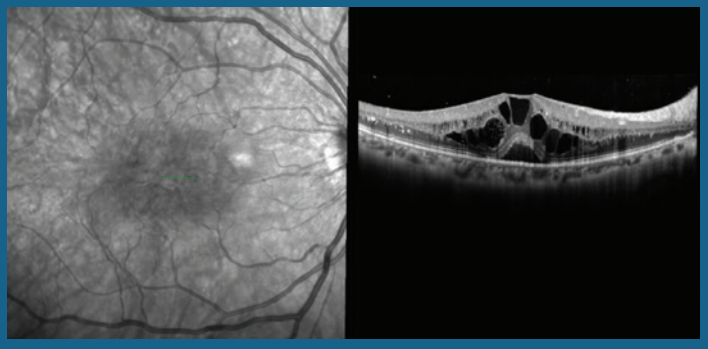
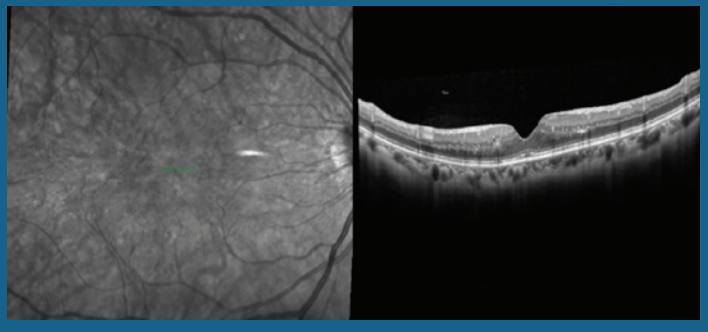
Supplement to RT Retina Today

November/
December 2021

Perspectives on OZURDEX® (dexamethasone intravitreal implant) 0.7 mg and Understanding IOP Elevations






John W. Kitchens, MD
(Moderator)


Blake A. Isernhagen, MD


Inder Paul Singh, MD


Lejla Vajzovic, MD

A panel of experts explores the indications, data, and efficacy of OZURDEX® and offers real-world examples of the use of OZURDEX® 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.

Perspectives on OZURDEX® (dexamethasone intravitreal implant) 0.7 mg and Understanding IOP Elevations

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TREATMENT WITH OZURDEX®

OZURDEX® (dexamethasone intravitreal implant 0.7 mg, Allergan/AbbVie) is approved to treat adults with diabetic macular edema (DME), macular edema (ME) following retinal vein occlusion, and posterior segment uveitis.[1] It has been used in clinical practice for more than 10 years.[2] This sustained-release, biodegradable implant slowly releases the corticosteroid dexamethasone to help reduce inflammation in the retina.[1] The proprietary drug delivery system includes a single-use intravitreal applicator that is preloaded with OZURDEX®.[1] OZURDEX® can be administered as an in-office procedure.

Recently, a panel of experts who have long-term experience with OZURDEX® convened to discuss management of intraocular pressure (IOP) elevation in patients who have undergone treatment with the implant. The key points of their discussion are highlighted in these articles.

1. OZURDEX® Prescribing Information.
2. US Department of Health and Human Services. NDA approval. NDA 22-315. Drugs @ FDA website. June 17, 2009. Accessed July 2, 2021. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022315s000ltr.pdf.

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Case Study: Intraretinal and Subretinal Fluid Treatment Challenge

This patient's journey was successful with 2 OZURDEX® treatments.

BY LEJLA VAJZOVIC, MD; WITH COMMENTARY FROM JOHN W. KITCHENS, MD, AND INDER PAUL SINGH, MD

CASE PRESENTATION

A 62-year-old woman with type 2 diabetes who has been on insulin therapy for 14 years was referred to me for a second opinion for DME management. She had moderate nonproliferative diabetic retinopathy and no cardiac or renal issues. The patient controlled her blood sugar well and had an HbA1c of 6%. In general, she was compliant with her care and received prior treatment.

The patient was pseudophakic. Therefore, she was not at risk for cataracts associated with steroids. On presentation, her vision was 20/60 OD and 20/30 OS, and her intraocular pressure (IOP) was within the normal range (14 mm Hg OU). There was a marked difference in central retinal thickness between the two eyes (650 µm OD and 325 µm OS), and the right eye had significant intraretinal and subretinal fluid (Figure 1). Cases such as this, in which subretinal fluid is present, can be challenging to control.

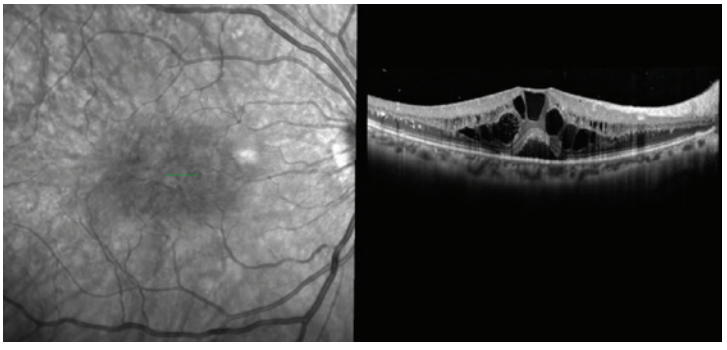


Figure 1. Optical coherence tomography (OCT) of the macula at the initial examination showed signs of intraretinal and subretinal fluid.

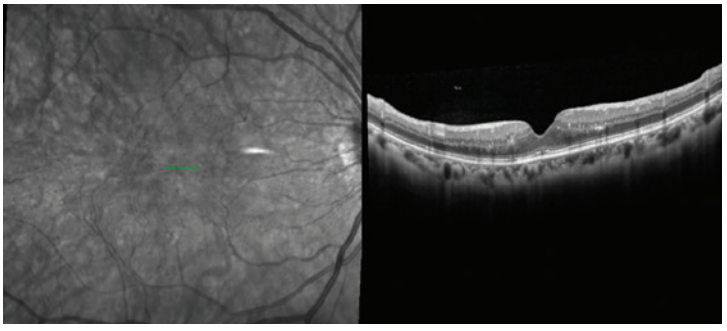


Figure 2. OCT of the macula at the 6-week follow-up showed no signs of intraretinal and subretinal fluid.

TREATMENT AND RESULTS

Prior to her visit, the patient received monthly treatments. At her initial examination, I suggested we initiate treatment with the dexamethasone intravitreal implant 0.7 mg (OZURDEX®, Allergan/AbbVie) OD because, from my clinical experience, this implant is a good treatment option for patients with intraretinal and subretinal fluid. The presence of subretinal fluid, for me, is a biomarker that inflammation is occurring. I think OZURDEX® is a way to intervene in a controlled, manageable fashion.

At 6 weeks, the patient's vision improved, to 20/32 OD, as did the central retinal thickness in that eye, which was reduced to 315 µm from 650 µm at her initial visit. There was no sign of intraretinal or subretinal fluid in the patient's right eye (Figure 2), and IOP in that eye was 31 mm Hg. I opted to start combination IOP-lowering drops BID in the patient's right eye. I often rely on a local optometrist or general ophthalmologist to help with controlling pressures in this range because I see patients from a large territory around Duke University. Three months after the initial OZURDEX® injection,

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.

