Supplement to September 2014

RETINA TODAY

Changing Patterns in Treatments of Diabetic Macular Edema for Patients Who Are Pseudophakic or Phakic and Scheduled for Cataract Surgery

Highlights from a roundtable discussion held during the 2014 meeting of the Association for Research in Vision and Ophthalmology in Orlando, FL.

Sponsored by Allergan, Inc.

Changing Patterns in Treatments of Diabetic Macular Edema for Patients Who Are Pseudophakic or Phakic and Scheduled for Cataract Surgery

The management of diabetic macular edema (DME) is evolving rapidly, and our treatment approaches often depend on many variables, including demographics, and payer mix. There are, however, some constants. Diabetic macular edema is a multifactorial disease with some modifiable factors. For example, metabolic control has been demonstrated to be important. With regard to treatment, the current standard of care is anti-VEGF therapy, but treatment patterns will continue to evolve as we learn more from studies and clinical experience, and as new therapies become available. This supplement to Retina Today *features a discussion in which panel members detail the factors that help determine treatment patterns for DME.*

—Victor H. Gonzalez, MD

MODERATOR

Victor H. Gonzalez, MD, is the founder and managing partner of Valley Retina Institute and a founding member of Valley Retina Research in McAllen, TX. Dr. Gonzalez is a consultant to and has received research support from Allergan, Inc. He may be reached at maculadoc@aol.com.

PANELISTS

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Pravin U. Dugel, MD, is a managing partner at Retinal Consultants of Arizona, a founding member of Spectra Eye Institute, and a clinical associate professor in the Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles. Dr. Dugel is a consultant to Allergan, Inc. He may be reached at pdugel@gmail.com.

Raj K. Maturi, MD, practices in Indianapolis, IN. He is an associate professor of ophthalmology at the Indiana School of Medicine. Dr. Maturi is a consultant to and has received research funding from Allergan, Inc. He may be reached at rmaturi@gmail.com.

Victor H. Gonzalez, MD: Retina specialists are physicians first and eye doctors second, and this is never more apparent than when we are treating patients who have diabetes. Dr. Avery, what do you do when you see a patient with diabetic retinopathy for the first time?

Robert L. Avery, MD: I emphasize the importance of metabolic control. I ask all of my patients what their hemoglobin A1c level is, because that is the best way for me to gauge how well a patient is controlling his or her diabetes. I do not end the conversation there. I also discuss the importance of controlling hypertension and lipids.

Raj K. Maturi, MD: I also ask patients how often they check their blood sugar. I have found some patients check it only once every 2 weeks or so, which certainly has an impact on their overall health and is a barrier to successful treatment of diabetic eye disease.

Pravin U. Dugel, MD: In addition to discussing metabolic control, I take a comprehensive medical history to find out if a patient has had a stroke, a heart attack, or some other arteriothromboembolic (ATE) issue. Those factors influence my treatment decisions.

Dr. Maturi: A patient's commitment to therapy has a significant effect on future compliance. Most patients with diabetes are of working age, and many either do not want to take time off from work to come to the office, or they simply cannot come in because of employers' restrictions. These factors represent significant barriers to successful treatment of diabetic eye disease.

> "Inflammation is an important factor [in DME]."
> —Pravin U. Dugel, MD

Dr. Dugel: I find involving family members is beneficial, particularly when I explain the patient's treatment plan. Treatment can be a significant burden for patients, and family support is important.

Dr. Gonzalez: I agree that metabolic control is important, particularly when a patient is undergoing treatment for DME. I also take a broad look at patients from head to toe, making sure they are not exhibiting signs of edema from other factors, such as heart or kidney disease.

Dr. Dugel, what is the role of VEGF in DME?

Dr. Dugel: VEGF suppression was first utilized to treat cancers of the colon and the breast. We think of anti-VEGF agents as antipermeability agents, but colon cancer and breast cancer do not have permeability issues. So why are we suppressing VEGF? According to VEGF biologists, the primary effect of VEGF suppression is to accelerate the normalization of vessels. The antipermeability effect is secondary. Clearly, there is more to treating DME than simply blocking VEGF. Inflammation is an important factor.

Please see important information about OZURDEX® on the following pages.

