

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-315

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OZURDEX™ (dexamethasone intravitreal implant)

Initial U.S. Approval: 1958

—INDICATIONS AND USAGE—

OZURDEX™ contains a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). (1)

—DOSAGE AND ADMINISTRATION—

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

—DOSAGE FORMS AND STRENGTHS—

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

—CONTRAINDICATIONS—

- Ocular or periocular infections. (4.1)
- Advanced glaucoma. (4.2)

—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. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. (5.2)

—ADVERSE REACTIONS—

The most common adverse reactions reported by ≥20% of patients included increased intraocular pressure and conjunctival hemorrhage. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: June 2009

*FULL PRESCRIBING INFORMATION:
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only.

2.2 Administration

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

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

4.2 Advanced Glaucoma

OZURDEX™ is contraindicated in patients with advanced glaucoma.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored following the injection. (see **PATIENT COUNSELING INFORMATION**, 17)

5.2 Potential Steroid-related Effects

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.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. Corticosteroids should not be used in active ocular herpes simplex.

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.

The following information is based on the combined clinical trial results from the initial 6 month masked period of two

randomized, sham-controlled, parallel studies.

Adverse reactions reported by greater than 2% of patients in the first six months

MeDRA Term	OZURDEX™ N=421(%)	Sham N=423(%)
Intraocular pressure increased	106 (25%)	5 (1%)
Conjunctival hemorrhage	85 (20%)	63 (15%)
Eye pain	31 (7%)	16 (4%)
Conjunctival hyperemia	28 (7%)	20 (5%)
Ocular hypertension	17 (4%)	3 (1%)
Cataract	15 (4%)	6 (1%)
Vitreous detachment	12 (3%)	8 (2%)
Headache	14 (3%)	7 (2%)

Increased IOP with **OZURDEX™** peaked at day 60 and returned to baseline levels by day 180. During the initial treatment period, 0.7% (3/421) of the patients who received **OZURDEX™** required laser or 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Topical dexamethasone has been shown to be teratogenic in mice, producing fetal resorptions and cleft palate. In the rabbit, dexamethasone produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1 mg/kg/day every other day for 28 days or at 10 mg/kg/day once or every other day on 3 or 5

days between gestation days 23 and 49 had fetuses with minor cranial abnormalities. A 1 mg/kg/dose in pregnant rhesus monkeys would be approximately 85 times higher than a **OZURDEX™** injection in humans (assuming 60 kg body weight).

There are no adequate and well-controlled studies in pregnant women. **OZURDEX™** (dexamethasone intravitreal implant) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of **OZURDEX™** in pediatric patients has not been established.

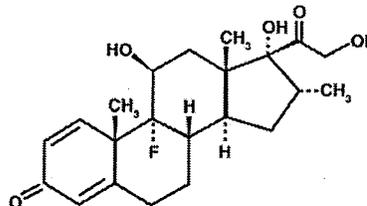
8.5 Geriatric Use

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 µg) dexamethasone in the **NOVADUR™** solid polymer drug delivery system. **OZURDEX™** is preloaded into a single-use, specially designed **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. **OZURDEX™** is preservative-free. The chemical name for dexamethasone is pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β,16α). Its structural formula is: MW 392.47; molecular formula: 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 potent 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 in the two, 6-month Phase 3 efficacy studies prior to dosing and on Days 7, 30, 60, and 90 following the intravitreal implant containing 0.35 mg or 0.7 mg dexamethasone. In both studies, the majority of plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ= 50 pg/mL). Plasma dexamethasone concentrations from 10 of 73 samples in the 0.7 mg dose group and from 2 of 42 samples in the 0.35 mg dose group were above the LLOQ, ranging from 52 pg/mL to 94 pg/mL. The highest plasma concentration value of 94

pg/mL was observed in one subject from the 0.7 mg group. 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.

14 CLINICAL STUDIES

The efficacy of **OZURDEX™** was assessed in two, multicenter, double-masked, randomized, parallel studies.

Following a single injection, **OZURDEX™** for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) demonstrated the following clinical results for the percent of patients with ≥ 15 letters of improvement from baseline in best-corrected visual acuity (BCVA):

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

Study Day	Study 1			Study 2		
	DEX 700 N=201	Sham N=202	p-value	DEX 700 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.

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-XXXX-XX.

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

**17 PATIENT COUNSELING
INFORMATION**

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

Patients may experience temporary visual blurring after receiving an intravitreal injection. They should not drive or use machines until this has resolved.

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