

# Important Information About Diabetic Macular Edema (DME) and Treatment



For patients with DME

## What you can expect with OZURDEX<sup>®</sup>

### Approved Uses

OZURDEX<sup>®</sup> (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

#### When Not to Use OZURDEX<sup>®</sup>

OZURDEX<sup>®</sup> should not be used if you have any infections in or around the eyes, 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 pages 9-12.

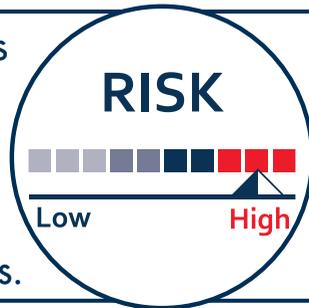
**Ozurdex<sup>®</sup>**  
(dexamethasone intravitreal  
implant) 0.7 mg

## Diabetes and vision

1.5 million Americans are diagnosed with diabetes every year.

Diabetic eye disease is the #1 cause of vision loss in working-age adults

All people with diabetes are at risk for diabetic eye disease such as diabetic retinopathy, which damages the blood vessels in the eyes.



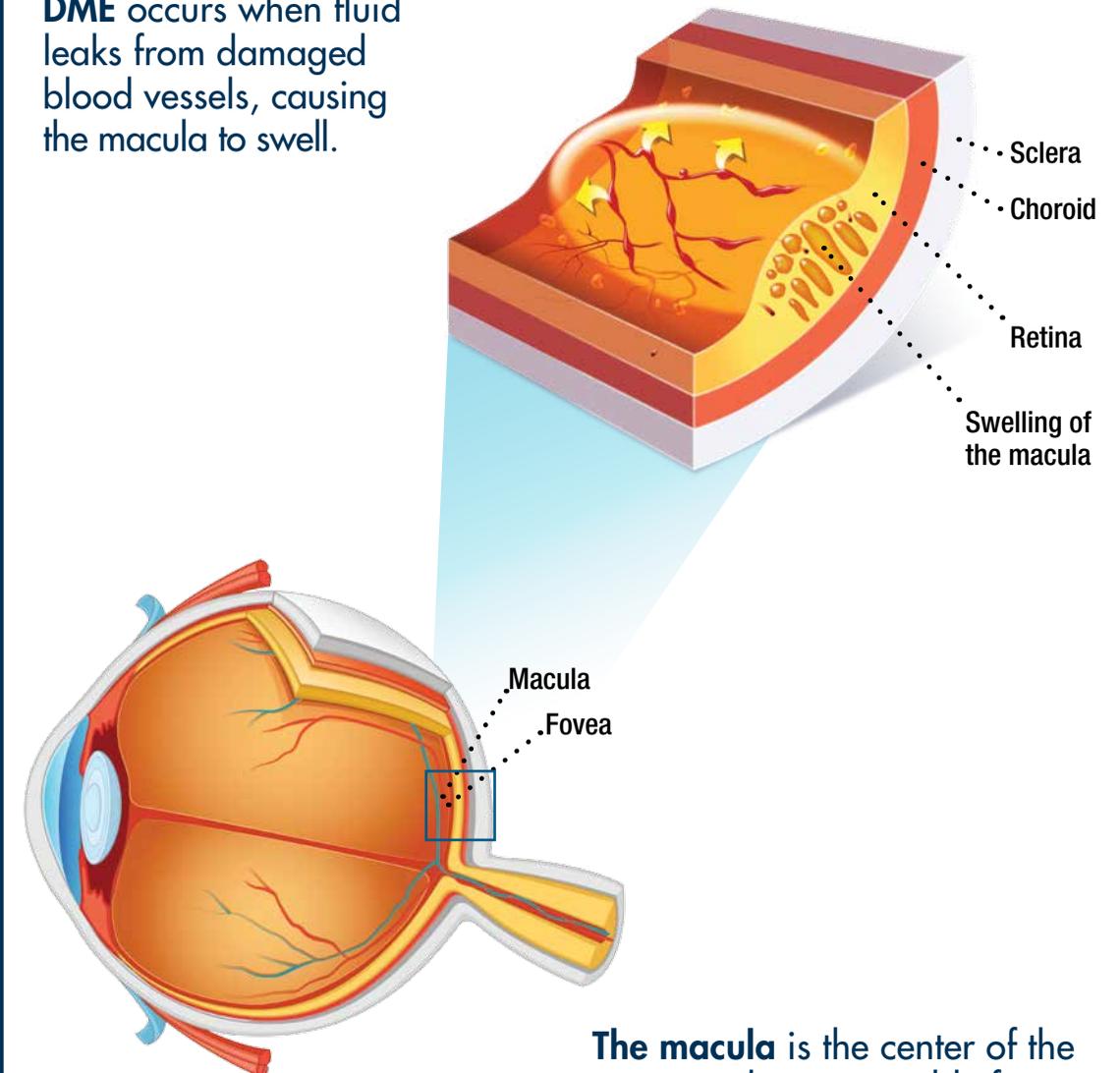
The longer a person has diabetes, the greater the risk.

DME develops in **HALF** of all people with diabetic retinopathy.



## The eye with DME

**DME** occurs when fluid leaks from damaged blood vessels, causing the macula to swell.



The **macula** is the center of the retina and is responsible for sharp, central vision.