TABLE. BEFORE AND AFTER TREATMENT WITH 2 OZURDEX® INJECTIONS

Visit	VA OD	CRT OD	IOP OD	IOP-lowering drops	Treatment OD
Initial	20/60	650 µm	14 mm Hg		OZURDEX®
6 weeks after 1 OZURDEX®	20/32	315 µm	31 mm Hg	X	Observe
2 months after 1 OZURDEX®	20/32	315 µm	12 mm Hg	X	Observe
3 months after 1 OZURDEX®	20/32	325 µm	8 mm Hg		Observe
4 months after 1 OZURDEX®	20/40	340 µm	15 mm Hg	X	OZURDEX® #2
3 months after second OZURDEX®	20/32	320 µm	9 mm Hg		Observe

the patient continued to do well in terms of vision and retinal thickness. Further, IOP improved on drop therapy alone, indicating to me it was being managed. I discontinued the IOP-lowering drops in the patient's right eye and scheduled another follow-up for the following month. At 4 months, the presence of intraretinal fluid was noted in the right eye, coinciding with a slight change in vision and retinal thickness. At this time, I opted for a second injection of OZURDEX®.

Knowing that the patient had a pressure elevation with the first injection, I restarted her on IOP-lowering drops right away. She was asked to follow up with her local optometrist at 6 to 8 weeks postinjection and with me at 3 months postinjection. At that time, she continued to do well. The fluid was minimally present, and IOP was lowered on IOP-lowering drops. We scheduled a follow-up for 4 months postinjection, and at that time, she completed another treatment with OZURDEX®.

CONCLUSION

The Table summarizes this patient's journey before and after treatment with 2 OZURDEX® injections. OZURDEX® provided a treatment option without the need for monthly injections. ■

CASE PRESENTATION DISCUSSION

JOHN W. KITCHENS, MD

I love how Dr. Vajzovic started this patient out of the gate on OZURDEX®. Dr. Vajzovic took the patient's history into account, and because she had a limited response to initial therapy, Dr. Vajzovic changed the direction of the patient's therapy with positive results. I also think it's great that Dr. Vajzovic referred this patient back to her local optometrist. In my own personal experience, I've learned that it is helpful to partner with as many local providers as possible to comanage these issues. We know that steroids can increase IOP and the risk of cataract formation, but our focus must be achieving optimal anatomical and visual outcomes. In this pseudophakic case, when you take development of cataract out of the picture, there was efficacy without the need for monthly injections.

INDER PAUL SINGH, MD

Dr. Vajzovic managed this case well. I think a beta-blocker and a carbonic anhydrase inhibitor (CAI) is a good combination to bring down the IOP in patients who are on steroid therapy. 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,[1] 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.

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.[2] In OHTS, patients with IOP between 24 to 32 mm Hg were randomized to treatment or observation.[2] The latter group is the key, because fewer than 10% of those subjects did go on to develop glaucoma compared to 4.4% of patients on medication.[2] Most people seem comfortable monitoring up to about 30 mm Hg even today.

I know IOP elevation can be concerning, but I believe you have time to bring those pressures down before they cause permanent damage. Once the pressure drops in patients with a healthy nerve, it is fine to stop IOP-lowering drops and continue to monitor. If IOP goes back up, you can always restart them on the drops. In the case Dr. Vajzovic shared, the patient experienced a rapid and robust reduction of IOP with IOP-lowering drops, and it stayed low.

1. American Academy of Ophthalmology. *Preferred Practice Pattern*® Guidelines. Primary open-angle glaucoma. San Francisco, CA: American Academy of Ophthalmology. 2020.
2. Kass MA, Heuer DK, Higginbotham EJ, et al; Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-713. doi: 10.1001/archopht.120.6.701.

Case Study: An Acute Decrease in Vision

Don't be afraid to initiate drop therapy to lower intraocular pressure (IOP).

BY BLAKE A. ISERNHAGEN, MD; WITH COMMENTARY FROM JOHN W. KITCHENS, MD; LEJLA VAJZOVIC, MD; AND INDER PAUL SINGH, MD

CASE PRESENTATION

In my practice, most of my dexamethasone intravitreal implant 0.7 mg (OZURDEX®, Allergan/AbbVie) patients have uveitis. One of my earliest experiences with OZURDEX® for DME, however, was for a 72-year-old man who had type 2 diabetes for the past 16 years. The first time he was seen in our practice, about 3 years after onset of DME, his HbA1c was 7.5%. The patient was pseudophakic, which is helpful when thinking about treatment with steroids, and he had a history of peripheral neuropathy, hypertension, and cardiovascular disease. He had received multiple previous treatments at 6- to 8-week intervals but had not undergone any focal or steroid therapies.

The patient called before his next scheduled appointment complaining of an acute decrease in vision in his right eye. On examination, a cystic change and the beginning of some buildup of subretinal fluid was noted on optical coherence tomography (OCT) (Figure 1). In his right eye, his vision had dropped to 20/50, central retinal thickness was elevated (432 µm), and his optic nerve was healthy with no significant cupping. His IOP was within a normal range in the right eye (13 mm Hg).

He had no family history of glaucoma, which is something I try to think about when I'm considering a steroid treatment. I decided to change gears and proceeded with the OZURDEX® injection in the patient's right eye. With other intravitreal extended-release steroid injections, a steroid challenge might be required. In my opinion, however, a steroid challenge is not needed with OZURDEX® because there is a low incidence of an elevation requiring surgical intervention.[1] I did not, therefore, initiate steroid treatment prior to the first injection.

Four weeks after the first injection, the patient's central retinal thickness decreased from 432 µm to 295 µm in the right eye, and his vision improved. He did, however, have a small elevation of IOP (26 mm Hg) in this eye. I didn't have a high level of concern, but I started the patient on a topical beta-blocker BID. At his next visit 4 months later, after 1 OZURDEX® injection, the patient's visual acuity in the right eye improved, IOP was controlled with a beta-blocker, and the nerve was still healthy (Figure 2). On OCT, the reaccumulation of intraretinal fluid in the right eye was observed. He was not overly symptomatic, but given his past history with

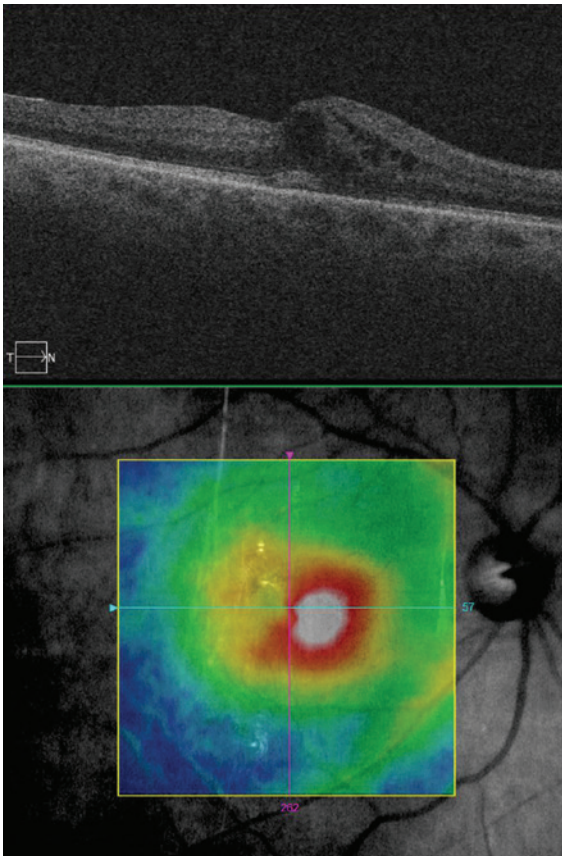


Figure 1. On OCT, the beginning of some buildup of subretinal fluid was noted in this patient.

