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

Treatment of Diabetic Macular Edema (DME) and Macular Edema (ME) Following Retinal Vein Occlusion (RVO)* With a Discussion on Use in Pseudophakic Patients With DME

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® 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.

*Retinal vein occlusion: branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

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

Treatment of Diabetic Macular Edema (DME) and Macular Edema (ME) Following Retinal Vein Occlusion (RVO) With a Discussion on Use in Pseudophakic Patients With DME

Recent studies have shown us that the inflammatory cascade is highly relevant in the development and persistence of ME and that interventions aimed at multiple inflammatory mediators help improve visual acuity.[1] Corticosteroids form the basis for such approaches in the clinic, although there is an appreciable risk of cataract progression and intraocular pressure (IOP) elevation associated with their use.[1,2] In the following article, a panel of experts will discuss these risks, adding important clinical context about safety concerns. Additionally, this supplement will include a focus on patients with RVO and DME and discuss pseudophakic patients with DME. In particular, we will discuss whether patients with a pseudophakic lens require any special treatment considerations for DME.

— Tarek S. Hassan, MD, Moderator

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IMPORTANT SAFETY INFORMATION (continued)

Contraindications (continued)

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

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

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

THE ROLE AND RELEVANCE OF INFLAMMATION IN MACULAR EDEMA

Tarek S. Hassan, MD: ME is a feature of many commonly occurring eye diseases, including diabetic eye disease and RVO. ME is the most common cause of visual impairment in RVO.[3] Corticosteroids, due to their anti-inflammatory properties, and anti–vascular endothelial growth factor (VEGF) therapy both play a prominent role in the therapy of ME.[4] Yet, while inflammatory mediators and VEGF each drive ME pathophysiology, it appears that one or the other may predominate in a given clinical presentation.[5]

Baruch D. Kuppermann, MD, PhD: The relative contributions of VEGF and inflammatory mediators are individualized, and they also vary in different disease states. For example, while VEGF and inflammatory mediators are key drivers of ME in RVO and DME, VEGF may be slightly more important in RVO due to the potential for induced hypoxia. In diabetic retinopathy (DR), there is growing evidence regarding the role of inflammatory mediators in the disease process.[6]

What is common to DME, RVO, and uveitis with respect to ME, though, is that it is the result of a cascade of events caused by vascular disease that is facilitated by inflammatory cytokines that lead to vasodilation, leukostasis, diapedesis, increased vascular permeability, and the accumulation of various inflammatory proteins.[7] Thus, while VEGF blockade is an important approach, we may need to address other clinical factors as well. Inflammation plays an important role, and this broader context should be considered.

Dr. Hassan: It has been proposed that the relative contributions of the inflammatory component and the VEGF might vary in DME.[5] Is there any evidence of this?

Amy C. Schefler, MD, FACS: I have found that patients in my practice who have longer-term DME need a multifactorial approach. That would suggest to me that perhaps another mediator is active, and that inflammation can also play a critical role.[5]

Dr. Hassan: I wonder if the chronicity of the eye disease is the only factor.[2,5,8] In some cases, it appears that the ME is driven by either VEGF or inflammation, whereas in others, both are factors.[9]

Eric D. Nudleman, MD, PhD: There are some interesting clinical trial data that are worth considering. In a subgroup analysis of the FAME trial, which was investigating the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera), patients who had chronic edema—defined as a 3-year duration or longer—had greater improvement on visual outcomes than those with DME less than 3 years.[10] The reason is uncertain, but it was suggested that fluocinolone was more beneficial in eyes with inflammatory disease, indicated by longer duration of active edema.[10]

Dr. Kuppermann: Interestingly, a reanalysis of the FAME trial suggested that the median duration of DME was less than 2 years; this observed effect in patients with chronic DME started to occur after about 2 years of median disease duration. Delaying initiation of anti-VEGF may have consequences for visual ability.[9] In the RISE/RIDE trial, patients who were crossed over to ranibizumab (Lucentis, Genentech) at 24 months did not gain as much vision as patients initially treated with anti-VEGF.[11] Taken together, these data support what Dr. Hassan is suggesting, that steroids may have an important place in therapy because of the role of inflammation in the pathophysiology of ME. Also, because the inflammatory response is a cascade, it intensifies over time and becomes more active as the DME persists, which may explain why we may see an effect in more chronic ME.[5]

There is another piece of evidence that speaks to the relative contributions of VEGF and inflammation in ME. Dong et al showed that VEGF is elevated in aqueous samples taken from eyes with DR, but other inflammatory cytokines also appeared to be prominently elevated as well. This suggests to me that, while VEGF is certainly a key player, the presence of a variety of cytokines suggest that inflammation is also important and DME may also be responsive to treatment with steroids.[12]

Dr. Hassan: Are there any clinical trial data that might help us predict who will respond to anti-VEGF?

Howard F. Fine, MD, MHSc: The data from the EARLY trial was a post-hoc analysis of the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol I data.[13] That can be helpful when thinking about who will be a good responder, a medium responder, or a poor responder to anti-VEGF therapy. In my clinic, I look at this a little bit differently.

My endpoint for therapy is to gain improvement in visual acuity and to get a dry macula.

ADDRESSING INFLAMMATION IN RVO

Dr. Hassan: The classic thinking in RVO is that the VEGF mediators are much more influential in ME. However, there is evidence that corticosteroid therapy targeted at multiple inflammatory cytokines also may help reduce ME in eyes with RVO.[4] The importance of treating inflammation is further supported by data from the GENEVA trial, in which 853 patients with central (CRVO) or branch (BRVO) RVO were randomized 1:1 to OZURDEX implant or sham. Time to achieve ≥ 15 letters (3-line) improvement in best corrected visual acuity (BCVA) cumulative response rate curves was significantly faster with OZURDEX compared to sham ($P < .01$).[14] Patients had a mean duration of ME of 157 days.[13] Overall, the proportion of patients achieving at least a 15-letter improvement from baseline BCVA was significantly greater in the OZURDEX group than in the sham group from day 30 through day 90 (Figure 1).[14,15] At 180 days, this difference was not statistically significant.[14]

Dr. Kuppermann:

The window of response from 30 to 90 days is actually pretty reflective of what we see in practice, with most patients responding early, by day 30, and the effect peaking by 60 days, then a continued clinical effect over the next month. I find the response to be quite predictable, and if there is a response to the first implant injection, I feel comfortable reusing it if needed.

Dr. Hassan: Is there a difference between BRVO and CRVO in how we should approach treatment?

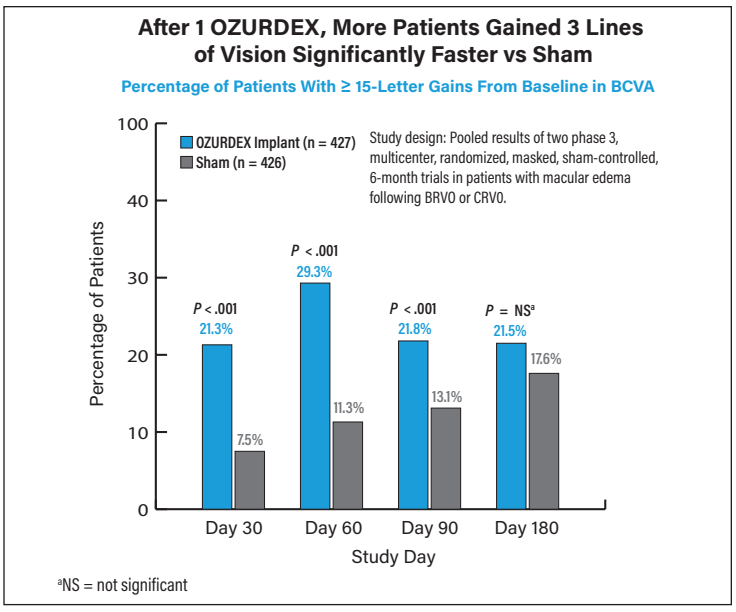


Figure 1. Percentage of patients with ≥ 15-letter gains from baseline in BCVA.[14,15]

Dr. Fine: Anti-VEGF is likely the first consideration in both BRVO and CRVO, but the reasons for evaluating therapy typically differ. There is a worse prognosis associated with CRVO,[3,9] so in many cases I start with anti-VEGF therapy, but I may also think about a dexamethasone implant to suppress the inflammation.[16]

Dr. Schefler: Certainly, the prognosis with treatment is better in BRVO compared to CRVO, and that is just the nature of these conditions. Still, as we saw in the GENEVA study data, the dexamethasone implant is effective for treating both BRVO and CRVO, with a peak effect around day 60 (Figure 2).[14,15]

Dr. Hassan: How long do you stick with a given treatment approach before escalating therapy?