## How DME affects vision

- ④ DME can lead to a loss of your vision (or blurry vision)
- ④ If your doctor finds DME early, you may not have any symptoms
- ④ 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



### What you can do to prevent or delay loss of vision due to DME



Good management of diabetes



Regular eye exams



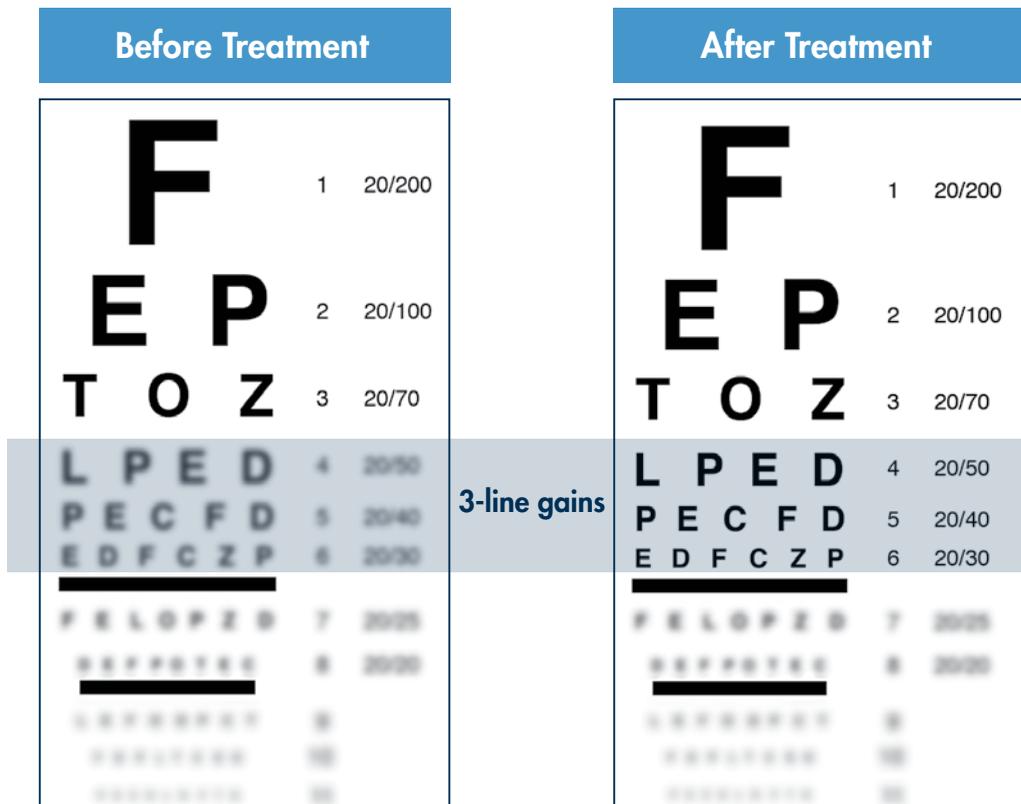
Appropriate follow up

## The effect of DME is measured by your visual acuity



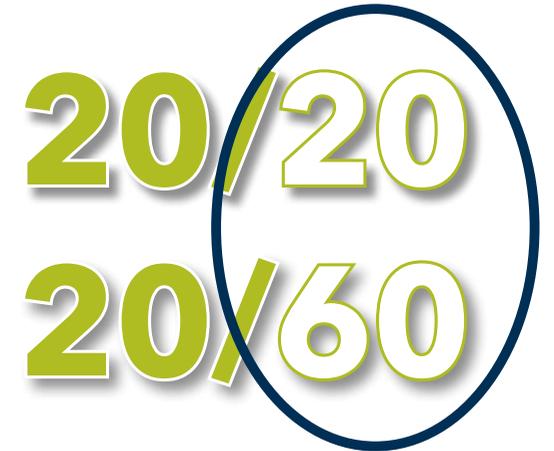
Visual acuity is the sharpness of vision. It is measured by the ability to read letters on an eye chart.

DME treatments can help improve visual acuity by increasing the number of lines a patient can read on an eye chart



## Visual acuity by the numbers

- 🕒 **20/20:** A person with 20/20 vision sees the same at a distance of 20 feet that someone with ideal vision sees at 20 feet
- 🕒 **20/60:** A person with 20/60 vision needs to be at a distance of 20 feet to see what a person with 20/20 vision can see at 60 feet
- 🕒 The second number increases as vision worsens



### Decreased visual acuity may affect your ability to:



Recognize faces



Obtain a driver license  
(20/40 vision is the minimum in 47 states)



Have vision to dial a telephone

## Treating DME with OZURDEX®

- 1 OZURDEX® is a prescription medicine approved by the U.S. Food and Drug Administration (FDA) to treat adults with diabetic macular edema
- 2 The tiny implant slowly releases medication over time, **without the need for monthly injections**. It will dissolve naturally and will not need to be removed
- 3 OZURDEX® treatment can help **reduce inflammation** in your retina and **improve your vision**

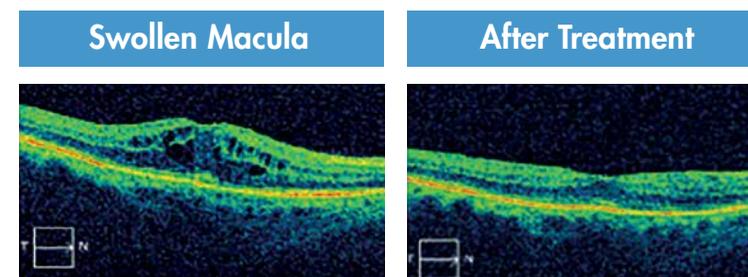


For more education and resources, visit [Ozurdex.com](http://Ozurdex.com).



## How OZURDEX® works

- 1 OZURDEX® is injected directly into the back of the eye, with minimal systemic absorption
- 2 Once injected, the implant dissolves slowly and releases a corticosteroid called dexamethasone
- 3 Corticosteroids, such as dexamethasone, reduce inflammation



## Safety Information

### Approved Uses

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

#### When Not to Use OZURDEX®

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

## Possible side effects of OZURDEX<sup>®</sup>

### Increased eye pressure

There is a chance of an increase in eye pressure that generally returns to where it started. If you experience this, you will be observed by your doctor to determine the need to be managed with eye drops and, rarely, with surgery.

### Cataracts

- ⦿ Cataract is a condition in which the lens of the eye becomes cloudy or opaque
- ⦿ It's possible a cataract could form if you have repeated treatments with OZURDEX<sup>®</sup>. If that happens, your vision may decrease, and you will need a procedure to remove the cataract and restore your vision

## Safety Information (continued)

### IMPORTANT SAFETY INFORMATION (continued)

#### When Not to Use OZURDEX<sup>®</sup> (continued)

OZURDEX<sup>®</sup> should not be used if you have glaucoma that has progressed to a cup-to-disc ratio of greater than 0.8.

