colleagues in a patient at risk, so that the retina specialist can continue to give treatment to the patient in an environment that has been medically assessed.

Dr. Singer: In these examples, you are still treating the patient. Dr. Bacharach, how often do you want to see these patients when you know we are going to continue using OZURDEX dexamethasone intravitreal implant and the patient is being managed on a topical drop?

Dr. Bacharach: The clinical context needs to be taken into consideration. But in general, if the pressure is deemed

reasonable for the health of that individualized nerve, we generally follow up about 12 weeks later. Once that patient is comanaged, we will be working together to give that patient their best chance at having improved vision without compromising the nerve.

Dr. Wolfe: It is my experience that we as retina specialists think our glaucoma colleagues are going to be upset if we have done something that may raise the IOP, when in reality, that is not the case. I have never sent a patient for a glaucoma referral only to be told it was ill-advised to inject the patient with a corticosteroid.

Dr. Bacharach: I agree. Do what you need to do to improve the retina condition and we will manage the pressure.

Dr. Moshfeghi: I think that if we try to manage the IOP ourselves, we might be stricter than a glaucoma specialist, which is all the more reason we should not do it.

Dr. Fortun: And we need to keep the patient informed throughout this process. We have had the discussion with the patient before we started the corticosteroid treatments, but now is the time to reassure them that the topical drop is likely what is going to be needed, as the rate of incisional surgery is low (0.3% in the MEAD study, 0.7% in the GENEVA study, and 1.3% in the HURON study).^{1,5,22}

Dr. Singer: We have touched on IOP elevations that make us uncomfortable. Having that glaucoma specialist on board really makes everybody feel better. But again, DME is a lifelong disease that is not going away anytime soon.²

Dr. Fortun: For me, if I have a history of the patient's IOP fluctuations from previous medical records and they have consistently been in that 12 mm Hg to 13 mm Hg range, and then

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions

Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX® (dexamethasone intravitreal implant), have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® 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 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.

Please see additional Important Safety Information on the following pages.

they jump to 23 mm Hg or 24 mm Hg after a corticosteroid injection—that worries me because in that patient, those levels may be damaging.

Dr. Bacharach: Good point—glaucoma is a very individualized disease and using an absolute number can be artificially reassuring. We talked about 30 mm Hg being a generalized cut-off to initiate treatment, but patients under 30 mm Hg may not be home free. It depends on the structural changes to the nerve and what their baseline numbers were.

Dr. Singer: If you have a cup-to-disc ratio greater than a 0.8, you should not start the patient on OZURDEX intravitreal implant,¹ and that is a patient who should be referred sooner rather than later.

Presuming we start topical treatment for steroid-induced elevated pressure, what class of drugs do you use?

Dr. Fortun: It is a question for me to ask my glaucoma specialist.

Dr. Wolfe: If I am starting drop therapy, I use a fixed combination drop.³

Dr. Moshfeghi: I also use combination drops if I am going to initiate therapy.

Dr. Singer: I use a combination IOP-lowering therapy. Some of my clinics are far away. I want the IOP to decrease in case there is an issue of the patient not being diligent to return for IOP checks.^{3,25,26} Based on Dr. Bacharach's comments, there does not seem to be a lot of value in step-wise therapy. Presuming there are no other comorbidities that would prevent or question the use of a combination drug, that is my go-to treatment.

What I like hearing from Dr. Bacharach's perspective also is that the rates of incisional surgery are very low in MEAD, GENEVA, and HURON.^{1,5,22}

Sequential increases in IOP were not seen at the safety visits at 3 weeks in the MEAD study.⁵ Nor did any patient in the OZURDEX dexamethasone intravitreal implant arm have a meaningful change in their optic nerve status.¹⁸ Figure 2 shows that during the course of the 3-year study, the percentage of eyes with first IOP increases of 10 mm Hg or more from baseline decreases from the first injection to the fourth injection. Have you found this in your patient populations as well?

Dr. Fortun: I have noticed that as well—you do not see recalcitrant steroid-induced IOP rises with OZURDEX dexamethasone implant.^{5,18} The majority of my OZURDEX cases have been managed with drops.¹

Dr. Wolfe: This is why I choose five cycles before I am confident to extend monitoring. I am conservative and I want those IOP elevations to be closer to zero.

