AUSTRALIAN PRODUCT INFORMATION – OZURDEX® (DEXAMETHASONE) INTRAVITREAL IMPLANT

1 NAME OF THE MEDICINE

Dexamethasone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OZURDEX® is a biodegradable intravitreal implant containing 700 µg dexamethasone in a solid polymer drug delivery system (DDS).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Intravitreal implant

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OZURDEX® is indicated for the treatment of:

- Diabetic macular oedema (DME).
- Macular oedema due to Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).
- Non-infectious uveitis affecting the posterior segment of the eye.

4.2 DOSE AND METHOD OF ADMINISTRATION

The safety and efficacy of OZURDEX® administered to both eyes on the same day has not been studied; and is not recommended.

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

Treatment with OZURDEX® for diabetic macular oedema, macular oedema following BRVO or CRVO, and non-infectious uveitis affecting the posterior segment of the eye is 700 µg per eye (entire contents of a single-use OZURDEX® device).

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefitting from continued treatment, OZURDEX® should be discontinued.

DME

In clinical trials, the majority of retreatments were administered between 5 and 7 months after a prior treatment (see **CLINICAL TRIALS**). Patients in the OZURDEX® arm of the pivotal trials received an average of 4 implants over 3 years. The protocol in the pivotal trials specified a 6-monthly dosing interval. There is currently no experience of the efficacy and safety of repeat administrations in DME beyond 7 implants.

RVO and Uveitis

OZURDEX® should be used in BRVO or CRVO patients with reduced visual acuity only when other treatments are considered inappropriate or ineffective.

Monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters and in the physician's opinion may benefit from retreatment without being exposed to significant risk.

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

There is only very limited information on repeat dosing intervals less than 6 months. There is currently no experience of repeat administrations in posterior segment non-infectious uveitis or beyond 2 implants in RVO.

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

Method of administration

The intravitreal injection procedure should be carried out under aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be carefully evaluated before performing the intravitreal procedure. The periocular skin, eyelid and ocular surface should be disinfected and adequate local anaesthesia and a broad-spectrum topical microbicide should be administered before the injection. Aseptic technique should be maintained at all times before and during the injection procedure.

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.

With the long axis of the applicator parallel to the limbus, enter the sclera at a shallow oblique angle with the bevel of the needle up (away from the sclera) to create a partial thickness tract 1-2 mm in length parallel to the limbus (no more than the length of the needle bevel). Re-direct the needle perpendicularly towards the center of the vitreous cavity; this creates a bi-planar self-sealing scleral puncture.

Advance the needle until the vitreous cavity is entered and the silicone sleeve is against the conjunctiva. Do not advance the needle past the point where the sleeve touches the conjunctiva. When re-directing into the vitreous cavity, allow for the fact that the DDS can be up to 6.5 mm long. Slowly depress the actuator button on the applicator until an audible or palpable click is noted (on occasion, a smaller, softer click is heard or felt while the button is only partially depressed).

Before withdrawing the applicator from the eye, ensure the button is fully depressed and has locked flush with the applicator surface. The speed of the DDS injection is proportional to the speed that the button is depressed. Withdraw the needle from the eye back-tracking along the original entry path if possible.

Following the intravitreal injection, patients may be treated with antibiotics.

Patients should be monitored. 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 2 and 7 days following the injection.

Each applicator can only be used for the treatment of a single eye.

4.3 CONTRAINDICATIONS

OZURDEX® is contraindicated in the following:

- patients with active or suspected ocular or periocular infection, 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
- aphakic eyes with rupture of the posterior lens capsule
- eyes with an anterior chamber intraocular lens (ACIOL), iris or transscleral fixated IOLs, and rupture of the posterior lens capsule
- patients with hypersensitivity to dexamethasone or to any other components of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Treatment with OZURDEX® is for intravitreal injection only.

Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, intraocular inflammation, increased IOP, and retinal detachment.

Monitoring:

Proper aseptic injection techniques must always be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased IOP occur. 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 or any of the above-mentioned events without delay.

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 into the anterior chamber might lead to corneal oedema. Persistent severe corneal oedema could progress to the need for corneal transplantation. Regular monitoring of such patients allows for early diagnosis and management of device migration.

Potential Steroid-related Effects:

Use of corticosteroids, including OZURDEX®, have been associated with posterior subcapsular cataracts, increased IOP, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Visual Disturbance

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.

Cataract:

The incidence of cataract increases after multiple corticosteroid injections.

IOP Increase:

As expected with ocular steroid treatment and intravitreal injections, IOP increases may be seen. The rise in IOP is normally manageable with IOP lowering medication (see ADVERSE EFFECTS). Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase between 45 and 60 days following an injection. Therefore, regular monitoring of IOP, irrespective of baseline IOP, is required and any elevation should be managed appropriately post-injection as needed. Patients of less than 45 years of age with macular oedema following RVO or non-infectious uveitis affecting the posterior segment of the eyes are more likely to experience increases in IOP.

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.

The safety and efficacy of OZURDEX® administered to both eyes on the same day has not been studied.

A limited number of subjects with Type 1 diabetes were investigated in the Phase 3 DME studies, and the response to OZURDEX® in these subjects was not significantly different to those subjects with Type 2 diabetes.

Anti-coagulant Therapy:

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 anti-coagulant therapy (6%).

In RVO1 and RVO2, anti-coagulant therapy was used in 2% of patients receiving OZURDEX®; there were no reports of haemorrhagic adverse events in these patients.

Anti-platelet Therapy:

Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in up to 56% of patients. For patients using concomitant and anti-platelet medication, haemorrhagic adverse events were reported in a slightly higher proportion of patients injected with OZURDEX® (up to 29%) compared with the Sham group (up to 23%), irrespective of indication or number of treatments. The most common haemorrhagic adverse event reported was conjunctival haemorrhage (up to 24%).

