

Patient Guide

Ozurdex[®]
(dexamethasone intravitreal
implant) 0.7 mg



For the treatment of
diabetic macular edema

IMPORTANT SAFETY INFORMATION

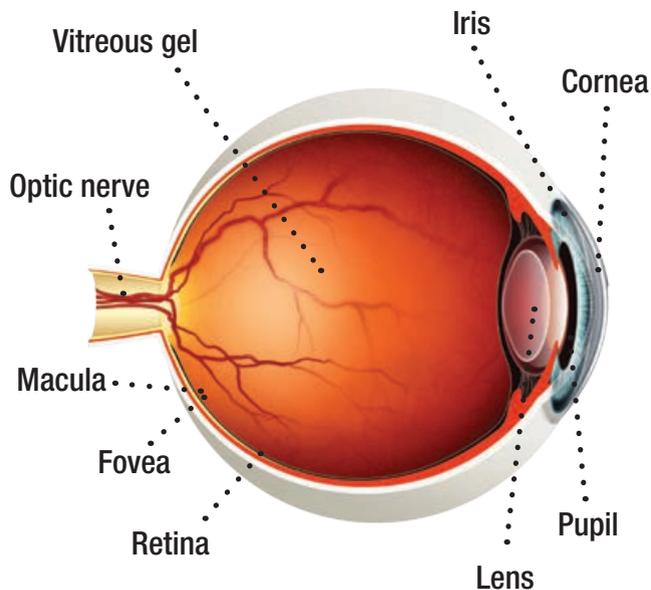
OZURDEX[®] (dexamethasone intravitreal implant) should not be used if you have any infections or diseases in the eye, or surrounding eye area, including most viral diseases of the cornea and conjunctiva, including active herpes viral infection of the eye, vaccinia, varicella, mycobacterial infections, and fungal diseases.

Please see additional Important Safety Information on page 7.

Your eyes



What makes up the eye?



How does the eye work?

Light enters through the cornea, passes through the opening in the iris, called the pupil, and then to the lens, which focuses light on the retina—the inner lining of the back of the eye. The retina is lined with light-sensitive cells, or photoreceptors, called rods and cones. The macula is the center of the retina, and it is responsible for sharp central vision. The fovea is a small depression in the macula that provides the sharpest vision of all. When light reaches the retina, the photoreceptors send impulses along the optic nerve to the brain, which interprets them as vision.

Why is a healthy retina important?

A healthy retina is essential for normal vision. A number of diseases can damage the retina, which may lead to impaired vision or loss of vision. One of these diseases is diabetic macular edema, which is a common cause of vision loss in people who have diabetes.

A photograph (called funduscopy) of a healthy retina.

