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NRMD

New Retina MD

Perspectives on Treatment With OZURDEX (dexamethasone intravitreal implant) 0.7 mg

Incidence and Risk of IOP Elevations

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.

Perspectives on Treatment With OZURDEX (dexamethasone intravitreal implant) 0.7 mg

Incidence and Risk of IOP Elevations

Ozurdex is approved for the treatment of diabetic macular edema (DME).[1] But some clinicians are concerned about elevated intraocular pressure (IOP) when it comes to treating with a corticosteroid. 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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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.

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.

WHAT IS GLAUCOMA?

Dr. Gross: An established and important risk factor for primary open-angle glaucoma (POAG) is elevated IOP. But the definition of glaucoma is characteristic damage to the structure and function of the optic nerve.[2,3] POAG is currently defined as a 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] IOP is not a part of this definition; the American Academy of Ophthalmology (AAO) *Preferred Practice Pattern* removed the term several years ago.[3,4] Normal-tension glaucoma can also meet these definitions.[3,5] There are slight differences between normal-tension and POAG, but at its core, glaucoma is damage that occurs with or without the presence of elevated IOP.[2,3] Does the retina community in general know that IOP is a risk factor but does not define the disease?

Dr. Eichenbaum: No. Most of my colleagues do not realize IOP has been excluded from the current AAO definition of glaucoma, myself included at one point.

Dr. Gross: Glaucoma specialists have recognized glaucoma as a progressive disease of the optic nerve for years. We are now at a point where generally both structural and functional changes need to be present, but each individual patient may be more sensitive to changes in one aspect over another. We have also progressed to a point where ocular hypertension is separate from glaucoma and has a separate *ICD-10* code.[2,3]

Dr. Kuppermann: Drug approvals use IOP as the surrogate endpoint in the evaluation of therapies to treat IOP associated with glaucoma, but we should not confuse that with IOP being part of the definition of glaucoma.[6] There are two different types of patients: there is a patient with glaucoma and a patient with elevated IOP without glaucoma. In the clinical trials for IOP-lowering medications, they were patients who had an elevated IOP associated with glaucoma such as open-angle glaucoma, as an example. However, elevated IOP alone does not define glaucoma.[3,7,8]

Dr. Gross: The vast majority of patients who develop glaucoma progress slowly.[2,7]

Dr. Eichenbaum: This circles back to the point made earlier that glaucoma is a disease that requires a diagnosis over a long time.[3] I let patients know that I am there to monitor their retinal disease, but I am not the physician who will be evaluating the health of their optic nerve or taking visual fields. I do check IOP in every patient on every visit and measure the vertical cup-to-disc ratio at dilated exams, but that is the extent of my glaucoma evaluation.

Dr. Singh: Can you make a snapshot diagnosis of glaucoma based on what the definition is here?

Dr. Gross: By definition, we consider glaucoma to be a progressive optic neuropathy.[3]

MEASURING IOP

Dr. Kuppermann: While we measure IOP, most retina specialists use Tono-Pen rather than applanation. As a glaucoma specialist, are you comfortable with the differences between the two?

Dr. Gross: The key for us is that you are consistent. We are really concerned about the change and magnitude of change. The instrument you use should control somewhat for that. People with higher pressures, older age, a family history of glaucoma, or who have a sibling or first-degree relative with glaucoma are at a higher risk for glaucoma damage, as are people of African or Latino descent.[3] I cannot reiterate enough that a high pressure does not necessarily guarantee damage has occurred or will occur.[2,3]

Rishi Singh, MD: There is a difference between IOP and glaucoma when considering the anatomic and visual field definitions,[3] yet this remains a confusing area for many ophthalmologists. For instance, the dexamethasone intravit-

IMPORTANT SAFETY INFORMATION (continued)
Contraindications (continued)

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.

Please see additional Important Safety Information on the following pages.

real implant 0.7 mg (OZURDEX; Allergan) is contraindicated in patients with glaucoma and a cup-to-disc ratio greater than 0.8,[1] but IOP is not part of the contraindication. In the warnings and precautions section of the label, it mentions the possibility of producing an increase of intraocular pressure and glaucoma.

David Eichenbaum, MD: The cup-to-disc ratio has to be greater than 0.8 to be a contraindication, but that must be in conjunction with a confirmed glaucoma diagnosis. Considering that, I would be hesitant to use corticosteroids in a patient with a cup-to-disc ratio greater than 0.8 without an appropriate glaucoma evaluation and completely benign findings.[1]

Dr. Singh: How retina specialists monitor and manage glaucoma differs from our glaucoma specialist colleagues. Dr. Faia, what is your perceived IOP elevation rate/incidence in your patient population who have been treated with steroid implants?

Lisa Faia, MD: It is not a high percentage.