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued)

Diabetic Macular Edema (continued)

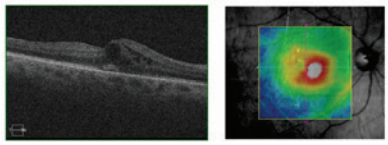
Increased Intraocular Pressure (continued): The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).

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.

Please see additional Important Safety Information on the following pages.

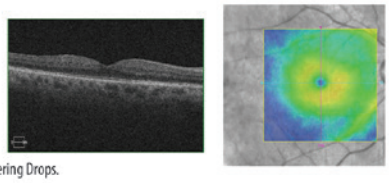
Initial Visit

	OD
VA	20/50
CRT	432 µm
IOP	13 mm Hg



4 Weeks After 1 OZURDEX® Injection

	OD
VA	20/32
CRT	295 µm
IOP	26 mm Hg



4 Weeks After 1 OZURDEX® Injection. Patient Began IOP-Lowering Drops.

4 Months After 1 OZURDEX® + IOP-Lowering Topical Drop

	OD
VA	20/32
CRT	318 µm
IOP	17 mm Hg

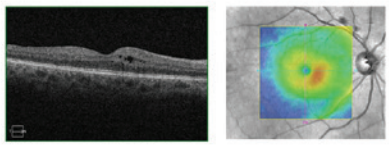


Figure 2. Summary of examinations at the patient's initial visit, 4 weeks, and 4 months after 1 injection of OZURDEX®. At 4 weeks, the patient started on topical IOP-lowering drops. At 4 months, the patient was brought back for an IOP of 17 mm Hg.

DME, I felt the best course of action was to proceed with a second OZURDEX® injection.

CONCLUSION

This case is encouraging because it shows how patients can respond to treatment with OZURDEX® and maintain control of pressure on a single beta-blocker. I felt comfortable knowing that, while there was a pressure elevation, it was well controlled and manageable. This patient, like most other patients with a similar history, didn't mind using 1 drop BID.

What I learned from this case is that it is okay to start patients on drop therapy to keep IOP in check, and most patients respond positively. With this regimen, I am comfortable knowing that the response is well known, pressure is unlikely to elevate significantly more than the initial evaluation, and pressure generally returns to baseline over time.[2] ■

CASE PRESENTATION DISCUSSION

JOHN W. KITCHENS, MD

Dr. Isernhagen did not hesitate to re-treat this patient when he started to have the early recurrence of edema. For me, when I start to see the pressure go up, I pause and think, "Should I give this patient another shot, or should I wait another month?" Most times, I will wait another month before proceeding with the second OZURDEX® treatment.

LEJLA VAJZOVIC, MD

Personally, I am comfortable reinjecting OZURDEX® because I know that if there is a pressure elevation, it is understandable. We saw that in the MEAD trial: If an elevation were to occur, it would typically be between 6 to 8 weeks after the injection, and the incidence and magnitude of the elevation did not increase after repeated injections.[1,2] I plan to bring patients back in 6 to 8 weeks after 1 OZURDEX® injection because trials have shown that about 15% of patients may develop a pressure elevation of 10 mm Hg.[3] Most eyes that develop elevated IOP can be managed with observation or topical treatment alone.[3]

INDER PAUL SINGH, MD

In the case that Dr. Isernhagen recounted, as well as the one Dr. Vajzovic shared, the patient's pressures came down and stayed down, even after the second injection. If a patient is controlled with topical drops, I feel comfortable knowing that IOP will be stable with a second and even a third round of OZURDEX®, even as the risk of cataract increases. When you have a healthy nerve, including a healthy rim and retinal nerve fiber layer, the eye can maintain a higher pressure in the low-20 mm Hg range and still accommodate for that for a period of time.[4]

1. Leske MC, Heija A, Hyman L, Bengtsson B, Dong L, Yang Z; EMGT Group. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(11):1965-1972. doi:10.1016/j.ophtha.2007.03.016
2. OZURDEX® Prescribing Information.
3. Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146. doi:10.1016/j.ophtha.2010.03.032
4. Kass MA, Heuer DK, Higginbotham EJ, et al; Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-713. doi:10.1001/archopht.120.6.701

1. Boyer DS, Yoon YH, Belfort R Jr, et al; Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1904-1914. doi:10.1016/j.ophtha.2014.04.024
2. OZURDEX® Prescribing Information.

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.

Understanding the Relationship Between Intraocular Pressure (IOP) and Glaucoma

A review of the key data on IOP and OZURDEX®

BY BLAKE A. ISERNHAGEN, MD; JOHN W. KITCHENS, MD; INDER PAUL SINGH, MD; AND LEJLA VAJZOVIC, MD

Ocular hypertension is defined as IOP that is higher than 21 mm Hg in an eye with a normal optic nerve and visual field.[1] Nearly 40% of patients with primary open-angle glaucoma (POAG), a chronic progressive optic neuropathy, may not present with elevated IOP.[2] In patients with POAG, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. It is associated with an open anterior chamber angle by gonioscopy.[2] Based on data from the Ocular Hypertension Treatment Study,[3] the majority (95.6%) of patients will not develop POAG with pressures that are between 24 and 32 mm Hg while receiving treatment with a topical ocular hypotensive medication.

BREAKING IT DOWN

It is important to recognize that elevated IOP is an independent risk factor for glaucoma,[2] but it does not equal glaucoma. Glaucoma can occur at normal pressures, and the majority of patients have enough biomechanical properties of the lamina cribrosa and optic nerve head to handle pressure fluctuations for a period of time.[4]

TABLE. MEAD, GENEVA, AND HURON IOP DATA

Indication	Study	Percentage of Patients With a ≥ 10 mm Hg IOP Increase From Baseline		Percentage of Patients With IOP ≥ 35 mm Hg		Percentage of Patients Requiring IOP-Lowering Surgery
		OZURDEX®	Sham	OZURDEX®	Sham	
Diabetic macular edema	**MEAD**[5] Pooled results from 2 multicenter, masked, randomized, sham-controlled, 3-year studies	28.1% (91/324)[a]	4.0% (13/328)[a]	6.2% (20/324)[a]	0.9% (3/328)[a]	0.3% (1/324)[8]
Macular edema following retinal vein occlusion	**GENEVA**[6] Pooled results from 2 multicenter, masked, sham-controlled, 6-month studies	26.6% (112/421)[a]	1.4% (6/423)[a]	5.9% (25/421)[a]	0% (0/423)[a]	0.2% (1/421)[d6]
Noninfectious posterior segment uveitis	**HURON**[7] Multicenter, masked, randomized, 26-week study	9.6% (7/73)[b]	0% (0/71)[b]	7.9% (6/76)[c]	1.3% (1/75)[c]	1.3% (1/77)[7]

[a]At any visit. [b]At week 8. [c]Overall. [d]Does not include surgeries due to neovascular glaucoma.

Source: Allergan Data on File, 2020.

IMPORTANT SAFETY INFORMATION (continued)

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.

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.

Chronic elevation, however, could become problematic, and that is when there is cause for concern. A small increase in IOP is expected, and it should be monitored.