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

OZURDEX<sup>®</sup> should not be used if you are allergic to any of its ingredients.

### Warnings and Precautions

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

Use of corticosteroids including OZURDEX<sup>®</sup> 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 as corticosteroids are not recommended in these patients.



## Safety Information (continued)

### Common Side Effects in Diabetic Macular Edema

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.

### Patient Counseling Information

After repeated injections with OZURDEX<sup>®</sup>, 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<sup>®</sup> that will need to be managed with eye drops, and rarely, with surgery.

In the days following injection with OZURDEX<sup>®</sup>, 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.



## Preparing for the procedure

### Before

- ④ Speak with your doctor about any questions/concerns you may have
- ④ Arrange to have somebody take you to and from your appointment
- ④ Create a list of all the prescription and over-the-counter medications you take

### During

- ④ The injection of OZURDEX<sup>®</sup> will only take a few moments
- ④ You will be awake
- ④ Your doctor will clean and numb the surface of the eye
- ④ Your doctor will inject OZURDEX<sup>®</sup> using a special applicator that's about the size of a pen
- ④ During the injection you may feel pressure
- ④ You may then hear a click when your doctor presses the button that releases the OZURDEX<sup>®</sup> implant in your eye

### After

- ④ Your doctor will check your eye, and then you will be ready to go home
- ④ Over time, you should notice an improvement in your vision. Your individual results may vary
- ④ If your eye becomes red, sensitive to light, painful, or develops a change in vision, please contact your eye doctor immediately

**Be sure to follow your doctor's instructions following the procedure.**

## Frequently Asked Questions

### **Q: How does OZURDEX<sup>®</sup> work?**

OZURDEX<sup>®</sup> is an implant that slowly dissolves over time and releases a corticosteroid called dexamethasone. This medication helps to reduce inflammation in the retina. OZURDEX<sup>®</sup> helps by improving visual acuity.

### **Q: How will my doctor administer OZURDEX<sup>®</sup>?**

The injection of the OZURDEX<sup>®</sup> implant will take only a few moments. The implant will be injected into the back part of your eye called the vitreous humor.

### **Q: How common are intravitreal injections?**

Intravitreal injections are frequently used to treat a variety of ophthalmic diseases. Your doctor is specially trained in giving eye injections.

### **Q: What can I expect during the injection procedure?**

You will be awake during the procedure. Your doctor will follow steps that clean the surface of the eye and then numb the area for your comfort.

### **Q: When the OZURDEX<sup>®</sup> implant is injected, will I feel anything?**

During the injection, you may feel some pressure. You may then hear a click when the doctor presses the button that releases the OZURDEX<sup>®</sup> implant into your eye.

### **Q: What results can I expect with OZURDEX<sup>®</sup>?**

- In two 3-year clinical trials, 328 people received OZURDEX<sup>®</sup> about every 6 months, based on their doctor's discretion, and 328 people received sham (control) treatment

- At the end of the 3-year studies, 20% (1 in 5) of OZURDEX<sup>®</sup> treated people gained  $\geq 15$  letters (3 or more lines) of vision on an eye chart compared to 11% (1 in 10) of control-treated people
- Your own individual results may vary; talk to your doctor

### **Q: What else should I know about the risks of OZURDEX<sup>®</sup> treatment?**

#### **Cataracts**

It's possible a cataract could form if you have repeated treatments with OZURDEX<sup>®</sup>. In clinical trials, after 1 injection, cataracts developed in about 10% (24 of 243) of OZURDEX<sup>®</sup> patients with natural lenses and 8% (18 of 230) of sham (control)-treated patients with natural lenses. After up to a maximum of 7 treatments over 3 years, cataracts occurred in 68% (166 of 243) of OZURDEX<sup>®</sup> treated patients with natural lenses and 21% (49 of 230) of sham (control)-treated patients with natural lenses. If a cataract forms, your vision may decrease, and you will need a procedure to remove the cataract and restore your vision.

#### **Increased eye pressure**

Also, you may develop increased pressure inside your eye with OZURDEX<sup>®</sup>. This will be observed by your doctor to determine the need to be managed with eye drops or, rarely, with surgery.

### **Q: What happens after the procedure?**

After the procedure, your doctor will check your eye, and then you will be ready to go home. Be sure to follow your doctor's instructions.



**Please see accompanying full Prescribing Information.**

### Information Sources

- Ali-Javadi M, Zarei-Ghanavati S. Cataracts in diabetic patients: a review article
- Boyd K. Who is at risk for diabetic retinopathy? American Ophthalmology Association website
- Diabetes and cataracts. American Academy of Ophthalmology website
- Diabetic eye disease: The number one cause of vision loss in working-age adults. National Eye Health Education Program
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- Facts about macular edema. National Eye Institute website
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- Segre L. What's an eye test? Eye charts and visual acuity explained. All About Vision website
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- Steinkuller PG. Legal vision requirements for drivers in the United States

**Ozurdex**<sup>®</sup>  
(dexamethasone intravitreal  
implant) 0.7 mg



# OZURDEX<sup>®</sup>

(dexamethasone intravitreal implant) 0.7 mg

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### OZURDEX<sup>®</sup> (dexamethasone intravitreal implant)

#### For Intravitreal Injection

Initial U.S. Approval: 1958

## INDICATIONS AND USAGE

OZURDEX<sup>®</sup> 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<sup>®</sup> 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2018

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Retinal Vein Occlusion
- 1.2 Posterior Segment Uveitis
- 1.3 Diabetic Macular Edema

### 2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Administration

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

- 4.1 Ocular or Periocular Infections
- 4.2 Glaucoma
- 4.3 Torn or Ruptured Posterior Lens Capsule
- 4.4 Hypersensitivity

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Intravitreal Injection-related Effects
- 5.2 Steroid-related Effects

### 6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\* 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**<sup>®</sup> (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**<sup>®</sup> is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

#### 1.3 Diabetic Macular Edema

**OZURDEX**<sup>®</sup> 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**<sup>®</sup> is administered to the other eye.