Dr. Eichenbaum: The MEAD studies found about 30% of patients who received OZURDEX had pressure elevations (Table 1).[9,10]

Ronald Gross, MD: Historically, the retina community has had a fear of using steroids. OZURDEX has been studied in large clinical trials in DME, RVO, and noninfectious posterior segment uveitis, and IOP elevations have been demonstrated as generally manageable.[9,12,13]

TABLE 1. OZURDEX ACROSS INDICATIONS

Indication	Study	Percentage of Eyes With ≥ 10 mm Hg IOP Increase From Baseline		Percentage of Eyes With IOP ≥ 35 mm Hg		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[9]	28.1% (91/324) at any visit[11]	4.0% (13/328) at any visit[11]	6.2% (20/324) at any visit[11]	0.9% (3/328) at any visit[11]	45 or 90 days after injection[10,11]	180 days after injection[10,11]
Macular edema following retinal vein occlusion	GENEVA—Pooled results from 2 multicenter, randomized, masked, sham-controlled, 6-month studies[12]	26.6% (112/421) at any visit[11]	1.4% (6/423) at any visit[11]	5.9% (25/421) at any visit[11]	0% (0/423) at any visit[11]	60 days after injection[11]	180 days after injection[11]
Noninfectious posterior segment uveitis	HURON—Multicenter, masked, randomized, 26-week study[13]	9.6% (7/73) at week 8[11]	0% (0/71) at week 8[11]	7.9% (6/76) overall[11]	1.3% (1/75) overall[11]	56 days after injection[11]	182 days after injection[11]

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 should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Dr. Singh: What role does the patient's history play in your decisions to use OZURDEX?

Dr. Faia: I look at the whole picture when it comes to the patient. I may be a little more liberal because of my experience with steroids and noninfectious posterior segment uveitis. If the patient has had a pressure rise in the past, I will talk to them about it and explain how these side effects can be manageable; I do consider cup-to-disc as well. If I am truly concerned, I will get an optical coherence tomography (OCT) of the nerve fiber layer. We do not do pachymetry in my office, but I will take that into consideration. I have a very frank discussion with the patient and discuss how previous pressure changes can be managed and/or are still managed. Then, I continue to discuss OZURDEX as an option.

Dr. Kuppermann: I work in an academic institution with an excellent glaucoma department. We are of the mindset that the physicians in the retina department will take care of the macula and the glaucoma physicians will take care of the nerve. We are trying to preserve or restore vision in patients who have already lost at least a part of their central vision. There is typically a reason I am considering using OZURDEX, and it is because the patient needs additional disease management.

Dr. Eichenbaum: Our practice is a multiphysician, multilocation referral practice, so my real hesitation is only in patients with a poor follow-up record with the referring physician. Those patients do not know exactly where I fit into their disease management, and they tend to have missed visits, high pressures, and poor pressure control if they have a steroid response following an injection.

Dr. Singh: How do we talk to patients about the steroids? For patients with DME who are not currently being treated, or who need a different treatment, are the consent processes different?

Dr. Faia: I do talk to patients about all the options. I allot more time for new patients. With repeated intravitreal injections, there have been some patients who then have an elevated IOP.[11,14] There is no guarantee the IOP will remain at baseline levels. With OZURDEX, I explain how long the effect generally lasts, and if the patient has a good history with follow-up, I might consider the steroid as a first injection. We always discuss the risk of elevated IOP, but also that it can be a manageable side effect that usually resolves on its own or can be managed with topical medication if necessary.[1]

Dr. Eichenbaum: I have a high comfort level with OZURDEX. It is my recommended first-line intravitreal steroid. When I use OZURDEX, I typically tell the patient that medication may be required to control the pressure and I bring the patient back for follow-up at 6 or 8 weeks, or more frequently as required by the patient's condition. That is the end of the conversation; otherwise it gets too technical and unrealistically anxiety provoking.

Dr. Kuppermann: Our institution mandates that patients sign a new consent form every time an injection is performed. On repeat injections, it is relatively perfunctory as I typically tell the patient we are going to do the same injection as before, and I briefly review the risk profile, but I do not get into great detail. Before the first injection, we have a detailed discussion about all the treatment options, but I defer a longer discussion until the patient needs a different approach. We have a significant discussion about stroke/death, infection, and retinal detachment risks, but we will not have a serious discussion about steroids and their related side effect profile until later in their treatment. At that point, there is a more in-depth consent discussion because it is a change in therapeutic approach with its own risk profile. If they are phakic, we discuss the possibility of cataracts and the effects of steroids on cataracts.[1] We discuss IOP elevations and how either I or the glaucoma specialist will handle that if necessary.

Dr. Singh: I have that same progressive discussion with patients. We all have switched within the class or gone to a steroid. We might submit preauthorizations before we switch, and that is a big part of our practice nowadays—billing and preauthorization. How do you address the patient in whom you

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%).

Please see additional Important Safety Information on the following pages.

have injected an OZURDEX intravitreal implant and there is a steroid response? What is your management in that patient?

