PRESCRIBING INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OZURDEX 700 micrograms intravitreal implant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 700 micrograms of dexamethasone

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravitreal implant in applicator.

White to off-white rod-shaped implant containing dexamethasone located in the needle of a disposable applicator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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;
- Macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein occlusion (CRVO);
- Inflammation of the posterior segment of the eye presenting as non-infectious uveitis.

4.2 Posology and method of administration

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

Posology

The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended.

DME

Patients treated with OZURDEX who have experienced an initial response and who in the ophthalmologist's opinion may benefit from retreatment without being exposed to significant risk may be considered for retreatment.

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

RVO and Uveitis

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the ophthalmologist'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.

For information concerning the current safety experience of repeat administrations beyond 2 implants in posterior segment non-infectious uveitis and Retinal Vein Occlusion, see section 4.8.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).

Special populations

Elderly

No dosage adjustment is required for older patients (≥ 65 years old).

Renal impairment

OZURDEX has not been studied in patients with renal impairment.

Hepatic impairment

OZURDEX has not been studied in patients with hepatic impairment.

Paediatric population

There is no relevant indication for the use of OZURDEX in children below 18 years of age.

Method of Administration

Single-use intravitreal implant in applicator for intravitreal use only.

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

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) (see section 4.4). A broad-spectrum topical antimicrobial should be given prior to and on the day of the

injection procedure. The patient should be instructed to self-administer broad spectrum antimicrobial drops daily for 3 days before and after each injection.

Before the injection, the periocular skin, eyelid and ocular surface should be disinfected (using for example drops of povidone iodine 5 % solution on the conjunctiva as it was done in the clinical trials for the approval of OZURDEX) and adequate local anaesthesia should be administered. 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. Once the foil pouch is opened the applicator should be used immediately. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

For instructions on the administration of the intravitreal implant, see section 6.6.

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

Following the intravitreal injection patients should continue to be treated with a broad-spectrum antimicrobial.

Following the intravitreal injection, patients should be monitored for elevation in intraocular

pressure and for endophthalmitis (see section 4.4). 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 must be instructed to report any symptoms suggestive of endophthalmitis without delay. Each applicator can only be used for the treatment of a single eye.

4.3 Contraindications

- Hypersensitivity to dexamethasone or to any of the ingredients of OZURDEX, listed in section 6.1.
- Active or suspected ocular or periocular infection, including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis) and a history thereof, vaccinia, varicella, mycobacterial infections and fungal diseases. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex and not be used in active ocular herpes simplex.
- Advanced glaucoma (where the disease cannot be adequately controlled by medications alone) or uncontrolled glaucoma.
- Patients with hypersensitivity to any of the ingredients.
- Aphakic eyes with rupture of the posterior lens capsule.
- Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated IOLs and ruptured posterior lens capsule.
- Communication between vitreous cavity and anterior chamber.

4.4 Special warnings and precautions for use

Intravitreal injection of OZURDEX, has been associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. In addition, patients must be monitored following the injection to

permit early treatment if an infection or increased intraocular pressure occurs. 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 must be instructed to report any symptoms suggestive of endophthalmitis or any of the other above-mentioned events without delay, e.g. eye pain, blurred vision etc.

All patients with a posterior capsule tear, e.g. those with a posterior lens (e.g. due to cataract surgery), and/or those who have an iris opening to the vitreous cavity (e.g. due to iridectomy) with or without a history of vitrectomy, are at risk of implant migration into the anterior chamber. These patients should be closely monitored to allow for early diagnosis and management of device migration. Implant migration to the anterior chamber may lead to corneal oedema. Persistent severe corneal oedema could progress to the need of corneal transplantation. Other than those patients contra-indicated where OZURDEX should not be used (see section 4.3), OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored to allow for early diagnosis and management ~~for any signs~~ of implant migration.

Use of OZURDEX, may induce cataracts (including posterior subcapsular cataracts), increased IOP, steroid induced glaucoma and may result in secondary ocular infections.

In the 3-year DME clinical studies, at baseline 87 % of patients with a phakic study eye treated with OZURDEX had pre-existing lens opacification e.g. early cataract. 59,2 % of patients with a phakic study eye treated with OZURDEX underwent cataract surgery in the study eye (see section 4.8).

After the first injection the incidence of cataract appears higher in patients with non-infectious uveitis of the posterior segment compared with BRVO/CRVO patients. In BRVO/CRVO clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second

injection (see section 4.8). One patient out of 368 required cataract surgery during the first treatment and three patients out of 302 during the second treatment. In the non-infectious uveitis study, one patient out of the 62 phakic patients underwent cataract surgery after a single injection.