Dr. Avery: Macular edema secondary to retinal vein occlusion (RVO) is a more VEGF-mediated disease, as is age-related macular degeneration (AMD). Studies have shown that inflammation is a strong contributing factor in DME.[1,2]

Steroids also indirectly affect VEGF, enabling us to address not just the inflammatory pathways but also the VEGF pathway.

Dr. Maturi: Researchers recently published a meta-analysis investigating molecular biomarkers of the vitreous associated with diabetic retinopathy.[3] They found interleukin (IL)-6, IL-8, erythropoietin, interferon (INF)-alpha, and platelet-derived growth factor (PDGF) are increased in people with diabetes; whereas, pigment epithelium-derived factor (PEDF) is decreased in people with DME and proliferative diabetic retinopathy. We do not yet know exactly what this means.

Liu and Feener examined the regulation and mechanisms of the plasma kallikrein-kinin system (KKS) in the retina and discussed potential strategies for targeting this pathway as a new therapeutic approach for treating diabetic retinopathy.[4] Ma et al found the bradykinin B1 and B2 receptor isoforms (B1R and B2R, respectively) are expressed in human retinas.[4]

Dr. Gonzalez: Most patients being treated for AMD are retired, whereas, people with DME are still working. A monthly schedule can be difficult. Most people with diabetes already spend about 25 days a year in physicians' offices.[5]

Dr. Maturi: I believe the eye can tolerate some edema without too much harm, but above a certain amount and over a certain duration, it causes significant harm.

Dr. Gonzalez: Dr. Dugel, what is your understanding of the disease process, and what is its impact on your decision whether or not to continue with a therapy?

Dr. Dugel: We now understand that DME is not a homogeneous disease. Based on various physiological factors, we can stage it. That is of consequence, because we may treat patients differently at different stages.

Dr. Maturi: In the MEAD study evaluating the dexamethasone intravitreal implant 0.7 mg (OZURDEX®, Allergan, Inc.), patients received an average of 4 treatments of intravitreal dexamethasone over the 3-year study period, and about 42% required at least 1 anti-glaucoma medicine for IOP control.[6,7] Only 1 patient in the 0.7-mg group required surgical trabeculectomy for steroid-induced IOP increase.[6,7]

Data showed an increase in mean IOP with each treatment cycle, but mean IOP generally returned to baseline between treatment cycles (at the end of the 6-month period).[7]

Dr. Dugel: OZURDEX® is a sustained-release intravitreal implant that biodegrades to lactic acid and glycolic acid.[6]

Dr. Gonzalez: Based on current knowledge, have you developed a profile of an ideal candidate for steroids?

> "In my opinion, candidates who are suitable for treatment with a steroid are those who are pseudophakic with no history of glaucoma, as well as those who are phakic and scheduled for cataract surgery."
> —Robert L. Avery, MD

What does your decision tree look like when choosing a treatment for DME?

Dr. Avery: In my opinion, candidates who are suitable for treatment with a steroid are those who are pseudophakic with no history of glaucoma, as well as those who are phakic and scheduled for cataract surgery.

Dr. Maturi: The one question I often ask myself is: Once patients are not responding to prior therapy, does it make sense to continue it?

Dr. Dugel: My goal is to find that sweet spot when improving vision is still possible with a change in therapy. I do not want to start thinking about combination therapy after the photoreceptor cells have died. I believe finding that ideal window of opportunity will be our next area of study.

Dr. Avery: OZURDEX® (dexamethasone intravitreal implant) will provide more fire power in our armamentarium for treating this difficult disease. In the clinical trials, treatment with OZURDEX® allowed a low frequency of injections. Up to 7 injections were permitted in the 3-year study design. In addition, by addressing multiple pathways, I think efficacy can improve.

Dr. Maturi: I appreciate having an additional tool in my arsenal. Knowing when to judiciously use all of our tools will be much more of an art than merely checking retinal thickness.

Dr. Dugel: We have established that DME is a diverse and complex disease with a natural life cycle that involves more than VEGF. I look forward to being able to individualize my treatment strategy based on the patient's risk:benefit ratio and disease stage.