Dr. Eichenbaum: I do not get a retinal nerve fiber layer (RNFL) OCT at baseline unless a patient has a preexisting glaucoma or ocular hypertension diagnosis. If the pressure rises in a patient with a normal optic nerve and history of previously normal intraocular pressures, that is often when I take my first RNFL OCT. 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.[11] If the pressure rises to 25 mm Hg or 30 mm Hg, I will start the patient on a single agent. I will keep the patient on that if I am planning repeat OZURDEX intravitreal implants. If the pressure rises to higher than 35 mm Hg and I cannot control it with a combination drop or a single agent, then the glaucoma specialist needs to take over. If the RNFL changes during the course of a year, I will refer to our glaucoma colleagues.

Dr. Faia: I also prefer to use a single agent if a patient has an elevated IOP after an injection. If pressures are above 30 mm Hg, I might put them on a combination drop and still try to manage it myself. But if that is not working, then I bring in the glaucoma specialists. Even if I get an RNFL OCT and it looks okay, I would like to see what the visual field is at baseline. I would prefer the glaucoma specialist interpret it because they are much better than I am. While 25 mm Hg does not seem to be high, if the patient normally runs somewhere in the mid-teens, that would be a concern for me, and then I will treat.

Dr. Singh: For you, Dr. Faia, is it the absolute difference as well as the number itself?

Dr. Faia: Yes.

Dr. Kuppermann: I also agree. One additional caveat is that it depends on when the IOP elevation is observed. I may not initiate IOP treatment if the pressure is 25 mm Hg and it is 2 months after the injection. I tend to be relatively circumspect if the optic nerve is healthy, because I know the pressure may come down. But if pressures are 30 mm Hg or higher,[1] I would initiate a therapeutic approach. I try to get to the glaucoma specialist earlier rather than later to let them have a chance to advise me. I want to make sure that I do not underrefer, I do not wait too long, do not miss something that I should have seen. So, 30 mm Hg may only be a number but it is my trigger point for treatment and potentially referral. At that point, I might put the patient on a combination drug.

Dr. Eichenbaum: Although I am comfortable treating patients with steroid response topically, I sometimes will send the patient back to their referring doctor before their regular scheduled visits if the pressure is up to a number where I think they should go back. The referring ophthalmologist is the one who will evaluate the formal visual field, the color nerve photos, and (maybe) perform a selective laser trabeculoplasty.[2,3] If I send the patient back early, I always precede that visit with a letter and an indication for the referral when my office makes that appointment.

Dr. Singh: Dr. Gross, when do you want us to refer these patients?

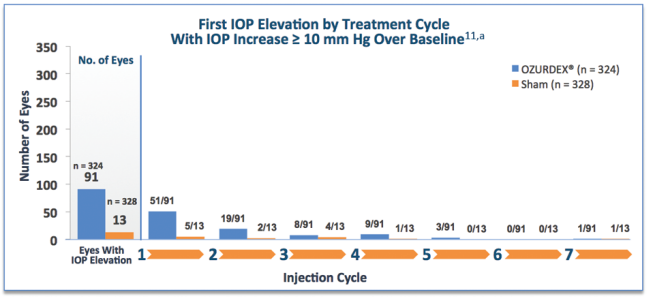
Dr. Gross: For most people, if damage is going to occur it is the culmination of high pressure, how long the pressure has been high, and the patient's susceptibility. The first two we know; it is that third variable that is unpredictable. As a glaucoma specialist, we are very comfortable with addressing any pressure issue that might arise. We want to reassure patients that the opportunity they have to see better may be with a steroid, and we can handle the pressure increases.

Dr. Singh: I find it interesting that, as retina specialists, we are completely comfortable using an OCT to image the macula, but we are hesitant to just move it over a bit and capture the RNFL as well.

Dr. Gross: As I am sure happens in the retina world, there are times when the OCT will indicate it is normal, but it is actually

Figure 1. In DME Patients with IOP Elevations, IOP Increases Typically Occurred During the First Treatment Cycle[11]

Ninety-one of 324 (28%) OZURDEX® patients experienced an IOP elevation ≥ 10 mm Hg from baseline versus 13 of 328 (4%) sham patients during the 3-year MEAD study[11]



[a]For patients who experienced repeated IOP elevations across multiple cycles, the patient is counted only once and is included in the respective cycle where the first IOP elevation was reported.

not, and vice versa. OCT can be misleading when it is being used as the sole diagnostic test. It is not a perfect test, but the real strength of it is that when substantial changes are uncovered, we have a much better insight about the causes.

MONITORING FOR GLAUCOMA

Dr. Singh: How often do you monitor for glaucoma if the pressure is not elevated?