Dr. Bacharach: What we have learned is that if they occur, these elevated IOP responses are typically going to happen within the first few cycles with OZURDEX intravitreal implant.⁵

VISUAL GAINS WITH OZURDEX

Dr. Singer: The data from the MEAD and GENEVA trials showed 19.5% and 21.5% of patients gained 3 lines of vision, respectively; data from the HURON trial showed significant reduction in vitreous haze in noninfectious posterior segment uveitis (see Table 3).^{5,23,24}

DISCUSSING STEROID THERAPY WITH PATIENTS

Dr. Singer: What is your approach with patients when you are considering initiating intravitreal steroid therapy for DME?

Dr. Moshfeghi: My patients have been very receptive to the idea. I usually recommend this for patients who require additional disease management. I tell them I am hopeful this

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%).

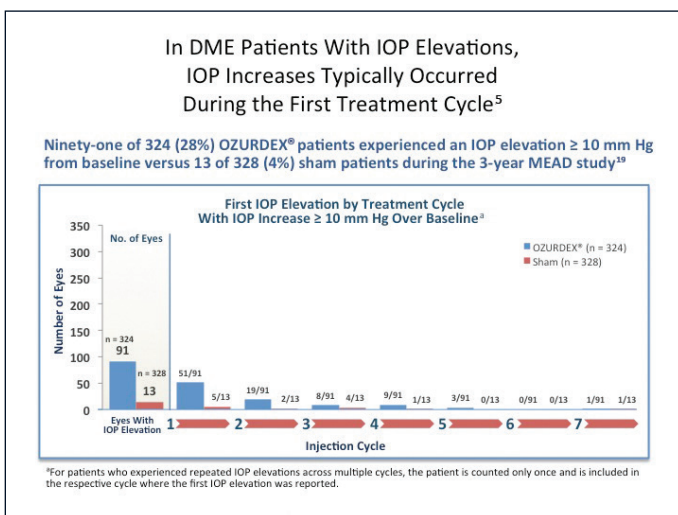


Figure 2. A subgroup analysis of the percent distribution of first IOP increase by injection cycle for those patients who had an IOP increase ≥ 10 mm Hg above baseline.⁵

approach will make some headway,¹ but that they may feel the needle when being injected. Then we discuss cataract and potential IOP elevations, but patients are more interested in the potential improvements.

Dr. Wolfe: I have a similar approach. I tell patients some will have pressure elevations but I try not to get into percentages. Instead, I let them know we are going to be paying close attention to the IOP and the optic nerve. These are patients who have been treated with another therapy first, and I am now going to try OZURDEX dexamethasone intravitreal implant.

Dr. Fortun: It is a good discussion when you are talking to the patient about trying to decrease the number of injections in treatment cycles and helping manage the disease. I tell

them we may be leaving something on the table that we will not be able to get back if we do not try now with a steroid. I do reassure patients that if their pressure goes up to a point where it needs to be medically managed, that it can be managed and usually with topical drops.¹ In my opinion, that trade-off is completely worthwhile.

Dr. Singer: My thoughts are that the patient required additional disease management, or the patient can try a treatment with fewer injections in treatment cycles. IOP associated with OZURDEX intravitreal implant was generally managed in the majority of patients with drops.¹ I do discuss the cataract formation with the phakic patients and let them know about cataract surgery.

Dr. Fortun: For those of us who use OZURDEX intravitreal implant frequently, over the years we have learned about IOP management.

Dr. Bacharach: It is our job to manage the patient and to achieve the best outcome with whatever tools we feel appropriate. That may sometimes include bringing in a glaucoma specialist to comanage any elevated IOP that causes concern.

CONCLUSION

Dr. Singer: Our panel discussion revealed a number of excellent observations. Glaucoma is a lot more than just elevated IOP. It is actually an optic neuropathy that is multifactorial, and in fact increased IOP is not in the American Academy of Ophthalmology's definition of glaucoma.^{3,4} When evaluating our retina patients to see if they may be developing glaucoma, one should evaluate the patient's risk factors, including family history, race, refractive error, and systemic conditions. When examining the patient one should look closely at the optic nerve for the size of the cup

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.

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).

Please see additional Important Safety Information on the following pages.