We do ourselves a disservice by calling IOP-lowering drops "glaucoma drops." It's a misnomer, and it's why patients come back and say, "I must have glaucoma because I'm on glaucoma drops." In reality, it is rare for patients who have a temporary rise in IOP to need more than topical antihypertensive medications to control IOP.[3]

STUDY DATA

OZURDEX® (dexamethasone intravitreal implant 0.7 mg, Allergan/AbbVie) helps to control inflammation in the retina. It is contraindicated in patients with glaucoma who have a cup-to-disc ratio greater than 0.8.[8] When prescribing OZURDEX® to patients, it is important to remember that they should be monitored for elevated IOP.

In pivotal clinical studies with OZURDEX®, IOP elevations of up to 35 mm Hg were low across indications.[5,6,9] Key data from studies in the literature shed some more light on this subject.

MEAD. The OZURDEX® MEAD studies were two 3-year, multicenter, masked, randomized, sham-controlled, phase 3 studies evaluating the safety and efficacy of the dexamethasone intravitreal implant for the treatment of diabetic macular edema (DME). A total of 1048 patients were enrolled; 351 received the dexamethasone intravitreal implant 0.7 mg, 347 the dexamethasone intravitreal implant 0.35 mg, and 350 received sham treatment. The data shown here are from the 0.7-mg and sham arms. The pooled results from the studies showed that an elevation of 10 mm Hg or greater from baseline at any visit occurred in 28.1% of patients who received OZURDEX® compared to 4.0% of sham patients.[7]

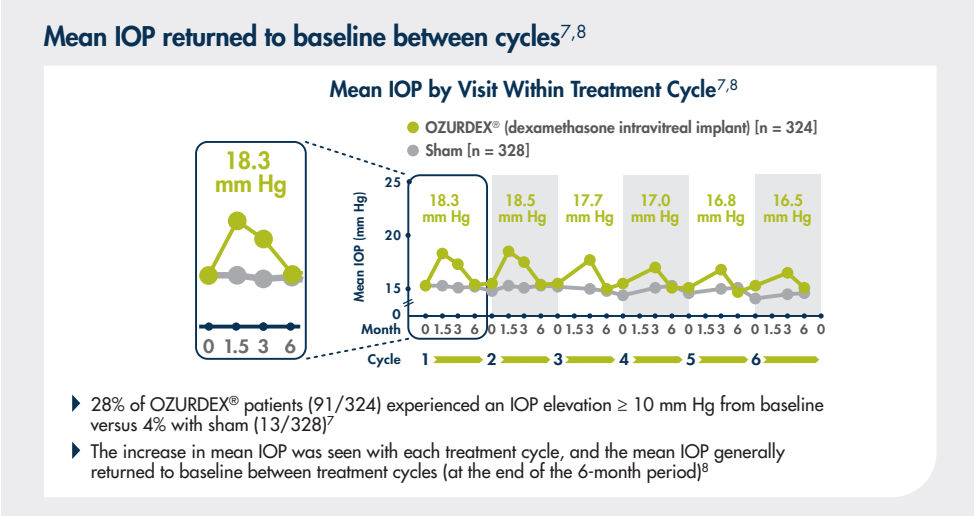


Figure 1. IOP elevations return to baseline between cycles.

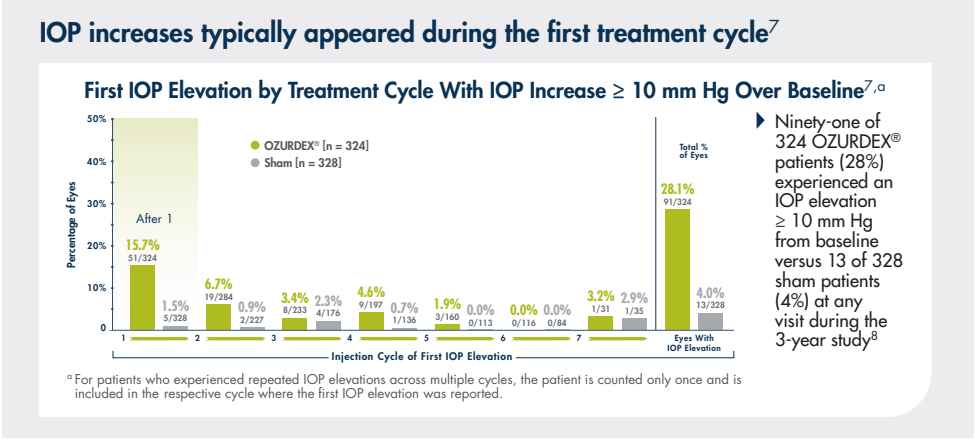


Figure 2. First occurrence of IOP elevation by treatment cycle.

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.

IOP elevations of 25 mm Hg or greater at any visit during the study occurred in 32% of patients treated with OZURDEX.®[5] That percentage dropped to 6.2% for IOP of 35 mm Hg or greater (Table).[5]

Of the patients who received OZURDEX,® 41.5% were subsequently treated with IOP-lowering medications versus 9.1% of patients who did not receive treatment.[5] The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles. Only 1 of 324 (0.1%) needed incisional surgery for a steroid-induced increase in IOP (Figures 1-4).[5]

GENEVA. Likewise, the GENEVA study showed that a low percentage of eyes had a notable change in IOP. In these two identical, multicenter, masked, randomized, 6-month, sham-controlled clinical trials, 1267 patients with vision loss due to macular edema associated with branch retinal vein occlusion (RVO) and central RVO were evaluated to determine the safety and efficacy of the dexamethasone intravitreal implant compared with sham. A total of 427 patients received a single treatment with the dexamethasone intravitreal implant 0.7 mg, 414 with the dexamethasone intravitreal implant 0.35 mg, and 426 received sham treatment. The pooled results of these studies showed that, at day 60, fewer than 5% of patients who received OZURDEX® had an IOP of 35 mm Hg or greater, and at day 180 it was nearing 0%.[6] The percentage of eyes in the implant groups with IOP of at least 25 mm Hg was about 15% at day 60 and close to 1% at day 180.[6] Further, the percentage of eyes in the implant groups with an increase in IOP of at least 10 mm Hg was about 15% at day 60 and closer to 1% at day 180 (Figure 5).[6,7]

Regarding surgical intervention, only 1 eye in the OZURDEX® group underwent IOP-lowering surgery.[6] Two eyes were treated for neovascular glaucoma, not for a treatment-related IOP elevation.[6]

When IOP increases occurred, they were typically managed with topical medication[7]

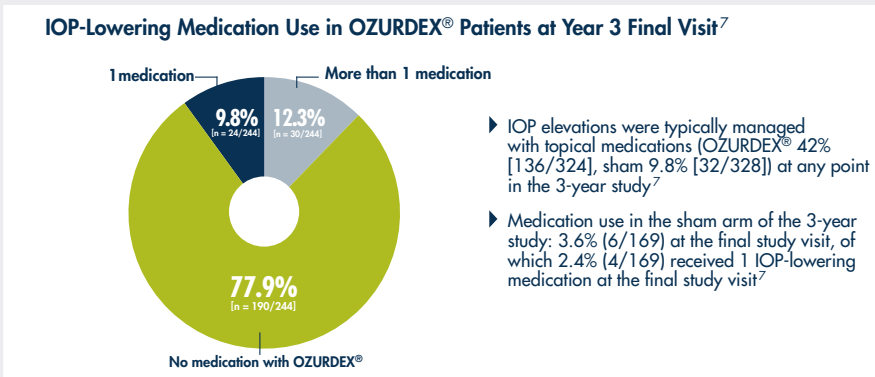


Figure 3. IOP-lowering medication use in OZURDEX® patients at year 3 final visit.