Dr. Eichenbaum: For DME, we have guidance from the MEAD study.[9,10] After an initial OZURDEX intravitreal implant, I see patients at about the 6- to 8-week mark, and I will do that for the first 2 to 3 OZURDEX intravitreal implants, or more frequently as required by the patient's condition. But if there has been no elevation in pressure during that time, I will easily extend them out to 3 months. There are data showing patients who are going to experience a pressure rise do so by the second injection.[1,11]

Dr. Faia: We are looking for spikes and usually see them fairly early in treatment. At the same time, I do emphasize the importance of going back to their general ophthalmologist or glaucoma specialist because I am not the proper person for glaucoma screening or follow-up. If the nerve looks abnormal or I notice a concerning abnormality, such as a hemorrhage, I will send them for a referral sooner if they do not have a comprehensive ophthalmologist or glaucoma specialist already.

Dr. Singh: What does the American Academy of Ophthalmology or the American Glaucoma Society recommend for glaucoma screening in this population?

Dr. Gross: There is no official guideline for glaucoma screening in patients with DME who have undergone a steroid injection.

Dr. Kuppermann: With our referred patients—especially those whom we are seeing for monthly treatment—they are somewhat resistant to going back to their referring doctor, as their treatment burden is already high. There has been an implicit transfer of care given that we are going to see these patients every 4 to 6 weeks for the rest of their lives. Sometimes it is difficult to even get them to see the referring physician for an annual visit. I always talk to the referring doctor and discuss the probable sequence of events and ask when they want to see the patient.

Dr. Faia: With OZURDEX patients, once you know they do not have a spike, you are not really seeing them as often. I do get pushback, but I remind patients they may need an update in glasses and we should try to maximize what vision they have.

Dr. Kuppermann: I have found the same thing with patients in my practice. Once a year they are willing to go back to their referring physician. More than that, there is resistance, quite honestly. They are viewing us as their primary eye care provider now. We need to have that detailed discussion during which we explain that the trade-off for coming in less often for an injection is that they may or may not need to see another eye care provider. And that is how I loop them back in.

Dr. Eichenbaum: When I am sending patients back sooner to their referring doctor, that is when I take the extra chair time,

which I think is a good investment. I explain that the eye has many parts, and I am a subspecialist. I explain that my concern is that I am noticing something I want another doctor to review, in the same fashion as when an attending physician recommended a referral to me to treat their diabetic condition.

ELEVATED IOP AND GLAUCOMA

Dr. Gross: The Ocular Hypertension Treatment Study (OHTS) found that, with an untreated IOP of 24 to 32 mm Hg, 9.5% of patients developed glaucoma damage in 5 years.[15] In OHTS, patients between 24 to 32 mm Hg were randomized to treatment or observation.[15] The latter group is the key, because less than 10% of those subjects did go on to develop glaucoma compared to 4.4% of patients on medication.[15] Most people seem comfortable monitoring up to about 30 mm Hg even today.

Glaucoma specialists have suggested 5 variables that could help identify people at greater risk of developing glaucoma, the first of which is disc size.[16,17] The mean vertical diameter of a normal optic disc measures 1.92 ± 0.29 mm.[17] When you are making the vertical slit on your slit lamp, correction factors may be needed depending on the power of the lens being used.

Second, consider the inner retinal rim[16-18]—typically damage will occur at the superior and inferior poles, so a vertical "ovalness" to the disc itself becomes a greater concern. Is there asymmetry? Is the vertical cup-to-disc ratio greater than the horizontal ratio?

Third, consider the RNFL.[16,19] Getting a baseline RNFL will give you some information.

Fourth, examine the disc for beta-zone parapapillary atrophy.[16,20-22] Studies have shown that the presence of beta-zone parapapillary atrophy increases the likelihood that glaucoma damage is present.[22] Additionally, the area of the disc in which the beta-zone parapapillary atrophy is present corresponds to the area of the disc damaged by glaucoma.

Finally, look for disc hemorrhages.[16,23-25] These can occur in the normal population (under 1% in the Beaver Dam study[26]), but in the glaucoma population, their presence indicates the probability of disease progression.

Dr. Eichenbaum: The Beaver Dam study[27] also found 7.3% of the healthy population has a retinal hemorrhage at some point. So, it is much more likely to have a benign retinal hemorrhage than a benign disc hemorrhage. The actual location of the hemorrhage on biomicroscopy and/or fundus photography is important.

Dr. Kuppermann: That is one of my triggers for referral—disc hemorrhage.

INTERPRETING VISUAL FIELDS

Dr. Gross: For a glaucoma suspect, everyone should be getting a visual field, preferably a SITA Standard; that is much better than a SITA Fast. This test may take a minute or two longer, but the quality of data is much better. There are false-positives and false-negatives, but the main points to evaluate are the probability plots.[28,29]

STEROID-INDUCED IOP ELEVATION

Dr. Gross: Elevated IOP, we presume, occurs as a result of increased resistance to outflow because of changes in the trabecular meshwork.[30] Elevated IOP may be facilitated by upregulation of glucocorticoid receptors on trabecular meshwork cells, altering the rate of protein synthesis and inhibiting degradation of the extracellular matrix.[14,30] There are several risk factors already identified, including existing POAG, family history, prior history of steroid IOP elevations, higher baseline IOP, high myopia, angle recession, and diabetes or connective tissue disease.[14,31-35]

For patients who have never had a steroid, you really will not know if they are steroid responders.

