DATA SHEET

1. PRODUCT NAME

OZURDEX® 700 µg implant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

dexamethasone 700 µg

For full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

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.

OZURDEX® is a biodegradable intravitreal implant containing 700 µg dexamethasone in the NOVADUR™ solid polymer drug delivery system. OZURDEX® is preloaded into a single-use, specially designed drug delivery system (DDS) applicator to facilitate injection of the rod-shaped implant directly into the vitreous. The polymer drug delivery system contains polyglactin [poly (D,L-lactide-coglycolide)] PLGA biodegradable polymer matrix. OZURDEX® is preservative-free.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OZURDEX® is indicated for the treatment of macular oedema due to retinal vein occlusion (RVO).

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

OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

4.2 Dose and method of administration

Single-use intravitreal implant in applicator for intravitreal use only. Treatment with OZURDEX® for retinal vein occlusion, diabetic macular oedema and uveitis is 700 µg per eye (entire contents of a single-use OZURDEX® device).

Repeat doses should 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. 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.

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

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

The recommended dose is one OZURDEX® implant to be administered intra-vitreally to the affected eye. 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.

The injection procedure should be carried out under aseptic conditions, which includes 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 prior to performing the intravitreal procedure. The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection and following the intravitreal injection, patients may be treated with antibiotics and 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.

Aseptic techniques should be maintained at all times prior to 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 centre 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 drug delivery system (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, make sure that 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 should be monitored for elevation in IOP and for endophthalmitis.

Paediatric Use

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

Use in Elderly

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

4.3 Contraindications

OZURDEX® is contraindicated in:

- 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.
- Advanced glaucoma (disease that cannot be adequately controlled by medications alone)
- Hypersensitivity to the active substance or to any of the excipients
- Aphakic eyes with ruptured posterior lens capsule
- Eyes with an Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated IOLs and ruptured posterior lens capsule.

4.4 Special warnings and precautions for use

General:

Any intravitreal injection, including ones with OZURDEX® can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure (IOP) and retinal detachment. 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 should occur. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

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

Use of corticosteroids, including those with OZURDEX®, has been associated with posterior subcapsular cataracts, increased IOP, and glaucoma. Use of corticosteroids may result in secondary ocular infections due to bacteria, fungi, or viruses.

As expected with ocular steroid treatment and intravitreal injections, increases in IOP may be seen. Therefore, elevation of IOP should be managed appropriately post injection as needed.

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

4.5 Interaction with other medicines and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Effects on Fertility:

The effect of OZURDEX® on fertility has not been investigated in studies in animals.

Use in Pregnancy: Category B3

Safety for use in pregnancy has not been established. There are no adequate data from the use of dexamethasone in pregnant women. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the recommended therapeutic dose. The potential risk for humans is unknown. OZURDEX® should not be used during pregnancy unless clearly necessary.

Use in Lactation:

Safety for use in lactation has not been established. 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.

Information for patients:

In the days following intravitreal injection of OZURDEX®, patients are at risk of potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patients should seek immediate care from an ophthalmologist.

4.8 Undesirable effects

Clinical Trials
Treatment of Retinal Vein Occlusion:

The clinical safety of OZURDEX® in RVO has been assessed in two Phase III randomised, double-masked, sham-controlled studies in patients with macular oedema following central retinal vein occlusion or branch retinal vein occlusion. A total of 427 patients were randomised to OZURDEX® and 426 to sham in the two Phase III studies. A total of 401 patients (94%) randomised and treated with OZURDEX® completed the initial treatment period (up to day 180).

A total of 47.3% of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX® were increased IOP (24.0%) and conjunctival haemorrhage (14.7%).

The adverse reaction profile for BRVO patients was similar to that observed for CRVO patients although the overall incidence of adverse reactions was higher for the subgroup of patients with CRVO.

The following undesirable effects, considered related to OZURDEX® treatment were reported during these two Phase III clinical trials:

Table 1 Summary of Adverse Reactions in the Phase III studies

System Organ class	Frequency	Undesirable effect
Nervous system disorders	uncommon	Headache
Eye disorders	very common	IOP increased, conjunctival haemorrhage*
	common	Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*
	uncommon	Retinal tear*, anterior chamber flare*

* Undesirable effects considered to be related to the intravitreal injection procedure rather than the dexamethasone implant

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) undesirable effects are presented according to System Organ Class in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 the temporary use of 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.

The adverse event profile of 100 patients analysed following a second injection of OZURDEX®, was similar to that following the first injection. The incidence of increased IOP was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. As expected, the overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

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 [(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 haemorrhage (6.0%, 17/283), and increased IOP (24.0%, 68/283).

Treatment of Diabetic Macular Oedema:

The clinical safety of OZURDEX® was assessed in 2 Phase III randomised, masked, Sham-controlled studies in patients with DME. 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 2:

Table 2 Summary of Adverse Reactions in Phase 3 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 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 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 peak mean IOP 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 in the OZURDEX® group required IOP-lowering medication(s) at baseline. In total, the collective proportion of patients in the OZURDEX® group 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% in the OZURDEX® group 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 IOP 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.