### 3 DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR**<sup>®</sup> solid polymer drug delivery system.

### 4 CONTRAINDICATIONS

#### 4.1 Ocular or Periocular Infections

**OZURDEX**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> use.

#### 4.4 Hypersensitivity

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

Following a second injection of **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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 <sup>®</sup> N=324 (%)	Sham N=328 (%)
<b>Ocular</b>		
Cataract <sup>1</sup>	166/243 <sup>2</sup> (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 (%)
<b>Non-ocular</b>		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

<sup>1</sup> 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.

<sup>2</sup> 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**

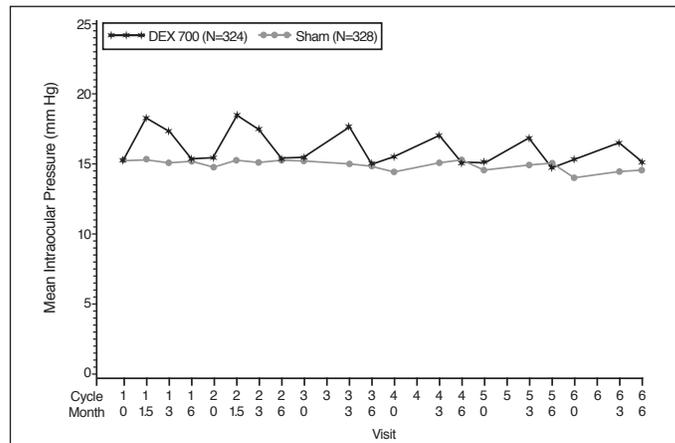
IOP	Treatment: N (%)	
	OZURDEX® N=324	Sham N=328
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

\* **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**

**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**<sup>®</sup> injection in humans (0.7 mg dexamethasone) on a mg/m<sup>2</sup> 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**<sup>®</sup> injection in humans (0.7 mg dexamethasone) on a mg/m<sup>2</sup> 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**<sup>®</sup> to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for **OZURDEX**<sup>®</sup> and any potential adverse effects on the breastfed child from **OZURDEX**<sup>®</sup>.

## 8.4 Pediatric Use

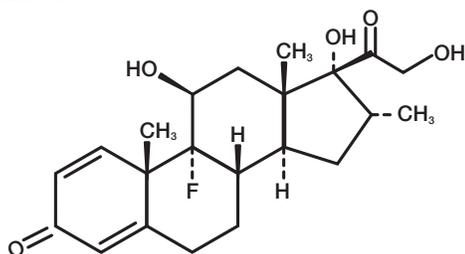
Safety and effectiveness of **OZURDEX**<sup>®</sup> in pediatric patients have not been established.

## 8.5 Geriatric Use

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

## 11 DESCRIPTION

**OZURDEX**<sup>®</sup> is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR**<sup>®</sup> solid polymer sustained-release drug delivery system. **OZURDEX**<sup>®</sup> is preloaded into a single-use, **DDS**<sup>®</sup> applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR**<sup>®</sup> 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 $\beta$ ,16 $\alpha$ ). Its structural formula is:



MW 392.47; molecular formula: C<sub>22</sub>H<sub>29</sub>FO<sub>5</sub>

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 [<sup>14</sup>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**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> demonstrated the following clinical results for the percent of patients with  $\geq 15$  letters of improvement from baseline in best-corrected visual acuity (BCVA):

**Table 4: Number (Percent) of Patients with  $\geq 15$  Letters Improvement from Baseline in BCVA**

Study Day	Study 1			Study 2		
	OZURDEX <sup>®</sup> N=201	Sham N=202	p-value*	OZURDEX <sup>®</sup> 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  $\geq 15$  letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with **OZURDEX**<sup>®</sup> compared to sham ( $p < 0.01$ ), with **OZURDEX**<sup>®</sup> treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a  $\geq 15$  letter (3-line) improvement in BCVA with **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> versus 7% for sham at week 8.

### Diabetic Macular Edema

The efficacy of **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> and 12.2% from Sham).

**Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCF<sup>a</sup>)**

Study	Outcomes	OZURDEX <sup>®</sup>	Sham	Estimated Difference (95% CI)
1 <sup>a</sup>	Mean (SD) Baseline BCVA (Letters)	56 (10)	57 (9)	
	Median (range) Baseline BCVA (Letters)	59 (34-95)	58 (34-74)	
	Gain of $\geq 15$ letters in BCVA (n(%))	34 (21%)	19 (12%)	9.3% (1.4%, 17.3%)
	Loss of $\geq 15$ 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 <sup>b</sup>	Mean (SD) Baseline BCVA (Letters)	55 (10)	56 (9)	
	Median (range) Baseline BCVA (Letters)	58 (34-72)	58 (36-82)	
	Gain of $\geq 15$ letters in BCVA (n(%))	30 (18%)	16 (10%)	8.4% (0.9%, 15.8%)
	Loss of $\geq 15$ 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)

