PRODUCT MONOGRAPH

Pr OZURDEX®

(dexamethasone)

Intravitreal Implant 0.7 mg

Corticosteroid

Allergan Inc.
Markham, ON
L6G 0B5

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[Pr]OZURDEX®

dexamethasone

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravitreal injection	Intravitreal implant 0.7 mg	None. For complete listing see the Dosage Forms, Composition and packaging section of the Product Monograph

INDICATIONS AND CLINICAL USE

OZURDEX® (dexamethasone intravitreal implant 0.7 mg) is indicated for:

- the treatment of macular edema following central retinal vein occlusion (CRVO).
- the treatment of non-infectious uveitis affecting the posterior segment of the eye.
- the treatment of adult patients with diabetic macular edema (DME) who are pseudophakic.

Geriatrics (> 65 years of age):
No dose adjustment is required for elderly patients.

Pediatrics (< 18 years of age):
OZURDEX® is not recommended for pediatric use. The safety and efficacy of OZURDEX® have not been studied in pediatric patients.

CONTRAINDICATIONS

- 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.
- Patients with advanced glaucoma.
- Patients with known hypersensitivity to any components of this product or to other corticosteroids.
- Patients who have aphakic eyes with rupture of the posterior lens capsule.

- Patients with ACIOL (Anterior Chamber Intraocular Lens) and rupture of the posterior lens capsule.

WARNINGS AND PRECAUTIONS

General

There is only very limited information on repeat dosing intervals less than 6 months and there is currently no experience of repeat administrations beyond 2 implants in patients with macular edema due to retinal vein occlusion (CRVO). Therefore, for macular edema following CRVO, no more than two consecutive OZURDEX® injections should be used, and an interval of approximately 6 months should be allowed between the two injections. (See **DOSAGE AND ADMINISTRATION**).

In patients with posterior segment uveitis, as there is no experience with more than one OZURDEX® injection, the use of a second OZURDEX® injection is not recommended. Caution should be exercised if a second injection is considered in cases where the possible benefits are believed to outweigh the risk to the patient. An interval of approximately 6 months should be allowed between the two injections.

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX®, should not be retreated.

Repeat doses should only be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk.

OZURDEX® has not been studied in patients with macular edema secondary to RVO with significant retinal ischemia, therefore OZURDEX® is not recommended in these patients.

The safety and efficacy of OZURDEX® administered to both eyes concurrently have not been studied, therefore administration to both eyes is not recommended.

OZURDEX® has not been studied in aphakic patients. Therefore, OZURDEX® should be used with caution in these patients.

Ophthalmologic

Intravitreal Injection-related Effects:

OZURDEX® must be administered by a qualified ophthalmologist experienced in intravitreal injections. Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients in whom the posterior capsule of the lens is absent or has a tear (e.g., occurring after cataract surgery) are at risk of implant migration into the anterior chamber. Proper aseptic injection techniques must always be used.

There have been reports of implant misplacement requiring surgical intervention.

Serious cases of dislocated implants moving into the anterior chamber have been reported, some of which required eye surgery. See ADVERSE REACTIONS - Post-Market Adverse Drug Reactions.

Several cases of hypotony of the eye (associated with vitreous leakage due to injection) were also reported, some of which were serious. See ADVERSE REACTIONS - Post-Market Adverse Drug Reactions.

Patients should be monitored regularly following the injection including monitoring of the 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 or any of the above mentioned events without delay. See **DOSAGE AND ADMINISTRATION**.

The most common haemorrhagic adverse reaction reported in patients receiving anti-platelet therapy was conjunctival haemorrhage (24%). OZURDEX® should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products. See Drug Interactions.

Potential Steroid-related Effects:
Prolonged use of corticosteroids may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and result in 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.

In clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see **ADVERSE REACTIONS**). Increase of IOP of ≥10 mmHg from baseline was also reported with maximum rates at 60 days following the OZURDEX® injection. Patients less than 45 years old were more likely to experience IOP increase. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post-injection as needed.

OZURDEX® is a biodegradable polymer matrix containing 700 µg micronized dexamethasone. However, implant residuals were reported in 34% of patients treated with OZURDEX® but also in 17% of patients treated with the sham. There does not appear to be residuals accumulation following the second implant. The possible impacts of implant residuals after OZURDEX® injection are unknown.

Peri-Operative Considerations
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 should be given prior to the

injection.

Sexual Function/Reproduction
No reproductive and developmental toxicity data are available for OZURDEX®. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application (Pregnancy Category C). Therefore, OZURDEX® is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Special Populations
Pregnant Women:
Topical dexamethasone has been shown to be teratogenic in mice (fetal resorptions and cleft palate) and rabbits (fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc). Pregnant rhesus monkeys treated with dexamethasone intramuscularly had fetuses with cranial abnormalities. See Toxicology.

There are no adequate and well-controlled studies in pregnant women. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women:
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. OZURDEX® is not recommended during breast feeding unless clearly necessary.

Pediatrics (< 18 years of age):
The safety and effectiveness of OZURDEX® has not been studied in pediatric patients.

Geriatrics (> 65 years of age):
No increased risk in the geriatric population was noted in the clinical studies with OZURDEX®.

Renal, Hepatic/Biliary/Pancreatic
No studies have been conducted to examine the pharmacokinetics of OZURDEX® in patients with renal, hepatic/biliary/pancreatic impairment.

Carcinogenesis and Mutagenesis
No carcinogenicity studies were performed. See Toxicology**.**

Endocrine and Metabolism
Disturbances on the corticosteroids HPA axis in humans were not evaluated for OZURDEX®.

Occupational Hazards
Patients may experience temporary visual blurring after receiving OZURDEX® by intravitreal injection. They should not drive or use machines until this has resolved.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions related to the prolonged use of ophthalmic dexamethasone include increased intraocular pressure (IOP), glaucoma with possible damage to the optic nerve, defects in visual acuity and visual field, 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.

Indication of Macular Edema due to CRVO

In two phase 3 studies assessing OZURDEX®, the most frequently reported adverse reactions with OZURDEX® were increased IOP (25.2 %) and conjunctival haemorrhage (20.2 %). Cataracts were also observed with OZURDEX®. Other events reported infrequently and believed to be due to the procedure included vitreous hemorrhage and conjunctival edema. Overall, a total of 62.9 % of patients experienced at least one adverse reaction based on the investigator's assessment.

Following the second OZURDEX® injection, the adverse event profile was similar to that following the first injection, except for the overall incidence of cataracts which increased significantly after one year, with subcapsular cataract reported in 13% of patients.

No significant differences in the safety profile were noted between patients with CRVO and those with BRVO, in relation to OZURDEX®.