Treatment of Uveitis

The clinical safety of OZURDEX® was assessed in a single, multi-center, masked and randomised, 26-week Phase III 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 III 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. During the treatment period, no patients required incisional surgery for raised IOP. Three patients required laser iridotomies in the study eye for the treatment of pupillary block, iris bombe, and raised IOP.

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 (see **Treatment of Retinal Vein Occlusion**).

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
Central serous chorioretinopathy

General disorders and administration site conditions

Complication of device insertion resulting in ocular tissue injury (implant misplacement)
Device dislocation with or without corneal oedema/ corneal decompensation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

No case of overdose has been reported in clinical trials and would not be expected due to its method of administration.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroid

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. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

5.2 Pharmacokinetic properties

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month retinal vein occlusion (RVO) efficacy studies prior to dosing and on days 1, 7, 30, 60, and 90 following the intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% 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.

In two Phase 3 diabetic macular oedema (DME) studies, 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 700 µg 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 350 µg dexamethasone 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.

The anatomy and physiology of the monkey eye is closely similar to the human eye. In both the monkey and human eyes, the vitreal clearance of dexamethasone is rapid and ocular concentrations will be controlled by DDS® delivery. In the monkey, the time course for release of dexamethasone into the vitreous humor showed considerable variability (standard deviations, 33-70% of the mean). However, the variability of mean dexamethasone exposure (AUC) in all ocular tissues (retina, iris, ciliary body, aqueous humour, and vitreous) over 3 months was relatively low (~30%).

In a 6-month monkey study following a single intravitreal injection of OZURDEX® the concentration of dexamethasone in vitreous humor (the half distal to the implant) peaked at 100 ng/mL at day 42 post-injection and was 5.57ng/mL at day 91. Dexamethasone remained detectable in the vitreous to 3 months post-injection, at which time release from the implant was complete. The rank order of dexamethasone exposure (AUC and C_{max}) was ciliary body > iris > retina > aqueous humor > vitreous humor > plasma.

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. This is consistent with results from rabbit and monkey ocular metabolism studies.

Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

The OZURDEX® matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, and then further degrades into carbon dioxide and water.

5.3 Preclinical safety data:

Carcinogenicity and Genotoxicity:

No carcinogenicity data are available for OZURDEX®. Dexamethasone was negative in some bacterial reverse gene mutation assays, but the results are not conclusive, and dexamethasone was found to be clastogenic both *in vitro* in human blood lymphocytes and *in vivo* in mice.

CLINICAL STUDIES

Retinal Vein Occlusion:

The efficacy of OZURDEX® in RVO was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies which together comprised 1,267 patients who were randomised to receive treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to

OZURDEX®**,** 414 to dexamethasone 350 µg and 426 patients to sham.

Based on the pooled analysis results, treatment with OZURDEX® implants showed statistically significantly greater incidence of responders, defined as patients achieving a ≥ 15 letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at 90 days following injection of a single implant, when compared with sham ($p < 0.001$).

The proportion of patients achieving the primary efficacy measure of ≥ 15 letter improvement from baseline in BCVA following injection of a single implant is 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 the incidence of responders 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 from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

Visit	OZURDEX® N = 427	Sham N = 426
Day 30	21.3 % [a]	7.5%
Day 60	29.3% [a]	11.3%
Day 90	21.8% [a]	13.1%
Day 180	21.5%	17.6%

[a] Proportion significantly higher with OZURDEX® compared to sham ($p < 0.001$)

The mean change from baseline BCVA was significantly greater with OZURDEX® compared to sham at all-time points.

In each Phase III study and the pooled analysis, the time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response curves were significantly different with OZURDEX® compared to sham ($p < 0.001$) with OZURDEX® treated patients achieving a 3-line improvement in BCVA earlier than sham treated patients.

OZURDEX® was numerically superior to sham in preventing vision loss as shown by a lower proportion of patients experiencing deterioration of vision of ≥ 15 letters in the OZURDEX® group throughout the 6-month assessment period.

In each of the Phase III studies and the pooled analysis, mean retinal thickness was significantly less, and the mean reduction from baseline was significantly greater, with OZURDEX® (-207.9 microns) compared to sham (-95.0 microns) at day 90 ($p < 0.001$, pooled data). The treatment effect as assessed by BCVA at day 90 was thus supported by this anatomical finding. By day 180 the mean retinal thickness reduction (-119.3 microns) compared with sham was not significant.

Patients who had a BCVA score of < 84 letters OR retinal thickness > 250 microns by optical coherence tomography (OCT) and in the investigator's opinion treatment would not put the patient at risk; were eligible to receive OZURDEX® treatment in an open label extension. Of the patients who were treated in the open label phase, 98% received an OZURDEX® injection between 5 and 7 months after the initial treatment.

As for the initial treatment, peak response 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 results in a lower proportion of responders at all-time points in the open label phase when compared with those receiving a second OZURDEX® injection.

Diabetic Macular Oedema

The clinical efficacy of OZURDEX® was assessed in two Phase 3 randomised, masked, sham-controlled studies in patients with DME. A total of 1,048 patients (351 OZURDEX®, 347 350 µg dexamethasone, and 350 Sham) were evaluated as the 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 mean average change from baseline during the study (AUC approach) in the study eye.

