Allergan

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)

----------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), for the treatment of non-infectious uveitis affecting the posterior segment of the eye, and for the treatment of patients with visual impairment due to diabetic macular edema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. (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)

• Aphakic eyes with ruptured posterior lens capsule. (4.3)

• Eyes with ACIOL, iris or transscleral fixated IOLs and rupture of the posterior lens capsule. (4.4)

• Hypersensitivity. (4.5)

----------WARNINGS AND PRECAUTIONS----------

• Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, retinal detachments, and implant migration into the anterior chamber. Patients should be monitored following the injection. (5.1)

• Patients who had a tear in the posterior lens capsule (e.g., due to cataract surgery), or who had an iris opening to the vitreous cavity (e.g., due to iridectomy) are at risk of implant migration into the anterior chamber. (5.2)

• 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. Visual disturbance may be reported with systemic and topical corticosteroid use. (5.3)

• Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex. (5.4)

----------ADVERSE REACTIONS----------

In controlled studies, the most common adverse reactions reported by 20-70% of patients were cataract, increased intraocular pressure and conjunctival haemorrhage. (7.1)

See 15 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS

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).

OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

OZURDEX® (dexamethasone intravitreal implant) is indicated for the treatment of patients with visual impairment due to diabetic macular edema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection only. The recommended dose is one **OZURDEX®** implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended.

In DME, retreatment may be performed after approximately 6 months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular edema.

There is currently no experience of the efficacy or safety of repeat administrations in DME beyond 7 implants.

There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

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). Disinfection of the periocular skin, eyelid, and ocular surface (for example, drops of povidone iodine 5% solution on the conjunctiva) and administration of adequate local 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.

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 Aphakic eyes with ruptured posterior lens capsule

OZURDEX® is contraindicated in aphakic eyes with ruptured posterior lens capsule.

4.4 Eyes with ACIOL, iris or transscleral fixated IOLs and ruptured posterior lens capsule

OZURDEX® is contraindicated in eyes with ACIOL (Anterior Chamber Intraocular Lens), iris or transscleral fixated IOLs and ruptured posterior lens capsule.

4.5 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

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

• In RVO, anti-coagulant therapy was used in 2% of patients receiving **OZURDEX®**; there were no reports of hemorrhagic adverse events in these patients. In DME, anti-coagulant therapy was used in 8% of patients. Among patients who used anti-coagulant therapy, the frequency of haemorrhagic adverse events was similar in the **OZURDEX®** and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of **OZURDEX®** treated patients reported haemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with **OZURDEX®** who received anti-coagulant therapy (11%) compared with those not receiving anticoagulant therapy (6%).

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 antiplatelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with **OZURDEX®** (up to 29%) compared with the control group (up to 23%), irrespective of indication or number of treatments. The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%).

OZURDEX® should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

5.1 Intravitreal Injection-related Effects

Intravitreal injections, including those with **OZURDEX®**, have been associated with endophthalmitis, introcular inflammation, increased intraocular pressure, and retinal detachment. Proper aseptic injection techniques must always be used.

In addition, patients should be monitored regularly following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay. **(see PATIENT COUNSELING INFORMATION, 15**)

5.2 Risk of Implant Migration

Patients who had a tear in the posterior lens capsule (e.g., due to cataract surgery), or who had an iris opening to the vitreous cavity (e.g., due to iridectomy) are at risk of implant migration into the anterior chamber. Implant migration to the anterior chamber might lead to corneal edema. Persistent severe corneal edema could progress to the need of corneal transplantation. Regular monitoring of such patients allows for early diagnosis of device migration.

5.3 Potential Steroid-related Effects

Use of corticosteroids, including those with **OZURDEX®**, have been associated with 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.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

5.4 Ocular Herpes Simplex

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 DRUG INTERACTIONS

No interaction studies have been performed.

7 ADVERSE REACTIONS

7.1 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.

Treatment of Macular Edema following BRVO or CRVO

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.

Table 1: Adverse reactions reported in ≥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%)
Vitreous hemorrhage	10 (2%)	12 (3%)
Conjunctival edema	9 (2%)	7 (2%)

Cataract and Intraocular Pressure in Studies

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 compared with 0.2% (1/423) with sham.