Dr. Singh: In MEAD, the rate was 28.1% (n = 91/324) at any visit; in GENEVA, the rate was 26.6% (n = 112/421) at any visit; and in HURON, the rate was 9.6% (n = 7/73) at week 8; the percentages of eyes with at least a 10 mm Hg increase from baseline is about what we have seen before.[9,12,13] (See Table 2 for primary efficacy results from each trial.)

Dr. Gross: What is important is that last column in Table 1—when IOP generally returns to baseline—so there is a

distinct difference between patients who have increased IOP with steroid and patients who have glaucoma.[10,11]

Dr. Eichenbaum: Glaucoma, which is a progressive optic neuropathy, is not necessarily always associated with an increase in IOP.[10]

Dr. Singh: When do you bring your patients back for follow-up?

Dr. Eichenbaum: At 6 to 8 weeks, and rarely sooner depending on the patient's condition.

Dr. Faia: Every 6 weeks or sooner depending on the patient's condition.

Dr. Kuppermann: The peak IOP has been observed at about the 2-month time point, based on the RVO clinical trials, and that time point is consistent with the known pharmacokinetics of dexamethasone release from the implant. IOP elevations may differ in real clinical practice.[36]

Dr. Singh: Before initiating a steroid treatment, do you routinely discuss family history and/or IOP rises?

Dr. Kuppermann: I ask if they have had glaucoma themselves in the past because I have been following the patient for a more limited period of time, and I may not necessarily know if they have a history of prior glaucoma.

Dr. Eichenbaum: We do query new patients about their parents and vision loss. Often, if the patient's parents went blind, the patient is unaware of the reason. Our electronic records will then note "family history of loss of vision." We may not know the cause, but we will know a first-degree relative went blind.

Dr. Faia: I ask specifically about family history. Most patients know if their parents have had cataract surgery or if they had glaucoma. Even if the patients do not remember the term "glaucoma," they do remember their parents taking daily eye drops for their condition. They do not know it was a bleb, but they will remember their parent had to have glaucoma surgery. For our diabetic cataract patients, I also ask if they remember being on drops and if anyone noted any increase in pressure readings. The family history of cataracts or glaucoma does not necessarily stop me from using OZURDEX, but it does become an important part of the conversation.

Dr. Kuppermann: Do you do that for every patient at baseline? Or only when you are contemplating OZURDEX?

Dr. Faia: We spend a little more time with our newer patients, and that is when we have that conversation. When we decide to use OZURDEX, I can quickly review the medical records and note Mom had glaucoma, Dad had cataracts. We do it at the baseline visit because we have less and less time during the follow-up visits.

Dr. Singh: What about OZURDEX and the return to baseline IOP?

Dr. Eichenbaum: That is one of the biggest factors for me. It is one of the reasons why I have adopted OZURDEX when it is time to initiate steroid therapy. The randomized, controlled MEAD study looked at repeated injections; when pressures did rise, they generally came down in a similar pattern.[9] For me, that is reassuring. I agree with Dr. Kuppermann that 8 weeks will better provide a more sensitive response than 6 weeks, but if there is no steroid response by 8 weeks, it is unlikely there will be one later on.[1]

Dr. Singh: Dr. Kuppermann, how does this issue weigh into your practice pattern for patients? Is it either reassuring or not reassuring that IOP generally returns to baseline?

Dr. Kuppermann: There is some variability among individual patients. The products are identical in the manufacturing facility, but the individual eye can vary. But that individual eye has its own reproducibility. If I see a pattern of IOP elevations, I will bring the patient back every 2 months. But if the patient has

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

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Please see additional Important Safety Information on the following pages.

TABLE 2. OZURDEX PRIMARY EFFICACY ENDPOINT RESULTS

Indication	Study	Measurement	OZURDEX (n = 328)	Sham (n = 328)	Estimated Difference (95% confidence interval [CI])
Diabetic macular edema	MEAD[9,11]	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[11,12]	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[11,13]	Percentage of patients with vitreous haze score of zero at week 8	46.8%[b]	11.8%	

[a]$P = .002$ vs sham; [b]$P < .001$ vs sham; [c]P = not significant.

undergone a series of injections without the concomitant IOP spike, then I am more focused on bringing them back when I am more likely to capture a recurrence of the edema.

THE TOPICAL STEROID CHALLENGE

Dr. Singh: Does anyone use a topical steroid in a patient before opting to use OZURDEX?