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

Use in hepatic impairment

OZURDEX® has not been studied in patients with hepatic impairment; however no special considerations are needed in this population.

Use in renal impairment

OZURDEX® has not been studied in patients with renal impairment; however no special considerations are needed in this population.

Use in the elderly

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

Paediatric use

The safety and efficacy of OZURDEX® in paediatric patients has not been established.

Effects on laboratory tests

There are no data available regarding the effects on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no fertility data available.

Use in pregnancy

Pregnancy Category B3

Studies in animals have shown teratogenic effects following topical ophthalmic administration. There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Long-term systemic treatment with glucocorticoids during pregnancy increases the risk for intra-uterine growth retardation and adrenal insufficiency of the newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment,

OZURDEX® is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Use in lactation

Dexamethasone is excreted in breast milk. No effects on the child are anticipated due to the route of administration and the resulting systemic levels. OZURDEX® should not be used by breastfeeding women unless clearly necessary.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

DME

The clinical safety of OZURDEX® was assessed in two Phase 3 randomised, masked, Sham-controlled studies in patients with diabetic macular oedema. In both studies, a total of 347 patients were randomised and received OZURDEX® and 350 received Sham.

The most frequent adverse reactions (dexamethasone or injection procedure) were defined as adverse reactions that occurred with a higher frequency in the OZURDEX® group compared to the Sham group and had a plausible mechanism of action as shown in Table 1:

Table 1: Summary of Adverse Reactions in Phase 3 DME Studies in ≥ 1% of Patients – Entire Study Period

	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)

Anterior chamber inflammation*	6 (1.7)	0 (0.0)
Visual acuity reduced	29 (8.4)	14 (4.0)

Note: "*" indicates 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 necrotising retinitis (0.3%).

Cataract and Raised Intraocular Pressure

The most frequently reported adverse reactions across the entire study period in the study eye of patients who received OZURDEX® were cataract and elevated IOP (see below).

In the three-year DME clinical studies, at baseline, 87% of patients with a phakic study eye treated with OZURDEX® had some degree of lens opacification/ early cataract. The incidence of all observed cataract types (i.e. cataract cortical, cataract diabetic, cataract nuclear, cataract subcapsular, cataract lenticular, cataract) was 68% in OZURDEX® treated patients with a phakic study eye across the three-year studies. 59% of patients with a phakic study eye required cataract surgery by the three-year final visit, with the majority performed in the 2nd and 3rd years.

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

28% of patients treated with OZURDEX® had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the three-year studies, with the majority of these patients requiring more than one medication. Peak usage (33%) occurred during the first 12 months and remained similar from year to year**.**

A total of 4 patients (1%) treated with OZURDEX® had procedures in the study eye for the treatment of IOP elevation. One patient treated with OZURDEX® required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation, 1 patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 1 patient had an iridotomy for narrow angle glaucoma and 1 patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

RVO

The clinical safety of OZURDEX® was assessed in three Phase 3 randomised, double-masked, Sham-controlled studies in patients with macular oedema following BRVO or CRVO. In Study RVO3, a total of 129 patients were randomised and received OZURDEX® and 130 received Sham. In Studies RVO1 and RVO2, a total of 421 patients were treated with OZURDEX® and 423 received Sham.

The most frequent adverse reactions (dexamethasone or injection procedure) were defined as adverse reactions in the initial masked treatment period, that occurred with a higher frequency in the OZURDEX® group compared to the Sham group or had a plausible mechanism of action as shown in Table 2:

Table 2: Summary of Adverse Reactions in Phase 3 RVO Studies in ≥ 1% of Patients

System Organ Class Preferred Term	Pooled Studies RVO 1 and RVO 2		Study RVO 3	
	OZURDEX® N = 421	**Sham N = 423**	**OZURDEX® N = 129**	**Sham N = 130**
Eye Disorders (Study Eye)				
Intraocular pressure increased	106 (25.2%)	5 (1.2%)	38 (29.5%)	3 (2.3%)
Conjunctival haemorrhage*	85 (20.2%)	63 (14.9%)	24 (18.6%)	5 (3.8%)
Eye pain*	31 (7.4%)	16 (3.8%)	3 (2.3%)	3 (2.3%)
Conjunctival hyperaemia*	28 (6.7%)	20 (4.7%)	17 (13.2%)	6 (4.6%)
Ocular hypertension	17 (4.0%)	3 (0.7%)	4 (3.1%)	0 (0.0%)
Cataract	15 (3.6%)	6 (1.4%)	0 (0.0%)	0 (0.0%)
Vitreous opacities* (including vitreous floaters)	17 (4.0%)	6 (1.4%)	0 (0.0%)	0 (0.0%)
Vitreous detachment*	12 (2.9%)	8 (1.9%)	1 (0.8%)	0 (0.0%)
Vitreous haemorrhage*	10 (2.4%)	12 (2.8%)	0 (0.0%)	3 (2.3%)
Conjunctival oedema*	9 (2.1%)	7 (1.7%)	4 (3.1%)	1 (0.8%)
Subcapsular cataract	7 (1.7%)	3 (0.7%)	0 (0.0%)	0 (0.0%)
Visual disturbance	7 (1.7%)	3 (0.7%)	0 (0.0%)	0 (0.0%)
Photopsia*	6 (1.4%)	3 (0.7%)	0 (0.0%)	0 (0.0%)
Anterior chamber cells*	5 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lenticular opacities	1 (0.2%)	1 (0.2%)	2 (1.6%)	0 (0.0%)
Nervous System Disorders				
Headache	14 (3.3%)	7 (1.7%)	3 (2.3%)	1 (0.8%)

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

Uncommon adverse reactions occurring in pooled studies RVO1 and RVO2 included anterior chamber flare (0.7% - injection procedure related) and retinal tear (0.5% - injection procedure related).