Dr. Fine: It really depends. With OZURDEX, if there is a response, I will continue to use it. I will know pretty quickly if it works or not before moving on to other treatment strategies.

Dr. Schefler: Because inflammation is such an important part of RVO, I have a low threshold for considering OZURDEX.

Dr. Hassan: What factors might we consider regarding the timing of a repeat OZURDEX injection?

Dr. Fine: RVO is a highly time-dependent disease.[17] I have found that there is a specific point at which the drug wears off and the edema can come back very quickly. That said, the acute nature of the ME also makes it a little forgiving, because even if the swelling recurs, repeat treatment is likely to improve the vision similar to how it did with the prior injections.[18] The goal should be to time the retreatment so the effect of the implant remains continuous without losing efficacy.[14,15]

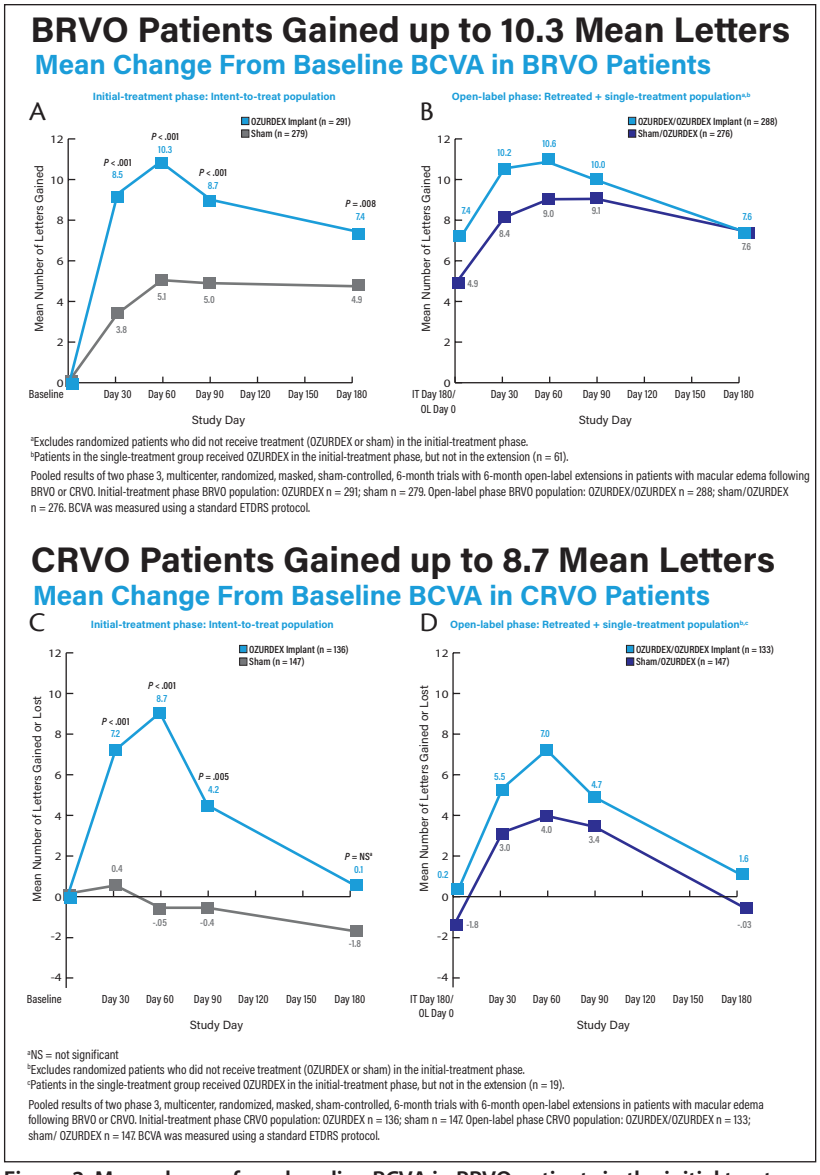
OZURDEX IOP AND CATARACT SAFETY INFORMATION IN RVO AND POSTERIOR SEGMENT UVEITIS

Combined results from the OZURDEX phase 3 RVO and posterior segment uveitis studies showed:

- 25% of OZURDEX patients (n = 497) versus 2% of sham patients (n = 498) experienced increased IOP; increased IOP with OZURDEX peaked at approximately week 8[16]
  - 1% of the patients who received OZURDEX (3/421) required surgical procedures for management of elevated IOP during the initial treatment period[16]
- 5% of OZURDEX patients versus 2% of sham patients experienced a cataract; following a second injection of OZURDEX in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year[16]

ME IN DME: MEAD TRIAL DATA IN CONTEXT

Dr. Hassan: The pivotal MEAD trial led the FDA to approve OZURDEX for treatment of DME based in part on the proportion of patients gaining ≥ 15 letters in BCVA from baseline at the patient's final efficacy assessment (Table 1).[15] The outcome was positive, yet I wonder if some of the



[a]Excludes randomized patients who did not receive treatment (OZURDEX or sham) in the initial-treatment phase.
[b]Patients in the single-treatment group received OZURDEX in the initial-treatment phase, but not in the extension (n = 61).

Pooled results of two phase 3, multicenter, randomized, masked, sham-controlled, 6-month trials with 6-month open-label extensions in patients with macular edema following BRVO or CRVO. Initial-treatment phase BRVO population: OZURDEX n = 291; sham n = 279. Open-label phase BRVO population: OZURDEX/OZURDEX n = 288; sham/OZURDEX n = 276. BCVA was measured using a standard ETDRS protocol.

[a]NS = not significant
[b]Excludes randomized patients who did not receive treatment (OZURDEX or sham) in the initial-treatment phase.
[c]Patients in the single-treatment group received OZURDEX in the initial-treatment phase, but not in the extension (n = 19).

Pooled results of two phase 3, multicenter, randomized, masked, sham-controlled, 6-month trials with 6-month open-label extensions in patients with macular edema following BRVO or CRVO. Initial-treatment phase CRVO population: OZURDEX n = 136; sham n = 147. Open-label phase CRVO population: OZURDEX/OZURDEX n = 133; sham/ OZURDEX n = 147. BCVA was measured using a standard ETDRS protocol.

Figure 2. Mean change from baseline BCVA in BRVO patients in the initial treatment phase (A) and open-label extension (B). Results are also presented in CRVO patients (C and D).[14,15]

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.

TABLE 1. VISUAL ACUITY OUTCOMES AT 39 MONTHS IN THE MEAD TRIAL.[15]

All Randomized Patients: Visual Acuity Outcomes at Month 39			
Measurement	**OZURDEX (n = 328)**	**Sham (n = 328)**	**Estimated Difference (95% Confidence Interval [CI])**
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	19.5% (64)	10.7% (35)	8.8% (3.4%, 14.3%)
Patients losing ≥ 15 letters in BCVA (n)	13.7% (45)	10.7% (35)	3.0% (-2.0%, 8.1%)
Mean change in BCVA (letters) (SD[a])	2.2 (15.88)	0.8 (12.72)	1.3 (-0.9, 3.4)
BCVA Baseline and Change From Baseline After 1 Treatment			
After 1 treatment (3-month visit)		6.0 letters gained in OZURDEX group 2.6 letters gained in sham group	

Pooled results of all DME randomized patients with last observation carried forward (LOCF) from two multicenter, masked, randomized, sham-controlled studies. 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 retreatment at month 36. Only 14% of the study patients completed the month 39 visit (16.8% from OZURDEX and 12.2% from sham).[15,19]

[a] Standard deviation.

baseline characteristics might be interesting to consider for context. For instance, the mean DME duration of the patients in the trial was 2 years, and I wonder if that may have influenced the results?