Indication of Posterior Segment Uveitis

In a single 6-month randomized study in adult patients with posterior segment uveitis, 76 patients received OZURDEX® (with 73 completing the 6-month follow-up), and 75 patients received a sham. Fifty-seven (57) patients with OZURDEX® (75%) experienced ocular adverse events, as compared to 60% of those with the sham. The most frequently reported adverse events were increased IOP (25 % with OZURDEX® and 7% with the sham) and conjunctival haemorrhage (30% with OZURDEX® and 21% with sham). Cataract was reported in 12% of patients with OZURDEX® and 5% of those with the sham. Other events included ocular discomfort, eye pain, and ocular hypertension. See table 2 below for less common adverse events.

Indication of Diabetic Macular Edema

In two phase 3 studies assessing OZURDEX®, the most frequently reported adverse reactions with OZURDEX® were cataracts (37.8%), intraocular pressure increased (30.8%), and conjunctival haemorrhage (21.0%). Incidences were generally higher with dexamethasone compared to sham, however there were no notable differences between the OZURDEX® and DEX 350-µg doses. Of note, cumulative study exposure (ie, patient years) was shorter in the sham group (665.5 patient years) than in the OZURDEX® and DEX 350 groups (853.9 and 880.2 patient years, respectively) due to more patient discontinuations after the second treatment in the sham group. Overall incidences of AEs and SAEs were similar across all three groups by

exposure-adjusted analysis

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Indication of Macular Edema due to CRVO

The following information in Table 1 is based on the combined clinical trial results from the initial 6 month masked period of two, multicenter, double-masked, randomized, sham-controlled, parallel studies in patients with macular edema due to BRVO or CRVO. Overall, 427 were randomized to receive OZURDEX® and 426 to receive a sham. A total of 401 patients (94%) randomized and treated with OZURDEX® completed the initial treatment period (up to day 180).

Table 1 Adverse Drug Reactions (>2%) after 6 Months Following One OZURDEX® Injection

MedDRA term	**OZURDEX®** N=421(%)	Sham N=423(%)
Ocular Reactions in the study eye		
Intraocular pressure increased	106 (25.2%)	5 (1.2%)
Conjunctival hemorrhage	85 (20.2%)	63 (14.9%)
Eye pain	31 (7.4%)	16 (3.8%)
Conjunctival hyperemia	28 (6.7%)	20 (4.7%)
Ocular hypertension	17 (4.0%)	3 (0.7%)
Cataract(*)	15 (3.6%)	6 (1.4%)
Vitreous detachment	12 (2.9%)	8 (1.9%)
Non-ocular Reactions		
Headache	14 (3.3%)	7 (1.7%)

(*) Following two OZURDEX® injections, cataracts were reported in **26%** of patients, with subcapsular cataracts reported in **13%** of patients.

Following the first OZURDEX® injection, increased IOP with OZURDEX® peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with topical IOP-lowering medications. 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 in the study eye compared with 0.2% (1/423) with sham.

In 341 patients analyzed following a second injection of OZURDEX® (6-month open-label phase), the increase in IOP was similar to the increase that was seen following the first injection during initial 6-month randomized phase, and likewise returned to baseline by the end of the 6-month open-label phase. However, compared to the initial 6 months, the overall incidence of cataracts was higher after 1 year, compared to the initial 6 months with subcapsular cataract reported in 13% of patients.

The adverse event profile for BRVO patients was similar to that observed for CRVO patients. Although, the overall incidence of adverse events was higher for patients with CRVO (79.7%) than BRVO (69.1%), there was no indication that OZURDEX® was more frequently associated with the occurrence of AEs in patients with CRVO than in patients with BRVO. That is, the difference in percentage of patients with AEs (overall) between OZURDEX® and sham was approximately 19% for patients with CRVO, and 14% for those with BRVO.

Indication of Posterior Segment Uveitis

The following information in Table 2 is based on results from a 6-month randomized, sham-controlled study assessing the effects of a single OZURDEX® injection in the treatment of patients with posterior segment uveitis:

Table 2 Ocular adverse events reported by ≥ 2% of patients with OZURDEX®

MedDRA Preferred Term	**OZURDEX® N = 76**	**Sham N = 75**
Overall Ocular adverse events	57 (75.0%)	45 (60.0%)
IOP increased	19 (2**5.0**%)	5 (6.7%)
Conjunctival Haemorrhage	23 (**30.3**%)	16 (21.3%)
Ocular Discomfort	10 (**13.2**%)	6 (8.0%)
Eye Pain	9 (11.8%)	10 (13.3%)
Cataract	11 (14.5%)	8 (10.7%)
Iridocyclitis	7 (9.2%)	4 (5.3%)
Ocular Hypertension	6 (7.9%)	0
Myodesopsia	6 (7.9%)	5 (6.7%)
Uveitis	6 (7.9%)	7 (9.3%)
Vision Blurred	5 (6.6%)	3 (4.0%)
Conjunctival Hyperaemia	5 (6.6%)	7 (9.3%)
Blepharitis	3 (3.9%)	0
Vitreous Opacities	3 (3.9%)	1 (1.3%)
Intermediate Uveitis	3 (3.9%)	1 (1.3%)
Conjunctival Oedema	3 (3.9%)	3 (4.0%)
Eye Irritation	3 (3.9%)	3 (4.0%)
Eye Pruritus	3 (3.9%)	5 (6.7%)
Macular Oedema	3 (3.9%)	6 (8.0%)
Iritis	2 (2.6%)	0

MedDRA Preferred Term	OZURDEX® N = 76	Sham N = 75
Maculopathy	2 (2.6%)	0
Anterior Chamber Cell	2 (2.6%)	1 (1.3%)
Dry Eye	2 (2.6%)	1 (1.3%)
Photopsia	2 (2.6%)	1 (1.3%)
Scleral Hyperaemia	2 (2.6%)	1 (1.3%)
Visual Impairment	2 (2.6%)	1 (1.3%)
Abnormal sensation in eye	2 (2.6%)	0
Eyelids Pruritus	2 (2.6%)	0
Retinal Detachment	2 (2.6%)	2 (2.7%)

Rates of adverse events of increased IOP with OZURDEX® peaked at week 8 and IOP returned to baseline by week 26. During the treatment period, 25 patients treated with OZURDEX® experienced IOP increases ≥ 10 mm Hg, most of which were controlled with topical IOP-lowering medications. However, three patients with elevated IOP required laser iridotomies in the study eye (pupillary block, iris bombe, and raised IOP).

Cataract surgery was performed in one patient with OZURDEX®.

Indication of Diabetic Macular Edema

The following information in Table 3 is based on the clinical safety of OZURDEX® which was assessed in 2 phase 3 randomized, masked, sham-controlled studies in patients with diabetic macular edema. In both studies, a total of 347 patients were randomized and received OZURDEX® and 350 received sham.