Increased intraocular pressure (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 the temporary use of topical IOP-lowering medicinal products. Over the initial treatment and open-label extension periods of the 1 year studies, IOP medications in the study eye were reported for 39.3% of patients in the OZURDEX® group and 32.7% in the Sham group. Less than 1% of patients who received OZURDEX® required laser or surgical procedures for management of elevated IOP in the study eye.

In the RVO clinical studies (RVO1 and RVO2), cataract was reported more frequently in patients with a phakic study eye receiving a second injection of OZURDEX®. 2 patients had lenticular opacities and there was no cataract adverse reaction or cataract surgery reported in Study RVO3.

In Studies RVO1 and RVO2, only 1 patient out of 368 with a phakic study eye required cataract surgery in the study eye during the first treatment and 3 patients out of 302 with a phakic study eye during the second treatment.

The adverse reaction profile of 341 patients analysed following a second injection of OZURDEX® in the open-label extension phase of Studies RVO1 and RVO2, was similar to that following the first injection. The incidence of increased IOP (32.6 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

Uveitis

The clinical safety of OZURDEX® was assessed in a single, multi-center, masked and randomised, 26-week Phase 3 study for 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.

The most frequent adverse reactions (dexamethasone or injection procedure) were defined as adverse reactions that occurred with a higher frequency in the OZURDEX® group compared to the Sham group or had a plausible mechanism of action as shown in Table 3:

Table 3: Summary of Adverse Reactions in Phase 3 Uveitis Study in ≥ 1% of Patients

	OZURDEX® N = 76	**Sham N = 75**
Eye Disorders (Study Eye)		
Conjunctival haemorrhage*	23 (30.3%)	16 (21.3%)
Intraocular pressure increased	19 (25.0%)	5 (6.7%)
Cataract	9 (11.8%)	4 (5.3%)
Myodesopsia	6 (7.9%)	5 (6.7%)
Blepharitis	3 (3.9%)	0 (0.0%)
Vitreous opacities	3 (3.9%)	1 (1.3%)
Abnormal sensation in eye*	2 (2.6%)	0 (0.0%)
Eyelid pruritus	2 (2.6%)	0 (0.0%)
Retinal detachment*	2 (2.6%)	2 (2.7%)
Scleral hyperaemia*	2 (2.6%)	1 (1.3%)
Visual impairment	2 (2.6%)	1 (1.3%)
Nervous System Disorders		
Migraine	2 (2.6%)	0 (0.0%)

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

The proportion of OZURDEX®-treated patients with increased IOP (≥ 25 mm Hg) peaked at week 3 and returned to baseline by week 26. IOP medications in the study eye were reported for 33.8% of patients in the OZURDEX® group and 13.2% in the Sham group. During the treatment period, no patients required incisional surgery for raised IOP. Two patients in the OZURDEX® treatment group required laser iridotomies in the study eye for the treatment of iris bombe and raised IOP compared to 0 patients in Sham group.

1 patient out of the 62 with a phakic study eye underwent cataract surgery in the study eye after a single injection of OZURDEX®.

The clinical safety of OZURDEX® was assessed in a multicentre, 24-month real world observational study in the treatment of macular oedema 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 [(44/178), for cataract formation and (57/178) for cataract progression] based on eyes with phakic lens status at baseline, vitreous haemorrhage (17/283), and increased IOP (68/283).

Post-marketing Experience

The following adverse reactions have been identified during post-marketing use of OZURDEX® in clinical practice. Because post-marketing 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

Central serous chorioretinopathy

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 oedema

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased oedema, fibrin deposition, capillary leakage, and migration of the inflammatory cells. Vascular endothelial growth factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF and modulate VEGF-mediated responses. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

OZURDEX® contains 700 µg micronised dexamethasone in a biodegradable polymer matrix that is injected directly into the posterior segment of the eye with an applicator. The polymer degrades into water and carbon dioxide over time, gradually releasing dexamethasone to the vitreous, allowing for sustained drug levels in the target area with a smaller total amount of drug administered than via other routes of corticosteroid administration. Furthermore, delivery of OZURDEX® 700 µg directly into the vitreous cavity reduces the potential for systemic effects compared to other routes of administration. The dose of dexamethasone delivered by OZURDEX® 700 µg every 6 months is less than the usual single daily physiologic replacement dose (0.75 mg).

Clinical trials

DME

The clinical efficacy of OZURDEX® was assessed in two Phase 3 randomised, masked, Sham-controlled studies in patients with diabetic macular oedema. A total of 1,048 patients (351 OZURDEX® [700 µg], 347 dexamethasone 350 µg, and 350 Sham) were evaluated as the intent-to-treat (ITT) population and received up to 7 treatments during the 3-year study period.

The primary endpoint in both studies was Best Corrected Visual Acuity (BCVA) using early treatment diabetic retinopathy study (ETDRS) method in the study eye at the qualification/baseline visit and each follow-up visit.

Patients were eligible for retreatment based upon central subfield retinal thickness > 175 microns by optical coherence tomography (OCT) or upon physician's interpretation for any evidence of residual retinal oedema consisting of intraretinal cysts or any regions of increased retinal thickening within or outside of the central subfield.

BCVA Average Change from Baseline (area under the curve [AUC] approach)

In Study DME1, the mean BCVA average change from baseline during the study was significantly greater with OZURDEX® compared to Sham (4.1 letters versus 1.9 letters, $p = 0.016$).