Dr. Fine: The cohort enrolled to MEAD would fit the profile of some of the tougher cases of DME that we would deal with in the clinic. In addition to the longer duration of DME, a majority had received other previous treatments, for example (Table 2).[19] In my view, there appears to be a bit more advanced disease at baseline in the MEAD trial study population in terms of severity of nonproliferative diabetic retinopathy (NPDR).[19]

Dr. Hassan: I think the high percentage of phakic patients, 75%,[15,19] might have had an impact on final acuity outcomes, as well (Figure 3). It is also important to acknowledge that there was a reinjection protocol of every 6 months with OZURDEX, based on physician's discretion after examination including OCT. In clinical practice, we may reinject at shorter intervals. These are variables that should be taken into consideration.

DME IN THE PSEUDOPHAKIC PATIENT

Dr. Hassan: Certain populations of patients appear to be particularly good candidates for earlier initiation of OZURDEX therapy. In MEAD, 20% of pseudophakic patients on OZURDEX gained 3 or more lines of BCVA at 39 months versus 11% of sham patients (estimated difference 8.4%; 95% CI: -2.2%, 19.0%), and this pseudophakic subset had a greater improvement in mean BCVA versus sham patients and the phakic subset of patients (Tables 3 and 4 and Figures 4 and 5).[16,19] Does that suggest we should consider the lens status in the treatment of patients with DME?

Dr. Fine: I do not think we need to change our treatment endpoint in a pseudophakic eye, but it might affect the approach. My treatment endpoint is always to improve visual acuity and achieve a dry macula. That is not always achievable, but pseudophakia might encourage me to think about using OZURDEX to treat edema.

Dr. Kuppermann: I attempt to treat until the macula is dry as well, but there is also a balance. If the excess macular thickness is 50 µm or less, and the vision is good after using anti-VEGF therapy, I would not be inclined to add OZURDEX in my treatment of DME.

Dr. Hassan: What other endpoints are important? How do you use OCT and/or vision to guide treatment decisions?

Dr. Schefler: In DME, I think it is important to not ignore vision. All of the variables we use in the clinic add up in our evaluation, and there may be other factors to consider as well.

EVALUATING AND MANAGING IOP ELEVATION

Dr. Hassan: Cataract progression and IOP elevation are two well-known risks associated with use of corticosteroid therapy.

TABLE 2. MEAD DME STUDY POPULATION.[15]

	OZURDEX (n = 328)	Sham (n = 328)		OZURDEX (n = 328)	Sham (n = 328)
Mean age, years (range)	**62.8 (33–85)**	**62.9 (26–88)**	**Diabetes type** (%)		
Gender (% male)	**62.8%**	**63.4%**	Type 1	**10.4%**	**8.5%**
Race (%)			Type 2	**88.7%**	**91.5%**
White	**71.0%**	**70.1%**	**Mean HbA1c (SD)**	**7.6** (1.15)	**7.5** (1.05)
Black	**4.9%**	**6.1%**	≤ 8% (%)	**67.1%**	**71.6%**
Asian	**16.5%**	**16.2%**	**Mean DME duration, months** (SD)	**24.0** (25.92)	**26.3** (26.11)
Hispanic	**4.3%**	**4.6%**			
Other	**3.4%**	**3.0%**	**DME subtype** (%)		
Lens status (%)			None	**0.6%**	**0.6%**
Pseudophakic	**25.0%**	**30.2%**	Focal	**35.1%**	**39.9%**
Phakic	**75.0%**	**69.8%**	Intermediate	**39.9%**	**35.7%**
Mean BCVA, letters (SD[a])	**55.7** (9.96)	**56.6** (8.77)	Diffuse	**19.5%**	**20.7%**
Median BCVA, letters (range)	**59.0** (34–95)	**58.0** (34–82)	**Severity of diabetic retinopathy** (%)		
Mean center subfield retinal thickness on OCT (SD)	**469.8** (156.99)	**468.7** (128.96)	Moderately severe or better nonproliferative diabetic retinopathy (NPDR)	**48.2%**	**49.7%**
			Severe or worse NPDR	**43.6%**	**42.1%**
Mean IOP, mm Hg (SD)	**15.3** (2.64)	**15.3** (3.09)	**Prior DME treatment** (%)		
Mean diabetes duration, years (SD)	**16.5** (9.15)	**15.9** (9.26)	Anti-VEGF[b]	**7.6%**	**7.9%**
			Intravitreal steroid	**17.7%**	**18.3%**
			Laser	**68.6%**	**72.3%**
			None	**26.5%**	**22.3%**

[a] *Standard deviation.*
[b] *Anti–vascular endothelial growth factor.*

While pseudophakic lens status obviates the former, IOP elevation is something that should be carefully considered for all patients. How common is IOP elevation after an OZURDEX implant?

Dr. Nudleman: I think what we saw in the MEAD trial, over the course of the 3-year study after up to seven implants, where 28% in the implant group compared with 4% in the sham group had an IOP elevation of 10 mm Hg or greater, is a fair representation of actual experience.[16] 15.7% experienced their first IOP elevation ≥ 10 mm Hg from baseline during the first cycle of treatments with OZURDEX.

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.[15]

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

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

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TABLE 3. PHAKIC PATIENTS: VISUAL ACUITY OUTCOMES AT MONTH 39.[16]

Measurement	OZURDEX (n = 246)	Sham (n = 229)	Estimated Difference (95% CI)
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	20% (48)	11% (24)	9.0% (2.7%, 15.4%)
Patients losing ≥ 15 letters in BCVA (n)	17% (41)	12% (28)	4.4% (-1.9%, 10.7%)
Mean change in BCVA (letters) (SD[a])	1.0 (16.9)	0.6 (12.9)	0.3 (-2.4, 3.0)

[a] Standard deviation.

TABLE 4. PSEUDOPHAKIC PATIENTS: VISUAL ACUITY OUTCOMES AT MONTH 39.[16]

Measurement	OZURDEX (n = 82)	Sham (n = 99)	Estimated Difference (95% CI)
Patients gaining ≥ 15 letters (3 lines) in BCVA (n)	20% (16)	11% (11)	8.4% (-2.2%, 19.0%)
Patients losing ≥ 15 letters in BCVA (n)	5% (4)	7% (7)	-2.2% (-9.1%, 4.7%)
Mean change in BCVA (letters) (SD[a])	5.8 (11.6)	1.4 (12.3)	4.2 (0.8, 7.6)

[a] Standard deviation.