The prevalence of conjunctival haemorrhage in patients with non-infectious uveitis of the posterior segment appears to be higher compared with BRVO/CRVO and DME. This could be attributable to the intravitreous injection procedure or to concomitant use of topical and/or systemic corticosteroid or non-steroidal anti-inflammatory medications. No treatment is required since spontaneous resolution occurs.

Increases in intraocular pressure (IOP) may occur. The rise in IOP is transient and usually manageable with IOP lowering medication (see section 4.8). 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 of intraocular pressure should be managed appropriately post injection as needed. Patients of less than 45 years of age with macular oedema following Retinal Vein Occlusion or inflammation of the posterior segment of the eye presenting as non-infectious uveitis are more likely to experience increases in IOP.

Corticosteroids should be used cautiously in patients with a history of ocular viral (e.g. herpes simplex) infection and not be used in active ocular herpes simplex.

The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended. If bilateral treatment is performed at the same time, this could lead to an increased systemic exposure.

OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischaemia. Therefore OZURDEX is not recommended.

In RVO, anti-coagulant therapy was used in 1,7 % of patients receiving OZURDEX; there were no reports of haemorrhagic 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 event 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 %).

Anti-platelet medicines, such as clopidogrel, were used at some stage during the clinical studies in up to 56 % of patients. For patients using concomitant 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 reaction reported was conjunctival haemorrhage (up to 24 %).

OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicines.

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, consider evaluating for 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.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been performed.

Systemic absorption of dexamethasone is minimal with OZURDEX and no interactions are anticipated.

Co-administration with inhibitors of CYP450 3A4 may increase the plasma concentrations and pharmacologic effects of corticosteroids, which are primarily metabolized by the isoenzyme. The interaction has been reported with potent inhibitors such as clarithromycin, erythromycin, itraconazole, nefazodone, cobicistat, and ritonavir during concomitant use of various corticosteroids, including inhaled, nasal, and ophthalmic formulations. Systemic corticosteroid adverse effects may occur following intensive or long-term continuous ophthalmic corticosteroid therapy. Cushing's syndrome and adrenal insufficiency have been attributed to the interaction.

Anti-coagulant therapy was used in 1,7 % of patients with macular oedema due to retinal vein occlusion; there were no reports of haemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40 % of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27 %) compared with the control group (20 %). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24 %). Anti-coagulant or anti-platelet therapy should not be used within two weeks before the injection of OZURDEX. OZURDEX should be used with great caution in patients taking anti-coagulant or anti-platelet medicinal products, and only if the expected benefits outweigh the potential risks to the patient.

Systemic medicines which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Medicines which inhibit CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP

3A4. Co-administration with other medicines that are metabolised by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

OZURDEX is not recommended during pregnancy.

Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). 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 new-born 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.

Breastfeeding

Safety in lactation has not been established.

OZURDEX is not recommended during breastfeeding.

Fertility

There is no fertility data available

4.7 Effects on ability to drive and use machines

Patients may experience temporary visual blurring after receiving OZURDEX by intravitreal injection (see section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

Tabulated list of adverse reactions

The adverse reactions considered related to OZURDEX treatment from the Phase III clinical trials (DME, BRVO/CRVO and uveitis) and spontaneous reporting are listed by MedDRA System organ class in the table below using the following convention:

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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

System organ class	Frequency	Adverse Reaction / Side Effect
Nervous system disorders	Common	Headache
	Uncommon	Migraine
Eye disorders	Very common	Increased intraocular pressure, cataract, conjunctival haemorrhage*
	Common	Ocular hypertension, subcapsular cataract, vitreous haemorrhage*, reduced visual acuity*, visual impairment/ disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema*, conjunctival hyperaemia
	Uncommon	Necrotising retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the

		eye* anterior chamber inflammation*, anterior chamber cells/flares*, abnormal sensation in eye*, eyelid pruritus, scleral hyperaemia*
General disorders and administration site conditions	Uncommon	Device dislocation* (migration of implant) with or without corneal oedema, complication of device insertion resulting in ocular tissue injury* (implant misplacement)

* Indicates adverse reactions considered to be related to the intravitreal injection procedure (the frequency of these adverse reactions is proportional to the number of treatments given)

Description of selected adverse reactions

Diabetic Macular Oedema

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

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 3-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 3-year studies. Fifty nine percent (59 %) of patients with a phakic study eye required cataract surgery by the 3-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.