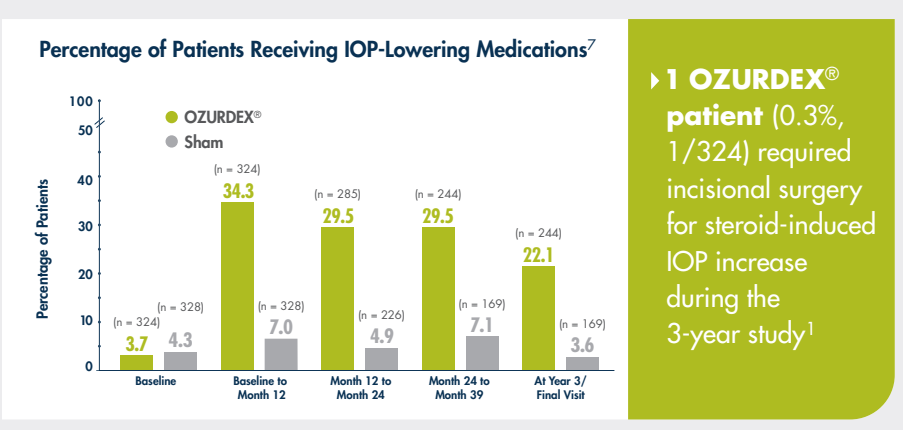


Figure 4. Percentage of patients receiving IOP-lowering medications.

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.

From the results of the GENEVA study, we can conclude that elevation of IOP is most likely to occur after the first treatment with the dexamethasone intravitreal implant.

The GENEVA study also showed some important data in terms of RVO. Patients with branch RVO and central RVO treated with OZURDEX® were at a reduced risk of further vision loss and actually increased their chance of improved visual acuity.[6] Further, the mean change in BCVA from baseline was higher than in patients who did not receive treatment.[6]

HURON. In this 26-week clinical trial, 153 patients randomized to a single treatment with OZURDEX® or sham were studied to evaluate the safety and efficacy of the treatment for noninfectious intermediate or posterior uveitis. The researchers found that intraocular inflammation improved after a single treatment with the implant and persisted for the study duration of 6 months.[9] Fewer than 5% and 10% of patients across all treatment groups developed an IOP of 35 mm Hg or greater and 25 mm Hg or greater, respectively, at any study visit.[9] Further, most patients were either observed only or treated with 1 medication throughout the 6-month period, with fewer than 8% requiring more than 1 medication.[9] Surgical intervention, including incisional surgery, laser trabeculoplasty, and cryotherapy for elevated IOP, was not indicated in any eye, confirming that the minimal incidence of elevation in IOP after treatment with OZURDEX® was typically transient and managed with either observation or 1 topical medication.[9]

IOP elevations of ≥ 10 mm Hg from baseline peaked at day 60 in 15.7% of OZURDEX® patients[7]

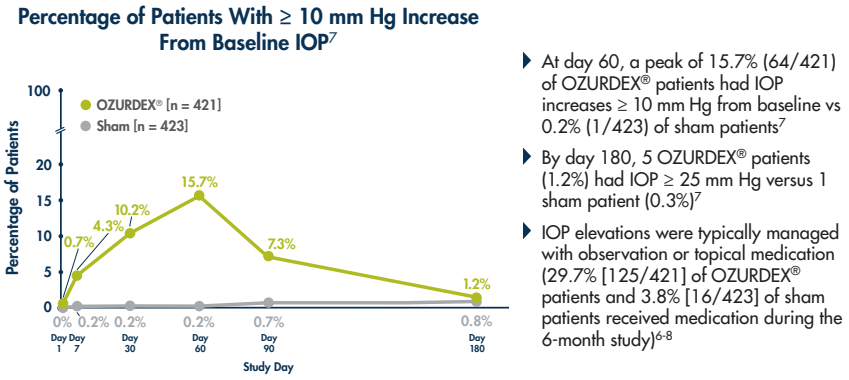


Figure 5. IOP elevations of ≥ 10 mm Hg from baseline peaked at day 60 in 15.7% of OZURDEX® patients.

CLINICAL EXPERIENCE

In our clinical experience, it is common to see an improvement not only in visual acuity but also in decreased retinal thickness over time in patients receiving OZURDEX®. In patients with diabetes specifically, we have found that ocular inflammation can be addressed with steroids. Other first-line options are available, but if patients do not respond well or if the central retinal thickness is not well controlled by the first few treatments, pivoting to OZURDEX® can be beneficial to achieve a successful outcome. In practice, patients with DME tend to respond to OZURDEX® treatments.

Further, when IOP elevations do occur, they are most likely to occur early in the treatment cycle.[7] In our experience, pressures generally return to baseline between treatment cycles. As a result, there is a low incidence of elevated IOP requiring surgery. These results reiterate how helpful steroids can be in patients with diabetes while providing them with a marked level of reduction of edema at 3 months after treatment with OZURDEX®.

The presence of subretinal fluid may be a biomarker for pursuing a more aggressive drying effect, which in

TALKING TO PATIENTS ABOUT IOP ELEVATIONS

- More time should be allotted to discuss IOP elevations with new patients. With repeated intravitreal injections, some patients will have an elevated IOP.[1,2]
- Always discuss the risk of elevated IOP, but also that it can be a main side effect that usually resolves on its own or can be managed with topical medication if necessary.[3]
- Tell the patient that medication may be required to control the pressure. End the conversation there; otherwise, it may get too technical and unrealistically anxiety provoking. Bring the patient back for follow-up at 6 or 8 weeks, or more frequently as required by the patient's condition.
- Consider family history as being just as much a risk factor as the others. Ask patients about family history, as that sometimes determines whether medication is needed.
- Race is a very strong risk factor. Prevalence rates of glaucoma are significantly higher in Black and Latino populations than in whites.[4,5] Those races tend to be underserved in the United States and the Western world for these diseases and, for that reason, this factor should be taken very seriously.

1. Data on file, Allergan.
2. Kiddee W, Trope GE, Sheng L, et al. Intraocular pressure monitoring post intravitreal steroids: a systematic review. *Surv Ophthalmol*. 2013;58(4):291-310. doi:10.1016/j.survophthal.2012.08.003
3. OZURDEX® Prescribing Information.
4. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991;109(8):1090-1095. doi:10.1001/archopht.1991.01080080050026
5. Varma R, Ying-Lai M, Francis BA, al; Los Angeles Latino Eye Study Group. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology*. 2004;111(8):1439-1448. doi:10.1016/j.ophtha.2004.01.025

our experience can be achieved with OZURDEX®. As demonstrated by the previous cases, patients can have a great response after a single treatment with OZURDEX®.