Table 3 Summary of Adverse Reactions in Phase 3 Studies in ≥ 2% of Patients – 3 Year Studies

	OZURDEX® N = 347	Sham N = 350
Eye Disorders (Study Eye)		
Cataract	131 (37.8%)	34 (9.7%)
Cataract subcapsular	41 (11.8%)	12 (3.4%)
Cataract nuclear	18 (5.2%)	8 (2.3%)
Lenticular opacities	16 (4.6%)	4 (1.1%)
Intraocular pressure increased	107 (30.8%)	12 (3.4%)
Ocular hypertension	21 (6.1%)	5 (1.4%)
Conjunctival haemorrhage*	73 (21.0%)	45 (12.9%)
Vitreous haemorrhage*	24 (6.9%)	25 (7.1%)
Eye pain*	18 (5.2%)	13 (3.7%)
Vitreous detachment*	17 (4.9%)	8 (2.3%)
Vitreous floaters*	17 (4.9%)	7 (2.0%)
Conjunctival oedema*	15 (4.3%)	4 (1.1%)
Vitreous opacities*	11 (3.2%)	3 (0.9%)

Note: "*" indicates adverse drug reactions considered to be related to the intravitreal injection procedure.

Cataract and Intraocular Pressure

At baseline, the percentage of patients who had a phakic study eye was 75.5% (262/347) in the OZURDEX® group and 71.6% (249/348) in the sham group. Among those, 87% in the OZURDEX® group and 83.9% in the sham group had pre-existing lens opacification. The incidence of cataract (i.e., cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, lenticular opacities, cataract) in patients who had a phakic study eye was higher in the OZURDEX® group (67.9%) compared with sham (20.4%). 59.2% of patients who had a phakic study eye treated with OZURDEX® required cataract surgery compared to 7.2% of the sham-treated patients with the majority of cataract surgeries reported in the 2nd and 3rd years.

The mean time to cataract being reported as an adverse event was approximately 16 months in the OZURDEX® group and approximately 10 months in the sham group. In OZURDEX® treated patients with a phakic study eye at baseline, the visual acuity achieved prior to cataract was re-established upon removal of the cataract.

In the OZURDEX® group, the rate of the adverse event of increased IOP did not increase from year to year.

Mean IOP in the study eye at baseline was the same in both treatment groups (15.3 mm Hg). The mean increase from baseline did not exceed 3.2 mm Hg across all visits in the OZURDEX® group, with mean IOP peaking observed at the 1.5 month visit post injection, and returning to approximately baseline levels by month 6 following each injection.

27.7% (96/347) of patients in the OZURDEX® group, and 3.7% (13/350) patients in the sham group had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At month 6 after each treatment, ≤ 1% of patients in each group had a ≥ 10 mm Hg IOP increase from baseline.

6.6% (23/347) of patients in the OZURDEX® group, and 0.9% (3/350) patients in the sham group had IOP ≥ 35 mm Hg in the study eye at 1 or more visits during the study). At month 6 after each treatment, no more than 1 patient in each group had IOP ≥ 35 mm Hg.

Elevations of IOP were more prevalent in the OZURDEX® group than in the sham group. Overall, 3.5% of patients required IOP-lowering medication(s) at baseline. In total, the collective proportion of patients who were prescribed a topical IOP-lowering medication(s) at any given point in time during year 1 was 32.9%, decreasing to 29.5% and 28.7% throughout the study periods of year 2 and 3 respectively. Of the final visit study population, 21.5% had been prescribed IOP-lowering medication(s).

One patient in the OZURDEX® group required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation.

Three patients in the OZURDEX® group and one in the sham group had concurrent procedures in the study eye for the treatment of IOP elevation. One patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 2 patients had an iridectomy (1 OZURDEX® and 1 sham), and 1 had an iridotomy. No patient required removal of the implant by vitrectomy to control IOP.

In summary, in the OZURDEX® group, the incidence of elevated intraocular pressure adverse events did not increase over time, the magnitude of the IOP elevation following OZURDEX® treatment did not increase upon repeated injection, and the proportion of patients using IOP-lowering medications in the study eye remained similar from year to year. These data suggest that there is no cumulative effect of OZURDEX® on IOP.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Indication of Macular Edema due to CRVO

Adverse drug reactions observed at an incidence of <2% in the two controlled clinical trials are provided below:

Ocular: Retinal tear*, anterior chamber flare*, visual disturbance, photopsia*, conjunctival edema*, vitreous hemorrhage*, vitreous opacities* (including vitreous floaters), anterior chamber cell*.

* considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

Indication of Posterior Segment Uveitis

OZURDEX®-related sterile endophthalmitis was reported in one patient. One case for each of

the following events were reported in patients treated with OZURDEX®: visual acuity reduced, choroiditis, visual field defect, hypotony of the eye, eye swelling / edema / erythema, eyelid ptosis, conjunctivitis allergic, anterior chamber flare, medical device complication (clot around an end of the study medication implant), and periorbital haematoma.

Indication of Diabetic Macular Edema
Uncommon adverse reactions included anterior chamber inflammation (1.7%- injection procedure related), endophthalmitis (0.6% - injection procedure related), glaucoma (0.9%) and necrotizing retinitis (0.3%).

Post-Market Adverse Drug Reactions
Reports of pain on injection associated with what was considered to be a blunt needle have been received. Reports of endophthalmitis considered to be injection related have been received (See **WARNINGS AND PRECAUTIONS, Ophthalmologic**).

Serious cases of implants dislocation into the anterior chamber (with or without corneal edema) have been reported.

Failures to insert the implant correctly (misplaced implants) with complications have been reported. and may require eye surgery (cataract surgery) and to remove surgically the implant.

Several cases of temporary hypotony of the eye have been reported, some of which were serious.

Reports of serious ocular hypertension requiring surgery (including vitrectomy to remove the implant) have been reported.

One report of serious vitreous adhesions with foveal traction syndrome has been reported.

Several cases of retinal detachment have been reported, some of which were serious.

DRUG INTERACTIONS

Overview
Drug interaction studies have not been conducted with OZURDEX®.

Anti-coagulant therapy was used in 1.7% of patients with macular edema due to retinal vein occlusion; there were no reports of hemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX® (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). Anti-coagulant or anti-platelet therapy should not be used within two weeks before the injection of OZURDEX®. OZURDEX® should be used with great caution in patients taking anti-coagulant or anti-platelet medicinal products, and only if the

expected benefits outweigh the potential risks to the patient.

Systemic drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-administration with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

Plasma dexamethasone concentration following intravitreal administration of OZURDEX® is expected to be significantly lower (at or below the limit of detection) compared to oral and IV administration, and therefore, is not expected to result in significant drug-drug interaction systemically.

Drug-Food, Drug-Herb, Drug-Laboratory Interactions
Drug-Food, Drug-Herb, and Drug-Laboratory interactions were not studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations
FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY.

OZURDEX® must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Administration to both eyes concurrently is not recommended.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs.

Dosing of OZURDEX® (dexamethasone intravitreal implant 0.7 mg) is recommended when there is evidence of macular edema or vascular leakage in the macula.

Dosing of OZURDEX® is also recommended when there is evidence of non-infectious uveitis affecting the posterior segment of the eye.