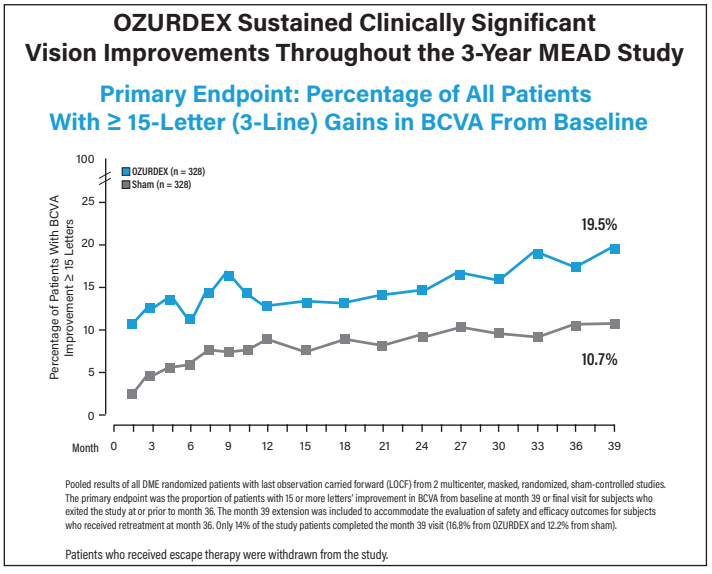


Figure 3. Percentage of patients with ≥ 15-letter (3-line) gains in BCVA from baseline in MEAD.[15]

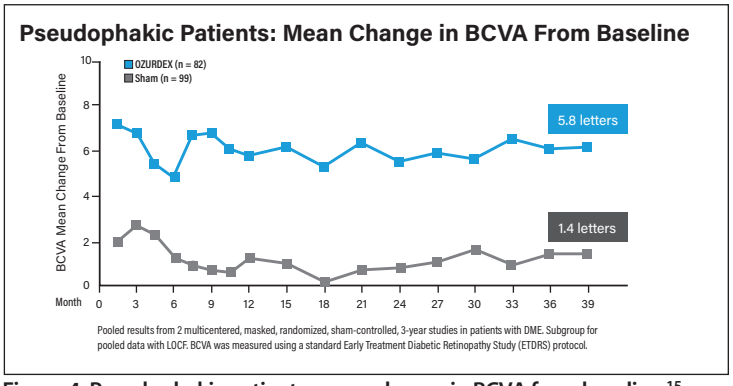


Figure 4. Pseudophakic patients: mean change in BCVA from baseline.[15]

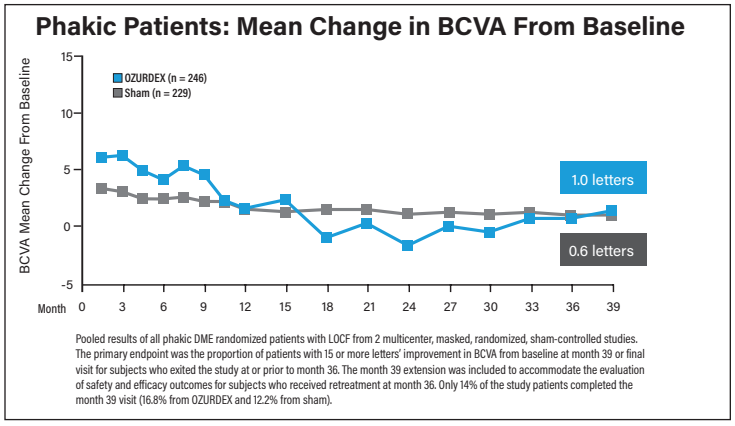


Figure 5. Phakic patients: mean change in BCVA from baseline.[15]

Dr. Hassan: How do you manage those patients?

Dr. Nudleman: If there is elevation, I want to see the patient back in about a week, because I want to see elevation on two consecutive visits before considering starting topical therapy.

Dr. Hassan: Does anyone use a benchmark, for example a pressure greater than 25 mm Hg?

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.

Dr. Fine: You have to consider the whole picture, because in that same patient, the cup-to-disc ratio might be 0.5 and the optic nerve looks healthy. If there is cupping and a pressure above target, I might be more aggressive about treating the elevation. I typically use a beta-blocker.

Dr. Schefler: We should make a distinction here because elevated ocular pressure does not always equal glaucoma. We should assess the whole health of the eye first. In MEAD, throughout the 3-year study, 28% of patients had an IOP elevation ≥ 10 mm Hg from baseline at some point during treatment compared with 4% of sham-treated patients. 42% of OZURDEX patients compared with 10% of sham patients needed any IOP-lowering medication during the study. Yet, over the course of the 3-year study, 0.3% of OZURDEX patients required incisional surgery for steroid-induced IOP increases, and 1.2% of OZURDEX patients needed any surgical intervention for elevated IOP as compared with 0.3% of sham-treated patients.[16] The goal is to save vision, and that should be the high priority.

Dr. Nudleman: I agree completely.

Dr. Hassan:

Returning to the MEAD data, after the first injection, 15.7% of OZURDEX eyes exhibited an elevated IOP of ≥ 10 mm Hg from baseline.[15,16] The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles.[15,16] I have noticed this same thing in clinical practice.

Dr. Fine: The nice thing about OZURDEX is that we have data to provide context for IOP elevations.

Dr. Hassan: Let us say that a patient experiences a rise in IOP to 30 mm Hg, and topical therapy is initiated. Once that pressure is back to target or something reasonable, will you reinject the implant?

Dr. Kuppermann: Yes. First, if I start topical therapy and lower the pressure to 20 or 25 mm Hg, I can start to taper because the pharmacokinetics of the implant suggest the steroid will not last long in the eye, with peak drug levels at 60 days post injection.[20] In clinical practice, it might be sufficient to observe patients, rather than use topical drops, in certain cases, to see if the IOP settles on its own.[15] Elevated IOP on its own can be a little misleading, and this is seen even in the MEAD trial, where there was an increase in mean IOP after each injection of the implant, but mean IOP generally returned to baseline between treatment cycles (Figure 6). Based on that, I try to manage each patient on an individualized basis in regard to IOP elevation.

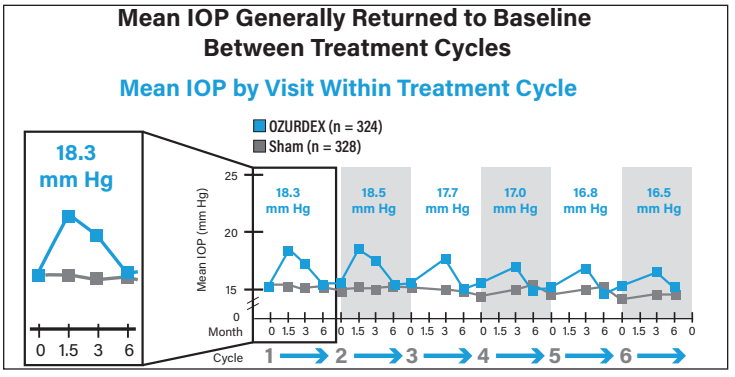


Figure 6. Mean IOP by visit within treatment cycle.[15,16]

Dr. Schefler: I think you can use the implant as the primary mode of therapy even after an IOP elevation. If the IOP is still elevated after 60 days, I have a conversation with the patient regarding their long-term goals and the need to try and achieve a dry macula and improve visual acuity. Generally speaking, though, having a patient on topical therapy for IOP is not a contraindication for reinjecting OZURDEX. Patients with glaucoma who have cup to disc ratios of greater than 0.8 is one of the contraindications.

Dr. Hassan: How do you manage the patient who is going to be reinjected with OZURDEX who had a previous IOP spike?

(Continued on page 15)

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%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® patients versus 4% of sham patients. 42% of the patients who received OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

Please see additional Important Safety Information on the following pages.

Case 1: Finding the Injection Sweet Spot

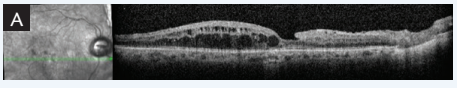
Eric D. Nudleman, MD, PhD

CASE BACKGROUND

2011 to 2013

This is a case of a 49-year-old white female with a 20-year history of poorly controlled type 2 diabetes, metabolic syndrome, hypertension, and hyperlipidemia. The patient had a membrane peel and received previous treatment for diabetic macular edema (DME). She underwent cataract surgery in the right eye (OD) in March 2013. She presented with DME OD. I began treatment with dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan).