CONCLUSION

There is a consistent theme across the MEAD, GENEVA, and HURON studies[5,6,9] that indicates that an IOP of 35 mm Hg or greater with OZURDEX® is uncommon. In our experience, these data do indeed play out in a clinical practice. As practitioners who see many patients with vision loss due to DME every day of the week, the data presented in this article further build our confidence that we can continue to treat our patients' vision with steroids. ■

1. Jonas JB, Wang N, Want YX, You QS, Yang D, Xu L. Ocular hypertension: general characteristics and estimated cerebrospinal fluid pressure. The Beijing Eye Study. *PLoS ONE*. 2014;9(7):e100533. doi:10.1371/journal.pone.0100533
2. American Academy of Ophthalmology. *Preferred Practice Pattern*® Guidelines. Primary open-angle glaucoma. San Francisco, CA: American Academy of Ophthalmology. 2020.
3. Kass MA, Heuer DK, Higginbotham EJ, et al; Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-713. doi:10.1001/archopht.120.6.701
4. Kim JH, Caprioli J. Intraocular pressure fluctuation: Is it important? *J Ophthalmic Vis Res*. 2018;13(2):170-174. doi:10.4103/jovr.jovr_35_18
5. Boyer DS, Yoon YH, Belfort R Jr, et al; OZURDEX MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904-1914. doi:10.1016/j.ophtha.2014.04.024
6. Haller JA, Bandello F, Belfort R Jr, et al; for OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146. doi:10.1016/j.ophtha.2010.03.032
7. Data on file, Allergan.
8. OZURDEX® Prescribing Information.
9. Lowder C, Belfort R Jr, Lightman S, et al; for OZURDEX HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545-553. doi:10.1001/archophthalmol.2010.339

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.

Key Practice Pearls

For retina specialists who are thinking about incorporating OZURDEX® into their armamentarium for patients with vision loss due to diabetic macular edema (DME), several practice pearls may help. Here, panelists share their top 5 pearls.

BY BLAKE A. ISERNHAGEN, MD; JOHN W. KITCHENS, MD; INDER PAUL SINGH, MD; AND LEJLA VAJZOVIC, MD

LEJLA VAJZOVIC, MD

The data outlined in the article "Understanding the Relationship Between Intraocular Pressure (IOP) and Glaucoma" (pg 7) highlights the decade-long experience with the dexamethasone intravitreal implant 0.7 mg (OZURDEX®, Allergan/AbbVie). The diabetes disease state is challenging, but a lot of the challenges have improved with the availability of OZURDEX®, particularly for patients with DME, but also for those with retinal vein occlusion and noninfectious uveitis affecting the posterior segment of the eye. Additionally, in patients in whom I have performed vitrectomy, OZURDEX® lasts 3 to 6 months[1] because it provides a steady release of medication. Overall, I think the efficacy and safety of OZURDEX® make it a great offering among the products we have to treat DME.

In my clinical practice, OZURDEX® has provided my patients with very predictable IOP levels. Further, if there is an elevation in IOP, it's transient and manageable with drops in most cases. Based on my experience, I have become very comfortable with this treatment, and I like it for many reasons. I find my patients like it as well because it is an option without the need for monthly treatments. As I mentioned in my case (see "Case Study: Intraretinal and Subretinal Fluid Treatment Challenge," pg 3), I bring patients back about 6 to 8 weeks after the initial appointment because the research has shown that about 25% of patients will develop a pressure elevation of at least 10 mm Hg after 1 OZURDEX®.[2] In most cases, an IOP-lowering drop is enough at this point to control the IOP, and I can postpone a subsequent treatment with OZURDEX® for 4 to 8 more weeks.

Practical Pearls

My top 5 practical pearls are as follows.

No. 1: One IOP-lowering drop may be enough to manage IOP. Typically, one IOP-lowering agent in topical form was enough to manage the elevated IOP in patients who received OZURDEX® in clinical studies. If it's not, involve your glaucoma team.

No. 2: Tell your patients who have elevated IOP to incorporate IOP-lowering drop use into their daily routine. Overall, I have found that patients are not bothered by the use of IOP-lowering drops in the morning and at night. I usually suggest that they remember to put the drops in when they brush their teeth, for instance, as a way to incorporate it into their routine in the morning and evening.

No. 3: Share the results with your patients. I think the efficacy of the OZURDEX® treatment really speaks to patients. I find that showing them their own preinjection and postinjection optical coherence tomography (OCT) images is educational, and seeing the results for themselves is more motivation for them to continue taking their IOP-lowering drops regularly and as prescribed.

No. 4: Know when to stop the IOP-lowering drops. If it were to elevate, the IOP will elevate about 6 to 8 weeks after the injection and then start to trend down. In my patients, it tends to trend down for about 3 to 6 months post injection. I feel comfortable at that point to stop the IOP-lowering drops as long as you continue to monitor patients and bring them back in 1 month for assessment of the retinal thickness.

No. 5: Pressure checks may not always be needed. Over time and with accumulated experience with OZURDEX®, some physicians may feel comfortable skipping pressure checks between injections in those patients who have not experienced an elevated IOP after the first few injections. For me, I feel very comfortable after the second injection because I know I will continue to see them regularly for management of their macular edema. I see these patients for 3- and 4-month follow-ups, and I feel confident that, if there were an issue with pressure, I would catch it with pressure checks and monitoring. Most of my patients have healthy optic nerves, so that's the other factor that makes me feel quite comfortable with skipping additional pressure checks in between injections.

1. OZURDEX® Prescribing Information.
2. Haller JA, Bandello F, Belfort R Jr, et al; for OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146. doi:10.1016/j.ophtha.2010.03.032

BLAKE A. ISERNHAGEN, MD

I was introduced to the dexamethasone intravitreal implant 0.7 mg (OZURDEX,® Allergan/AbbVie) at the end of my residency about 5 years ago. I used OZURDEX® throughout my medical and surgical retina fellowships; as I continue to use it frequently in practice today, I get more comfortable with it. Over time, I have become more confident in prescribing the treatment earlier, and I think my top 5 practical pearls outline why this is.

Top Pearls

No. 1: Don't be afraid to initiate treatment with OZURDEX® earlier than you have been. Patients with diabetes have a lot of inflammation. I would encourage practitioners to be thinking of OZURDEX® and steroid sooner in their patients with DME.

No. 2: Take the time to understand and monitor an IOP elevation in patients with retinal disease treated with OZURDEX®. Prescribe IOP-lowering drops and keep patients on the drops after the second injection and as long as steroids are being used.

No. 3: Get a baseline OCT of the retinal nerve fiber layer. Further, take a repeat OCT about every 6 to 12 months to make sure that nothing is happening behind the scenes, so to speak. We all know that not all patients are 100% compliant, so I like to be safe and have repeat OCTs to compare.

No. 4: Surgical intervention will not be required for nearly all patients. It is important to remember that most patients who experience elevated IOP with OZURDEX® can be managed with IOP-lowering topical therapy alone and that few require a surgical intervention.[1-3] Being on IOP-lowering drops is not a risk for surgical intervention. Knowing that gave me a lot of confidence in using OZURDEX® in more of my patients. We have a lot of weapons to fight elevated IOP, and knowing that most patients do well with topical IOP-lowering agents gave me the comfort to treat these patients aggressively.

No. 5: Communicate with patients. The main thing that I try to always remind myself is to communicate the successes with patients. Remind them of their progress, and make sure they are refilling their IOP-lowering drop prescriptions. Just because their pressure is good today does not mean it will be good the day after. I think communication with the patient is really important to reduce the IOP elevation.