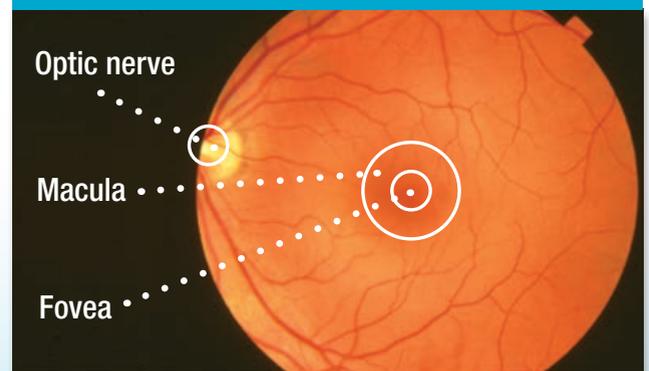


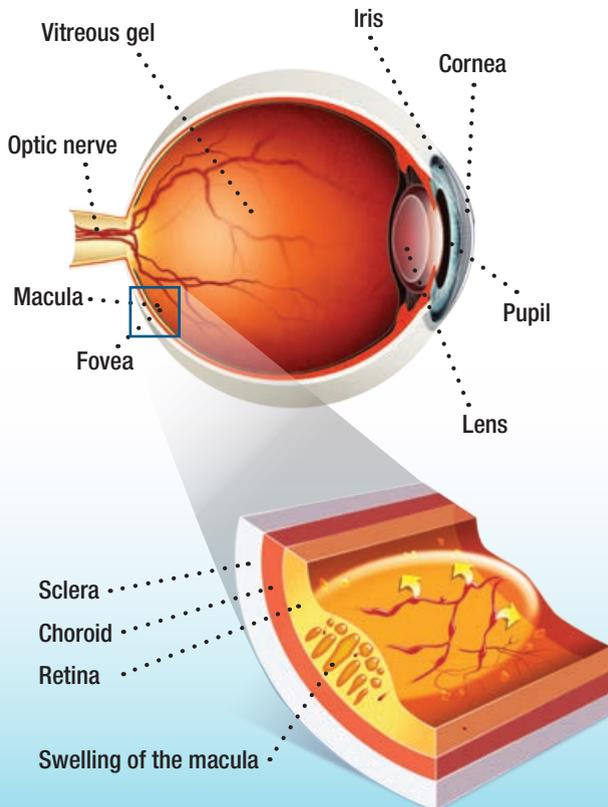
Image from the National Eye Institute online archive.

Your condition

What is diabetic macular edema?

Diabetes is a problem with how your body uses sugars (glucose), leading to high blood sugar levels. Over time, high blood sugar can damage the small blood vessels in the eye (capillaries), which can lead to inflammation. Fluid leaking from these blood vessels may cause the central part of the retina (the macula) to swell, and this is called diabetic macular edema (DME).

The Eye With DME



Symptoms of DME

If your doctor finds DME early, you may not have any symptoms. If DME worsens, it can lead to blurry central vision. The blurriness can range from mild to severe. DME can cause significant vision loss over time.

Range of visual impairment due to DME



Mild blurry vision



Moderate blurry vision



Severe blurry vision

Your treatment

Why did my doctor choose OZURDEX® (dexamethasone intravitreal implant)?

OZURDEX® (dexamethasone intravitreal implant) is a prescription medicine approved by the U.S. Food and Drug Administration (FDA) to treat adults with diabetic macular edema. Your doctor will discuss with you the reasons why OZURDEX® was selected as well as the benefits and risks of treatment.

You can learn more about OZURDEX® in the following pages, including pages dedicated to **Important Safety Information**—facts you should be familiar with as an OZURDEX® patient.

How does the OZURDEX® intravitreal implant work?

OZURDEX® is a biodegradable implant that provides sustained release of the corticosteroid dexamethasone. Corticosteroids, such as dexamethasone, block chemical pathways that lead to inflammation, leakage from the retinal blood vessels, and swelling (edema) of the retina.

APPROVED USE

OZURDEX® (dexamethasone intravitreal implant) is a prescription medicine that is an implant injected into the eye (vitreous) and used:

— To treat adults with diabetic macular edema

IMPORTANT SAFETY INFORMATION

OZURDEX® should not be used if you have any infections or diseases in the eye, or surrounding eye area, including most viral diseases of the cornea and conjunctiva, including active herpes viral infection of the eye, vaccinia, varicella, mycobacterial infections, and fungal diseases.

OZURDEX® should not be used if you have glaucoma.

OZURDEX® should not be used if you have a posterior lens capsule that is torn or ruptured.

Please see additional Important Safety Information on page 9.



Your treatment

What is a biodegradable implant?

A biodegradable implant is one that doesn't need to be removed after it releases medication. OZURDEX® (dexamethasone intravitreal implant) uses advanced NOVADUR® drug delivery technology, in which biodegradable material is combined with the active drug dexamethasone to form a tiny rod-shaped implant. Inside the eye, the implant is slowly dissolved by the vitreous gel that fills the eye, releasing dexamethasone.

How is OZURDEX® administered?

The OZURDEX® implant is so tiny that it can be injected into the eye (vitreous) with a procedure in your doctor's office. Each implant is already inside a special applicator device that is needed to perform the insertion. The implant will be injected into the vitreous humor inside your eye. This is known as an intravitreal injection.

Are intravitreal injections common?

Yes. Intravitreal injections are now used to deliver medication to treat many types of eye conditions. Your Retina Specialist is specially trained in giving eye injections.

Will I receive OZURDEX® more than once?

The OZURDEX® implant slowly dissolves, releasing medication. As the level of medication decreases over time, swelling or inflammation may affect your vision again. If this occurs, your doctor may recommend another OZURDEX® injection.