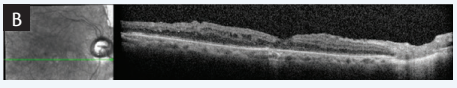
Initial Visit



- The patient's VA was 20/50 OD, and central retinal thickness (CRT) was 312 µm (A)
- Treated with OZURDEX OD

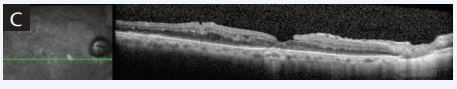
FIRST INJECTION

1 Month Post OZURDEX



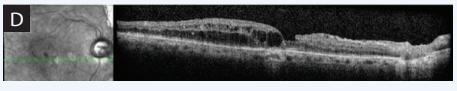
- The patient's VA was 20/40+2, CRT was 251 µm, and IOP was 15 mm Hg (B)

3 Months Post OZURDEX



- The patient's VA was 20/40+3, CRT was 232 µm, and IOP was 12 mm Hg (C)

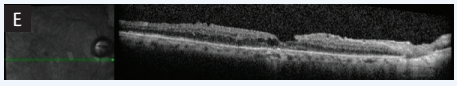
4.5 Months Post OZURDEX



- Some VA was lost by month 3 (VA was 20/50), CRT was 306 µm, and IOP was 13 mm Hg (D)
- I administered a second treatment with OZURDEX OD

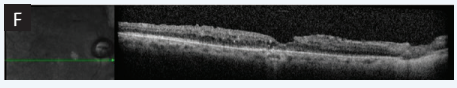
SECOND INJECTION

1 Month Post Second OZURDEX



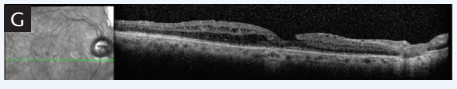
- The patient's VA was 20/40+2, CRT was 231 µm, and IOP was 12 mm Hg (E)

3 Months Post Second OZURDEX



- The patient's VA was 20/40, CRT was 229 µm, and IOP was 17 mm Hg (F)

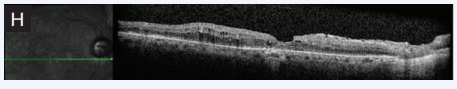
4.5 Months Post Second OZURDEX



- The patient's VA was 20/50, CRT was 274 µm, and IOP was 21 mm Hg (G)
- I administered a third injection with OZURDEX, as there was reduced VA

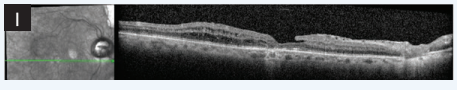
THIRD INJECTION

1 Month Post Third OZURDEX



- The patient's VA was 20/40, CRT was 243 µm, and IOP was 14 mm Hg (H)

3 Months Post Third OZURDEX



- The patient's VA was 20/40, CRT was 226 µm, and IOP was 21 mm Hg (I)

(Continued on next page)

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued)

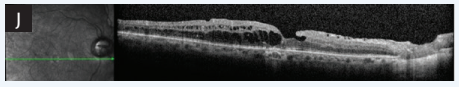
Diabetic Macular Edema (continued)

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.

4.5 Months Post Third OZURDEX

- The patient's VA was 20/50, CRT was 329 µm, and IOP was 18 mm Hg (J)

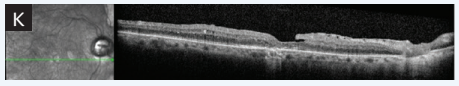


- I administered a fourth injection with OZURDEX, as there was reduced VA

FOURTH INJECTION

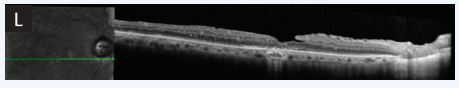
1 Month Post Fourth OZURDEX

- The patient's VA was 20/40+2, CRT was 237 µm, and IOP was 19 mm Hg (K)



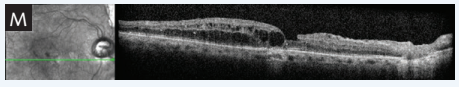
3 Months Post Fourth OZURDEX

- The patient's VA was 20/40+3, CRT was 232 µm, and IOP was 20 mm Hg (L)



4.5 Months Post Fourth OZURDEX

- The patient's VA was 20/50, CRT was 259 µm, and IOP was 17 mm Hg (M)

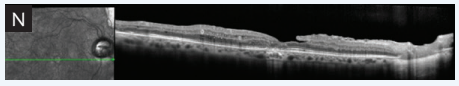


- I administered a fifth injection of OZURDEX, as there was reduced VA

FIFTH INJECTION

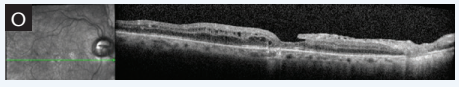
1 Month Post Fifth OZURDEX

- The patient's VA was 20/40+2, CRT was 232 µm, and IOP was 20 mm Hg (N)



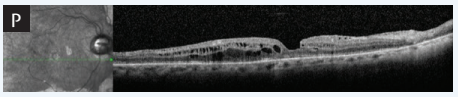
3 Months Post Fifth OZURDEX

- The patient's VA was 20/40, CRT was 240 µm, and IOP was 20 mm Hg (O)



4.5 Months Post Fifth OZURDEX

- The patient's VA was 20/50, CRT was 283 µm, and IOP was 17 mm Hg (P)

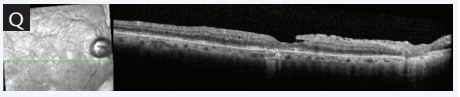


- I administered a sixth injection with OZURDEX, as there was reduced VA

SIXTH INJECTION

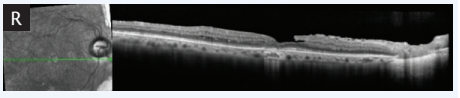
1 Month Post Sixth OZURDEX

- The patient's VA was 20/40, CRT was 228 µm, and IOP was down to 16 mm Hg (Q)



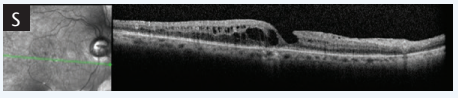
3 Months Post Sixth OZURDEX

- The patient's VA was 20/40, CRT was 216 µm, and IOP was back up to 20 mm Hg (R)



4.5 Months Post Sixth OZURDEX

- The patient's VA was 20/50, CRT was 346 µm, and IOP was 17 mm Hg (S)

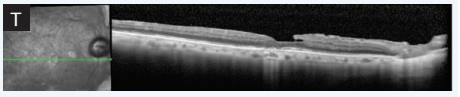


- I administered a seventh injection with OZURDEX, as there was reduced VA

SEVENTH INJECTION

1 Month Post Seventh OZURDEX

- The patient's VA was 20/40+2, CRT was 245 µm, and IOP was 18 mm Hg (T)



DISCUSSION

- Monotherapy with OZURDEX improved vision
- Her pattern was predictable—improved VA until month 4.5, when she required another OZURDEX injection
- The patient maintained improvements in VA for 2 years with OZURDEX every 4.5 months

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.

Case 2: OZURDEX in a Case of DME

Baruch D. Kuppermann, MD, PhD

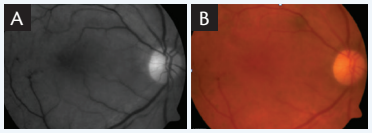
CASE BACKGROUND

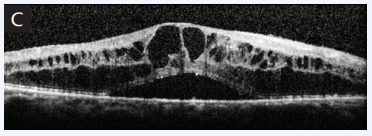
This is a case of a 65-year-old female with diabetic macular edema (DME) OD.