In Study DME2, the mean BCVA average change from baseline during the study was 2.9 letters with OZURDEX® compared to 2.0 letters with Sham; the difference was not statistically significant ($p = 0.366$).

In the pooled analysis, the mean BCVA average change from baseline during the study was significantly greater with OZURDEX® compared to Sham (3.5 letters versus 2.0 letters, $p = 0.023$).

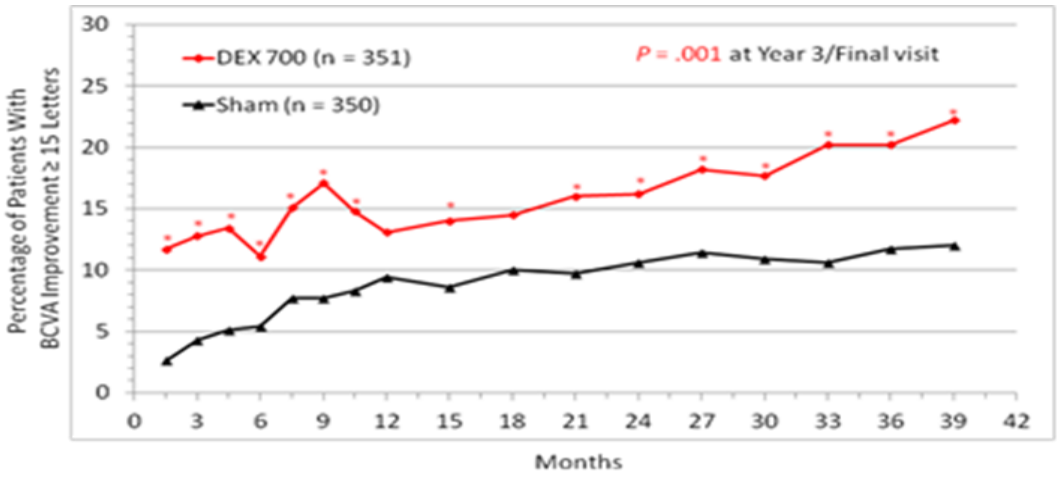
BCVA Improvement ≥ 15 Letters from Baseline

In Study DME1 the proportion of patients with 15 or more letters improvement in BCVA from baseline was significantly higher with OZURDEX® (22.1%) compared with Sham (13.3%) at the year 3 final visit, p = 0.038.

In Study DME2 the proportion of patients with 15 or more letters improvement in BCVA from baseline was significantly higher with OZURDEX® (22.3%) compared with Sham (10.8%) at the year 3 final visit, p = 0.003.

In the pooled analysis, the proportion of patients with 15 or more letters improvement from baseline was significantly higher with OZURDEX® (22.2%) compared to Sham (12.0%) at the year 3 final visit (p < 0.001) and significantly higher with OZURDEX® compared to Sham at 15 of the 17 study visits. The treatment benefit of OZURDEX® in vision improvement was seen throughout the 3-year study period.

Figure 1: Percent of Patients with ≥ 15 Letters Improvement from Baseline BCVA in the Study Eye (Pooled Studies, ITT Population)



* indicates statistically significant (p ≤ 0.05) difference between OZURDEX® versus Sham
Note: Missing values are imputed by last observation carried forward at the follow-up visits.

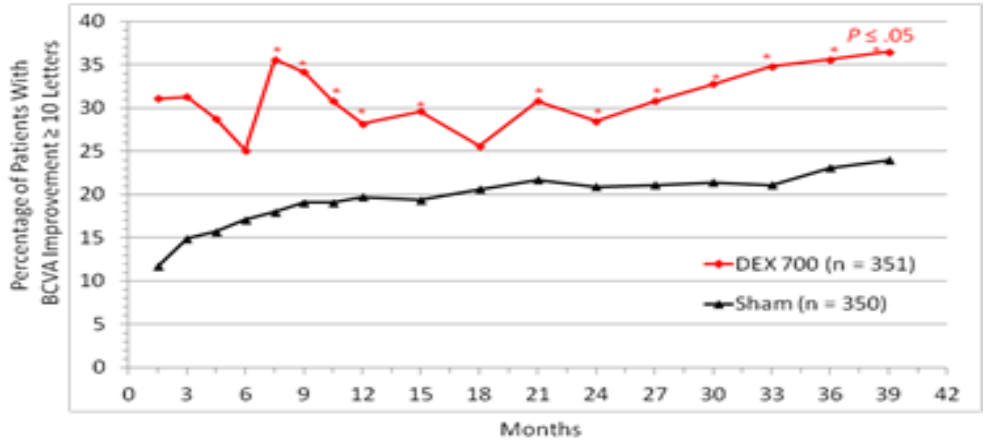
BCVA Improvement of 10 or More Letters from Baseline

In Study DME1, the proportion of patients with 10 or more letters improvement in BCVA was significantly higher with OZURDEX® compared to Sham at 14 of the 17 study visits. At the end of the study, significantly greater proportions of patients receiving OZURDEX® (38.7%) showed a 10-letter improvement compared to Sham (23.0%), p = 0.002.

In Study DME2, the proportion of patients with 10 or more letters improvement in BCVA was significantly higher with OZURDEX® compared to Sham at 10 of the 17 study visits. At the end of the 3-year study, a significantly greater proportion of patients receiving OZURDEX® (34.6%) showed a ≥ 10-letter improvement compared to Sham (24.9%), p = 0.040.