OZURDEX® should not be used in patients with:

- active or suspected ocular or periocular infections (See **CONTRAINDICATIONS**).
- advanced glaucoma.
- aphakic eyes with rupture of the posterior lens capsule
- anterior chamber intraocular lens and rupture of the posterior lens capsule
- known hypersensitivity to any components of this product or to other corticosteroids.

Recommended Dose and Dosage Adjustment

The recommended dose for the treatment of macular edema following Central Retinal Vein Occlusion (CRVO) is one OZURDEX® implant (entire contents of one single use OZURDEX® 0.7 mg device).

The recommended dose for the treatment of adult patients with non-infectious uveitis of the posterior segment of the eye is 700 µg per eye (entire contents of single use OZURDEX® 0.7 mg device).

The recommended dose for the treatment of diabetic macular edema is 700 µg per eye (entire contents of single use OZURDEX® 0.7 mg device).

Reinjection of OZURDEX® for diabetic macular edema is recommended when there is a presence of macular edema (see **Clinical Studies**).

There is only very limited information on repeat dosing intervals less than 6 months (see CLINICAL TRIALS) and there is currently no experience of repeat administrations beyond 2 implants for CRVO and uveitis. Therefore, no more than two consecutive OZURDEX® injections should be used, and an interval of approximately 6 months should be allowed between the two injections.

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX®, should not be retreated.

Repeat doses should only be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk.

Missed Dose

Missed dose with OZURDEX® has not been reported in clinical trials and would not be expected due to its method of administration.

Administration

Single-use intravitreal implant in applicator for intravitreal use only. Each applicator can only be used for the treatment of a single eye.

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). Disinfection of the periocular skin, eyelid, and ocular surface (including drops of povidone iodine 5% solution on the conjunctiva) and administration of adequate local anesthesia and are recommended 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 redirected 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.

Immediately after injecting OZURDEX®, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualization is possible in the large majority of cases. In cases in which the implant cannot be visualized, take a sterile cotton applicator and lightly depress over the injection site to bring the implant into view.

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.

OVERDOSAGE

Overdose with OZURDEX® (dexamethasone intravitreal implant 0.7 mg) has not been reported in clinical trials and would not be expected due to its method of administration.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dexamethasone is a glucocorticoid receptor agonist. Although the mechanism of action of dexamethasone in ocular inflammatory disease is most likely due to its potent anti-inflammatory activity, the mechanism of action in the treatment of posterior segment diseases is not completely understood. However, dexamethasone has been reported to inhibit the expression of vascular endothelial growth factor (VEGF), a potent promoter of vascular permeability.

Pharmacodynamics

OZURDEX® is a biodegradable polymer matrix containing 700 µg micronized dexamethasone placed directly into the posterior segment of the eye with an applicator. The polymer degrades over time, gradually releasing dexamethasone directly to the vitreous, and therefore, OZURDEX® may reduce the potential for systemic effects compared with other routes of

administration.

Pharmacokinetics

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month RVO efficacy studies prior to dosing and on day 7, 30, 60, and 90 following the intravitreal implant containing 700 µg dexamethasone. Eighty-six percent of the plasma dexamethasone concentration values for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/mL). The highest plasma concentration value of 0.094 ng/mL was observed in one subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In the phase 3 DME studies, blood samples were obtained from a subgroup of patients at predose, days 1, 7, and 21, and months 1.5 and 3 to determine plasma dexamethasone concentrations. In both studies, the majority of concentrations were below the LLOQ of 0.05 ng/mL. Plasma dexamethasone concentrations from 5 of 52 samples in the OZURDEX® group and from 0 of 60 samples in the DEX 350 group were above the LLOQ, ranging from 0.0599 ng/mL to 0.102 ng/mL.

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.

STORAGE AND STABILITY

Store at controlled room temperature 15º -30º C and protected from excessive heat.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OZURDEX® (dexamethasone intravitreal implant 0.7 mg) is a biodegradable intravitreal implant containing 700 µg dexamethasone in a solid polymer drug delivery system. OZURDEX® is preloaded into a sterile, single-use, specially designed drug delivery system applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The polymer drug delivery system contains PLGA biodegradable polymer matrix (NOVADUR™): Resomer® RG 502, Poly (D,L-lactide-co-glycolide), 50:50 PLGA ester terminated; and Resomer® RG 502 H, Poly (D,L-lactide-co-glycolide),50:50 PLGA acid terminated. OZURDEX® is preservative-free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

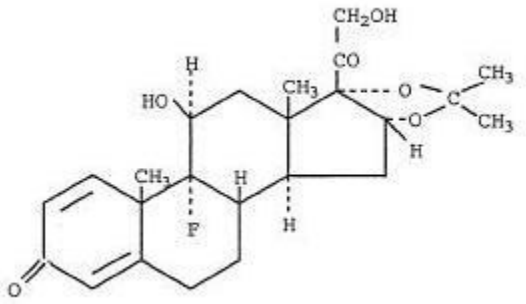
Drug Substance

Proper name: dexamethasone

Chemical name: pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydoxy-16-methyl-,(11β,16α)

Molecular formula and molecular mass: $C_{22}H_{29}FO_5$ and 392.47

Structural formula:



Physicochemical properties:	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.
Polymorphism:	Polymorph Form B.
Melting Range:	The anhydrous dexamethasone crystalline melts at a temperature range of 253-255ºC (onset).
Optical Rotation:	A one percent dexamethasone solution (m/V) in dioxane displays a specific rotation between +72º and +80º at 25ºC.

CLINICAL TRIALS

Study demographics and trial design

Indication of Macular Edema due to CRVO

Table 4 Summary of Patient Demographics for 2 Phase 3 Studies, 206207-008 and 206207-009

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
206207-008	Multicentre, masked, randomized, sham-controlled, parallel groups	OZURDEX® 0.7 mg and Dexamethasone 0.35 mg applicator system; and sham needleless applicator system Intravitreal injection 6-month masked initial treatment followed by 6-month open-label extension	n = 599 OZURDEX® 0.7 mg = 201 Dexamethasone 0.35 mg = 196 Sham = 202	65.5 years (32 to 91)	M 327 (54.6%) F 272 (45.4%)
206207-009	Multicentre, masked, randomized, sham-controlled, parallel groups	OZURDEX® 0.7 mg and Dexamethasone 0.35 mg applicator system; and sham needleless applicator system Intravitreal injection 6-month masked initial treatment followed by 6-month open-label extension	n = 668 OZURDEX® 0.7 mg = 226 Dexamethasone 0.35 mg = 218 Sham = 224	63.6 years (31 to 96)	M 350 (52.4%) F 318 (47.6%)

In two identical studies (study 206207-008 and study 206207-009), 1267 adult patients with either CRVO (approximately 1 third of the patients) or BRVO (approximately 2 thirds of the patients) were randomized to OZURDEX® 0.7 mg (n=427), or a Sham (n=426), or to a lower strength dexamethasone implant 0.35 mg (n=414).