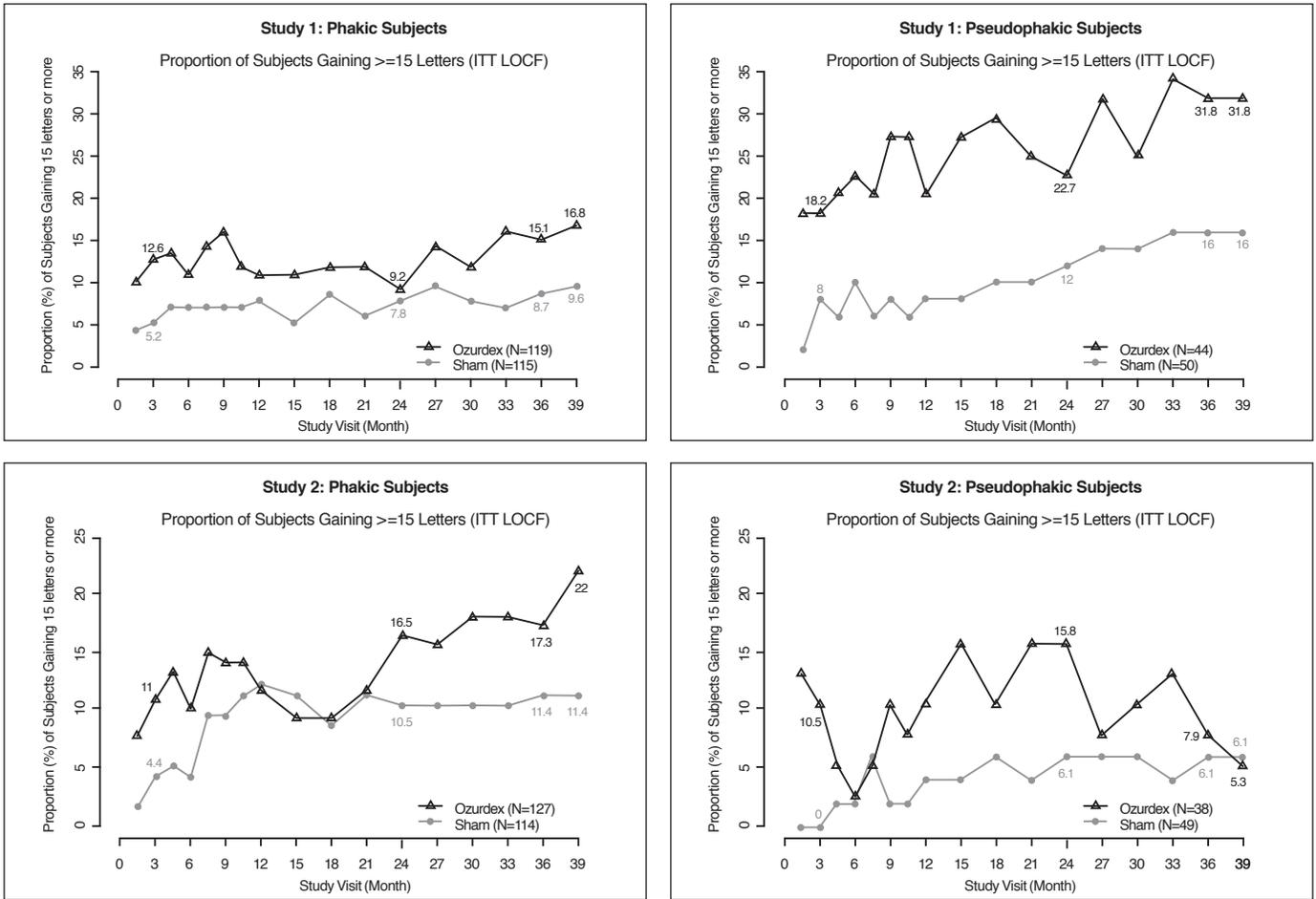
<sup>a</sup>Study 1: **OZURDEX**<sup>®</sup> N=163; Sham, N=165

<sup>b</sup>Study 2: **OZURDEX**<sup>®</sup> N=165; Sham, N=163

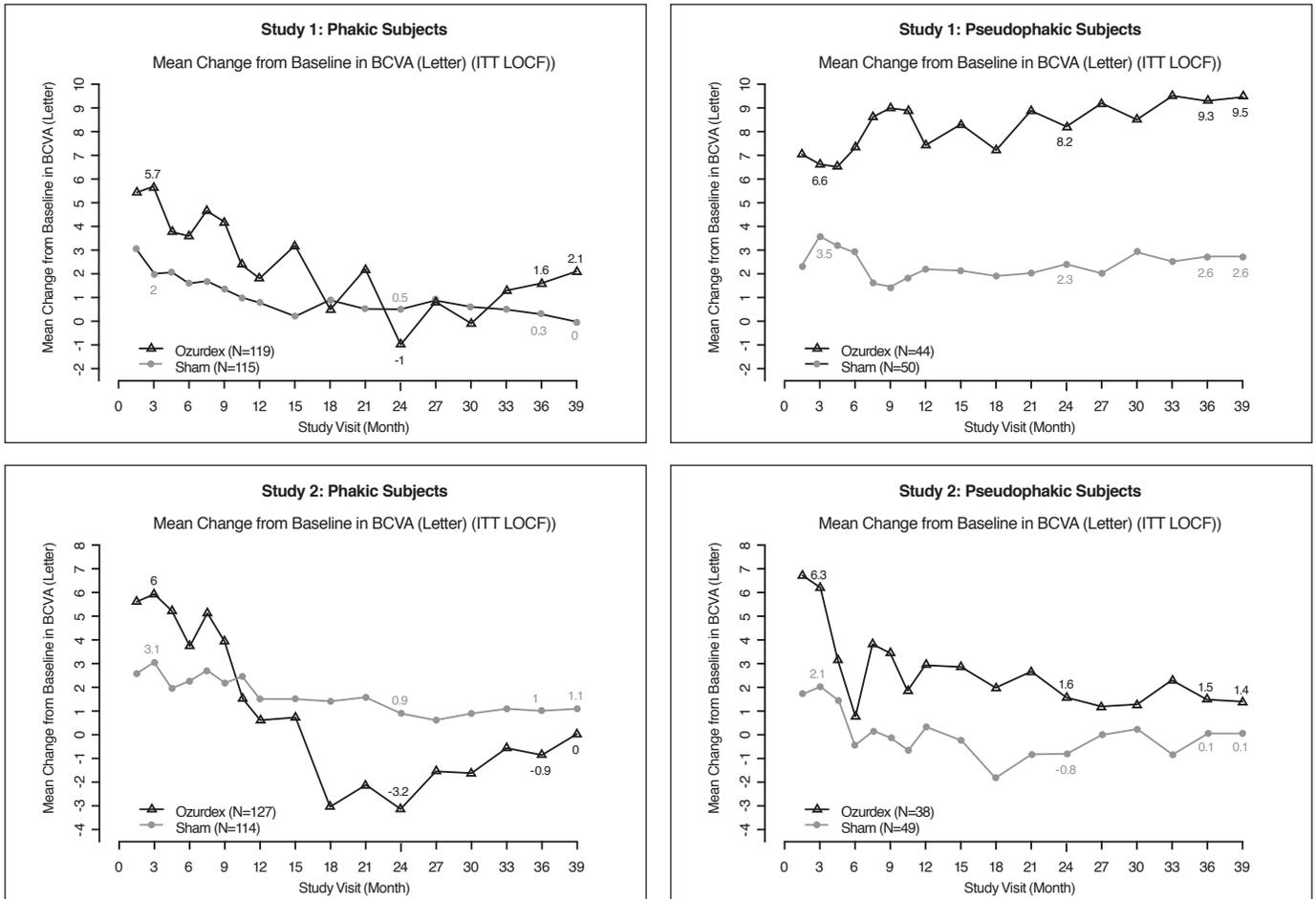
<sup>c</sup>14% (16.8% from **OZURDEX**<sup>®</sup> and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