Dr. Eichenbaum: There is a misconception that clinical or IOP response to a topical steroid would be indicative of the response to intravitreal OZURDEX. I do not use a topical steroid on a patient before an OZURDEX intravitreal implant. Some of that is because we typically use prednisolone as an ophthalmic topical steroid, and dexamethasone may not generate the same response with regard to an IOP response. Also,

OZURDEX is placed far from the trabecular meshwork, and topical prednisolone is essentially placed on the trabecular meshwork.[37-39]

Dr. Singh: When you see that IOP spike, do you go back and check the pressure yourself? Or, do you rely on the technician?

Dr. Gross: I think if you have well-trained technicians, particularly with tonometry, I would rely on their readings. I will recheck if the numbers do not make sense to me.

MANAGING IOP ELEVATIONS

Dr. Eichenbaum: In patients who are OZURDEX responders, do you put patients on glaucoma medications consistently, or do you periodically take them off?

Dr. Faia: I alternate depending on the patient's condition. If I know they are going to have a response, I may prescribe the topical medications for the first 6 to 8 weeks.

Dr. Kuppermann: I treat them episodically, too. They may not necessarily need topical treatments continuously.

Dr. Singh: I put them on and leave them on topical medications if they have had an IOP elevation.

Dr. Eichenbaum: I do as well, because I find the patients are confused otherwise.

Dr. Faia: I tell patients to use the one bottle of IOP-lowering medicine until it runs out, which is usually around 2 months.

Dr. Eichenbaum: That is good. That is very clear.

Dr. Singh: Reviewing the incisional surgery rates in the OZURDEX DME studies (0.3% in MEAD), was that something you expected to see, Dr. Gross?[9,12,13]

Dr. Gross: I was surprised. I thought it would be a much higher rate.

Dr. Singh: What have you seen in your practices? One of the interesting things about OZURDEX is that it is a sequential IOP rise but not cumulative, as observed in the DME trials.[1,10] Dr. Gross, do you agree?

Dr. Gross: Yes. In the vast majority of patients, the elevated IOP is related to the potency of steroid at the target tissue.[40]

Dr. Eichenbaum: I call to speak with my referring general ophthalmologist if I am concerned, and I ask if they can confirm the changes I have noted during the past 2 years in the superior pole, or the visual field. I do ask the general ophthalmologist to repeat the field and consider a referral to a glaucoma specialist because treating progressive glaucoma is outside my area of expertise.

Dr. Faia: It is very delicate—I want to preserve the relationship with both the patient and the referring doctor. I will call and note that Mrs. Jones is responding to OZURDEX, and that I want to keep using it on her, so I ask the referring doctor to periodically recheck the visual field as I want to ensure I am not creating damage. I try to put the onus on me.

VISION GAINS

Dr. Singh: When have you seen OZURDEX work well in your patients? We know from MEAD and GENEVA the percentage of 3-line gainers.[9,11,12] Have you found similar results?

Dr. Faia: For DME, if the patient needs additional disease management, I will use OZURDEX.

Dr. Kuppermann: It is individualized and based on the patient's response. When I see the anatomic result after an OZURDEX treatment, I frequently wonder why I did not consider the treatment earlier.

Dr. Singh: But have you seen nonresponse to a steroid?

Dr. Eichenbaum: I have seen an incomplete response to steroids.

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.

Please see additional Important Safety Information on the following page.

PEARLS FOR USE

Dr. Singh: What are some of your pearls for ophthalmologists who have not yet used OZURDEX?

Dr. Gross: If the patients' vision can benefit, consider OZURDEX; IOP is a secondary concern. The most important concern is their vision. And if retina specialists can address that, glaucoma specialists can deal with the IOP.

Dr. Eichenbaum: Look for patients who need additional disease management, and OZURDEX is an option in those patients.

Dr. Kuppermann: We do not like to cause cataracts or IOP elevations, but the bottom line is visual acuity and the macula need to be addressed—the sooner the better. ■

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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

RECENT MAJOR CHANGES

• Indications and Usage (1.3)	9/2014
• Contraindications (4.2, 4.3, 4.4)	9/2014
• Warnings and Precautions (5.2)	9/2014

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 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 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.