IMPORTANT SAFETY INFORMATION (continued)

You should not use OZURDEX® (dexamethasone intravitreal implant) if you are allergic to any of its ingredients.

Injections into the vitreous in the eye, including those with OZURDEX®, are associated with serious eye infection (endophthalmitis), eye inflammation, increased eye pressure, and retinal detachments. Your eye doctor may monitor you regularly after the injection.

Use of corticosteroids including OZURDEX® may produce subcapsular cataracts, increased eye pressure, glaucoma, and may increase the establishment of secondary eye infections due to bacteria, fungi, or viruses. Let your doctor know if you have a history of ocular herpes simplex.

Please see additional Important Safety Information on page 11.



Your treatment

What results can I expect with OZURDEX® (dexamethasone intravitreal implant)?

In 2 clinical studies, 328 patients were treated with OZURDEX®, and another 328 patients received simulated injections. Patients were eligible to receive an injection about once every 6 months for 3 years, at the physician's discretion. At the end of the studies:

- 20% (1 in 5) of those who received OZURDEX® gained 3 or more lines of vision on the eye chart
- In comparison, 11% (about 1 in 10) of patients who received simulated injections had similar gains

After an injection, vision improvements peaked at about 3 months and then lowered. Patients received additional injections throughout the studies to continue vision improvement.

For some patients in the studies, vision decreased. Talk to your doctor to learn more about how this may apply to you. It's important to remember that each case of DME is unique. Your own results may vary.

Is there anyone who should not be given OZURDEX®?

You should not receive OZURDEX® (dexamethasone intravitreal implant) if:

- You have any infections or diseases in the eye, or surrounding eye area, including most viral diseases of the cornea and conjunctiva, including active herpes viral infection of the eye, vaccinia, varicella, mycobacterial infections, and fungal diseases

Is there anyone who should not be given OZURDEX®? (continued)

- You have glaucoma
- You have a posterior lens capsule that is torn or ruptured
- You are allergic to any of its ingredients

IMPORTANT SAFETY INFORMATION (continued)

The most common side effects reported in patients include: cataract, increased eye pressure, conjunctival blood spot, reduced vision, inflammation of the conjunctiva, specks that float in the field of vision, swelling of the conjunctiva, dry eye, vitreous detachment, vitreous opacities, retinal aneurysm, foreign body sensation, corneal erosion, inflammation of the cornea, anterior chamber inflammation, retinal tear, drooping eyelid, high blood pressure, and bronchitis.

After repeated injections with OZURDEX® (dexamethasone intravitreal implant), a cataract may occur. If this occurs, your vision will decrease and you will need an operation to remove the cataract and restore your vision.

Please see additional Important Safety Information on page 13.



Your intravitreal injection

What happens during the injection procedure?

You will be awake during the procedure. Your doctor will follow steps that include ensuring the surface of the eye is clean and numbing the surface of the eye to help keep you comfortable. OZURDEX® (dexamethasone intravitreal implant) is injected using a special applicator device that's about the size of a pen. The applicator is designed to help your doctor deliver OZURDEX® to the vitreous where the medication is needed. As the injection occurs, you may feel some pressure. You may then hear a click when your doctor presses the button that releases the OZURDEX® implant in your eye.

Are there any risks associated with intravitreal injections?

Injections into the vitreous in the eye, including those with OZURDEX®, are associated with serious eye infection (endophthalmitis), eye inflammation, increased eye pressure, and retinal detachments. Your eye doctor may monitor you regularly after the injection.

Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased eye pressure, glaucoma, and may increase the establishment of secondary eye infections due to bacteria, fungi, or viruses. Let your doctor know if you have a history of ocular herpes simplex.

The most common side effects reported in patients include: cataract, increased eye pressure, conjunctival blood spot, reduced vision, inflammation of the conjunctiva, specks that float in the field of vision, swelling of the conjunctiva, dry eye, vitreous detachment, vitreous opacities, retinal aneurysm, foreign body sensation, corneal erosion, inflammation of the cornea, anterior chamber inflammation, retinal tear, drooping eyelid, high blood pressure, and bronchitis.