Patients were eligible for retreatment based upon central subfield retinal thickness >175 microns by 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 (AUC approach)
In study 1, 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 2, 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).

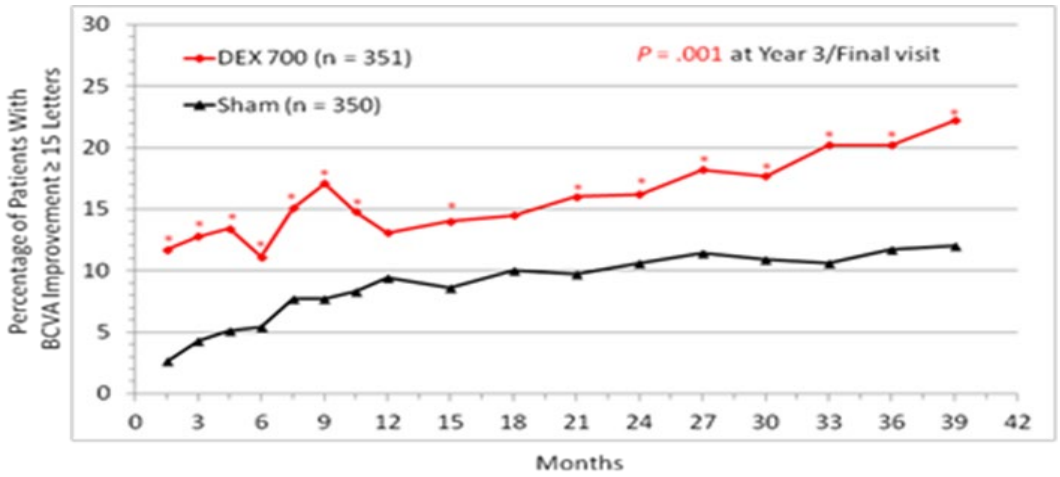
In the pooled analysis, the mean BCVA average change from baseline during the study was significantly greater with OZURDEX® compared to Sham (3.5 letters versus 2.0 letters, p = 0.023).

BCVA Improvement ≥ 15 Letters from Baseline
In Study 1, 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 2, 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.

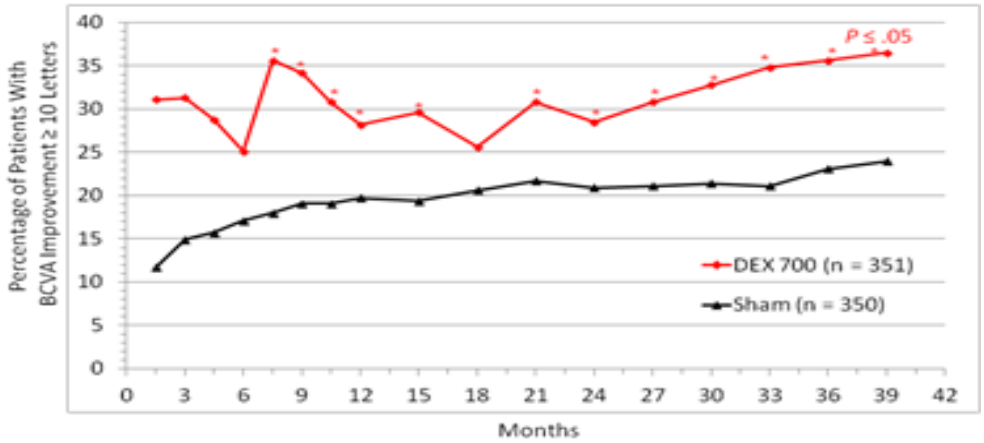
BCVA Improvement of 10 or More Letters from Baseline

In study 1, 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 2, 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 ≤ 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 1, 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 2, 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.

Mean decreases in retinal thickness at the centre subfield were consistently greater with OZURDEX® than with Sham throughout the study. 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 1,080 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%).

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.

A total of 229 patients were randomised to receive a single treatment of OZURDEX®, 350 µg dexamethasone or Sham. Of these, a total of 77 were randomised to receive OZURDEX®, 76 to 350 µg dexamethasone 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 5.

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 OZURDEX® 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 5.

Table 5 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 proportion of patients requiring escape medications from baseline to week 8 was nearly threefold less with OZURDEX® (7.8%) compared to Sham (22.4%), p=0.012.

There is no experience of repeat administration in posterior segment non-infectious uveitis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ester terminated 50:50 poly D, L-lactide-co-glycolide
Acid terminated 50:50 poly D, L-lactide-co-glycolide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

OZURDEX® has a shelf life of 3 years.

6.4 Special precautions for storage

Store below 25ºC. 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 consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab.

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

6.6 Special precautions for disposal

Not applicable

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
NEW ZEALAND
PH: 0800 900 030

9. DATE OF FIRST APPROVAL

16 December 2010

10. DATE OF REVISION OF THE TEXT

24 September 2025

SUMMARY TABLE OF CHANGES

Sections changed	**Summary of new information**
4.8	Inclusion of corneal decomposition and revision to website to report any suspected adverse reactions