1. Haller JA, Bandello F, Belfort R Jr, et al; for OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010;117(6):1134-1146. doi:10.1016/j.ophtha.2010.03.032
2. OZURDEX® Prescribing Information.
3. Lowder C, Belfort R Jr, Lightman S, et al; for OZURDEX HURON Study Group. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545-553. doi:10.1001/archophthalmol.2010.339

INDER PAUL SINGH, MD

Even as a glaucoma specialist, I treat a lot of patients with diabetes and retinal pathology. We send many of those patients to a retina specialist, but we do anti-VEGF and steroid injections like dexamethasone intravitreal implant 0.7 mg (OZURDEX,® Allergan/AbbVie) because there are not a lot of retina specialists in our area, and it is helpful to them if we are able to treat certain low-risk cases. When I started using OZURDEX,® I was surprised at how results looked after injection. It does not take long to get comfortable prescribing OZURDEX,® and with time you quickly find how to successfully manage patients with vision loss due to DME.

Applying 5 Practical Pearls

No. 1: You can treat elevated IOP the same way we, as glaucoma specialists, would. If a patient were referred to me with an elevated IOP from steroid, I would manage them with topical drops. If patients are responding to the topical drops, that may be all the treatment that is needed.

No. 2: First and foremost, focus on the patients' macula. 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 improve 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. It is my experience that retina specialists may think glaucoma colleagues are going to be upset if retina specialists have done something that may raise the IOP, when in reality, that is not the case. I gladly accept a glaucoma referral for a patient who needed and could benefit from a corticosteroid injection, knowing it can improve macular function.

DOCUMENT WHAT WORKS FOR YOUR PATIENT.

Patients receive so many injections, especially those with diabetes. In our practice, we make specific notes in patients' electronic health records (EHR) that act as reminders. I use that area to document personal things like if the patient is battling cancer or if they recently lost a loved one. Most commonly, however, I use that area in the EHR to document what type of therapy works for that patient. On occasion, I go back and look at the visit after the steroid shot to see if the patient improved, and in many cases they did! It is critically important to remind yourself (and your partners) when steroids worked for a patient.

– John W. Kitchens, MD

No. 3: After their first injection, patients should be monitored at the 6- to 8-week mark. This is a common timepoint for elevated IOP to occur. Usually, you'll get a sense of the patient's potential for a rise after the first injection. If the IOP is stable, I'm not too worried about them going forward. If it is elevated, however, I treat them accordingly and have them come back for an IOP check within 2 weeks.

No. 4: Remember that the incidence of an elevation in IOP after the first injection of OZURDEX® does not increase with repeated injections.[1] There is one caveat: In patients with a family history of glaucoma, heavily pigmentated trabecular meshwork, or a history of inflammation in the past, a significant rise in IOP is more likely. Closely monitoring those patients is therefore important.

No. 5: When a patient is diagnosed with glaucoma, they have had high elevation of pressure for a long period of time. Glaucoma develops slowly and is a progressive disease. 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 glaucoma specialists, we are very comfortable with addressing any pressure issue that might arise. The use of an IOP-lowering drop, in patients with a healthy nerve, is typically more than enough to bring the pressure back down.

1. Data on file, Allergan.

JOHN W. KITCHENS, MD

I do a lot of general retina in my practice, but I also treat patients with diabetes. In these patients, I use OZURDEX® quite frequently. I think many retina specialists can get concerned when IOP elevation occurs in this population, but it is important to remember that we don't have the perspective of glaucoma specialists; patients are going to be monitored.

Five Important Pearls

No. 1: Don't forget that steroids are an option. In other words, many retina specialists often don't even consider steroids until patients are a year or more into therapy.

No. 2: In some cases, optimal dryness of the retina is best achieved with a multimodal approach. Sometimes, especially in tough cases, a multimodal approach might be necessary.

No. 3: Document what works for your patient. Patients receive so many injections, especially those with diabetes. In our practice, we make specific notes in patients' electronic health records (EHR) that act as reminders. I use that area to document personal things like if the patient is battling cancer or if they recently lost a loved one. Most commonly, however, I use that area in the EHR to document what type of therapy works for that patient. On occasion, I go back and look at the visit after the steroid shot to see if the patient improved, and in many cases they did! It is critically important to remind yourself (and your partners) when steroids worked for a patient.

No. 4: Concentrate on the unresolved DME. Cataracts can impact our patients significantly, but only rarely do they cause blindness.[1] Unresolved DME, however, is much more likely to cause an eventual loss of vision that can be permanent.[2] My grandmother used to say to my parents when they did not reprimand me for poor behavior, "Spare the rod, spoil the child." I like to say, "Spare the cataract, spoil the macula" when it comes to leaving edema out of fear for the development of lens opacity.

No. 5: There is a technique for injecting OZURDEX®. For many early users of intravitreal injections, the idea of a larger needle and the trigger release mechanism is daunting. It can be more complicated than a needle and syringe, but it can be mastered easily. First, practice with a sample injector. AbbVie/Allergan is more than happy to bring injectors and trial eyes to a surgeon's office to help them gain experience with the device. ■

1. Khairallah M, Kahloun R, Bourne R, et al; Vision Loss Expert Group of the Global Burden of Disease Study. Number of people blind or visually impaired by cataract worldwide and in world regions, 1990 to 2010. *Invest Ophthalmol Vis Sci*. 2015;56:6762-6769. doi: 10.1167/iovs.15-17201
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis*. 2015;2:17. doi: 10.1186/s40662-015-0026-2

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: 10/2020

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 Trials Experience

Because clinical trials 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

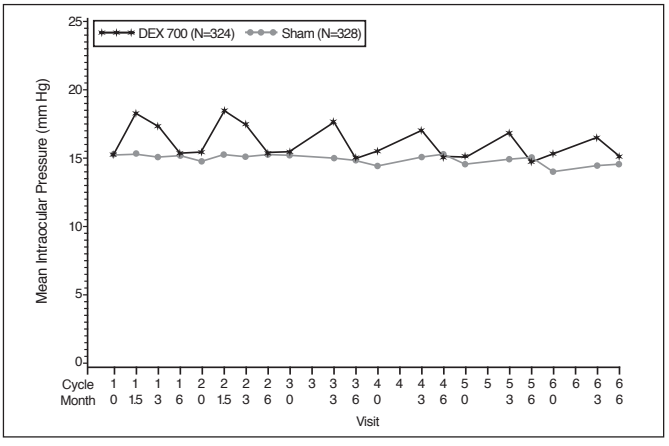
IOP	Treatment: N (%)	
	OZURDEX® N=324	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* **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 resulting in ocular tissue injury including sclera, subconjunctiva, lens and retina (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/m^2 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/m^2 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

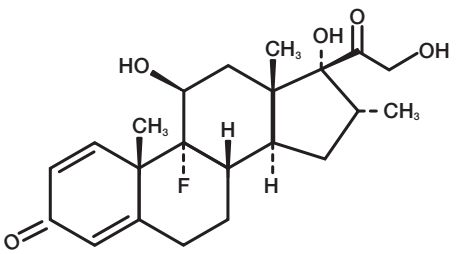
Safety and effectiveness of **OZURDEX**® in pediatric patients have not been established.