1. Yoshimura T, Sonoda KH, Sugahara M, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS One.* 2009;4(12):e8158.
2. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology.* 2009;116(1):73-79.
3. McAuley AK, SanFilippo PG, Hewitt AW, et al. Vitreous biomarkers in diabetic retinopathy: a systematic review and meta-analysis. *J Diabetes Complications.* 2014;28:419-425.
4. Liu J, Feener EP. Plasma kallikrein-kinin system and diabetic retinopathy. *Biol Chem.* 2013;394:319-328.
5. Wallick CJ, Hansen RN, Campbell J, et al. Increased health care utilization among patients with diabetic macular edema compared with diabetic patients without edema. Poster presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 5, 2014; Orlando, FL.
6. 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; in press.
7. OZURDEX® [package insert]. Irvine, CA: Allergan, Inc.; 2014.

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

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions
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.

Please see additional Important Safety Information on the following pages.

CASE 1

Dr. Maturi: This 64-year-old-man was diagnosed with diabetes about 18 years ago, and his metabolic control has been poor for 1 year. He does not monitor his blood sugar at home; he reports his A1c is always between 6.2 and 7.0. He has a history of hypertension and hypercholesterolemia, both of which are controlled with medication. Vision in his right eye is stable; vision in his left eye has been blurry intermittently for 2 to 3 weeks. He had previous treatment and was pseudophakic.

Three months after dexamethasone injection, the edema had improved, but after 6 months, it recurred, and I treated the patient again. Three months after the second injection, some edema recurred, and a third implant was injected.

We are finding that some patients with chronic disease may show an initial response to dexamethasone that does not persist. Multiple treatments with dexamethasone may be needed to show a benefit.

In this patient, after 3 dexamethasone implants, the edema was stable, and the retina was relatively stable. Fluorescein angiography also showed improvement (Figure 1). Over the 12 months of treatment with

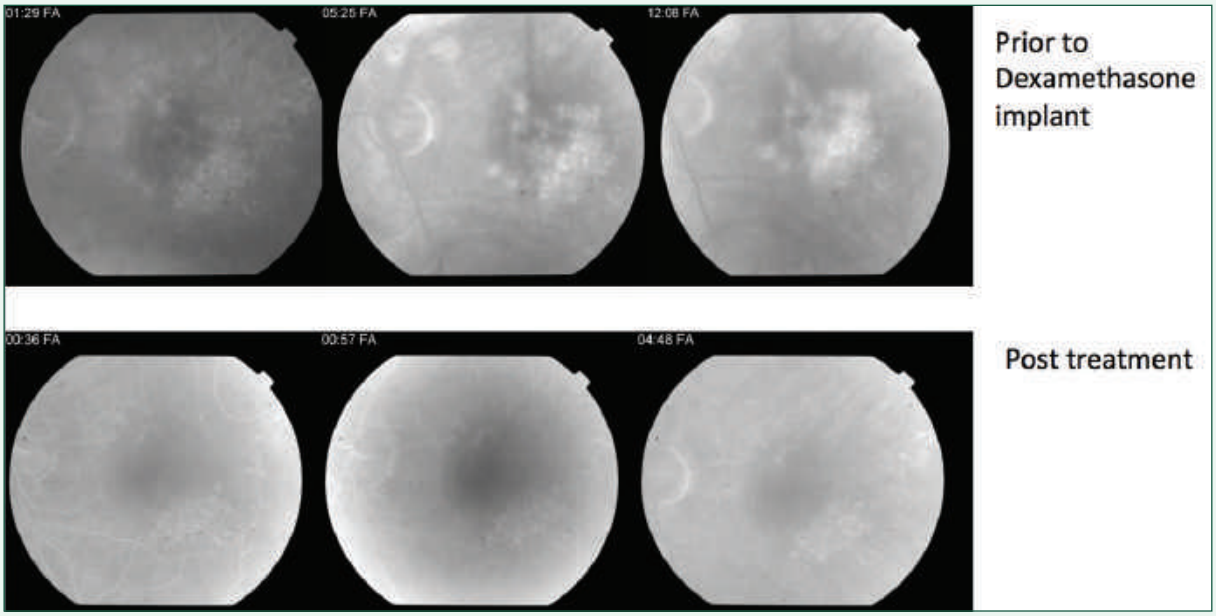


Figure 1. After 3 dexamethasone implants in 12 months, the edema was stable. Fluorescein angiography also showed improvement.

IMPORTANT SAFETY INFORMATION (continued)
Adverse Reactions (continued)
Diabetic Macular Edema
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%), intraocular pressure increased (35%), 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%), and hypertension (13%).