In the pooled analysis, the proportion of patients with 10 or more letters improvement in BCVA was significantly higher with OZURDEX® compared with Sham at 16 of the 17 study visits. By the end of the 3-year study, 36.5% of patients receiving OZURDEX® showed a 10-letter improvement compared to 24.0% of patients receiving Sham ($p < 0.001$).

Figure 2: Percent of Patients with ≥ 10 Letters Improvement from Baseline BCVA in the Study Eye (Pooled Studies, ITT Population)



* indicates statistically significant ($p \leq 0.05$) difference between OZURDEX® versus Sham
Note: Missing values are imputed by last observation carried forward at the follow-up visits

BCVA 20/40 or Better

In the pooled analysis, the proportion of patients achieving a BCVA of 20/40 or better in the study eye was significantly greater with OZURDEX® compared to Sham at 10 of the 17 study visits. At the year 3/final visit, the proportion of patients achieving BCVA 20/40 or better was significantly higher with OZURDEX® (28.8% [101/351]) compared to Sham (21.4% [75/350]), $p = 0.025$.

Time to BCVA ≥ 15 Letters Improvement

In each of the Phase 3 studies and the pooled analysis, OZURDEX® was shown to have a rapid onset of action, as demonstrated by the time to BCVA 15-letter improvement from baseline in the study eye. The response time distributions in the OZURDEX® group was significantly earlier compared with Sham, indicating an earlier onset of BCVA improvement in the OZURDEX® group, with separation of curves at the first efficacy visit and no crossover during the study.

Retinal Thickness in the Center Subfield using OCT

In Study DME1, the mean average decrease from baseline during the study in central subfield retinal thickness was significantly greater with OZURDEX® (101.1 µm) versus Sham (37.8 µm), $p < 0.001$.

In Study DME2, the mean average decrease from baseline during the study in central subfield retinal thickness was significantly greater with OZURDEX® (120.7 µm) versus Sham (45.8 µm), $p < 0.001$.

In the pooled studies, the improvement in vision with OZURDEX® during the 3-year study was associated with a rapid and sustained improvement in anatomical outcomes, as demonstrated by OCT. The mean average decrease from baseline during the study in the central subfield retinal thickness was significantly greater with OZURDEX® (111.6 µm) compared to Sham (41.9 µm), $p < 0.001$.

In the pooled studies, mean decreases in retinal thickness at the center subfield were consistently greater with OZURDEX® than with Sham throughout the studies. Statistically significant mean improvements with OZURDEX® compared to Sham were observed at every visit during the 3-year study.

Retreatment intervals

In the pooled Phase 3 studies, during the course of the 3-year study period, a total of 1080 study retreatments for OZURDEX® were administered. Approximately 80% of the retreatments were administered between 5 to 7 months after the prior treatment and 19.9% were after 7 months.

Discontinuations

A total of 35.9% of OZURDEX® treated patients discontinued study participation for any reason during the study compared with 56.6% of Sham patients. Discontinuation rates due to adverse events were similar across treatment and Sham groups (12.8% vs 11.1%). Discontinuation due to lack of efficacy was higher in the Sham group (6.6% vs 24.0%).

RVO

A branch retinal vein occlusion (BRVO) is a blockage of the portion of the circulation that drains the retina of blood. Central retinal vein occlusion (CRVO) is closure of the central retinal vein (located at the optic nerve) which collects all of the blood after it passes through the capillaries. The clinical efficacy of a single administration of OZURDEX® in patients with macular oedema following CRVO or BRVO was assessed in three Phase 3 randomised, masked, Sham-controlled studies with masked treatment for 6 months. Study enrolment included male or female patients, at least 18 years or age with macular oedema due to BRVO or CRVO, best-corrected visual acuity (BCVA) baseline score between 34 and 68 letters by ETDRS, and retinal thickness of ≥300µm by optical coherence tomography (OCT). Patients were eligible to receive a second treatment during open-label extensions for 2 to 6 months. In Study RVO3 a total of 259 patients (129 OZURDEX® and 130 Sham) were treated. In

Studies RVO1 and RVO2, a total of 1,267 patients (427 OZURDEX®, 414 dexamethasone 350 µg, and 426 Sham) were treated.

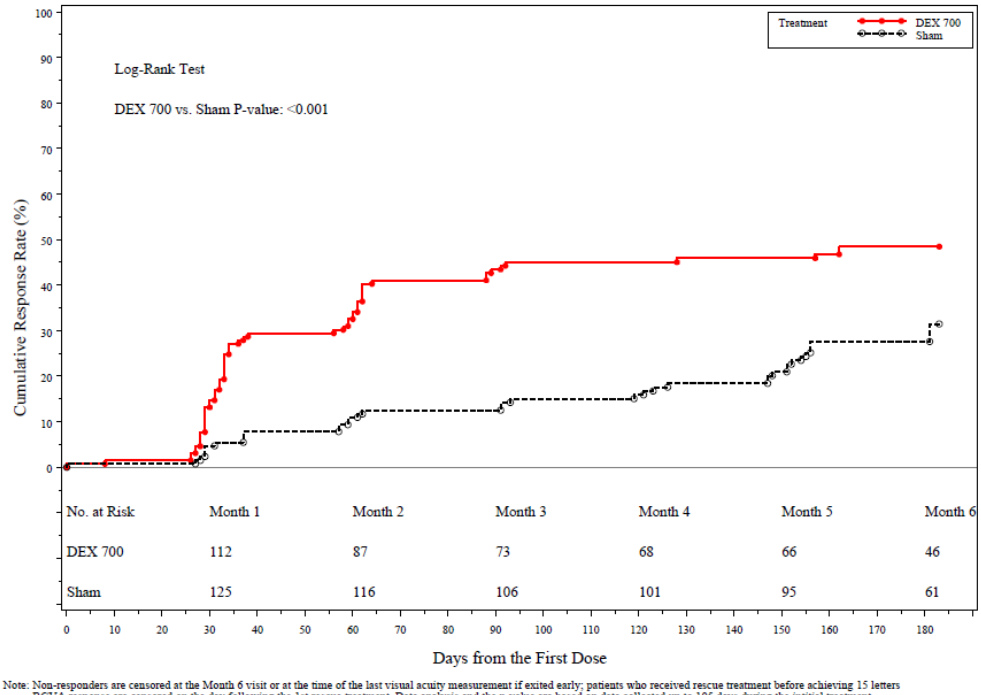
Primary efficacy endpoints were the following:

- the time to achieve a response of 15 or more letters improvement in BCVA from baseline in the study eye during the initial treatment period from day 0 to day 180 using the Kaplan Meier survival analysis (Studies RVO3 and RVO1)
- the proportion of patients with a BCVA improvement of 15 or more letters from baseline in the study eye at initial treatment day 180 (Study RVO2)

Time to achieve ≥ 15 Letters Improvement in BCVA

OZURDEX® was shown to have a rapid onset of action, as demonstrated by the time to BCVA 15-letter improvement from baseline in the study eye. The time to achieve ≥ 15 letters improvement in BCVA was significantly improved with OZURDEX® compared to Sham. The cumulative response rates of patients achieving a 3-line improvement were consistently higher with OZURDEX® starting from day 30 (month 1) to the end of the initial treatment period for the RVO3 study (see Figure 3), and consistently higher with OZURDEX® starting from day 30, further separated at day 60, with the treatment difference maintained through the end of day 180, for pooled RVO1 and RVO2 studies (see Figure 4).

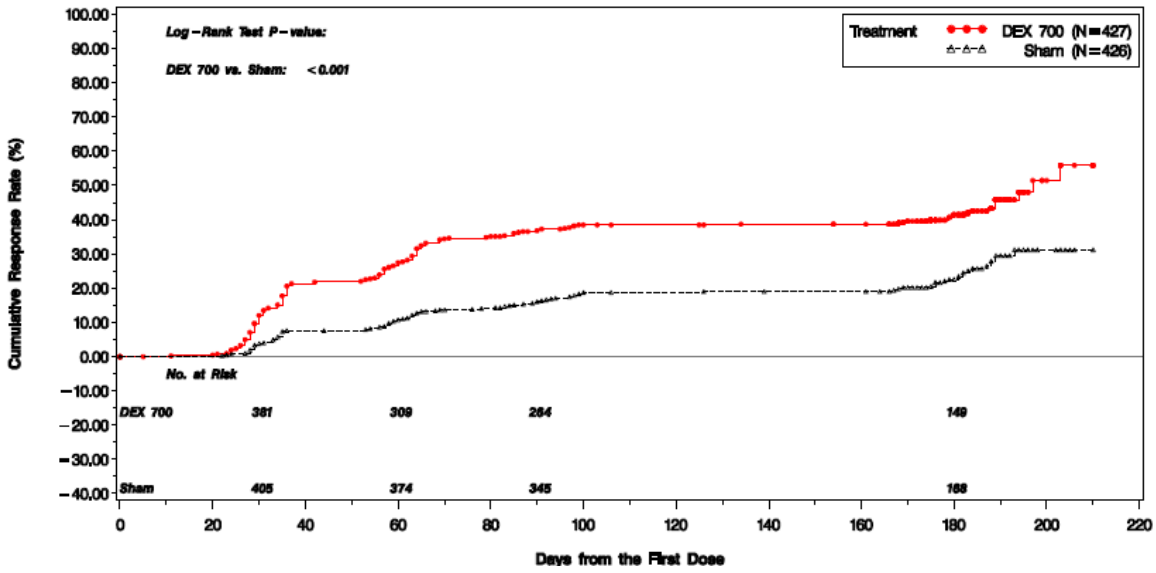
Figure 3: Time to Achieve ≥ 15 Letters Improvement in BCVA (Study RVO3, mITT Population*)



Note: Non-responders are censored at the Month 6 visit or at the time of the last visual acuity measurement if exited early; patients who received rescue treatment before achieving 15 letters BCVA response are censored on the day following the 1st rescue treatment. Data analysis and the p-value are based on data collected up to 195 days during the initial treatment.

* mITT (modified intent-to-treat): all randomised and treated patients. A total of 262 patients were randomised and enrolled in the study. There were 129 patients treated in the DEX 700 group, and 130 patients treated in the Sham group. Three patients were enrolled and randomised but not treated.

Figure 4: Time to Achieve ≥ 15 Letters Improvement in BCVA (Pooled Studies RVO1 and RVO2, ITT Population)



Proportion of Patients with BCVA ≥ 15 Letters Improvement

In all three studies, the proportion of patients with ≥ 15 letters improvement in BCVA from baseline was significantly higher with OZURDEX® compared to Sham at days 30, 60, and 90 ($p < 0.001$), as shown in Table 4. A treatment effect was seen at the first observation time point of day 30. The maximum treatment effect was observed at day 60 and the difference in response rates was statistically significant favouring OZURDEX® compared with Sham at all time-points to day 90 following injection. There continued to be a numerically greater proportion of responders for a ≥ 15 letter improvement from baseline in BCVA in patients treated with OZURDEX® compared with Sham at day 180.