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  $\geq 15$  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<sup>c</sup>)**

Subgroup (Pooled)	Outcomes	OZURDEX <sup>®</sup>	Sham	Estimated Difference (95% CI)
<sup>a</sup> 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)
<sup>b</sup> 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)

<sup>a</sup>Pseudophakic: OZURDEX<sup>®</sup>, N=82; Sham, N=99

<sup>b</sup>Phakic: OZURDEX<sup>®</sup>, N=246; Sham, N=229

<sup>c</sup>14% (16.8% from OZURDEX<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup>. 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<sup>®</sup> 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<sup>®</sup>, 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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v1.0USPI3348

# OZURDEX<sup>®</sup>

(dexamethasone intravitreal implant) 0.7 mg

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**OZURDEX<sup>®</sup> (dexamethasone intravitreal implant), for intravitreal injection**

Initial U.S. Approval: 1958

## INDICATIONS AND USAGE

OZURDEX<sup>®</sup> 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<sup>®</sup> 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2020

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Retinal Vein Occlusion
- 1.2 Posterior Segment Uveitis
- 1.3 Diabetic Macular Edema

### 2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Administration

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

- 4.1 Ocular or Periocular Infections
- 4.2 Glaucoma
- 4.3 Torn or Ruptured Posterior Lens Capsule
- 4.4 Hypersensitivity

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Intravitreal Injection-related Effects
- 5.2 Steroid-related Effects

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

\* 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**<sup>®</sup> (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**<sup>®</sup> is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

#### 1.3 Diabetic Macular Edema

**OZURDEX**<sup>®</sup> 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**<sup>®</sup> is administered to the other eye.

### 3 DOSAGE FORMS AND STRENGTHS

Intravitreal implant containing dexamethasone 0.7 mg in the **NOVADUR**<sup>®</sup> solid polymer drug delivery system.

### 4 CONTRAINDICATIONS

#### 4.1 Ocular or Periocular Infections

**OZURDEX**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> use.

#### 4.4 Hypersensitivity

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

Following a second injection of **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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 <sup>®</sup> N=324 (%)	Sham N=328 (%)
<b>Ocular</b>		
Cataract <sup>1</sup>	166/243 <sup>2</sup> (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 (%)
<b>Non-ocular</b>		
Hypertension	41 (13%)	21 (6%)
Bronchitis	15 (5%)	8 (2%)

<sup>1</sup> 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.

<sup>2</sup> 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**

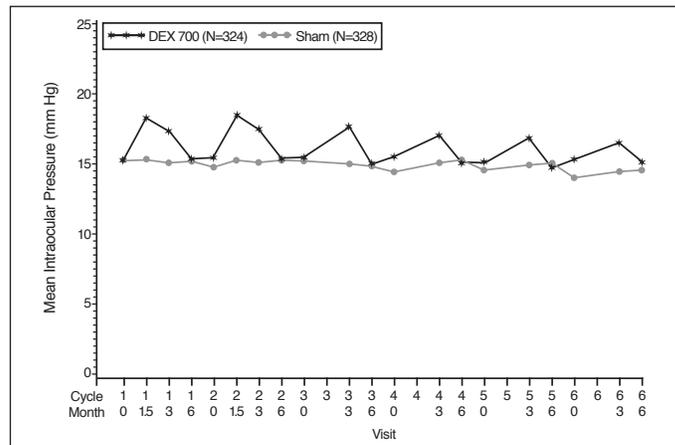
IOP	Treatment: N (%)	
	OZURDEX® N=324	Sham N=328
IOP elevation ≥10 mm Hg from Baseline at any visit	91 (28%)	13 (4%)
≥30 mm Hg IOP at any visit	50 (15%)	5 (2%)
Any IOP lowering medication	136 (42%)	32 (10%)
Any surgical intervention for elevated IOP*	4 (1.2%)	1 (0.3%)

\* **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**<sup>®</sup> (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**<sup>®</sup> injection in humans (0.7 mg dexamethasone) on a mg/m<sup>2</sup> 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**<sup>®</sup> injection in humans (0.7 mg dexamethasone) on a mg/m<sup>2</sup> 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**<sup>®</sup> to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for **OZURDEX**<sup>®</sup> and any potential adverse effects on the breastfed child from **OZURDEX**<sup>®</sup>.

## 8.4 Pediatric Use

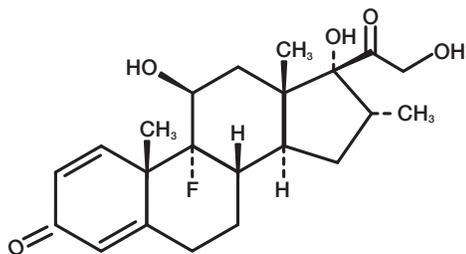
Safety and effectiveness of **OZURDEX**<sup>®</sup> in pediatric patients have not been established.