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.

Increased Intraocular Pressure: Approximately 42% of the patients who received OZURDEX® were subsequently treated with IOP-lowering medications during the study. In the sham control group, IOP-lowering medications were used in approximately 10% of patients.

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

CASE 1 (Continued)

3 dexamethasone injections, the patient's visual acuity fluctuated greatly during the 12-month period.

The other reason I shared this case was because the MEAD investigators administered injections of dexamethasone every 6 months. Based on those data, as well as my clinical experience, it is clear that dexamethasone does not last a full 6 months in most patients. Sometimes, we must treat again after 3 to 4 months to maintain a dry macula. Reinjection of OZURDEX® (dexamethasone intravitreal implant) is recommended at the physician's discretion when residual macular edema is present.

CASE 2

Dr. Dugel: This 55-year-old man has poorly controlled diabetes, a history of hypertension controlled with medication, and hypothyroidism. His left eye was pseudophakic.

After prior therapy, dense edema persisted, and the patient's visual acuity remained at 20/200 OS (Figure 2). At that point, a dexamethasone implant was injected. The anatomic response was good, but the visual acuity was not (Figure 3). It appears inflammation was involved.

There are two important take-aways from this case. First, we must avoid treating too late. If we treat too late, we have missed the sweet spot for a good visual outcome. Second, we must look at biomarkers with some skepticism. Most of us are looking only at retinal thickness on OCT. I believe we should not rely solely on the OCT maps but instead look at the slices. We want to be treating to preserve the outer retina. At the end of the day, a certain amount of fluid, particularly intraretinal fluid, can be present and vision will still be good.

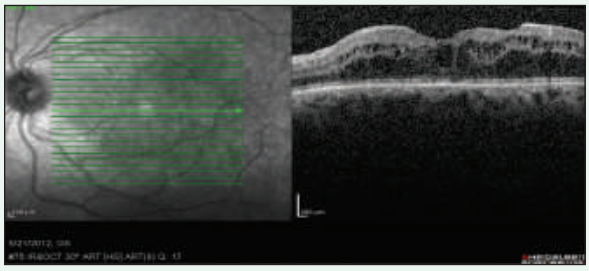


Figure 2. After multiple treatments with previous therapy, dense edema persisted.

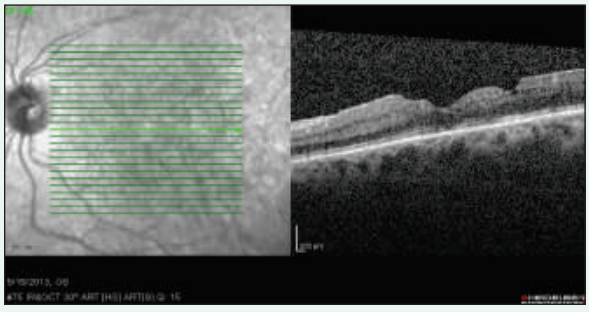


Figure 3. Anatomic response was good at day 28.

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)
Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

- Indications and Usage (1.3) 06/2014

INDICATIONS AND USAGE

OZURDEX® is a corticosteroid indicated for:

- The treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1)
- The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
- The treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery (1.3)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection only. (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)
- Advanced glaucoma (4.2)
- Non-intact 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)
- The implant may migrate to the anterior chamber if the posterior lens capsule is not intact. (5.3)

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported by 20–70% of patients were cataract, increased intraocular pressure and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

1.2 Posterior Segment Uveitis

OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

1.3 Diabetic Macular Edema

OZURDEX® is indicated for the treatment of diabetic macular edema in patients who are pseudophakic or are phakic and scheduled for cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only.

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 Advanced Glaucoma

OZURDEX® is contraindicated in patients with advanced glaucoma.

4.3 Non-intact Posterior Lens Capsule

OZURDEX® is contraindicated in patients whose posterior lens capsule is not intact.

4.4 Hypersensitivity

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

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 should be used cautiously in patients with a history of ocular herpes simplex.