TABLE 3. OZURDEX PRIMARY EFFICACY ENDPOINT RESULTS					
Indication	Study	Measurement	OZURDEX (n = 328)	Sham (n = 328)	Estimated Difference (95% confidence interval [CI])
Diabetic macular edema	MEAD ^{5,22}	Patients gaining ≥ 15 letters (3 lines) in BCVA (n) at month 39	19.5% ^a (64/328)	10.7% (35/328)	8.8% (3.4%, 14.3%)
		Patients losing ≥ 15 letters in BCVA (n) at month 39	13.7% (45/328)	10.7% (35/328)	3.0% (-2.0%, 8.1%)
		Mean change in BCVA (letters) (standard deviation) at month 39	2.2 (15.88)	0.8 (12.72)	1.3 (-0.9, 3.4)
Indication	Study	Measurement	OZURDEX (n = 427)	Sham (n = 426)	
Macular edema following retinal vein occlusion	GENEVA ^{5,23}	Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 30	21.3% ^b	7.5%	
		Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 60	29.3% ^b	11.3%	
		Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 90	21.8% ^b	13.1%	
		Patients gaining ≥ 15 letters (3 lines) in BCVA from baseline, day 180	21.5% ^c	17.6%	
Indication	Study	Measurement	OZURDEX (n = 77)	Sham (n = 76)	
Noninfectious posterior segment uveitis	HURON ^{5,24}	Percentage of patients with vitreous haze score of zero at week 8	46.8% ^b	11.8%	

^aP = .002 vs sham; ^bP < .001 vs sham; ^cP = not significant.

and whether the neuroretinal rim is healthy. In addition, one should note the presence of hemorrhages and peripapillary atrophy. In terms of IOP, steroid treatment induces increases

that usually return to baseline.^{5,18} In general, the sustained-released OZURDEX intravitreal implant is less likely to cause cumulative increases in IOP.¹ When monitoring for IOP

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. 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.

increases, consider examining patients 6 to 8 weeks after injection, or more frequently as required by the patient's condition, since that is when the pressure spike is usually going to occur.^{5,18,22}

In addition, when treating patients that have increases in IOP, consider adding an OCT of the optic nerve to the OCT of the macula that is typically ordered to monitor macular edema.

If the physician has any concerns about the IOP or possible glaucoma, be sure and involve a glaucoma specialist. This will make both the patient and physician feel more assured. ■

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This supplement to *Retina Today* is sponsored and edited by Allergan.

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%).

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

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

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OZU104942-v2 05/19 163842

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 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)

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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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 periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

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

4.2 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

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

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

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

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

MedDRA Term	OZURDEX [®] N=324 (%)	Sham N=328 (%)
Ocular		
Cataract ¹	166/243 ² (68%)	49/230 (21%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)

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

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

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

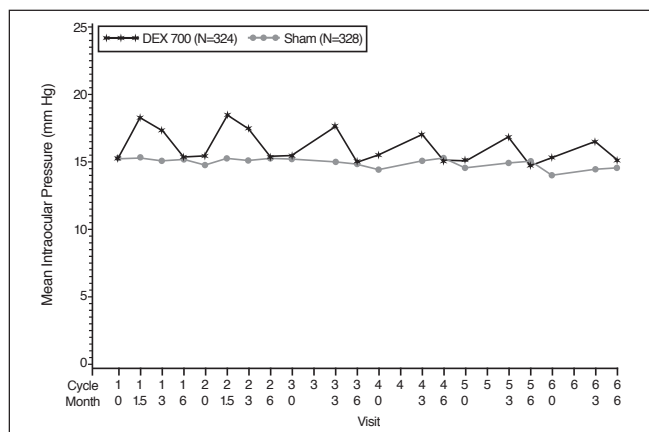
IOP	Treatment: N (%)	
	OZURDEX® N=324	Sham N=328
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* **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

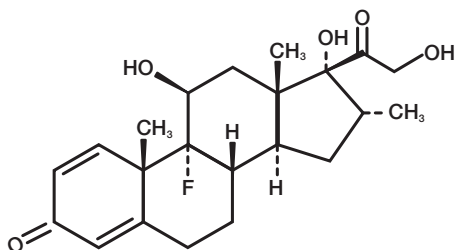
Safety and effectiveness of **OZURDEX**[®] in pediatric patients have not been established.

