SCHEDULING STATUS
Schedule 4

PROPRIETARY NAME AND DOSAGE FORM
OZURDEX intravitreal implant

COMPOSITION
One OZURDEX intravitreal implant contains:
Dexamethasone 700 µg
Excipients: Ester terminated 50:50 poly D,L-lactide-co-glycolide; acid terminated 50:50 poly D,L-lactide-co-glycolide.

PHARMACOLOGICAL CLASSIFICATION
A. 15.2. Ophthalmic preparations with corticosteroids

PHARMACOLOGICAL ACTION
Pharmacodynamic Properties
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.

Pharmacokinetic Properties
Plasma concentrations were obtained from a subset of 21 patients in the two, 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. 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 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. 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.

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.

There is limited data on the use of more than one application (refer to DOSAGE AND DIRECTIONS FOR USE).

CONTRA-INDICATIONS

- Hypersensitivity to dexamethasone or to any of the ingredients of OZURDEX.
- 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).
- 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.

WARNINGS AND SPECIAL PRECAUTIONS

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. 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. 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 CONTRA-INDICATIONS), OZURDEX should be used with caution and only following a careful risk benefit assessment. These patients should be closely monitored 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 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 SIDE EFFECTS).

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 SIDE EFFECTS). 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.

Conjunctival haemorrhage in patients with non-infectious uveitis of the posterior segment 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 SIDE 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 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 are more likely to experience increases in IOP.

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.

Effects on ability to drive and use machines
Patients may experience temporary visual blurring after receiving OZURDEX by intravitreal injection (see SIDE EFFECTS). They should not drive or use machines until this has resolved.

INTERACTIONS
No interaction studies have been performed.
Systemic absorption is minimal, but formal interactions studies have not been performed.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.
OZURDEX is not recommended during pregnancy or breastfeeding.

DOSAGE AND DIRECTIONS FOR USE
Single-use intravitreal implant in applicator for intravitreal use only.
Each applicator can only be used for the treatment of a single eye.
OZURDEX must be administered by a qualified 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.

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 of repeat administration 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.

Method of Administration
The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) (See WARNINGS AND SPECIAL PRECAUTIONS). A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure. 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.

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 WARNINGS AND SPECIAL PRECAUTIONS.) 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.

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

SIDE EFFECTS
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)

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. 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.

The mean increase from baseline IOP did not exceed 3,2 mmHg across all visits 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 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

During Phase III clinical trials, 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 edema following RVO and non-infectious uveitis affecting the posterior segment of the eye. The most frequent adverse reactions observed in this study were consistent with the most frequent adverse reactions from clinical trials. Stratifications by injection frequency revealed increases in the incidence of adverse reactions among patients who received > 2 injections compared to patients who received ≤ 2 injections. The most frequent adverse reactions for patients who received > 2 injections included cataract [(24,7 %, 44/178) for cataract formation and (32,0 %, 57/178) for cataract progression] based on eyes with phakic lens status at baseline, vitreous 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’.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending medical practitioner.

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

PRESENTATION

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.

STORAGE INSTRUCTIONS

Store at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

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.

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

REGISTRATION NUMBER

44/15.2/0045

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Allergan Pharmaceuticals (Pty) Ltd
30 New Road (entrance off Bavaria Road)
Randjespark Ext 11, Midrand, 1682
Johannesburg, Gauteng
SOUTH AFRICA

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of registration: 7 December 2012

Date of most recently revised Professional Information as approved by the Authority: 25 November 2016