5.3 Risk of Implant Migration
Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including **OZURDEX®** include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis
The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

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

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

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

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

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

Table 2: Adverse Reactions Reported by ≥ 1% of Patients

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Ocular		
Cataract[1]	166/243[2] (68%)	49/230 (21%)
Intraocular pressure increased[3]	115 (35%)	16 (5%)
Conjunctival hemorrhage	73 (23%)	44 (13%)
Visual acuity reduced	28 (9%)	13 (4%)
Conjunctivitis	19 (6%)	8 (2%)
Vitreous floaters	16 (5%)	6 (2%)
Conjunctival edema	15 (5%)	4 (1%)
Dry eye	15 (5%)	7 (2%)
Vitreous detachment	14 (4%)	8 (2%)
Vitreous opacities	11 (3%)	3 (1%)
Retinal aneurysm	10 (3%)	5 (2%)
Foreign body sensation	7 (2%)	4 (1%)
Corneal erosion	7 (2%)	3 (1%)
Keratitis	6 (2%)	3 (1%)
Anterior Chamber Inflammation	6 (2%)	0 (0%)

Table 2: Adverse Reactions Reported by ≥ 1% of Patients (continued)

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)

[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.

[3] Includes IOP increased and ocular hypertension.

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.

Increased Intraocular Pressure

Table 3: Summary of Elevated IOP Related Adverse Reactions

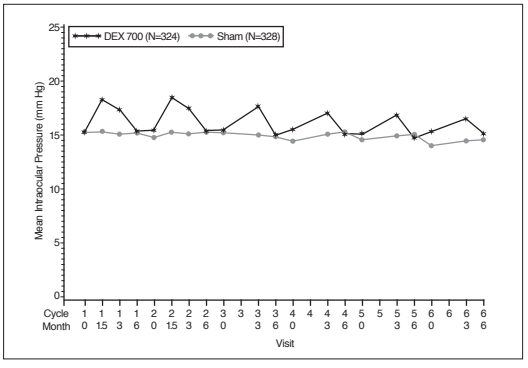
IOP	Treatment: N (%)	
	OZURDEX® N=324	**Sham N=328**
Any IOP Related AE	120 (37%)	18 (6%)
≥10 mm Hg IOP Change from Baseline at any visit	91 (28%)	13 (4%)
≥25 mm Hg IOP at any visit	106 (33%)	15 (5%)
≥35 mm Hg IOP at any visit	20 (6%)	3 (1%)
Glaucoma	4 (1.2%)	1 (0.3%)
IOP lowering procedure*	4 (1.2%)	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

Approximately 42% of the patients who received **OZURDEX**® were subsequently treated with IOP lowering medications during the study. In the sham control group, IOP lowering medications were used in approximately 10% of patients.

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

Figure 1: Mean IOP during the study



6.2 Postmarketing Experience

The following reactions have been identified during post-marketing use of **OZURDEX**® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **OZURDEX**®, or a combination of these factors, include: complication of device insertion (implant misplacement), device dislocation with or without corneal edema,

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal treatment with **OZURDEX**® is low *[see Clinical Pharmacology (12.3)]*. It is not known whether intravitreal treatment with **OZURDEX**® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **OZURDEX**® is administered to a nursing woman.

8.4 Pediatric Use

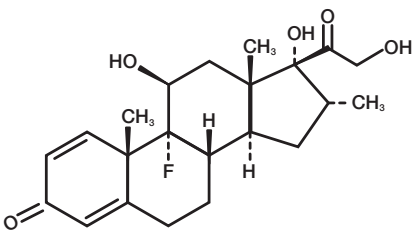
Safety and effectiveness of **OZURDEX**® in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

OZURDEX® is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR**® solid polymer sustained-release drug delivery system. **OZURDEX**® is preloaded into a single-use, **DDS**® applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR**® system contains poly (D,L-lactide-co-glycolide) PLGA intravitreal polymer matrix without a preservative. The chemical name for dexamethasone is Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α)-. Its structural formula is:



MW 392.47; molecular formula: $C_{22}H_{29}FO_5$

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.

12.3 Pharmacokinetics

Plasma concentrations were obtained from 21 patients with macular edema due to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), and 21 patients with diabetic macular edema (DME) prior to dosing and at 4 to 5 additional post-dose timepoints on Days 1, 7, 21, 30, 45, 60, and 90 following the administration of the first intravitreal implant containing 0.7 mg dexamethasone. In RVO and DME patients, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ = 50 pg/mL). Plasma dexamethasone concentrations from 12% of samples were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In an *in vitro* metabolism study, following the incubation of [^{14}C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies in animals have been conducted to determine whether **OZURDEX**® (dexamethasone intravitreal implant) has the potential for carcinogenesis.