The main selection criteria were: A duration of macular edema prior to baseline of 6 weeks to 9 months for CRVO patients and of 6 weeks to 12 months for BRVO patients, Best Corrected Visual Acuity (BCVA) score was between 34 and 68 letters (EDTRS), and Central retinal thickness ≥ 300 um by OCT. Note that patients with significant retinal ischemia were not allowed into the study.

After OZURDEX® injection, patients were monitored from initial treatment through to day 180 including scheduled visits on days 30, 60, 90, and 180.

At the end of the first 6-month period, patients were eligible to receive a second OZURDEX® implant in a 6 month open label extension if they had a BCVA < 84 letters, or a central retinal thickness > 250 µm.

Indication of Posterior Segment Uveitis

Table 5 Summary of patient demographics for 1 phase 3 Study, 206207-014

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
206207-014	Multicentre, masked, randomized, randomized patient and examiner-masked sham control	OZURDEX® and 350 µg applicator system; and sham needleless applicator system Intravitreal injection 8 weeks with an 18-week masked extension	OZURDEX® n = 77 DEX 350 = 76 Sham = 76	44.8 years (18 to 82)	M 84 (36.7%) F 145 (63.3%)

In a single, multicenter, masked, randomized study for the treatment of non-infectious uveitis affecting the posterior segment of the eye (study 206207-014), 229 adult patients were randomized to receive either OZURDEX® (N = 77), or Sham (N = 76), or a lower strength dexamethasone implant 0.35 mg (n=76). Most patients had intermediate uveitis (80%), and only 20% had posterior uveitis.

Inclusion criteria included a best-corrected (ETDRS) visual acuity score of 10 to 75 letters inclusive (Snellen equivalent approximately 20/640 – 20/32) in the study eye.

Main exclusion criteria were IOP > 21 mm Hg, ocular hypertension or glaucoma, use of anti glaucoma medications ≤ 4 weeks prior to treatment, periocular corticosteroid injections ≤ 8 weeks prior to treatment, intravitreal injections ≤ 26 weeks prior to treatment, previous use of Retisert™, and intraocular surgery ≤ 90 days prior to treatment. Other exclusion criteria included history of pars plana vitrectomy or herpetic infection, and presence of active ocular infection, or scleral thinning (or ectasia), uncontrolled systemic disease or HIV infection. Women who were pregnant, nursing, or planning a pregnancy, or who were of childbearing potential and not using contraception, were also excluded.

The primary efficacy analysis was the proportion of patients with vitreous haze score of 0 at

week 8 (primary time point). Other analyses included the proportion of patients with ≥ 15-letter visual score (BCVA) improvement, and the proportion of patients with ≥ 2-unit improvement from baseline in vitreous haze score.

The mean (range) age was 44.8 (18 to 82) years, and 8.3% were over the age of 65 years. The majority of patients were female (63.3%) and Caucasian (60.7%).

Indication of Diabetic Macular Edema (DME)

Table 6 Summary of Patient Demographics for 2 Phase 3 Studies, 206207-010 and 206207-011

Study #	Trial design	Dosage, route of administration and duration	# Patients by Arm Entered into ITT/ Completed	Mean age (Range)	Gender
206207-010	Multicentre, masked, randomized, sham-controlled	OZURDEX® 0.7 mg and Dexamethasone 0.35 mg applicator system; and sham needleless applicator system Intravitreal injection Up to 7 treatments during the 3-year study period	OZURDEX® 163/107 DEX 350 166/118 Sham 165/70	63.0 years (26 to 84)	**M** 304 (61.5%) **F** 190 (38.5%)
206207-011	Multicentre, masked, randomized, sham-controlled	OZURDEX® 0.7 mg and Dexamethasone 0.35 mg applicator system; and sham needleless applicator system Intravitreal injection Up to 7 treatments during the 3-year study period	OZURDEX® 188/118 DEX 350 181/112 Sham 185/82	61.9 years (25 to 88)	**M** 332 (59.9%) **F** 222 (40.1%)

The phase 3 studies included elements necessary for a valid ascertainment of the effectiveness of treatment. A parallel-group design minimized possible confounding effects that are inherent in other study designs (e.g., crossover). The studies were randomized and masked to minimize investigator and patient bias.

Patients were randomized in a 1:1:1 ratio to OZURDEX®, DEX 350, or sham on day 0, and received up to 7 treatments during the 3-year study period. Starting from the month 6 visit, patients were evaluated for retreatment eligibility every 3 months, but the study treatment

procedure was not to be performed more often than approximately every 6 months.

Patients who had confirmed 15 or more letters decrease in BCVA from baseline in the study eye attributable to macular edema (eg, not due to cataract or media opacity) were exited from the study at the investigator's discretion and considered to be a treatment failure. Patients who had received escape therapy in the study eye were considered to be study treatment failures, were no longer eligible to receive study medication, and were withdrawn from the study based on when they last received study treatment. A patient may have been withdrawn from the study at either the patient or the investigator's discretion at any point for any reason. Patients who underwent cataract surgery were to continue in the study.

Patients were masked to the study treatment assignment which was maintained for the duration of the trial. Study treatment procedures and postinsertion safety evaluations were performed by a treating investigator at each site. Follow-up investigators, site personnel including the visual acuity examiner, optical coherence tomography (OCT)/fluorescein angiography technicians, and evaluators at the central reading facility were masked, and had no knowledge of study treatment assignment.

Key inclusion criteria for the phase 3 studies were male or female, at least 18 years of age, diagnosis of diabetes mellitus (type 1 or type 2), blood HbA1c >10%, clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy, BCVA score between 34 and 68 letters in the study eye, and retinal thickness of ≥ 300 μm by OCT.

Further analyses were performed on 187 patients in the ITT population with a pseudophakic lens in the study eye at baseline; 86 in the DEX 700 group and 101 in the Sham group. The baseline characteristics of the pseudophakic subpopulation and the ITT population were generally similar, including mean BCVA (55.5 vs. 56.2 letters, respectively) and central retinal thickness (462.7 vs. 463.6 microns, respectively).

Study results

Indication of Macular Edema due to CRVO

Demographic and baseline characteristics were not significantly different among the treatment groups. Approximately 50% of patients were over 65, and 75% were Caucasian. For the majority of patients, the duration of macular edema was between 90 and 179 days, with 17% of patients with durations less than 90 days.

The efficacy of OZURDEX® was assessed based on patients treated with OZURDEX® (N=427) as compared to sham (N=426), using the study eye and the ITT population (with Last Observation Carried Forward for missing values). Efficacy analyses were performed separately for CRVO patients and BRVO patients, Among 570 patients with macular edema (ME) due to BRVO, 291 were randomized to OZURDEX®, and 279 to sham, and among 283 patients with ME due to CRVO, 136 were randomized to OZURDEX®, and 147 to sham.

The treatment benefits of OZURDEX® were larger in patients with macular edema due to

CRVO, as compared to those with BRVO. Only results in CRVO patients are presented below.