FIRST INJECTION

First Visit

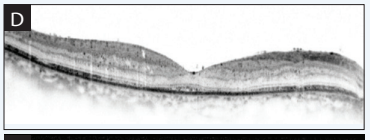
- The patient's VA was 20/100, and CRT was 846 µm (A, B, C)
- I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan)





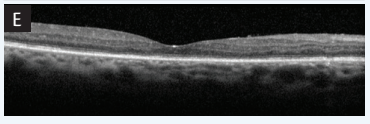
4 Weeks Post OZURDEX

- The patient's VA was 20/60, and CRT was 227 µm (D)



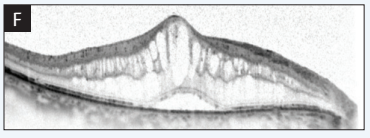
11 Weeks Post OZURDEX

- The patient's VA was 20/50, and CRT was 209 µm (E)



24 Weeks Post OZURDEX

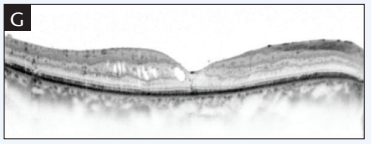
- The patient's VA was 20/50, and CRT was 752 µm (F)
- A second OZURDEX injection was required (we required insurance approval prior to administering the injection)



SECOND INJECTION

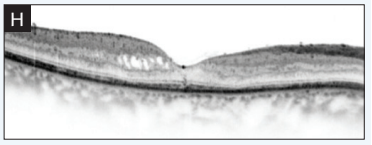
5 Weeks Post Second OZURDEX

- The patient's VA was 20/60, and CRT was 244 µm (G)



12 Weeks Post Second OZURDEX

- The patient's VA was 20/40, and CRT was 222 µm (H)



DISCUSSION

- I generally wind up using a steroid with a presentation such as this, with that much edema

IMPORTANT SAFETY INFORMATION

Contraindications

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

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

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.

Warnings and Precautions

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

Case 3: OZURDEX in a Case of DME

Amy C. Schefler, MD, FACS

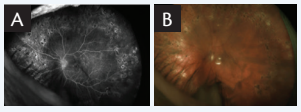
CASE BACKGROUND

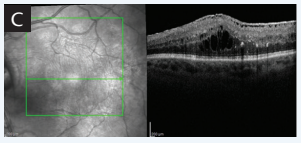
This is a case of a 68-year-old white female with a history of diabetes, hypertension, and hypercholesterolemia. She takes several prescription medications and presents with diabetic macular edema (DME) in the left eye (OS).

FIRST INJECTION

First Visit

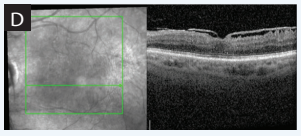
- The patient's VA was 20/80, CRT was 563 µm, and IOP was 11 mm Hg (A, B, C)
- I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan) OS





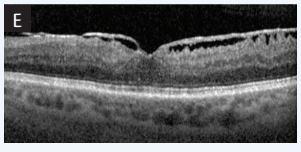
1 Month Post OZURDEX

- The patient's VA was 20/50, CRT was 332 µm, and IOP was 18 mm Hg (D)



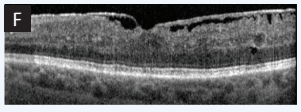
3 Months Post OZURDEX

- The patient's VA was 20/40, CRT was 339 µm, and IOP was 13 mm Hg (E)
- No treatment needed at this time



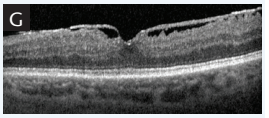
4 Months Post OZURDEX

- The patient's VA was 20/40+1, CRT was 353 µm, and IOP was 13 mm Hg (F)
- No treatment needed at this time



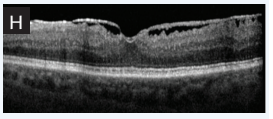
6 Months Post OZURDEX

- The patient's VA was 20/30+1, CRT was 343 µm, and IOP was 15 mm Hg (G)
- No treatment needed at this time



7 Months Post First OZURDEX

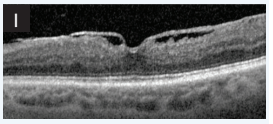
- The patient's VA was 20/40, CRT was 348 µm, and IOP was 17 mm Hg (H)
- I administered a second injection of OZURDEX



SECOND INJECTION

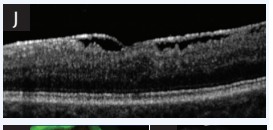
2 Months Post Second OZURDEX

- The patient's VA was 20/30-2, CRT was 330 µm, and IOP was 15 mm Hg (I)
- No treatment needed at this time



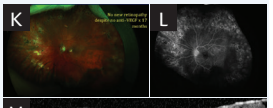
5 Months Post Second OZURDEX

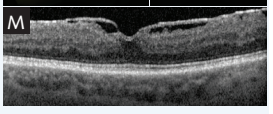
- The patient's VA was 20/30+2, CRT was 339 µm, and IOP was 15 mm Hg (J)
- No treatment needed at this time



8 Months Post Second OZURDEX

- The patient's VA was 20/40+1, CRT was 327 µm, and IOP was 15 mm Hg (K, L, M)
- No treatment needed at this time





DISCUSSION

- There was no new retinopathy
- This patient continues to hold steady today

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Steroid-related Effects: Use of corticosteroids including OZURDEX® (dexamethasone intravitreal implant) may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids 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.

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® 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%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® patients versus 4% of sham patients. 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients.

Please see additional Important Safety Information on the following pages.

Case 4: Improvement in DME Without Monthly Injections

Howard F. Fine, MD, MHSc

CASE BACKGROUND

This is a case of a 68-year-old southeast Asian female who presents with diabetic macular edema (DME) OS. She presented with pseudophakic OS postoperatively 2 years earlier. Her past medical history includes hypertension, hyperlipidemia, renal insufficiency, and coronary disease.

FIRST INJECTION

First Visit

- The patient's VA was 20/150, CRT was 745 µm, and IOP was 17 mm Hg (A)
- I administered the first injection of dexamethasone intravitreal implant 0.7 mg (OZURDEX, Allergan)

5 Weeks Post First OZURDEX

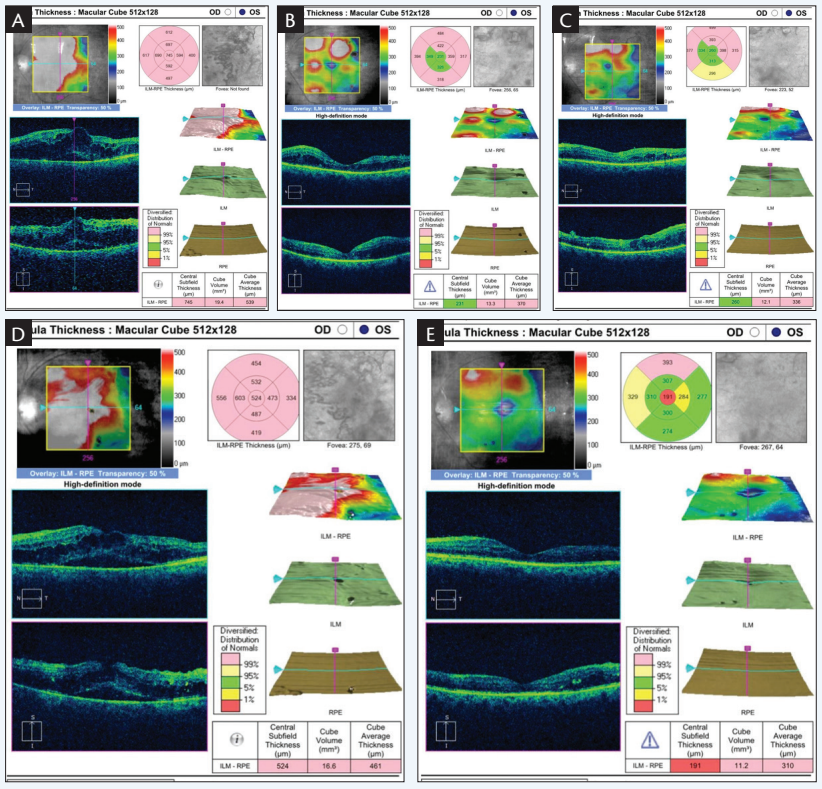
- The patient's VA was 20/70, CRT was 231 µm, and IOP was 16 mm Hg (B)
- No treatment needed at this time

14 Weeks Post First OZURDEX

- The patient's VA was 20/60, CRT was 260 µm, and IOP was 16 mm Hg (C)
- No treatment needed at this time

18 Weeks Post First OZURDEX

- The patient's VA was 20/100, CRT was 524 µm, and IOP was 18 mm Hg (D)
- I administered a second injection of OZURDEX



SECOND INJECTION

7 Weeks Post Second OZURDEX

- The patient's VA was 20/40, CRT was 191 µm, and IOP was 15 mm Hg (E)
- No treatment needed at this time

(Continued on next page)

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.