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:



MW 392.47; molecular formula: C₂₂H₂₉FO₅

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexamethasone, a 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.

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

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

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

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

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

Posterior Segment Uveitis

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

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

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^c)

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

^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

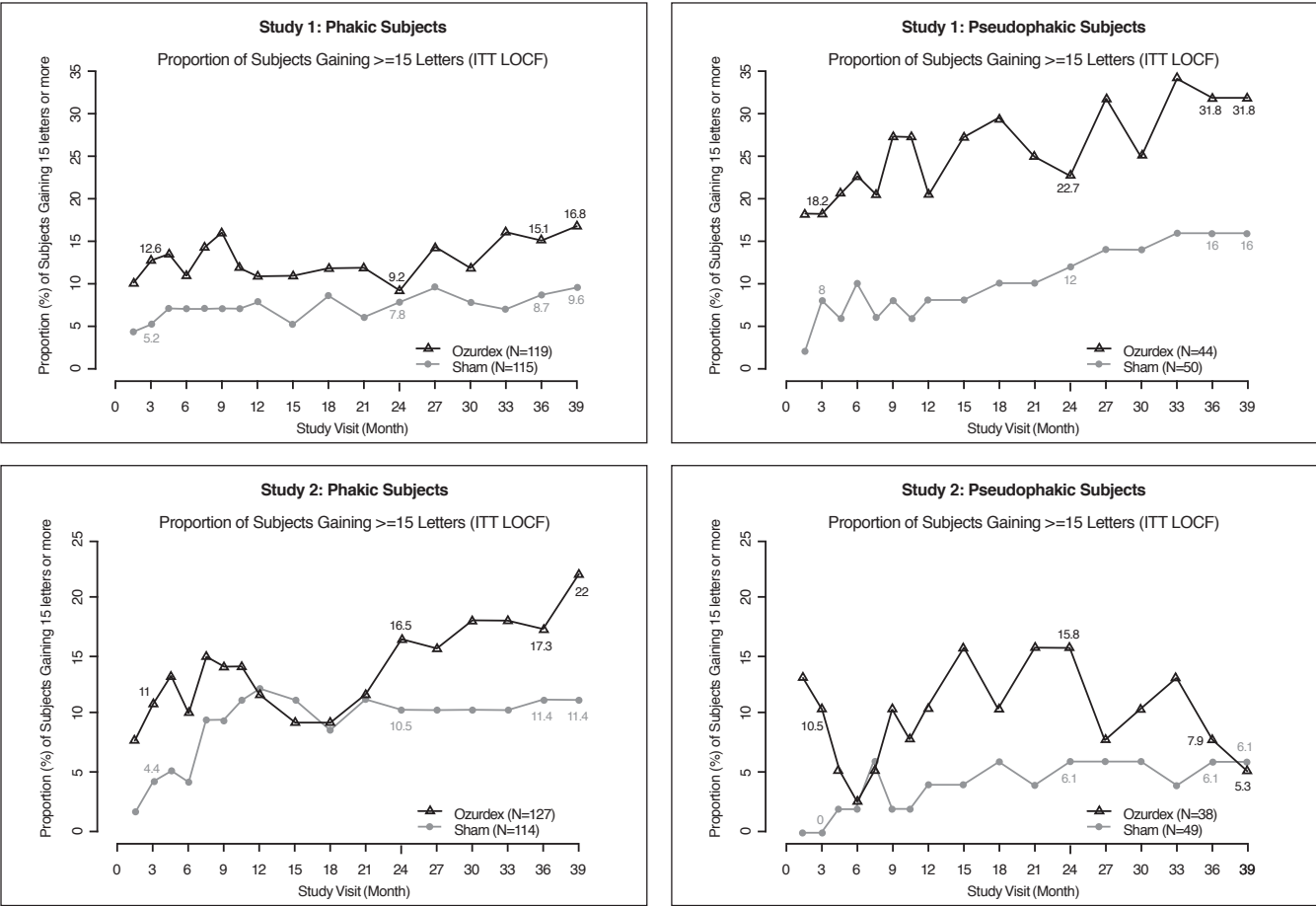
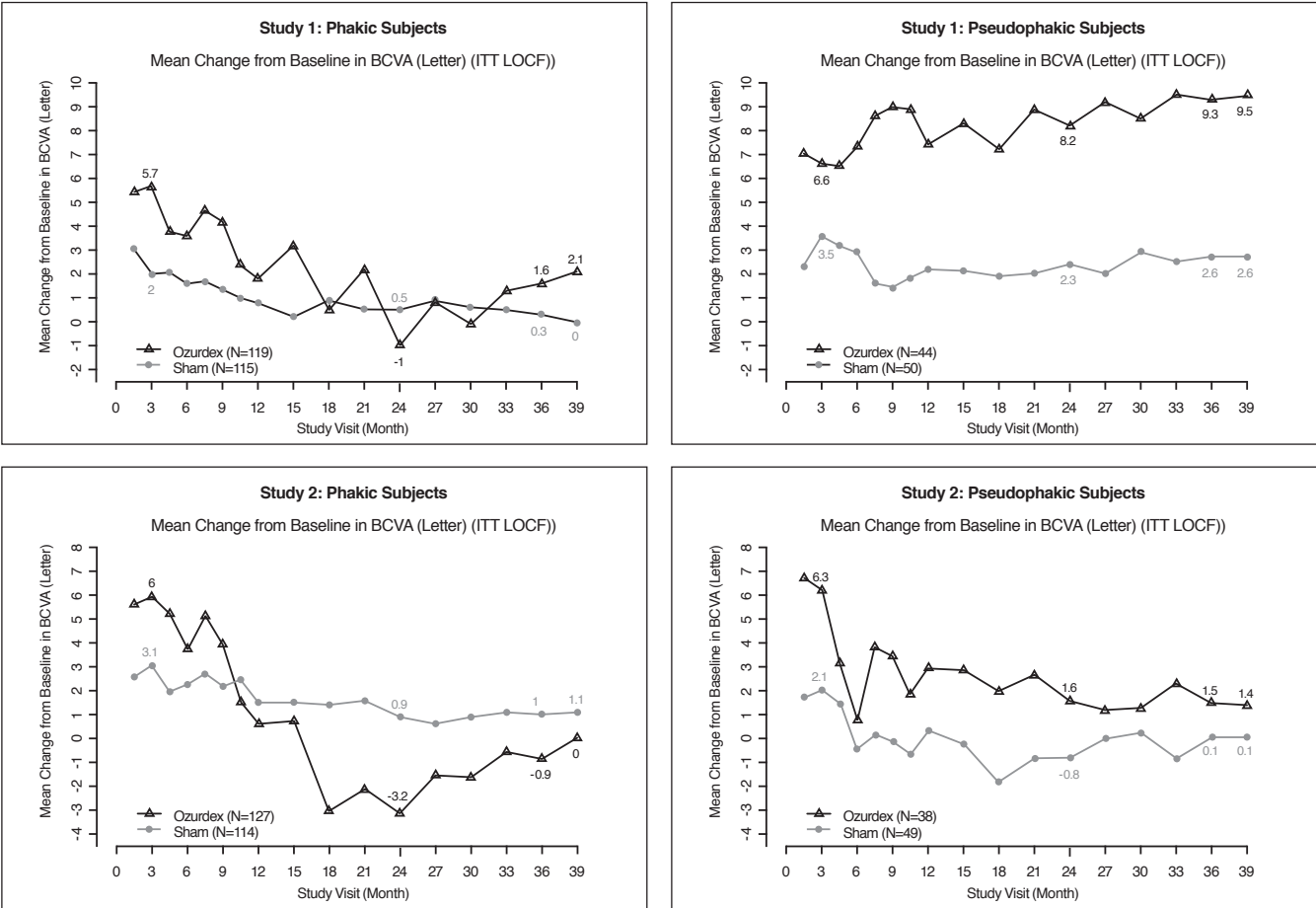


Figure 3: Mean BCVA Change from Baseline



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 LOCF^c)

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

^aPseudophakic: **OZURDEX[®]**, N=82; Sham, N=99

^bPhakic: **OZURDEX[®]**, N=246; Sham, N=229

^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 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 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with **OZURDEX[®]**. 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[®]** 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[®]**, 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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