OZURDEX® injection showed a statistically significantly greater proportion of patients achieving a ≥ 15-letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at day 30, and 60.

Table 7 Proportion of Patients with ≥15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, CRVO Study Population)

Visit	OZURDEX® N = 136	Sham N = 147	Difference
Day 30	21.3% *	6.8%	14.5%
Day 60	28.7% *	8.8%	19.8%
Day 90	17.6%	10.2%	7.4%
Day 180	18.4%	12.2%	6.1%

* Proportion significantly higher with OZURDEX® compared to sham ($p < 0.001$)

The proportion of patients with vision loss from baseline of ≥ 15-letter in BCVA was smaller with OZURDEX® as compared to sham (maximum difference of 7.2% at day 60).

Table 8 Proportion of Patients with ≥15-letter Vision Loss from Baseline BCVA (Pooled, CRVO Study Population)

Visit	OZURDEX® N = 136	Sham N = 147	Difference
Day 30	3.7%	6.8%	**-3.1%**
Day 60	3.7%*	10.9%	**-7.2%**
Day 90	8.1%	13.6%	**-5.5%**
Day 180	14.0%	20.4%	**-6.4%**

* Proportion statistically significantly lower with OZURDEX® compared to sham ($p \leq 0.02$)

The mean change from baseline BCVA was statistically significantly greater with OZURDEX® compared to sham up to day 90. The improvements peaked at day 60 with a difference among groups of 9.3 letters (Table 9) in favour of OZURDEX® as compared to the sham.

Table 9 Baseline and Mean Change from Baseline in Number of Letters Read Correctly (Pooled, CRVO Study Population)

	OZURDEX® N=136	Sham N=147	Difference
Baseline	52.4	53.3	-
Change from baseline			
Day 30	7.2*	0.4	**6.9**
Day 60	8.7*	-0.5	**9.3**
Day 90	4.2*	-0.4	**4.6**
Day 180	0.1	-1.8	**1.9**

* Mean change from baseline statistically significantly greater with OZURDEX® compared to sham ($p \leq 0.005$)

Indication of Posterior Segment Uveitis

The efficacy of a single injection of OZURDEX® was assessed in a 6-month single, multicenter, masked, randomized study for the treatment of non-infectious uveitis affecting the posterior segment of the eye (study 206207-014).

Approximately 80% of patients had intermediate uveitis and 20% posterior uveitis. At baseline, 83% of patients had a vitreal haze score of +1.5 to 2, and 17% a score of +3 or +4. Over 40% of patients in each treatment group had received medications for the treatment of ocular inflammation in the study eye prior to the trial.

The efficacy analysis using the ITT population (with Last Observation Carried Forward for missing values), showed that 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) and persisting through week 26. Additionally, the proportion of patients showing ≥2-unit improvement from baseline in vitreous haze score, and the proportion of patients with ≥15 letters improvement from baseline in best-corrected visual acuity (BCVA) were statistically significantly higher with OZURDEX® compared to sham throughout the 26-week period (Table 10).

Table 10 Comparison of Efficacy Results for OZURDEX® (N=77) vs. Sham (N=76) / p-value*

	Primary efficacy endpoint	Secondary efficacy endpoints	
Study Week	**Percent of patients with vitreous haze score of 0**	**Percent of patients with ≥ 15-letter improvement in BCVA from baseline**	**Percent of patients with ≥ 2-unit improvement from baseline in vitreous haze score**
Week 3	23% vs. 12% 0.061	33% vs. 4% < 0.001	21% vs.8% 0.023
Week 6	43% vs. 9% < 0.001	42% vs. 8% < 0.001	40% vs. 12% < 0.001
Week 8	47% vs. 12% < 0.001	43% vs. 7% < 0.001	44% vs. 12% < 0.001
Week 12	46% vs. 13% < 0.001	42% vs. 13% < 0.001	42% vs. 13% < 0.001
Week 16	40% vs. 21% 0.01	39% vs. 13% < 0.001	40% vs. 17% 0.002
Week 20	39% vs. 20% 0.009	40% vs. 13% < 0.001	42% vs. 15% < 0.001
Week 26	31% vs. 15% 0.014	38% vs. 13% < 0.001	34% vs. 12% 0.001

*p-values were based on Pearson's chi-square test or Fisher's exact test.

Indication of Diabetic Macular Edema (DME)

The clinical efficacy of OZURDEX® was assessed in 2 phase 3 randomized, masked, sham-controlled studies (Studies 206207-010 and 206207-011) in patients with diabetic macular edema. A total of 1,048 patients (351 OZURDEX®, 347 DEX 350, and 350 sham) were evaluated as the ITT population and received up to 7 treatments during the 3-year study period.

A clinical benefit was established in these two studies in the ITT population. In patients with a phakic study eye, however, vision improvement was confounded by cataract formation or progression which occurred on average during the 2nd year of the study and was not reestablished until the cataract was removed. The group which benefited from OZURDEX® treatment the most were patients who were pseudophakic at baseline, and therefore, only the results in this patient population are presented below.

In the pooled subgroup of patients with a pseudophakic study eye at baseline, the proportion of patients with 15 or more letters improvement in BCVA from baseline was significantly higher with DEX 700 (23.3%) compared with Sham (10.9%) at the year 3/final visit, p = 0.024.

The mean BCVA average change from baseline during the study (AUC approach) was significantly greater with DEX 700 (6.5 letters) compared to Sham (1.7 letters), p < 0.001.

The mean average decrease from baseline in OCT central subfield retinal thickness during the study (AUC approach) was significantly greater with DEX 700 (131.8 µm) compared to Sham (50.8 µm), $p < 0.001$.

The efficacy results for the pseudophakic patients subgroup by study and pooled analyses are presented in Table 11 below.

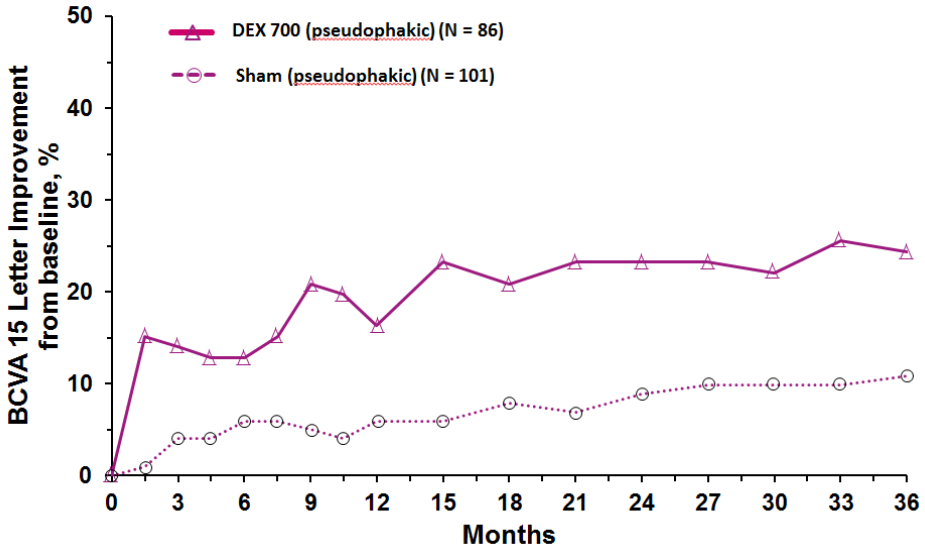
Table 11 Efficacy in Pseudophakic Patients (Studies 206207-010, 206207-011, and Pooled Analyses)