Table 4: Proportion of Patients with ≥ 15 Letters Improvement in BCVA in the Study Eye (Study RVO3, mITT* Population; Studies RVO1 and RVO2, ITT Population)

	Pooled Studies RVO 1 and RVO 2		Study RVO 3	
	OZURDEX®	Sham	OZURDEX®	Sham
Visit	N = 427	N = 426	N = 129	N = 130
Day 30	21.3%[a]	7.5%	28.7%[a]	5.4%
Day 60	29.3%[a]	11.3%	34.9%[a]	11.5%
Day 90	21.8%[a]	13.1%	33.3%[a]	13.1%
Day 180	21.5%	17.6%	23.3%	20.8%

[a] Proportion significantly higher with dexamethasone compared to Sham ($p < 0.001$)
* mITT (modified intent-to-treat): all randomised and treated patients

Mean Change from Baseline in BCVA

In Study RVO3, the mean changes from baseline BCVA in the study eye peaked at day 60 and were significantly greater with OZURDEX® compared to Sham at initial treatment days 30, 60, and 90 ($p < 0.001$) (see Table 5).

For the pooled analysis of Studies RVO1 and RVO2, the mean change from baseline BCVA was significantly greater with OZURDEX® compared to Sham at days 30, 60, 90, and 180 (see Table 5). The magnitude of improvement peaked at day 60 with nearly 10 letters with OZURDEX® compared to approximately 3 letters with Sham. At day 90, improvements of more than 7 letters increase were maintained with OZURDEX® compared to the nearly constant change to 3 letters at every visit with Sham.

Table 5: Mean Change from Baseline in BCVA in the Study Eye (Study RVO 3, mITT* Population; Studies RVO 1 and RVO 2, ITT Population)

	Pooled Studies RVO 1 and RVO 2		Study RVO 3	
Visit	**OZURDEX® N = 226**	**Sham N = 224**	**OZURDEX® N = 129**	**Sham N = 130**
Day 30	8.1[a]	2.6	9.1[a]	2.0
Day 60	9.8[a]	3.1	10.6[a]	1.7
Day 90	7.2[a]	3.2	7.7[a]	1.8
Day 180	5.1[b]	2.6	3.2	4.0

a Mean change from baseline significantly greater with OZURDEX® compared to Sham ($p < 0.001$)

b Mean change from baseline significantly greater with OZURDEX® compared to Sham ($p = 0.006$)

* mITT (modified intent-to-treat): all randomised and treated patients

Retinal Thickness in the Center Subfield using OCT

In Study RVO3, mean decreases in retinal thickness at the center subfield were significantly greater with OZURDEX® than with Sham at days 30, 60, and 90 ($p < 0.001$), though not at day 180. In the pooled RVO1 and RVO2 studies, the mean decrease in retinal thickness was significantly greater with OZURDEX® (-207.9 µm) than with Sham (-95.0 µm) at day 90 ($p < 0.001$), though not at day 180.

6-month Open-label Extension (Studies RVO1 and RVO2)

Eligibility criteria for second injection:

While remaining masked of the initial randomised treatment, patients were eligible for an OZURDEX® treatment at day 180if they had a BCVA score of <84 OR retinal thickness > 250 µm by OCT. 98% received an OZURDEX® injection between 5 and 7 months after the initial treatment. Of the 427 patients who received an initial treatment of OZURDEX®, 341 patients were retreated at day 180.

Peak BCVA improvement was seen at Day 60 in the open-label phase.

The cumulative response rates were higher throughout the open-label phase in those patients receiving two consecutive OZURDEX® injections compared with those patients who had not received an OZURDEX® injection in the initial phase. The proportion of responders at each time point was always greater after the second treatment compared with the first treatment. Whereas, delaying treatment for 6 months (i.e. patients who received Sham as their first treatment) resulted in a lower proportion of responders at all timepoints in the open label phase when compared with those first receiving OZURDEX®.

Uveitis

The clinical efficacy of OZURDEX® has been assessed in a single, multicentre, masked, randomised Phase 3 study for the treatment of non-infectious uveitis affecting the posterior segment of the eye. Study enrolment included male or female patients, at least 18 years of age, vitreous haze ≥+1.5 at both screening and baseline visits in the study eye, BCVA in the study eye of 10 to 75 letters using ETDRS method.

A total of 229 patients were randomised to receive a single treatment of OZURDEX®, dexamethasone 350 µg or Sham. Of these, a total of 77 were randomised to receive OZURDEX®, 76 to dexamethasone 350 µg and 76 to Sham, and evaluated as the ITT population.

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

The proportion of patients with vitreous haze score of 0 in the study eye at week 8 (primary endpoint) was 4-fold higher with OZURDEX® (46.8%) compared to Sham (11.8%), $p < 0.001$. Statistical superiority was observed at week 6 and maintained up to and including week 26 ($p \leq 0.014$) as shown in Table 6.

Secondary endpoints included the time to vitreous haze score of 0, and patients demonstrating at least 15 letters improvement from baseline BCVA throughout the 26-week period.

Time to vitreous haze score of 0 was significantly different for the OZURDEX® group compared to Sham group ($p < 0.001$), with patients receiving dexamethasone showing an earlier onset and greater treatment response.

The reduction in vitreous haze was accompanied by an improvement in visual acuity. The proportion of patients with at least 15 letters improvement from baseline BCVA in the study eye at week 8 was more than 6-fold higher with OZURDEX® (42.9%) compared to Sham (6.6%), $p < 0.001$. Statistical superiority was achieved at week 3 and maintained up to and including week 26 ($p < 0.001$) as shown in Table 6.