## 8.5 Geriatric Use

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

## 11 DESCRIPTION

**OZURDEX**<sup>®</sup> is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the **NOVADUR**<sup>®</sup> solid polymer sustained-release drug delivery system. **OZURDEX**<sup>®</sup> is preloaded into a single-use, **DDS**<sup>®</sup> applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The **NOVADUR**<sup>®</sup> 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 $\beta$ ,16 $\alpha$ )-. Its structural formula is:



MW 392.47; molecular formula: C<sub>22</sub>H<sub>29</sub>FO<sub>5</sub>

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 [<sup>14</sup>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**<sup>®</sup> (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**<sup>®</sup> 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**<sup>®</sup> demonstrated the following clinical results for the percent of patients with  $\geq 15$  letters of improvement from baseline in best-corrected visual acuity (BCVA):

**Table 4: Number (Percent) of Patients with  $\geq 15$  Letters Improvement from Baseline in BCVA**

Study Day	Study 1			Study 2		
	OZURDEX <sup>®</sup> N=201	Sham N=202	p-value*	OZURDEX <sup>®</sup> 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  $\geq 15$  letters (3-line) improvement in BCVA cumulative response rate curves were significantly faster with **OZURDEX**<sup>®</sup> compared to sham ( $p < 0.01$ ), with **OZURDEX**<sup>®</sup> treated patients achieving a 3-line improvement in BCVA earlier than sham-treated patients.

The onset of a  $\geq 15$  letter (3-line) improvement in BCVA with **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> versus 7% for sham at week 8.

### Diabetic Macular Edema

The efficacy of **OZURDEX**<sup>®</sup> 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**<sup>®</sup> 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**<sup>®</sup> and 12.2% from Sham).

**Table 5: Visual Acuity outcomes at Month 39 (All randomized subjects with LOCF<sup>a</sup>)**

Study	Outcomes	OZURDEX <sup>®</sup>	Sham	Estimated Difference (95% CI)
1 <sup>a</sup>	Mean (SD) Baseline BCVA (Letters)	56 (10)	57 (9)	
	Median (range) Baseline BCVA (Letters)	59 (34-95)	58 (34-74)	
	Gain of $\geq 15$ letters in BCVA (n(%))	34 (21%)	19 (12%)	9.3% (1.4%, 17.3%)
	Loss of $\geq 15$ 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 <sup>b</sup>	Mean (SD) Baseline BCVA (Letters)	55 (10)	56 (9)	
	Median (range) Baseline BCVA (Letters)	58 (34-72)	58 (36-82)	
	Gain of $\geq 15$ letters in BCVA (n(%))	30 (18%)	16 (10%)	8.4% (0.9%, 15.8%)
	Loss of $\geq 15$ 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)

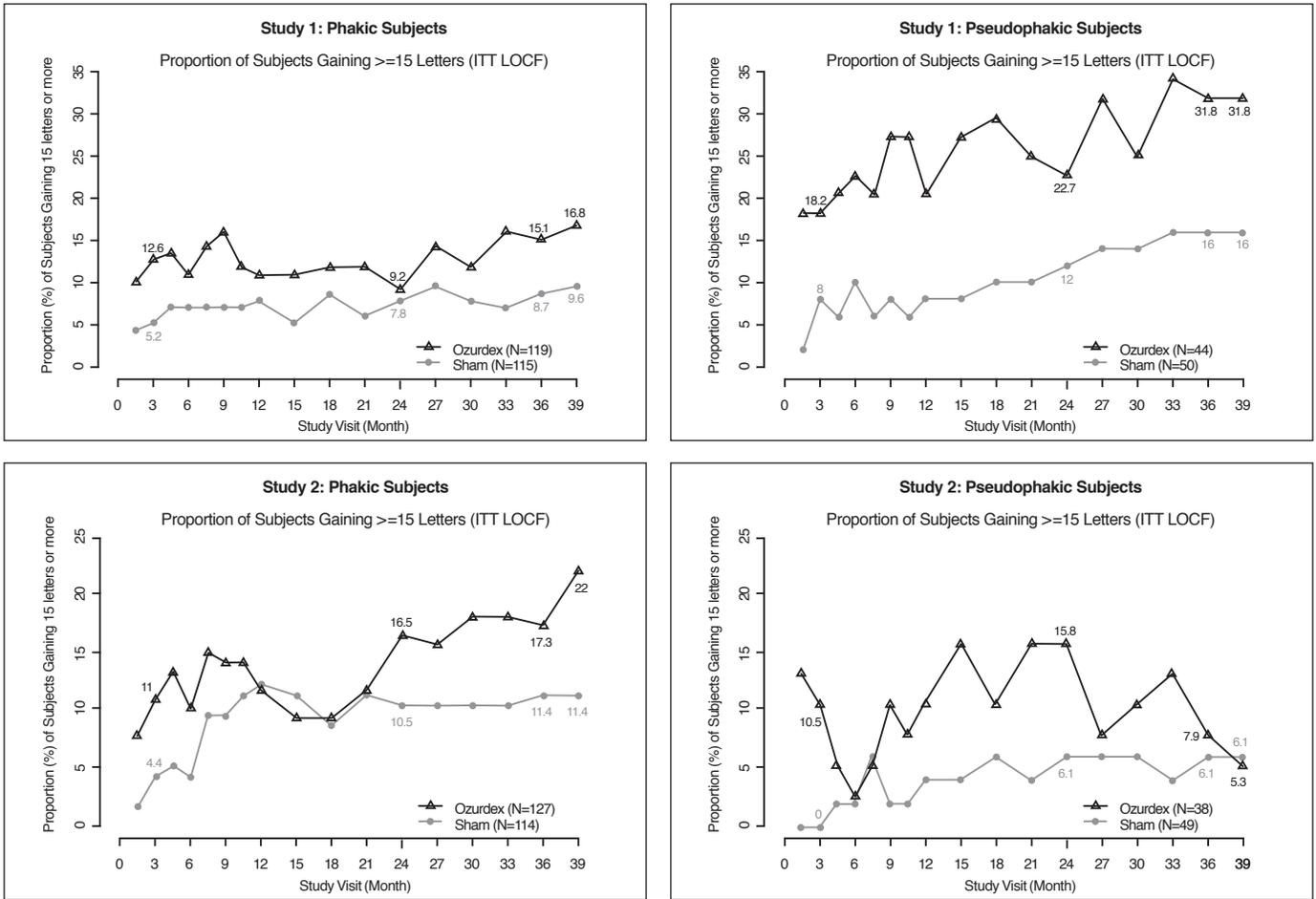
<sup>a</sup>Study 1: **OZURDEX**<sup>®</sup> N=163; Sham, N=165