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

Systemic effects with **OZURDEX®** would be expected to be negligible due to low systemic levels (below the lower level of quantitation). The adverse event profile for BRVO patients was generally similar to that observed for CRVO patients, and to the overall population. The overall incidence of adverse events was higher for the subgroup of patients with CRVO, which is consistent with the nature of the disease as patients with CRVO are more likely to develop ocular adverse events than patients with BRVO, even when not treated

The clinical safety of **OZURDEX®** was further assessed in a 6-month open-label (OL) extension of both the two phase 3 studies.

For those events reported at a rate of ≥ 1%, the types of events and their incidence following the second injection were similar to those seen following the first injection with the exception of subcapsular cataract which were higher in patients who had received **OZURDEX®** as their first injection followed by **OZURDEX®** as the second injection. For events reported in ≤ 1% of patients, mostly in only 1 or 2 patients per group, some differences between the first and second injection were seen. Review of these differences does not suggest a safety signal associated with repeat treatments

CONSTANCE 206207-025 (24-Month Post Approval Observational Study)

The clinical safety of DEX 700 was assessed in a multicenter, 24-month real world observational study in the treatment of macular edema following RVO and non-infectious uveitis affecting the posterior segment of the eye. The most frequent adverse reactions observed in this study were consistent with the most frequent adverse reactions from clinical trials. Stratifications by injection frequency revealed increases in the incidence of adverse reactions among patients who received >2 injections compared to patients who received ≤2 injections. The most frequent adverse reactions for patients who received >2 injections included cataract [(24.7%, 44/178) for cataract formation and (32.0%, 57/178) for cataract progression] based on eyes with phakic lens status at baseline, vitreous hemorrhage (6.0%, 17/283), and increased IOP (24.0%, 68/283) **.**

Treatment of Uveitis

The clinical safety of **OZURDEX®** was assessed in a multi-center, masked, and randomized, 26-week phase 3 study in the treatment of non-infectious uveitis affecting the posterior segment of the eye. A total of 76 patients were treated with **OZURDEX®** and 75 were treated with sham.

Table 2: Adverse reactions reported by greater than 2% of patients in a Phase 3 Study

	OZURDEX® **N = 76**	**Sham** **N = 75**
Eye Disorders (Study Eye)		
Conjunctival haemorrhage*	23 (30%)	13 (21%)
Intraocular pressure increased	19 (25%)	5 (7%)
Ocular discomfort*	10 (13%)	6 (8%)
Cataract	9 (12%)	4 (5%)
Myodesopsia	6 (8%)	5 (7%)
Vitreous opacities	3 (4%)	1 (1.3%)
Scleral hyperaemia	2 (3%)	1 (1%)
Visual impairment	2 (3%)	1 (1%)
Abnormal sensation in eye	2 (3%)	0 (0%)
Eyelids pruritis	2 (2.6%)	0 (0%)
Nervous System Disorders		
Migraine	2 (3%)	0 (0%)

***injection-related**

The proportion of **OZURDEX®**-treated patients with increased IOP (≥ 25 mm Hg) peaked at week 3 and returned to baseline by week 26. During the treatment period, no patients required incisional surgery for glaucoma. Three patients required laser iridotomies in the study eye for the treatment of pupillary block, iris bombe, and raised IOP.

CONSTANCE 206207-025 (24-Month Post Approval Observational Study)

Refer to CONSTANCE Study Results under RVO.

Treatment of Diabetic Macular Edema

The clinical safety of **OZURDEX®** 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 ≥ 1% 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 edema*	15 (4.3%)	4 (1.1%)
Vitreous opacities*	11 (3.2%)	3 (0.9%)
Anterior chamber inflammation*	6 (1.7%)	0 (0.0%)
Visual acuity reduced	29 (8.4%)	14 (4.0%)

* Adverse drug reactions considered to be related to the intravitreal injection procedure

Uncommon adverse reactions included endophthalmitis (0.6% - injection procedure related), glaucoma (0.9%) and necrotizing retinitis (0.3%).

Cataract and Intraocular Pressure in Studies

At baseline, the percentage of patients who had a phakic study eye was 75.5% (262/347) in the **OZURDEX®** group and 71.8% (250/348) 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 (ie. 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.

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.

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.

7.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of **OZURDEX®** in clinical practice. Because postmarketing reporting of these reactions is voluntary and from a population

of uncertain size, it is not always possible to reliably estimate the frequency of these reactions. The reactions have been chosen for inclusion due to a combination of the frequency of reporting and/or possible causal connection to **OZURDEX®**.

Eye disorders: Endophthalmitis, hypotony of eye (associated with vitreous leakage due to injection), Retinal detachment, Vision, blurred.