	Study 206206-010		Study 206206-011		Pooled Studies -010 and -011	
Endpoint	DEX 700 (N = 44)	Sham (N = 50)	DEX 700 (N = 42)	Sham (N = 51)	DEX 700 (N = 86)	Sham (N = 101)
BCVA ≥ 15-letter improvement from baseline at year 3/final visit (%)	34.1	16.0	11.9	5.9	23.3	10.9
P-value	0.042		0.461		0.024	
Mean BCVA average change over 3 years, AUC approach (letters)	8.1	2.1	4.9	1.3	6.5	1.7
P-value	< 0.001		0.018		< 0.001	
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-137.4	-43.3	-125.9	-58.3	-131.8	-50.8
P-value	< 0.001		0.007		< 0.001	

AUC = area under the curve; BCVA = best-corrected visual acuity; OCT = optical coherence tomography

Source: CSR 206207-010, Tables 14.5-14.2, 14.5-14.4, and 14.2-10.9, CSR 206207-011, Tables 14.5-14.2, 14.5-14.4, and 14.2-10.9; Module 5.3.5.3, ISE Tables 2-209.2, 2-209.4, and 2-5.7

Figure 1 **Proportion of Patients With 15 or More Letters Improvement in BCVA From Baseline by Visit (Pooled Studies 206027-010 and 206207-011, Pseudophakic Patient Subpopulation)**



DETAILED PHARMACOLOGY

Pharmacodynamics

The OZURDEX® implant is a biodegradable polymer matrix containing micronized dexamethasone, a potent glucocorticoid which is the pharmacologically-active component of OZURDEX®. It is administered to the vitreous cavity via the OZURDEX® Applicator system, where it is released from the polymer matrix and is available within the vitreous to diffuse to retinal target cells and bind with high affinity to the glucocorticoid receptor. The end result is the upregulation or down-regulation of multiple proteins, many of which are responsible for the potent anti-inflammatory and immunosuppressant properties of dexamethasone.

Vascular endothelial growth factor (VEGF) is a vasoactive cytokine that has been linked to macular edema and that promotes the breakdown of the blood-retinal and blood-aqueous barriers. Glucocorticoids, such as dexamethasone and triamcinolone acetonide, were shown to suppress the expression of VEGF protein.

Pharmacokinetics

In a 6 month monkey study following a single intravitreal injection of OZURDEX® the dexamethasone vitreous humor C_{max} was 100 ng/mL at day 42 post-injection and 5.57ng/mL at day 91. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humor > aqueous humor > plasma.

In an *in vitro* melanin binding study, dexamethasone did not demonstrate any significant binding to synthetic melanin. In an *in vitro* metabolism study, following the incubation of [^{14}C]-

dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed.

TOXICOLOGY

No mutagenicity, carcinogenicity, reproductive or developmental toxicity studies are available for OZURDEX®.

Five toxicology studies were performed with for the assessment of the toxicity of OZURDEX®. Three were single-dose toxicity studies in New Zealand White (NZW) rabbits (two studies with duration of 7 weeks (X7I062G and X8I310G) and one with a duration of 9 month (P0701002)). In addition, two 9-month repeat-dose studies were performed (one in NZW rabbits (TX05030), and one in Cynomolgus monkeys (TX05029)).

Lens opacities were noted in the 9-month rabbit study (Study TX05030), but were not observed in any of the other studies. In all the studies, there were no significant or unexpected other drug-related ocular adverse effects.

In one rabbit study (Study P0701002) transient systemic effects were noted: decrease in body weight, lymphoid depletion (thymus, cecal tonsils and spleen), hepatocellular swelling and degeneration, atrophy of the adrenal glands, increases in serum levels of alkaline phosphatase, alanine aminotransferase, and cholesterol. Changes in serum levels of creatinine, total protein, and globulin levels were also noted. No systemic effects were noted in the other toxicity studies. Note that these effects were transient and reversible after day 60 or 90.

Carcinogenicity

No carcinogenicity studies on OZURDEX® or dexamethasone have been performed.

Mutagenicity

No studies of the mutagenic potential of OZURDEX® have been conducted. Studies evaluating the mutagenic potential of dexamethasone in bacteria and mammalian cells in vitro have been negative. An in vivo mouse micronucleus test was also negative. The polymer used in OZURDEX® has been widely used in implantable medical devices.

Reproductive and Developmental Toxicity

No studies of the reproductive or developmental toxicity are available for OZURDEX®.

Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application. In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc. Pregnant rhesus monkeys treated with dexamethasone sodium phosphate intramuscularly at 1.0 mg/kg/day every other day for 28 days or at 10.0 mg/kg/day once or every other day on 3 or 5 days between gestation Days 23 and 49 had fetuses with findings limited to minor cranial abnormalities. A

1.0 mg/kg/day dose in pregnant rhesus monkeys would be approximately 85 times higher than a 700 µg DEX PS DDS® implant in humans (assuming 60 kg body weight).

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PART III: CONSUMER INFORMATION

PrOZURDEX®
dexamethasone

This leaflet is part III of a three-part "Product Monograph" published when OZURDEX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OZURDEX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
OZURDEX® is used to treat vision loss caused by a blockage of veins in the eye. This blockage leads to a build up of fluid causing swelling in the area of the retina (the light-sensitive layer at the back of the eye) called the macula. The swelling may lead to damage to the macula which affects your central vision which is used for tasks like reading.

OZURDEX® is used to treat non-infectious uveitis of the posterior segment of the eye (inflammation of the uvea - back part of the eye). This inflammation leads to a decrease of vision and/or the presence of floaters in the eye, (black dots or wispy lines that move across the field of vision).

Vision loss due to diabetic macular edema (DME), if you have already had an operation for cataract.
Diabetic macular edema is a swelling of the light-sensitive layer at the back of the eye called the macula. DME is a condition that affects some people with diabetes.

What it does:
OZURDEX® works by reducing swelling of the macula which helps to lessen or prevent more damage to the macula.

OZURDEX® also works by reducing the inflammation of the back of the eye.

When it should not be used:
- if you are allergic (hypersensitive) to dexamethasone or any of the other ingredients of OZURDEX®
- if you have an infection of any kind in or around your eye (bacterial, viral or fungal)
- if you have glaucoma or high pressure inside your eye which is not controlled properly with the medicines you may be taking
- if you have aphakic eyes (eyes without natural or artificial lens) with rupture in posterior lens capsule or you have anterior chamber intraocular lens and rupture of the posterior lens capsule.