Twenty eight percent (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 3-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 four 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, one patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, one patient had an iridotomy for narrow angle glaucoma and one patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

BRVO/CRVO

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

The majority of patients (47,3 %) experienced at least one adverse event. The most frequently

reported events in patients who received OZURDEX were increased intraocular pressure (24,0 %) and conjunctival haemorrhage (14,7 %).

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

Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not required 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 reaction profile of 341 patients analysed following a second injection of OZURDEX, was similar to that following the first injection. A total of 54 % of patients experienced at least one adverse reaction. The incidence of increased IOP (24,9 %) 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.

The use of corticosteroids may produce glaucoma and may enhance the establishment of secondary ocular infections.

Post-approval observational study

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).

Uveitis

The clinical safety of OZURDEX in patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis, has been assessed in a single, multicentre, masked, randomised study.

A total of 77 patients were randomised to receive OZURDEX and 76 to receive sham. A total of 73 patients (95 %) randomised and treated with OZURDEX completed the 26-week study.

The most frequently reported adverse reactions in the study eye of patients who received OZURDEX were conjunctival haemorrhage (30,3 %), increased intraocular pressure (25,0 %) and cataract (11,8 %).

Post-approval observational study

Refer to ‘Post-approval observational study’ under ‘BRVO/CRVO’.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

You can also report side effects to AbbVie (Pty) Ltd via this e-mail address:

MEAPV@abbvie.com

4.9 Overdose

If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending medical practitioner.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A. 15.2. Ophthalmic preparations with corticosteroids

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage and phagocytic migration of the inflammatory response. 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.

Clinical efficacy and safety

Diabetic Macular Oedema

The efficacy of OZURDEX was assessed in two 3-year, multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1048 patients (studies 206207-010 and 206207-011). A total of 351 were randomised to OZURDEX (DEX700), 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 oedema 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 DEX700 group compared to sham (7 % vs 24 %).

The primary and key secondary endpoints for studies 206207-010 and 011 are presented in Table 2. The vision improvement in the OZURDEX group was confounded by cataract formation. Vision improvement was re-established upon removal of cataract.

Table 2. Efficacy in studies 206207-010 and 206207-011 (ITT population)

Endpoint	**Study 206207-010**		**Study 206207-011**		**Pooled Studies 206207-010 and 206207-011**	
	DEX 700 N = 163	**Sham N = 165**	**DEX 700 N = 188**	**Sham N = 185**	**DEX 700 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 centre 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 3.

Table 3. Efficacy in pseudophakic patients (pooled studies 206207-010 and 206207-011)

Endpoint	**DEX 700 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 centre 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 4.

Table 4. Efficacy in patients with any prior treatment (pooled studies 206207-010 and 206207-011)

Endpoint	**DEX 700 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 centre subfield mean average change over 3 years, AUC approach (µm)	-126,1	-39,0	< 0,001

BRVO/CRVO

The efficacy of OZURDEX was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1267 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 5. 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 5. 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 of 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 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 an 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.

Uveitis

The clinical efficacy of OZURDEX has been assessed in a single, multicentre, masked, randomised study for the treatment of non-infectious ocular inflammation of the posterior segment in patients with uveitis.

A total of 229 patients were randomised to receive dexamethasone 350 µg or 700 µg implants or sham. Of these, a total of 77 were randomised to receive OZURDEX, 76 to dexamethasone 350 µg and 76 to sham. A total of 95 % of patients completed the 26-week study.

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 maintained up to and including week 26 ($p \leq 0,014$) as shown in Table 6.

The cumulative response rate curves (time to vitreous haze score of 0) were significantly different for the OZURDEX group compared to the 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.

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 %), $p = 0,012$.

Table 6. Proportion of patients with vitreous haze score of zero and ≥ 15 letters improvement from baseline best corrected visual acuity in the study eye (ITT population)

Visit	Vitreous Haze Score of Zero		BCVA improvement from baseline of ≥15 letters	
	DEX 700 N = 77	Sham N = 76	DEX 700 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] $p = 0,014$

5.2 Pharmacokinetic Properties

Plasma concentrations were obtained from a subset of 21 patients in the two RVO, 6-month efficacy studies prior to dosing and on day 7, 30, 60 and 90 following intravitreal injection of a single intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent (95 %) 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. Plasma dexamethasone concentration did not appear to be related to age, body weight or sex of patients.