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%)

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 (%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
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

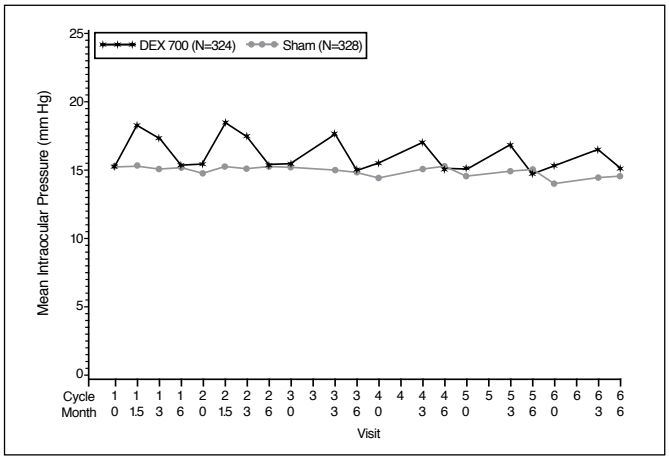
IOP	Treatment: N (%)	
	OZURDEX® N=324	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* 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

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

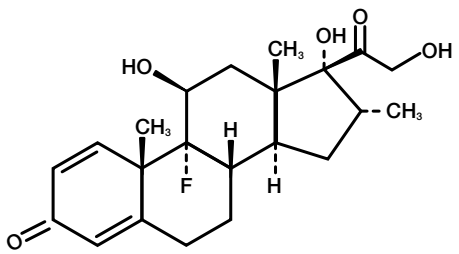
Safety and effectiveness of **OZURDEX®** in pediatric patients have not been established.

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:



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 [^{14}C]-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.

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 1			Study 2		
Study Day	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)

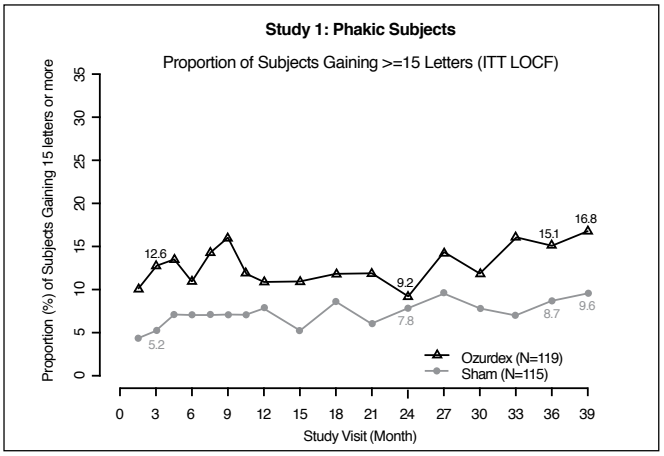
[a]Study 1: OZURDEX®, N=163; Sham, N=165

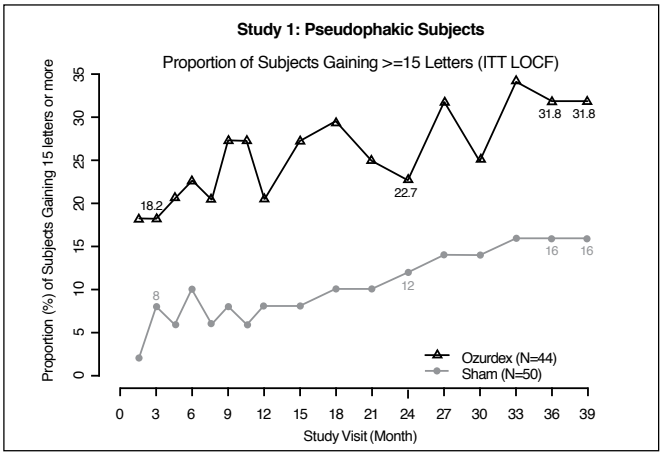
[b]Study 2: OZURDEX®, N=165; Sham, N=163

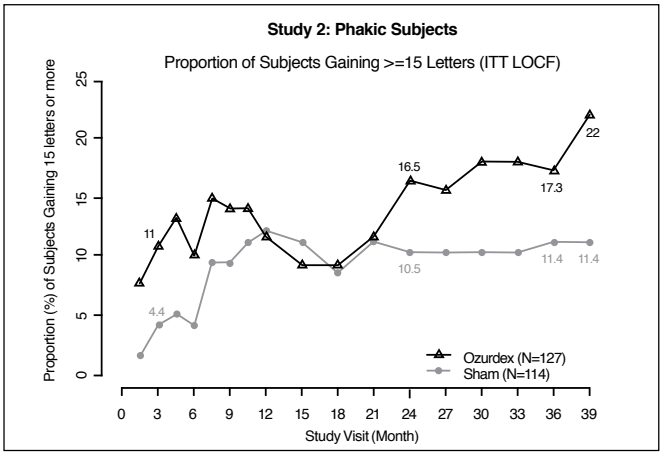
[c]14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