Ask your doctor if you are not sure if you have these conditions.

What the medicinal ingredient is:
The active substance in OZURDEX® is dexamethasone. Dexamethasone belongs to a group of medicines called corticosteroids. Each implant contains 700 micrograms of dexamethasone.

What the important nonmedicinal ingredients are:
The only nonmedicinal ingredient in OZURDEX® is a hair-like biodegradable polymer called Resomer®.

What dosage forms it comes in:
OZURDEX® is a small implant given by injection under local anaesthetic into the back of the eye by your eye doctor. OZURDEX® is supplied in a pack with the implant already inside a specially-designed applicator which will be used once and then thrown away.

WARNINGS AND PRECAUTIONS

Before the use of OZURDEX®, talk to your doctor or pharmacist if:
- you have any infection inside or around the eye.
- you have had a herpes simplex infection in your eye before (an ulcer on the eye that has been there a long time, or sores on the eye).
- you are taking any medication to thin the blood or any other medication (See Interactions with This Medication)
- you are pregnant or planning to become pregnant
- you are breast feeding or planning to breast feed
- you had recent eye surgery, or plan to have one
- you're allergic to any of the ingredients in OZURDEX® or to other corticosteroids
- if you had a cataract surgery

After the use of OZURDEX®, occasionally the following may occur or get worse after OZURDEX® treatment:
- an infection inside or around the eye,
- redness (inflammation) inside the eye
- glaucoma and/or increased pressure in the eye,
- detachment of the layer in the back of the eye (retinal detachment), or
- clouding of the lens (cataract),
- misplacement of implant requiring surgical intervention.

It is important to identify and treat these conditions as soon as possible. Please tell your doctor immediately if you have any concerns with your eye or experience the following signs:
- Blurred or decreased vision
- Eye pain or increased discomfort
- Worsening eye redness
- A feeling of spots in front of the eye (called 'floaters')
- Increased sensitivity to light

In some patients the pressure in the eye may increase for a short period straight after the injection. This is something you may not notice, so your doctor might monitor this after your injection.

Children and adolescent (below 18 years of age):
The use of OZURDEX® in children and adolescents is not recommended.

Pregnancy and breast-feeding:
If you are pregnant or planning to become pregnant, or if you are breast-feeding or planning to breast-feed, please discuss this with your doctor before OZURDEX® treatment. Always ask your doctor for advice before taking any medicine.

Driving and using machines:
After OZURDEX® treatment you may experience some blurred vision for a short time. If this happens, do not drive or use any tools or machines until it has gone.

INTERACTIONS WITH THIS MEDICATION

Ask your doctor for advice if you are taking any medicine, including blood thinners, barbiturates, phenytoin, carbamazepine, rifampin, ketoconazole, erythromycin and indinavir.

No interaction studies have been performed.

PROPER USE OF THIS MEDICATION

Usual adult dose:
The OZURDEX® injection will be given by your doctor.

The usual dose is one implant to be given by injection into your eye. Six months after the injection, and depending on the effect of OZURDEX®, your doctor may or may not want to give you a subsequent OZURDEX® injection if in the doctor's opinion you may benefit from retreatment without being exposed to significant risk.

No more than two consecutive OZURDEX® injections should be used, and an interval of approximately 6 months should be allowed between the two injections.

Your doctor may ask you to use antibiotic eye drops regularly for a number of days before and/or after each injection to prevent any eye infection. Please follow these instructions carefully.

On the day of the injection, your doctor may use antibiotic eye drops and give you a local anaesthetic to reduce or prevent any pain. You may hear a 'click' during the injection of OZURDEX®; this is normal.

Consult your doctor for the appropriate time to re-insert contact lenses following the OZURDEX® injection.

There are detailed instructions for your doctor on how to carry out the OZURDEX® injection at the end of this leaflet.

Overdose:
No case of overdose has been reported.

Missed Dose:
If you miss your appointment to receive OZURDEX®, contact your doctor or hospital as soon as possible to reschedule your appointment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very common	Occurs in more than 1 out of 10 patients
Common	Occurs in between 1 and 10 out of every 100 patients
Uncommon	Occurs in between 1 and 10 out of every 1,000 patients

The following side effects may be seen with OZURDEX® when used to treat swelling of the light-sensitive layer at the back of the eye (i.e. macula, part of the retina):
Very common:
- Increased pressure in the eye
- Bleeding on the surface of the eye

Common:
- Clouding of the lens (cataract), which may sometimes require surgery
- Glaucoma and/or high pressure in the eye (high intraocular pressure)
- Detachment of the jelly inside the eye from the light-sensitive layer at the back of the eye (vitreous detachment)
- Bleeding into the inside of the eye
- Vision blurred or decreased (difficulties in seeing clearly)
- A feeling of spots in front of the eye (including 'floaters')
- Eye pain
- Seeing flashes of light
- Swelling on the surface of the eye
- A feeling of looking through mist or fog
- Redness of the eye

Uncommon:
- Tear of the light-sensitive layer at the back of the eye (retinal tear)
- Increased protein in the front of the eye due to inflammation (anterior chamber flare)
- Headache

The following side effects may be seen with OZURDEX® when used to treat inflammation of the back of the eye (i.e. uvea, uveitis):

Very common:
- High pressure in the eye
- Clouding of the lens (cataract)

Common:
- Abnormal feeling in the eye
- Inflammation and itchiness of the eyelid
- Redness of the white of the eye
- Difficulties in seeing clearly
- A feeling of spots in front of the eye (including 'floaters')
- Migraine

The following side effects may be seen with OZURDEX® when used to diabetic macular edema (DME):

Very common:
- Increased pressure in the eye
- Clouding of the lens (cataract)
- Bleeding on the surface of the eye*

Common:
- High pressure in the eye
- Bleeding into the inside of the eye*
- Detachment of the jelly inside the eye from the light-sensitive layer at the back of the eye (vitreous detachment)
- A feeling of spots in front of the eye (including 'floaters')*
- A feeling of looking through mist or fog*
- Eye pain*
- Swelling on the surface of the eye*

Uncommon:
- A severe inflammation at the back of the eye (usually due to viral infection)
- Inflammation inside the eye
- Glaucoma

**Some of these side effects may be caused by the injection procedure and not the OZURDEX implant itself*

The following adverse events were reported after OZURDEX® was marketed: implant migration, low eye pressure and infection inside the eye.

Some of these side effects may be caused by the injection procedure and not the OZURDEX® implant itself.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

This is not a complete list of side effects. For any unexpected effects while taking OZURDEX®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use OZURDEX® after the expiry date which is stated on the carton and the pouch after EXP:. The expiry date refers to the last day of that month.

Store at controlled room temperature 15º -30º C and protected from excessive heat.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Allergan Inc., at: 1-800-668-6424.

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