<sup>b</sup>Study 2: **OZURDEX**<sup>®</sup> N=165; Sham, N=163

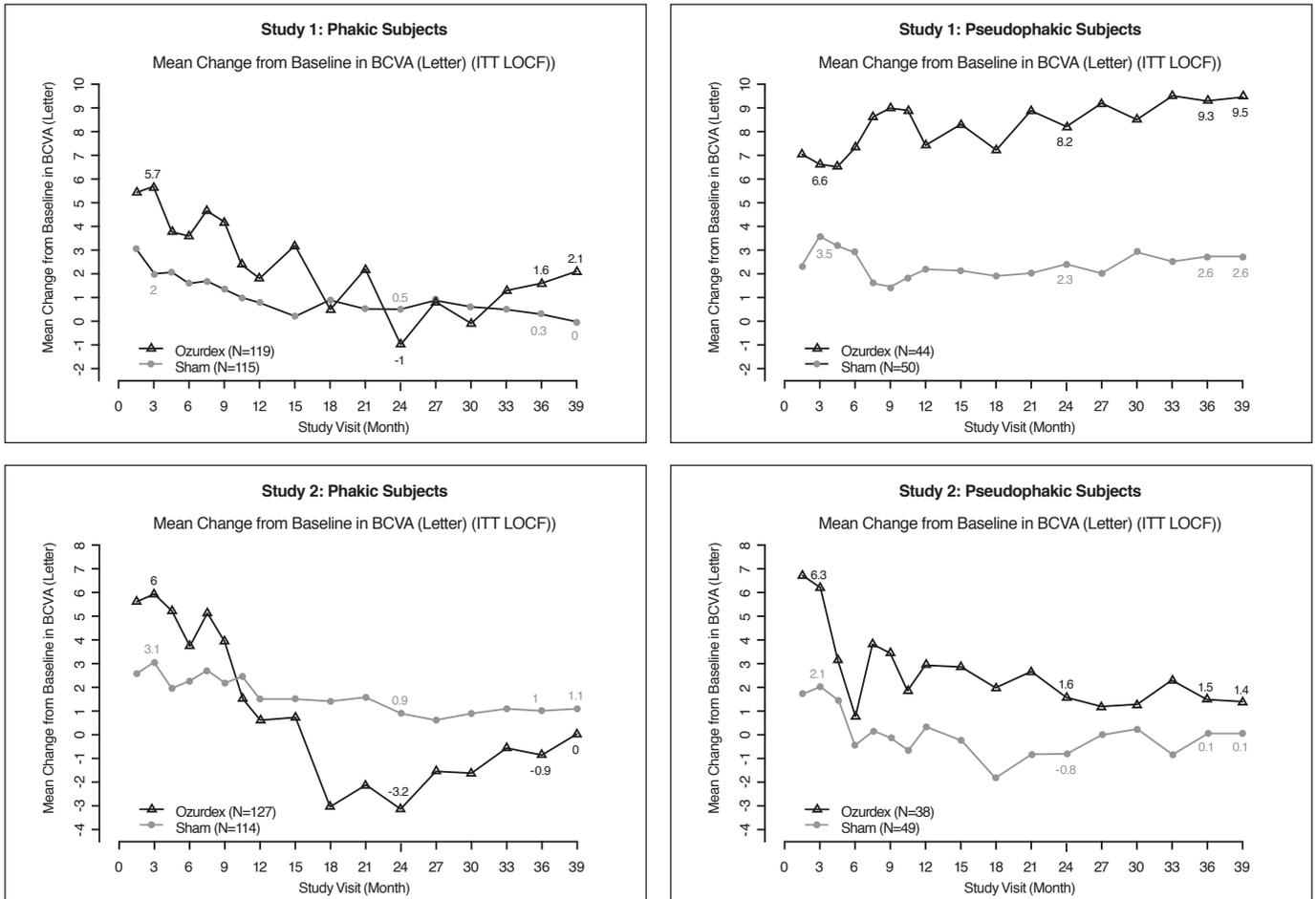
<sup>c</sup>14% (16.8% from **OZURDEX**<sup>®</sup> and 12.2% from Sham) of patients had BCVA outcome at Month 39, for the remaining patients, the data at Month 36 or earlier was carried forward.

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  $\geq 15$  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<sup>c</sup>)**

Subgroup (Pooled)	Outcomes	OZURDEX <sup>®</sup>	Sham	Estimated Difference (95% CI)
<sup>a</sup> 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)
<sup>b</sup> 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)

<sup>a</sup>Pseudophakic: **OZURDEX<sup>®</sup>**, N=82; Sham, N=99

<sup>b</sup>Phakic: **OZURDEX<sup>®</sup>**, N=246; Sham, N=229

<sup>c</sup>14% (16.8% from **OZURDEX<sup>®</sup>** 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<sup>®</sup>** (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°C to 30°C (59°F to 86°F).

## 17 PATIENT COUNSELING INFORMATION

### Steroid-related Effects

Advise patients that a cataract may occur after repeated treatment with **OZURDEX<sup>®</sup>**. 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<sup>®</sup>** 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<sup>®</sup>**, 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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