Plasma concentrations were obtained from a subgroup of patients in diabetic macular oedema pivotal clinical studies prior to dosing and on days 1, 7, and 21, and months 1,5 and 3 following intravitreal injection of a single intravitreal implant containing 350 µg or 700 µg dexamethasone.

One hundred percent (100 %) of the plasma dexamethasone concentration values for the 350 µg dose group and 90 % for the 700 µg dose group were below the lower limit of quantitation (0,05 ng/ml). The highest plasma concentration value of 0,102 ng/ml was observed in 1 subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In a 6-month monkey study following a single intravitreal injection the dexamethasone vitreous humour C_{max} was 100 ng/ml at day 42 post-injection and 5,57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humour > aqueous humour > plasma. Dexamethasone was released in the monkey vitreous up to 6 months.

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

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at doses considered sufficiently in excess of the maximum dose for human indicating little relevance to clinical use.

No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for OZURDEX. Dexamethasone has been shown to be teratogenic in mice and rabbits following

topical ophthalmic application.

Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

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

3 years

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

One pack contains:

One sustained release sterile implantable rod-shaped implant containing 700 µg of dexamethasone, located in the stainless steel needle of a disposable applicator.

The applicator consists of a stainless steel plunger within a needle where the implant is held in place by a silicone sleeve. 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. The foil pouch is packaged in an outer carton.

6.6 Special precautions for disposal and other handling

Do not use after the expiry date on the label.

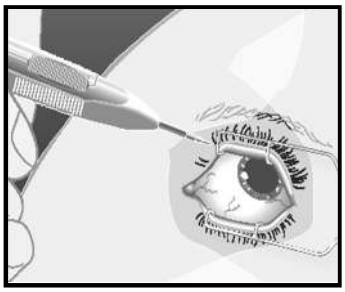
OZURDEX is for single use only. Each applicator can only be used for the treatment of a single eye.

If the seal of the foil pouch containing the applicator is damaged, do not use.

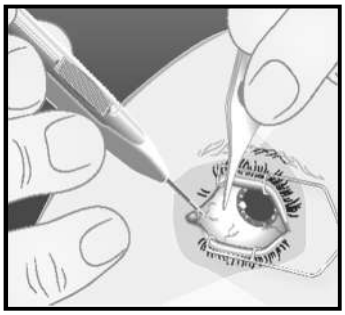
Once the foil pouch is opened the applicator should be used immediately.

Administering OZURDEX

1) Hold the long axis of the applicator parallel to the limbus.



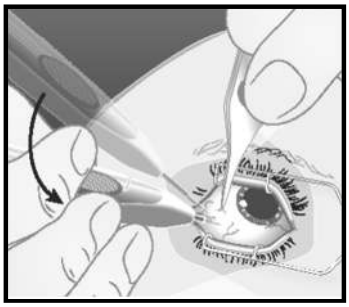
2) Allow the applicator to meet the sclera at an oblique angle with the bevel of the needle facing up, away from the sclera. Push the tip about 1 mm into the sclera, keeping it parallel to the limbus.



3) Redirect towards the centre of the eye into the vitreous cavity. This will create a shelved scleral path.

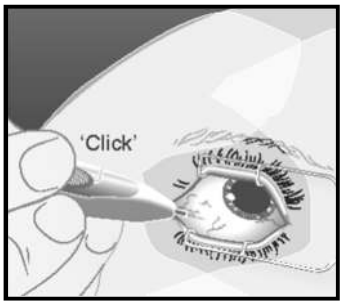
Advance the needle until you enter the vitreous cavity.

Do not advance the needle past the point where the sleeve of the applicator touches the conjunctiva.

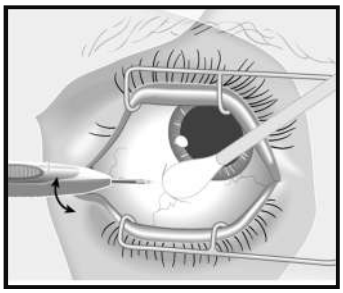


4) Depress the actuator button slowly until you hear a click.

Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface.



5) Withdraw the applicator in the same direction that you used to enter the vitreous.



6) Dispose of the applicator safely immediately after treatment.

The OZURDEX applicator is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Building 7

Waterfall Corporate Campus

74 Waterfall Drive

Midrand

1685

8. REGISTRATION NUMBER

44/15.2/0045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 December 2012

10. DATE OF REVISION OF TEXT

21 April 2023