General disorders and administration site conditions: Complication of device insertion resulting in ocular tissue injury (implant misplacement).

Device dislocation with or without corneal edema (drug implant migration).

8 OVERDOSE

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

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Safety for use in pregnancy and lactation has not been established. There are no adequate data from the use of dexamethasone in pregnant women. 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 an **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.

9.2 Nursing Mothers

It is not known whether ocular administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Low level dexamethasone systemic exposure was detected following intraocular implantation of **OZURDEX®** in non-pregnant rabbits and monkeys. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. **OZURDEX®** should not be used during lactation unless clearly necessary.

9.3 Pediatric Use

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

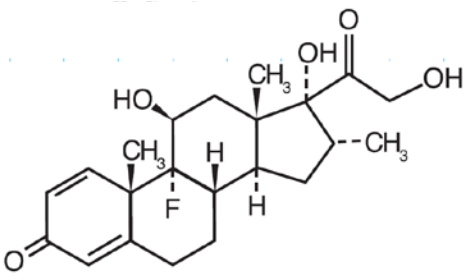
9.4 Geriatric Use

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

10 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-trihydoxy-16-methyl-,(11β,16α). Its structural formula is: MW 392.47; molecular formula: $C_{22}H_{29}FO_5$.



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

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

Contains: Active: dexamethasone 700 μg; **Inactives:** 50:50 PLGA ester; 50:50 PLGA acid.

11 CLINICAL PHARMACOLOGY

11.1 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.

11.2 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 0.35 mg or 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 (RVO:10 of 73 samples in the 0.7 mg dose group and 2 of 42 samples in the 0.35 mg dose group; DME: 5 of 52 samples in 0.7mg dose group and 0 of 60 samples in 0.35mg dose group) were above the LLOQ, ranging from 52 pg/mL to 102 pg/mL. The highest plasma concentration value of 94 pg/ mL was observed in one subject from the RVO 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 [^{14}C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humor, and sclera tissues for 18 hours, no metabolites were observed.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Adequate fertility studies have not been conducted in animals.

13 CLINICAL STUDIES

Macular Edema following BRVO or CRVO

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):

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

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

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

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

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

Uveitis

The clinical efficacy of **OZURDEX®** was assessed in a phase 3 randomized, masked, sham-controlled study assessing in the treatment of non-infectious ocular inflammation of the posterior segment in patients with intermediate or posterior uveitis. A total of 225 patients were randomized and evaluated as the ITT population.

In the study, eligible patients were ≥ 18 years of age and were diagnosed with non-infectious intermediate or posterior uveitis in at least one eye. Each patient received **OZURDEX®**, or sham on day 0 and was monitored through week 26.

The primary efficacy endpoint was the proportion of patients with vitreous haze score of 0 in the study eye at week 8 (primary time point) to week 26. Vitreous haze was graded by assigning scores ranging from 0 = no inflammation to +4 = optic nerve head not visible.

Secondary efficacy endpoints included the proportion of patients with a ≥ 1-unit improvement in vitreous haze and patients demonstrating at least 15 letters improvement from baseline BCVA throughout the 26-week period.

As presented in table below, after a single injection, the percent of patients reaching a vitreous haze score of 0 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 at least a 1-unit improvement from baseline in vitreous haze score and demonstrating at least 15 letters improvement from baseline in BCVA was statistically significantly higher with **OZURDEX®** compared to sham throughout the 26-week period. The onset of a ≥ 15-letter improvement in BCVA with **OZURDEX®** occurred by week 3 after implantation in approximately 33% of subjects and the duration of effect persisted through 26 weeks of the study.

Table 5: Comparison of Efficacy Results for OZURDEX® (N = 77) vs. Sham (N = 76) / p-value*

Study Week	Efficacy Endpoint		
	Percent of Patients with Vitreous Haze Score = 0	**Percent of Patients with ≥ 1-unit Improvement in Vitreous Haze Score from Baseline**	**Percent of Patients with ≥ 15-letter Improvement in BCVA from Baseline**
Week 3	23% vs. 12% 0.061	70% vs. 37% < 0.001	33% vs. 4% < 0.001
Week 6	43% vs. 9% < 0.001	91% vs. 46% < 0.001	42% vs. 8% < 0.001
Week 8	47% vs. 12% < 0.001	95% vs. 45% < 0.001	43% vs. 7% < 0.001
Week 12	46% vs. 13% < 0.001	91% vs. 53% < 0.001	42%vs. 13% < 0.001
Week 16	40% vs. 21% 0.010	87% vs. 54% < 0.001	39% vs. 13% < 0.001
Week 20	39% vs. 20% 0.009	86% vs. 51% < 0.001	40% vs. 13% < 0.001
Week 26	31% vs. 15% 0.014	82% vs. 51% < 0.001	38% vs. 13% < 0.001

* P-values were based on Pearson's chi-square test or Fischer's exact test.