After repeated injections with OZURDEX® (dexamethasone intravitreal implant), a cataract may occur. If this occurs, your vision will decrease and you will need an operation to remove the cataract and restore your vision. You may develop increased eye pressure with OZURDEX® that will need to be managed with eye drops, and rarely, with surgery.

These are not the only risks associated with intravitreal injections. If you experience other side effects, you should immediately contact your eye doctor. Your Retina Specialist will discuss the possible risks with you before performing the injection.

IMPORTANT SAFETY INFORMATION (continued)

You may develop increased eye pressure with OZURDEX® (dexamethasone intravitreal implant) that will need to be managed with eye drops, and rarely, with surgery.

In the days following injection with OZURDEX®, you may be at risk for potential complications including in particular, but not limited to, the development of serious eye infection or increased eye pressure. If your eye becomes red, sensitive to light, painful, or develops a change in vision, you should seek immediate care from your eye doctor. You may experience temporary visual blurring after receiving an injection and should not drive or use machinery until your vision has resolved.

Please see the full Prescribing Information in the pocket of this booklet.

Be aware and follow up

How may OZURDEX® (dexamethasone intravitreal implant) affect eye pressure?

Corticosteroids, such as OZURDEX®, can cause the fluid pressure inside the eye to increase. This is not something you can feel. So, following the injection, your doctor should regularly monitor your eye pressure. If you experience this side effect, treatment such as medicated eye drops or surgery may be required to lower the pressure.

Can OZURDEX® cause cataracts?

In clinical trials, 68% of OZURDEX® patients with natural lenses (166 of 243) developed cataracts, compared with 21% of patients with natural lenses who received simulated injections (49 of 230). After repeated injections with OZURDEX®, a cataract may occur. If this occurs, your vision will decrease and you will need an operation to remove the cataract and restore your vision. You may develop increased eye pressure with OZURDEX® that will need to be managed with eye drops, and rarely, with surgery.

Your "to do" list

Before injection _____

Day of injection _____

After injection _____

Doctor's instructions

You should return to the office as follows:

To help assess the effectiveness and safety of your treatment, please note any of the following:

- Vision improvement
- Eye becomes red, sensitive to light, painful, or develops a change in vision — please contact your eye doctor immediately

Change	Date and Time

IMPORTANT SAFETY INFORMATION

The most common side effects reported in patients include: cataract, increased eye pressure, conjunctival blood spot, reduced vision, inflammation of the conjunctiva, specks that float in the field of vision, swelling of the conjunctiva, dry eye, vitreous detachment, vitreous opacities, retinal aneurysm, foreign body sensation, corneal erosion, inflammation of the cornea, anterior chamber inflammation, retinal tear, drooping eyelid, high blood pressure, and bronchitis.

Please see additional Important Safety Information on back cover.

For the treatment of diabetic macular edema

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IMPORTANT SAFETY INFORMATION (continued)

After repeated injections with OZURDEX[®], a cataract may occur. If this occurs, your vision will decrease and you will need an operation to remove the cataract and restore your vision. You may develop increased eye pressure with OZURDEX[®] that will need to be managed with eye drops, and rarely, with surgery.

**Please see the full Prescribing Information
in the pocket of this booklet.**

Visit www.Ozurdex.com for more information.



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OZURDEX®

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OZURDEX® safely and effectively. See full prescribing information for OZURDEX®.

OZURDEX® (dexamethasone intravitreal implant)

For Intravitreal Injection

Initial U.S. Approval: 1958

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

OZURDEX® is a corticosteroid indicated for:

- The treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) (1.1)
- The treatment of non-infectious uveitis affecting the posterior segment of the eye (1.2)
- The treatment of diabetic macular edema (1.3)

DOSAGE AND ADMINISTRATION

- For ophthalmic intravitreal injection. (2.1)
- The intravitreal injection procedure should be carried out under controlled aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR®** solid polymer drug delivery system. (3)

CONTRAINDICATIONS

- Ocular or periocular infections (4.1)
- Glaucoma (4.2)
- Torn or ruptured posterior lens capsule (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. (5.2)

ADVERSE REACTIONS

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

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

See 17 for **PATIENT COUNSELING INFORMATION**.