Although no adequate studies have been conducted to determine the mutagenic potential of **OZURDEX**®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells *in vitro* or in the *in vivo* mouse micronucleus test.

Adequate fertility studies have not been conducted in animals.

14 CLINICAL STUDIES

Retinal Vein Occlusion

The efficacy of **OZURDEX®** for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, **OZURDEX®** demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

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

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

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

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

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

Posterior Segment Uveitis

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

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

Diabetic Macular Edema

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

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

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

Study	Outcomes	OZURDEX®	Sham	Estimated Difference (95% CI)
1[a]	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]	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)

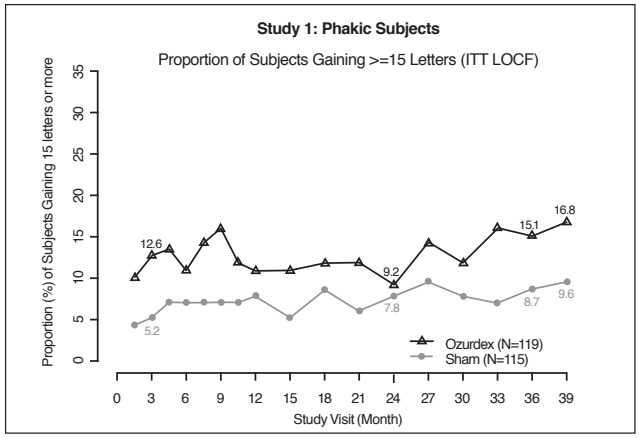
[a]Study 1: OZURDEX®, N=163; Sham, N=165

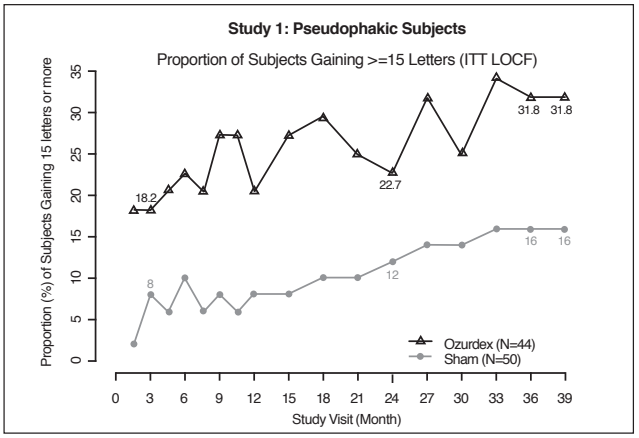
[b]Study 2: OZURDEX®, N=165; Sham, N=163

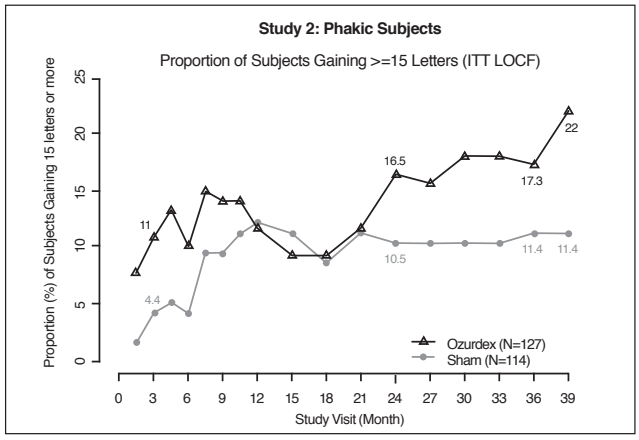
[c]14% (16.8% from OZURDEX® and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