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: $C_{22}H_{29}FO_5$

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

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 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

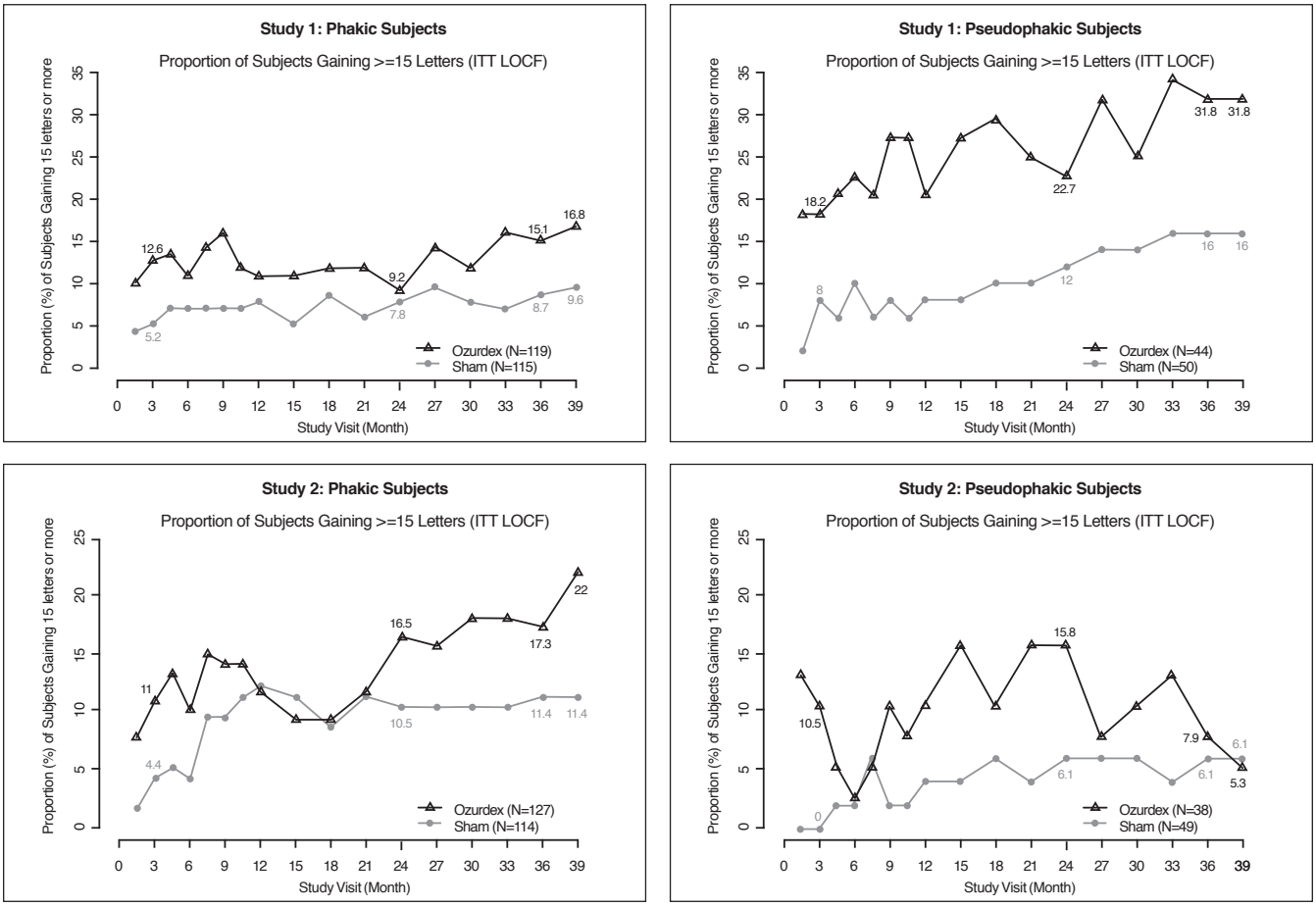
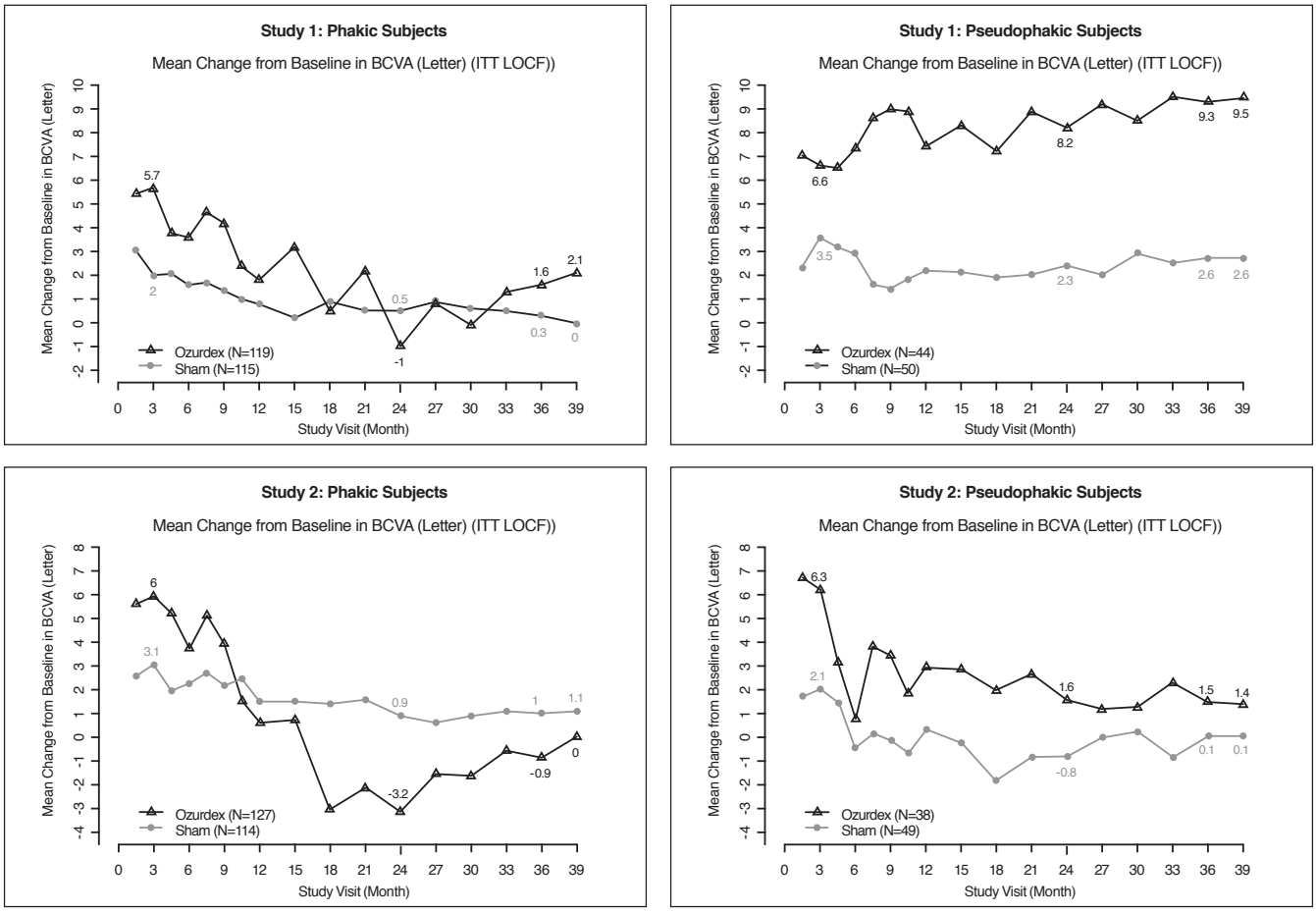


Figure 3: Mean BCVA Change from Baseline



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 15ºC to 30ºC (59ºF to 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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v2.0USPI3348

US-OZU-220037 02/2022 015976