Revised: 9/2014

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- 1.2 Posterior Segment Uveitis
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Retinal Vein Occlusion

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

1.2 Posterior Segment Uveitis

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

1.3 Diabetic Macular Edema

OZURDEX[®] is indicated for the treatment of diabetic macular edema.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection.

2.2 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid and ocular surface are recommended to be given prior to the injection.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

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

4.2 Glaucoma

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

4.3 Torn or Ruptured Posterior Lens Capsule

OZURDEX[®] is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for **OZURDEX**[®] use.

4.4 Hypersensitivity

OZURDEX[®] is contraindicated in patients with known hypersensitivity to any components of this product [see *Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections, including those with **OZURDEX**[®], have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [see *Patient Counseling Information (17)*].

5.2 Steroid-related Effects

Use of corticosteroids including **OZURDEX**[®] may produce posterior subcapsular cataracts, increased intraocular pressure, and

glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see *Adverse Reactions* (6.1)].

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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

Retinal Vein Occlusion and Posterior Segment Uveitis

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

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

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

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

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

Diabetic Macular Edema

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

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

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

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

MedDRA Term	OZURDEX® N=324 (%)	Sham N=328 (%)
Retinal tear	5 (2%)	2 (1%)
Eyelid ptosis	5 (2%)	2 (1%)
Non-ocular		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

¹ Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of **OZURDEX®** subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

² 243 of the 324 **OZURDEX®** subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 3: Summary of Elevated Intraocular Pressure (IOP) Related Adverse Reactions

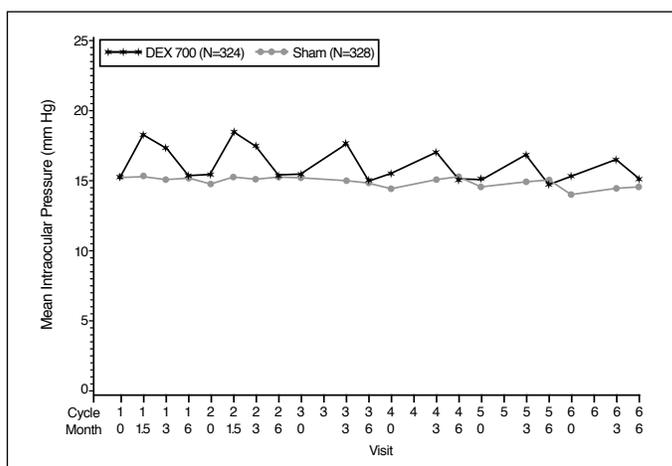
IOP	Treatment: N (%)	
	OZURDEX® N=324	Sham N=328
IOP elevation ≥ 10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥ 30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculectomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy

Sham: 1 laser iridotomy

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

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 243 of the 324 **OZURDEX®** subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **OZURDEX®** group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the **OZURDEX®** group and 12 months in the Sham group. Among these patients, 61% of **OZURDEX®** subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for **OZURDEX®** group and 20 for Sham) of the studies.

6.2 Postmarketing Experience

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Animal Data

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

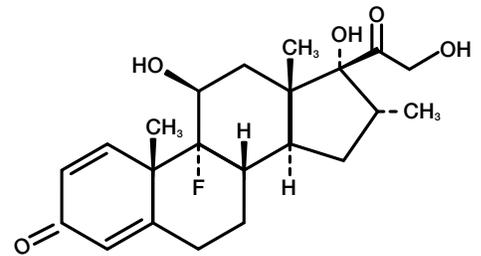
8.5 Geriatric Use

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

11 DESCRIPTION

OZURDEX[®] is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR**[®] solid polymer sustained-release drug delivery system.

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



MW 392.47; molecular formula: C₂₂H₂₉FO₅

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Posterior Segment Uveitis

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

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

Diabetic Macular Edema

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

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

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

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

^aStudy 1: OZURDEX[®] N=163; Sham, N=165

^bStudy 2: OZURDEX[®] N=165; Sham, N=163

^c14% (16.8% from OZURDEX[®] and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 2 and Figure 3. The occurrence of cataracts impacted visual acuity during the study. The visual acuity improvement from baseline increases during a treatment cycle, peaks at approximately 3 Months posttreatment and diminishes thereafter. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the final study visit.