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® 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.

18 Weeks Post Second OZURDEX

- The patient's VA was 20/40, CRT was 215 µm, and IOP was 18 mm Hg (F)
- I administered a third injection of OZURDEX

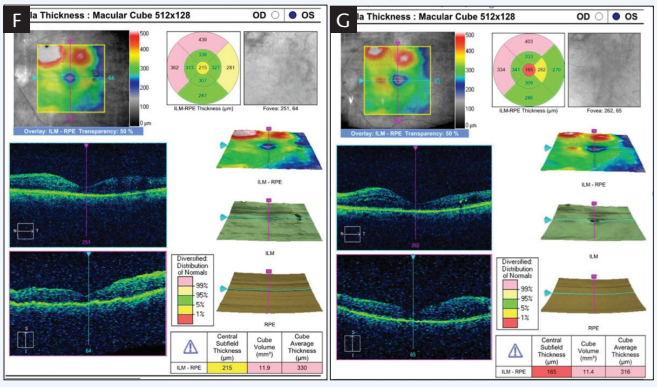
THIRD INJECTION

7 Weeks Post Third Injection OZURDEX

- The patient's VA was 20/30, CRT was 165 µm, and IOP was 16 mm Hg (G)
- No treatment needed at this time

DISCUSSION

- OZURDEX improved VA: from 20/70 to 20/40 to 20/30
- The patient experienced improvement in her DME without the need for monthly injections



(Continued from page 9)

Dr. Fine: I will usually start that patient on an IOP-lowering medication before I reinject, just to be cautious.

Dr. Kuppermann: I would consider the status of the optic nerve. If it is healthy, there may not be a need for topical therapy. As well, if the IOP is being controlled by some other measure, topical therapy might not be warranted.

Dr. Hassan: Is there a role for a topical steroid trial before injecting the implant?

Dr. Schefler: Unless there is compromise to the posterior capsule, in which case there is potential for anterior segment migration, then no, I do not see any reason why you would not start with the dexamethasone implant.

Dr. Kuppermann: In most settings, I am most comfortable starting with OZURDEX, which is approved for intraocular use.[16]

Dr. Fine: With the OZURDEX NOVADUR technology, you can be assured the patient is getting the exact dose inside the eye.

Dr. Kuppermann: I agree with that and would add that IOP elevation, should it occur, is manageable after a dexamethasone implant. In the clinical trials, there was a 15.7% rate of first IOP

IMPORTANT SAFETY INFORMATION

Contraindications

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

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

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 Dosage and Administration on the following page.

elevation ≥ 10 mm Hg from baseline associated with the first injection of the implant.[15] But if the IOP does elevate, topical drops can be effective management.[16]

Dr. Fine:

There is another reason to believe that outcomes of steroid challenges are not definitive. There are a number of genes that regulate steroid response, and they appear to be specific to specific types of steroids. For example, response to dexamethasone has different genes dictating the response than with triamcinolone.[21] And so, a steroid challenge is not a guarantee that a patient will be a responder to one steroid versus another.

INTRODUCING THE IMPLANT TO PATIENTS

Dr. Hassan: There are a couple of key points to introduce when we discuss OZURDEX as a potential treatment for patients, namely that swelling can be caused by a number of factors, and that OZURDEX works to reduce inflammation in the retina and thereby improve visual acuity.[22] I think it is also worthwhile to explain a little bit about the actual procedure, that we will be injecting the implant into the back of the eye, and that it will resorb on its own, and there is no need for a second procedure to remove the implant.[23] As far as safety concerns, I introduce the potential for cataract progression in phakic patients, especially after repeat injections, and elevated IOP ≥ 10 mm Hg, which occurred in 28% of patients on OZURDEX in the 3-year MEAD trial and typically was first seen after the initial implant.[16] In MEAD, the rate of IOP elevation greater than or equal to 10 mm Hg was 15.7% of patients on OZURDEX in the first treatment cycle.[16,19]

Dr. Nudleman: In addition to that, I also tell patients that in clinical trials, OZURDEX improved visual acuity without need for monthly injections.[19]

Dr. Fine: As far as the actual procedure goes, I also tell patients they may hear a click when we inject the OZURDEX implant[16] because I do not want them to be startled when that happens.

CONCLUSION

Dr. Hassan: OZURDEX is an effective treatment for DME, which as we have discussed, can be caused by a number of different pathologic entities.[14,19] While IOP elevation is a concern, most cases are manageable with topical medication.[14,16] As we have learned, it may be possible to observe some patients with IOP elevation off of medication if the optic nerve is healthy and there are no additional concerns.

INTRODUCING OZURDEX TO YOUR PATIENTS

- The swelling in your retina can be caused by several factors.[22]
- OZURDEX is a corticosteroid and works to help reduce the inflammation in your retina. OZURDEX helps by improving visual acuity.[16]
- OZURDEX is a tiny implant that slowly releases medication over time without monthly injections. It will dissolve over months and will not need to be removed.[16]
- OZURDEX is injected directly into the back of the eye with minimal systemic absorption.[23]
- There is a chance of an increase in eye pressure that generally returns to where it started. If you experience this, it will need to be managed with eye drops, and rarely, with surgery.[16]
- After repeated OZURDEX injections, a cataract may occur. If this occurs, your vision will decrease, and you will need a procedure to remove the cataract and restore your vision.[16]
- In clinical studies, OZURDEX improved vision in patients without the need for monthly injections.[16]

Overall, the inflammatory cascade is highly relevant to the formation of edema in the macula, and OZURDEX offers us a mechanism to address this.[7,16] ■

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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.

Please see accompanying full Prescribing Information on the following pages.

OZU113932-v3 05/21 010943

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

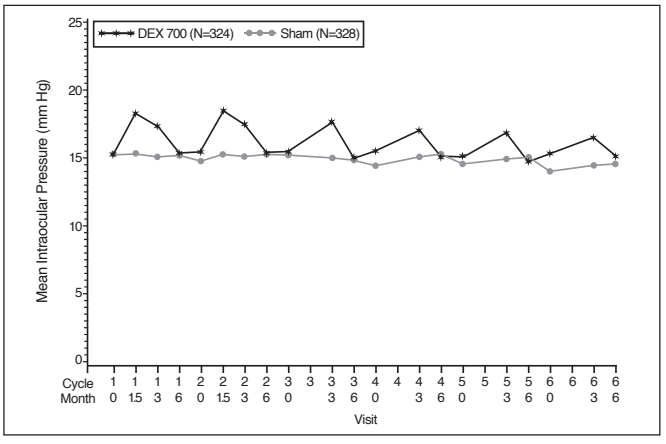
IOP	Treatment: N (%)	
	OZURDEX® N=324	**Sham N=328**
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* **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

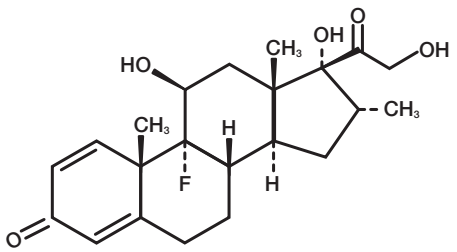
Safety and effectiveness of **OZURDEX**® in pediatric patients have not been established.