Table 6: Proportion of Patients with Vitreous Haze Score of Zero or ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (ITT Population)

Visit	Vitreous Haze Score of Zero		Proportion of Patients with BCVA ≥ 15 Letters Improvement	
	OZURDEX® N = 77	Sham N = 76	OZURDEX® N = 77	Sham N = 76
Week 3	23.4%	11.8%	32.5%[a]	3.9%
Week 6	42.9%[a]	9.2%	41.6%[a]	7.9%
Week 8	46.8%[a]	11.8%	42.9%[a]	6.6%
Week 12	45.5%[a]	13.2%	41.6%[a]	13.2%
Week 16	40.3%[b]	21.1%	39.0%[a]	13.2%
Week 20	39.0%[c]	19.7%	40.3%[a]	13.2%
Week 26	31.2%[d]	14.5%	37.7%[a]	13.2%

[a] $p < 0.001$; [b] $p = 0.010$; [c] $p = 0.009$; [d] $p = 0.014$

The percent of patients requiring escape medications from baseline to week 8 was nearly 3-fold less with OZURDEX® (7.8%) compared to Sham (22.4%), p=0.012.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

In two Phase 3 diabetic macular oedema studies (DME1 and DME2), adult patients with a diagnosis of Type 1 or Type 2 diabetes mellitus and clinically observable macular oedema associated with diabetic retinopathy were randomised in a 1:1:1 ratio to OZURDEX®, 350 µg dexamethasone, or Sham DEX PS DDS needleless applicator. 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 lower limit of quantitation (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 dexamethasone 350 µg group were above the LLOQ, ranging from 0.0599 ng/mL to 0.102 ng/mL. The highest plasma concentration value of 0.102 ng/mL was observed in one subject from the 0.7 mg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In the Phase 3 retinal vein occlusion Studies RVO1 and RVO2, blood samples were obtained from a subgroup of patients at predose and days 1, 7, 30, 60, and 90 to determine plasma dexamethasone concentrations. In both studies, the majority of concentrations were below the LLOQ of 0.05 ng/mL. Both studies showed that Plasma concentrations from 10 of 73 samples in the OZURDEX® group and from 2 of 42 samples in the dexamethasone 350 µg group were above the LLOQ, ranging from 0.0521 ng/mL to 0.0940 ng/mL.

In monkeys, following single bilateral intravitreal implantation of OZURDEX®, dexamethasone was released in two phases. The first phase provided high concentrations of

dexamethasone, with peak concentrations of dexamethasone observed in the vitreous humour and retina 60 days post-injection. This was followed by a second phase in which low concentrations of dexamethasone were released, extending the therapeutic period to 6 months.

Metabolism

In an in vitro metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies. Systemically, dexamethasone is subject to metabolism by CYP3A4 in the liver.

Excretion

Dexamethasone is predominantly cleared from the vitreous humour by diffusion into the retina/choroid/sclera membrane. Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Studies evaluating the mutagenic potential of dexamethasone in bacteria and mammalian cells in vitro have been negative. Assays for clastogenicity conducted in vitro and in vivo (mouse bone marrow micronucleus test) have returned mixed results, but the observed positive findings are considered likely to be confounded by the drug's pharmacological activity. The available data support that dexamethasone, as well as the polymeric component of OZURDEX®, do not pose a genotoxic hazard to patients.

Carcinogenicity

No studies on the carcinogenic potential of OZURDEX® have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OZURDEX® is preloaded into a single-use, specially designed DDS applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The polymer DDS contains polyglactin [poly (D,L-lactide-coglycolide)] PLGA biodegradable polymer matrix. OZURDEX® is preservative-free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from excessive heat.

6.5 NATURE AND CONTENTS OF CONTAINER

1 pack contains: 1 sustained-release sterile implantable rod-shaped implant containing 700 µg of dexamethasone, located in the needle (stainless steel) of a disposable applicator.

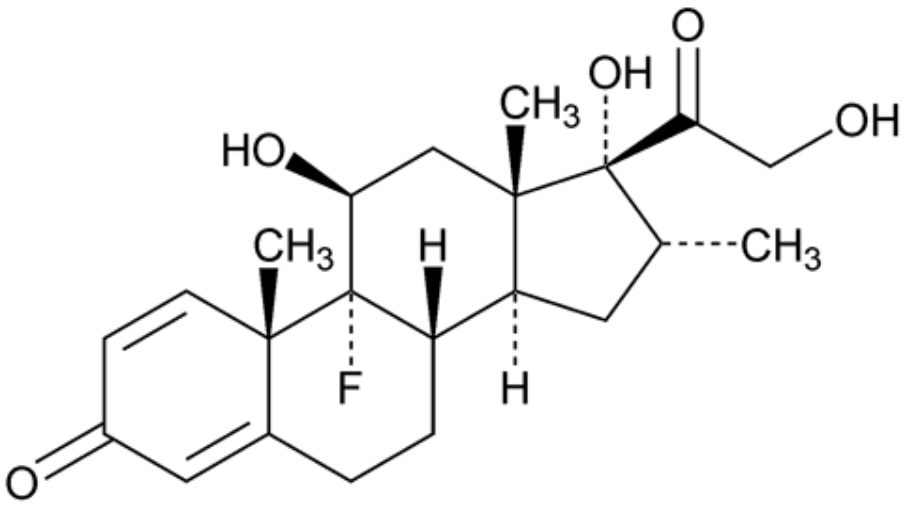
The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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

Molecular weight: 392.47

Empirical formula: $C_{22}H_{29}FO_5$

Dexamethasone is a white to cream-coloured crystalline powder with not more than a slight odour and is practically insoluble in water and very soluble in alcohol.

CAS number

50-02-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
AUSTRALIA
Ph: 1800 043 460
www.abbvie.com.au

9 DATE OF FIRST APPROVAL

04 June 2015

10 DATE OF REVISION

27 Sep 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Inclusion of central serous chorioretinopathy