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







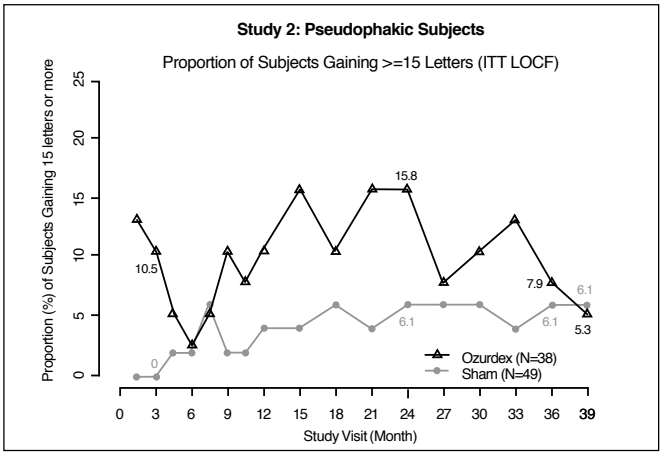
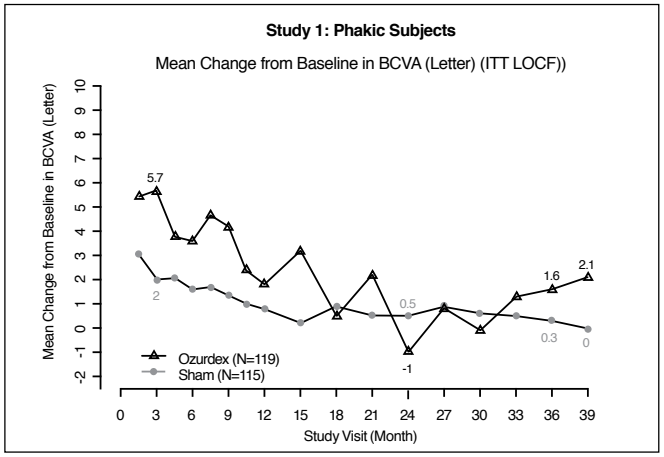
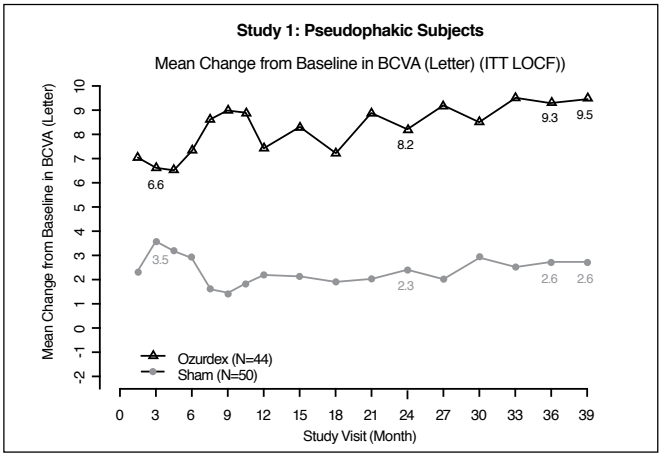
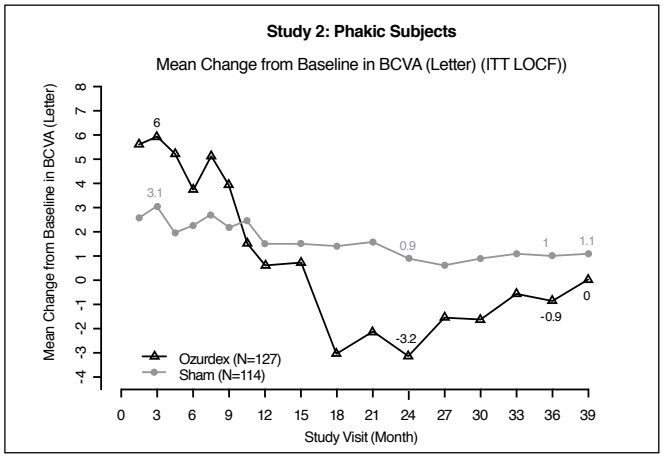
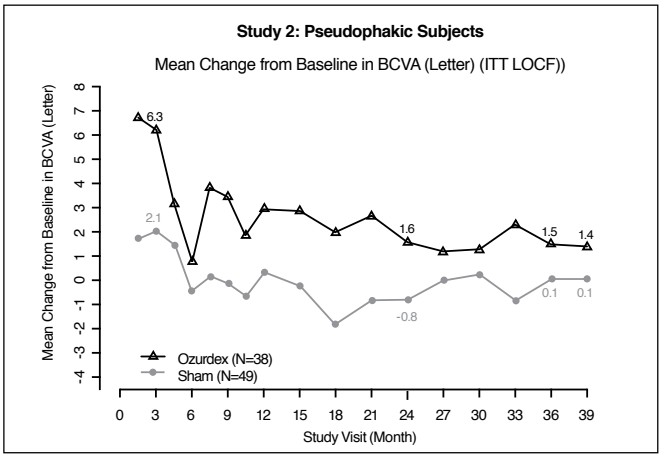


Figure 3: Mean BCVA Change from Baseline









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 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)

[a]Pseudophakic: OZURDEX®, N=82; Sham, N=99

[b]Phakic: OZURDEX®, N=246; Sham, N=229

[c]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

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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