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)

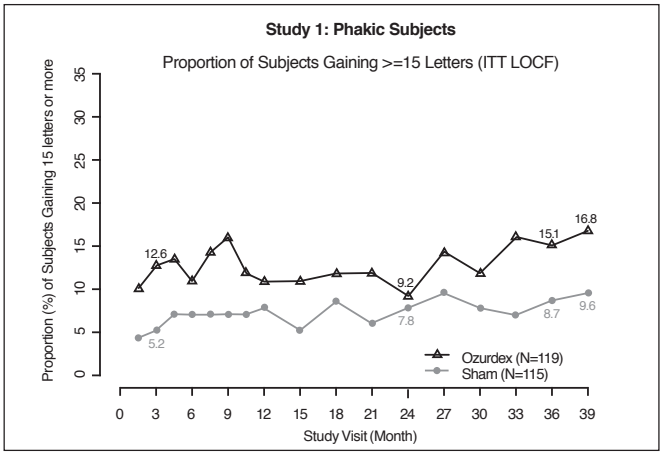
[a]Study 1: **OZURDEX®**; N=163; Sham, N=165

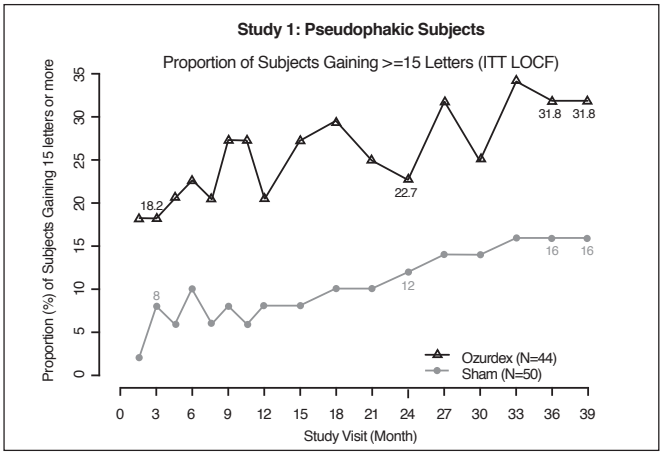
[b]Study 2: **OZURDEX®**; N=165; Sham, N=163

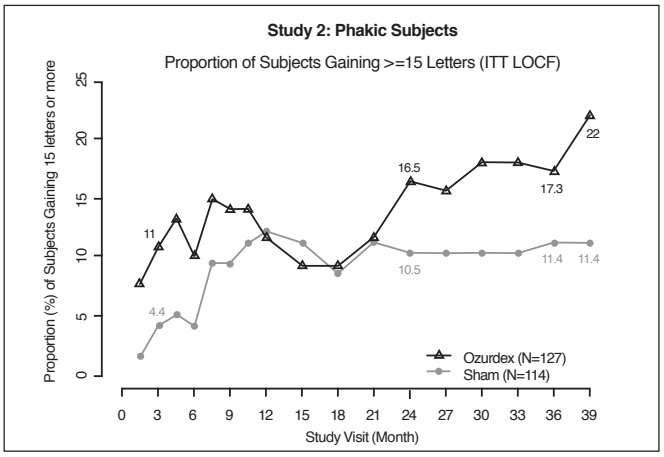
[c]14% (16.8% from **OZURDEX®** and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

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







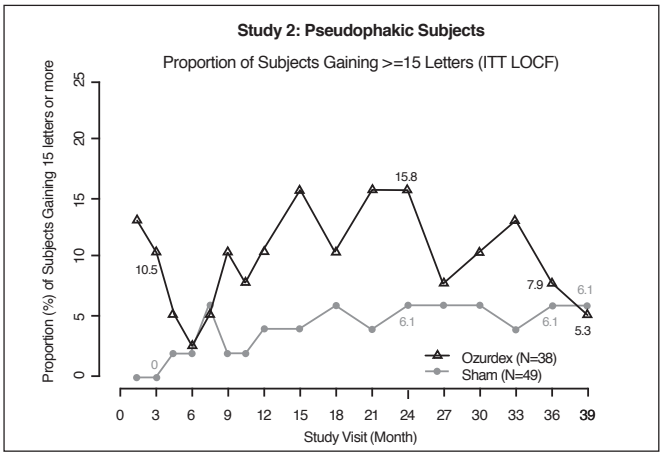
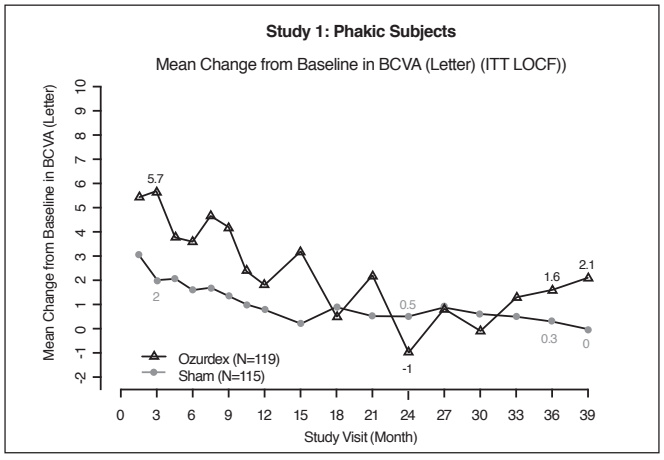
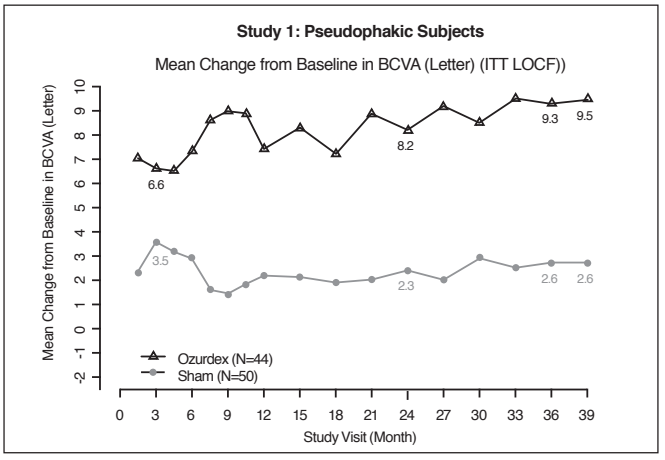
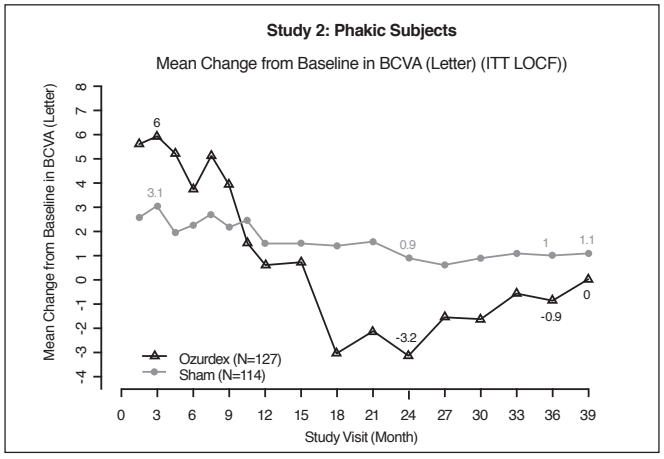
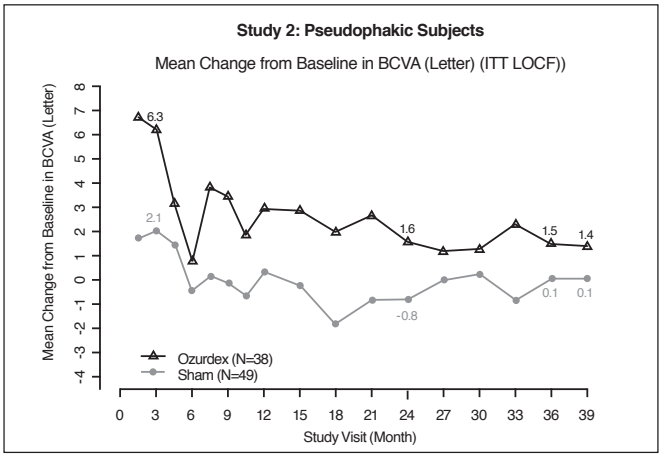


Figure 3: Mean BCVA Change from Baseline









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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