Diabetic Macular Edema

The efficacy of **OZURDEX®** was assessed in two 3 year, multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,048 patients (studies 206207-010 and 206207-011). A total of 351 were randomised to **OZURDEX®**, 347 to dexamethasone 350 µg and 350 patients to sham.

Patients were eligible for retreatment based upon central subfield retinal thickness >175 microns by optical coherence tomography (OCT) or upon investigators interpretation of the OCT for any evidence of residual retinal edema consisting of intraretinal cysts or any regions of increased retinal thickening within or outside of the central subfield. Patients received up to 7 treatments at intervals no more frequently than approximately every 6 months.

Escape therapy was permitted at the investigators discretion at any stage but led to subsequent withdrawal from the studies.

A total of 36% of **OZURDEX®** treated patients discontinued study participation for any reason during the study compared with 57% of sham patients. Discontinuation rates due to adverse events were similar across treatment and sham groups (13% vs 11%). Discontinuation due to lack of efficacy was lower in the **OZURDEX®** group compared to sham (7% vs 24%).

The primary and key secondary endpoints for studies 206207-010 and 011 are presented in Table 6. The vision improvement in the **OZURDEX®** group was confounded by cataract formation. Vision improvement was re-established upon removal of cataract.

Table 6: Efficacy in studies 206207-010 and 206207-011 (ITT population)

Endpoint	Study 206207-010		Study 206207-011		Pooled Studies 206207-010 and 206207-011	
	OZURDEX® N = 163	Sham N = 165	**OZURDEX®** N = 188	Sham N = 185	**OZURDEX®** N = 351	Sham N = 350
Mean BCVA average change over 3 years, AUC approach (letters)	4.1	1.9	2.9	2.0	3.5	2.0
P-value	0.016		0.366		0.023	
BCVA ≥ 15-letter improvement from baseline at Year 3/Final (%)	22.1	13.3	22.3	10.8	22.2	12.0
P-value	0.038		0.003		< 0.001	
Mean BCVA change from baseline at year 3/final visit (letters)	4.1	0.8	1.3	-0.0	2.6	0.4
P-value	0.020		0.505		0.054	
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-101.1	-37.8	-120.7	-45.8	-111.6	-41.9
P-value	<0.001		< 0.001		< 0.001	

The primary and key secondary endpoints for the pooled analysis for pseudophakic patients are presented in Table 7.

Table 7: Efficacy in pseudophakic patients (pooled studies 206207-010 and 206207-011)

Endpoint	**OZURDEX®** N = 86	Sham N = 101	P-value
Mean BCVA average change over 3 years, AUC approach (letters)	6.5	1.7	< 0.001
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	23.3	10.9	0.024
Mean BCVA change from baseline at year 3/Final visit	6.1	1.1	0.004
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-131.8	-50.8	< 0.001

The primary and key secondary endpoints for the pooled analysis for patients with any prior treatment are presented in Table 8.

Table 8: Efficacy in patients with any prior treatment (pooled studies 206207-010 and 206207-011)

Endpoint	**OZURDEX®** N = 247	Sham N = 261	P-value
Mean BCVA average change over 3 years, AUC approach (letters)	3.2	1.5	0.024
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	21.5	11.1	0.002
Mean BCVA change from baseline at year 3/Final visit	2.7	0.1	0.055
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (µm)	-126.1	-39.0	< 0.001

14 HOW SUPPLIED/STORAGE AND HANDLING

OZURDEX® (dexamethasone intravitreal implant) 0.7 mg is supplied in a foil pouch with 1 single-use plastic applicator.

Storage: Store at or below 30°C.

15 PATIENT COUNSELING INFORMATION

Steroid-related Effects

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

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

Intravitreal Injection-related Effects

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

When to Seek Physician Advice

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

Driving and Using Machines

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

Manufactured by:

Allergan Pharmaceuticals Ireland

Castlebar Road, Westport, Co. Mayo, Ireland.

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Date of Revision: Apr 2019