Figure 2: Proportion of Subjects with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye

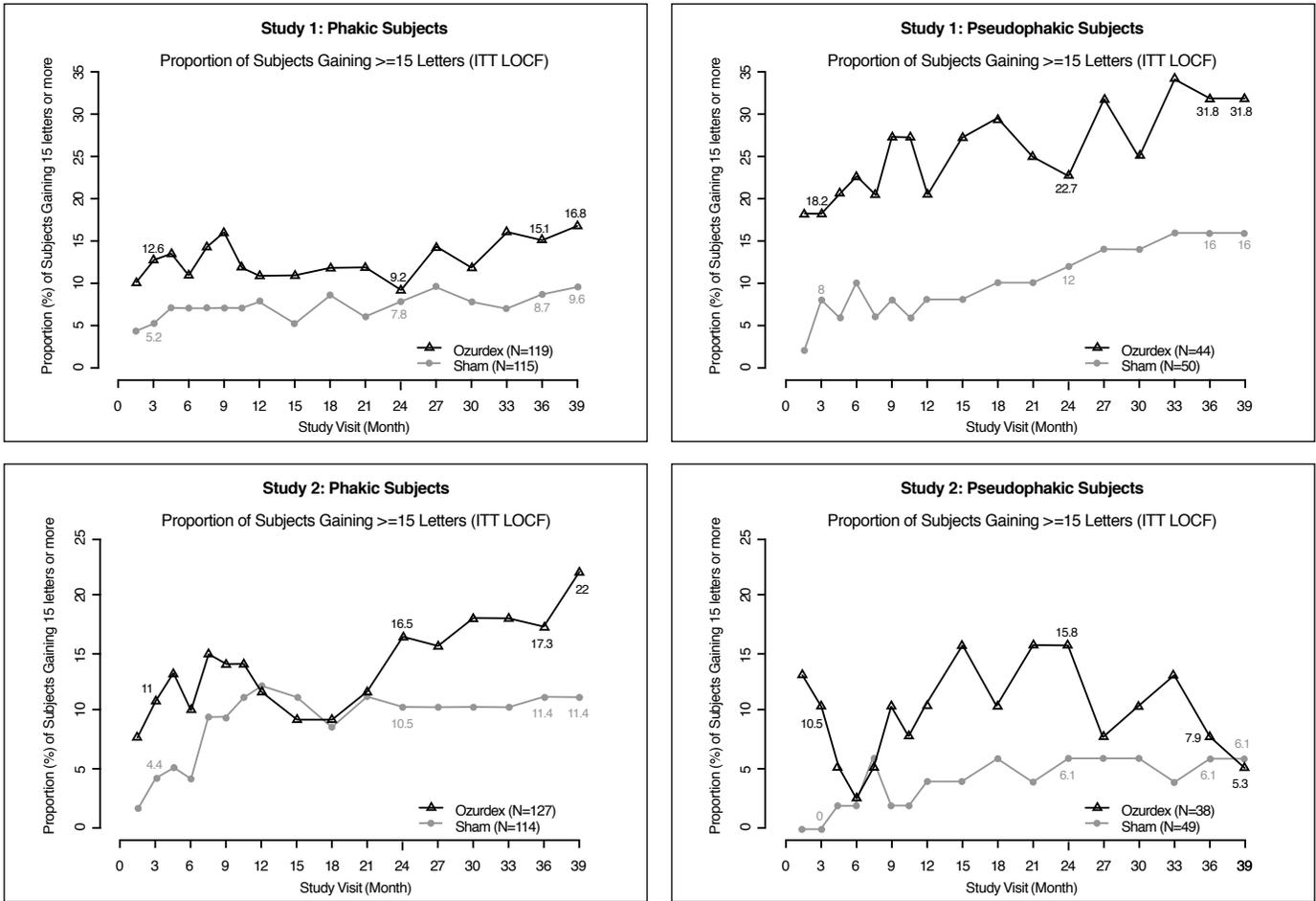
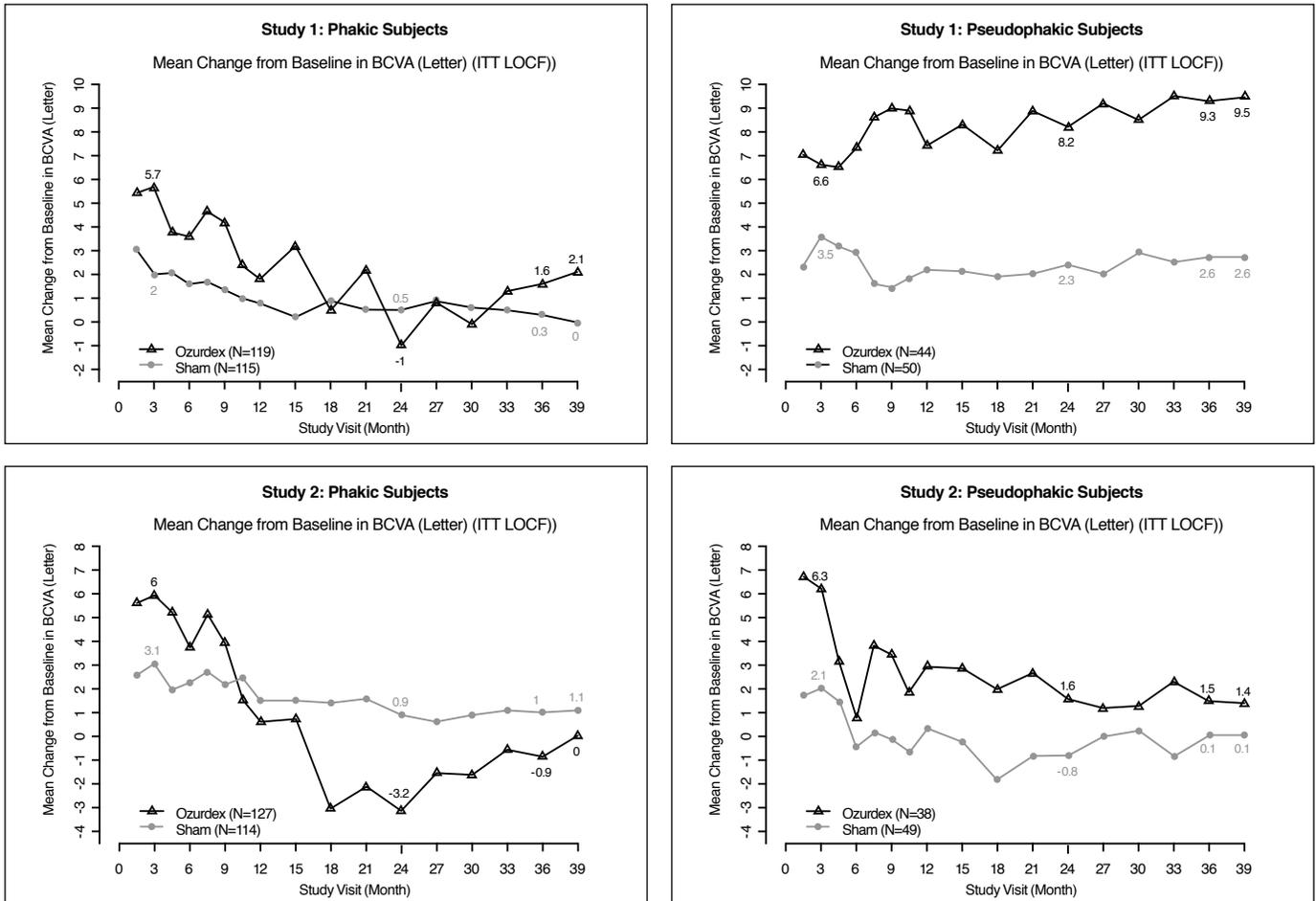


Figure 3: Mean BCVA Change from Baseline



The best corrected visual acuity outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 39 are presented in Table 6.

Table 6: Visual Acuity outcomes at Month 39 (Subgroup for pooled data with LOCF^c)

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

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

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

^c14% (16.8% from OZURDEX[®] and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients the data at Month 36 or earlier was used in the analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX[®] (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator, NDC 0023-3348-07.

Storage: Store at 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects

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

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

Intravitreal Injection-related Effects

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

When to Seek Physician Advice

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

Driving and Using Machines

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

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