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







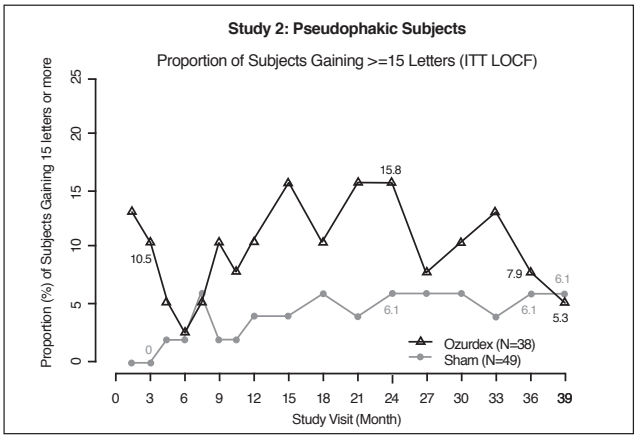
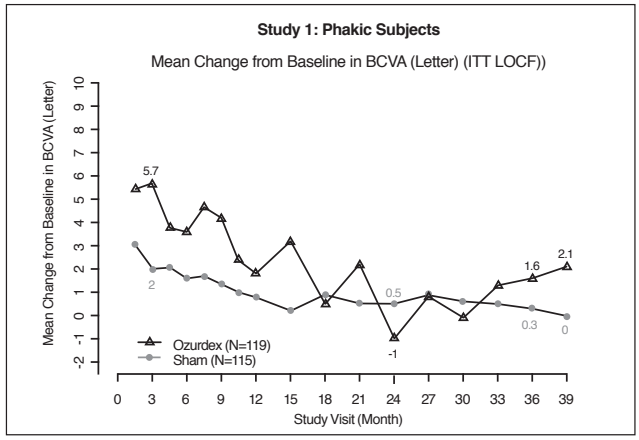
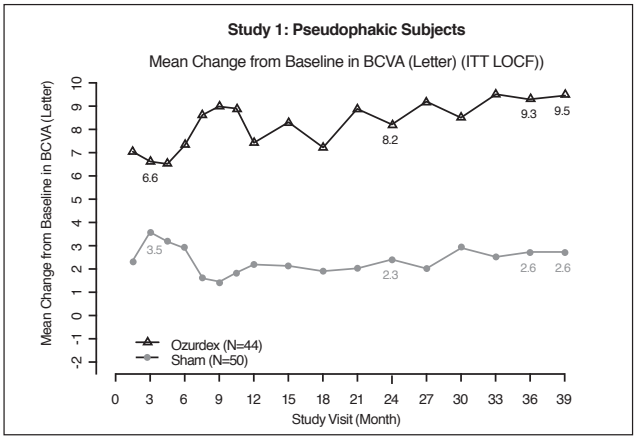
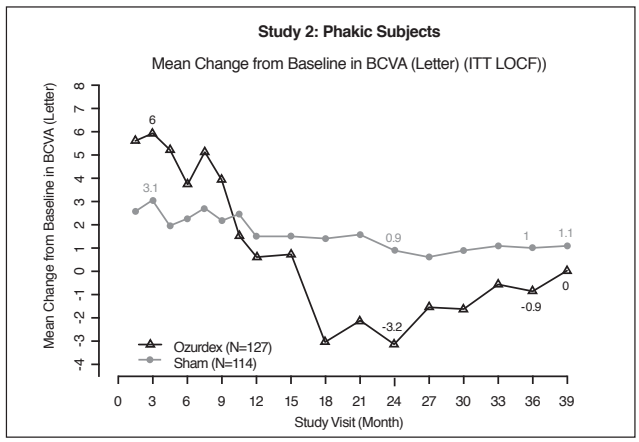
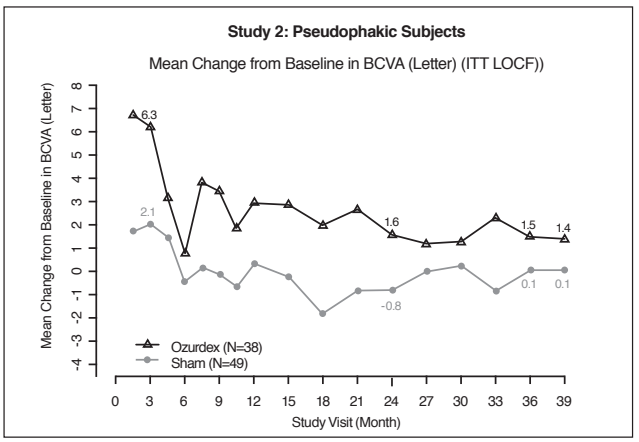


Figure 3 Mean BCVA Change from Baseline









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 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects

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

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

Intravitreal Injection-related Effects

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

When to Seek Physician Advice

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

Driving and Using Machines

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

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