ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator

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.

Disposable injection device, containing a rod-shaped implant. which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length.

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) (see section 5.1)
- 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 (see section 4.4).

DME
Patients treated with OZURDEX who have experienced an initial response and in the physician's opinion may benefit from retreatment without being exposed to significant risk should 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 currently 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 physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).

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 (see section 5.1).

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 (≥65 years old)
No dose adjustment is required for elderly patients.

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

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

Paediatric population
There is no relevant use of OZURDEX in the paediatric population in

- diabetic macular oedema
- macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of OZURDEX in uveitis in the paediatric population have not been established. No data are available.

Method of administration
OZURDEX is a 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).

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 (see section 6.6). 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients as 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), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.
- Aphakic eyes with ruptured posterior lens capsule.
- Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured posterior lens capsule.

4.4 Special warnings and precautions for use

Intravitreous injections, including those with OZURDEX, can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure 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 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 above mentioned events without delay, e.g. eye pain, blurred vision etc. (see section 4.8).

All patients with posterior capsule tear, such as 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 for corneal transplantation. Other than those patients contraindicated (see section 4.3) where OZURDEX should not be used, 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 of device migration.

Use of corticosteroids, including 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, 59% 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). Only 1 patient out of 368 required cataract surgery during the first treatment and 3 patients out of 302 during the second treatment. In the non-infectious uveitis study, 1 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.

As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. The rise in IOP is normally 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 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.

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

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

In RVO, anti-coagulant therapy was used in 2% 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 events was similar in the OZURDEX and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of OZURDEX treated patients reported haemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with OZURDEX who received anti-coagulant therapy (11%) compared with those not receiving anticoagulant therapy (6%).

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

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

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 medicinal products and other forms of interaction

No interaction studies have been performed.
Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

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 newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment, OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding
Dexamethasone is excreted in breast milk No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive and use machines

OZURDEX may have a moderate influence on the ability to drive and use machines. Patients may experience temporarily reduced vision 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

Summary of the safety profile
The most commonly-reported adverse events reported following treatment with OZURDEX are those frequently observed with ophthalmic steroid treatment or intravitreal injections (elevated IOP, cataract formation and conjunctival or vitreal haemorrhage respectively).

Less frequently reported, but more serious, adverse reactions include endophthalmitis, necrotizing retinitis, retinal detachment and retinal tear.

With the exception of headache and migraine, no systemic adverse drug reactions were identified with the use of OZURDEX.

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 Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous system disorders	Common	Headache
	Uncommon	Migraine
Eye disorders	Very common	Intraocular pressure increased**, cataract**, conjunctival haemorrhage*
	Common	Ocular hypertension, cataract subcapsular, vitreous haemorrhage**, visual acuity reduced*, visual impairment/ disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema* conjunctival hyperaemia*
	Uncommon	Necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the eye*, anterior chamber inflammation*, anterior chamber cells/ flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*
General disorders and administration site conditions	Uncommon	Device dislocation* (migration of implant) with or without corneal oedema (see also section 4.4), 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).
** in a 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 these adverse events were reported more frequently among patients who received >2 injections vs patients who received ≤2 injections; cataract formation (24.7% vs 17.7%), cataract progression (32.0% vs 13.1%), vitreous haemorrhage (6.0% vs 2.0%), and increased IOP (24.0% vs 16.6%).

Description of selected adverse reactions
Diabetic Macular Oedema

The clinical safety of OZURDEX in patients with diabetic macular oedema was assessed in two phase 3 randomized, double-masked, sham-controlled studies. In both studies, a total of 347 patients were randomized 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.

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

28% of patients treated with OZURDEX had a ≥ 10 mm Hg IOP increase from baseline at one or more

visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the 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 4 patients (1%) treated with OZURDEX had procedures in the study eye for the treatment of IOP elevation. One patient treated with OZURDEX required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation, 1 patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 1 patient had an iridotomy for narrow angle glaucoma and 1 patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

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. A total of 427 patients were randomised to receive OZURDEX and 426 to receive 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 intraocular pressure (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.

Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. 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.

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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinflammatory agents, ATC code: S01BA01

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 1,048 patients (studies 206207-010 and 206207-011). A total of 351 were randomised to OZURDEX, 347 to dexamethasone 350 µg and 350 patients to sham.

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

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

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

The primary and key secondary endpoints for studies 206207-010 and 011 are presented in Table 2. The vision improvement in the DEX700 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 center subfield mean average change over 3 years, AUC approach (µm)	-101.1	-37.8	-120.7	-45.8	-111.6	-41.9
P-value	<0.001		< 0.001		< 0.001	

The primary and key secondary endpoints for the pooled analysis for pseudophakic patients are presented in Table 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 center subfield mean average change over 3 years, AUC approach (µm)	-131.8	-50.8	< 0.001

The primary and key secondary endpoints for the pooled analysis for patients with any prior treatment are presented in Table 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 center 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 1,267 patients who were randomized 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] $p = 0.014$

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with OZURDEX in all subsets of the paediatric population for retinal vascular occlusion and also for diabetic macular oedema (see section 4.2 for information on paediatric use).

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 days 7, 30, 60 and 90 following intravitreal injection of a single 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. 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 the two DME pivotal 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 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 of OZURDEX 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.

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

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, 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each pack contains:

One sustained release sterile implantable rod shaped implant containing 700 micrograms 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.

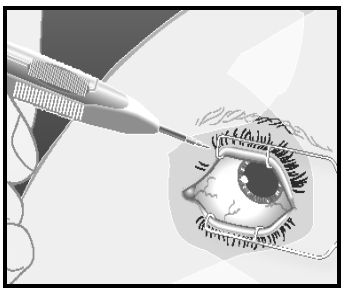
6.6 Special precautions for disposal and other handling

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

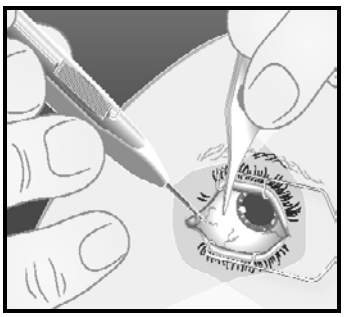
If the seal of the foil pouch containing the applicator is damaged, the applicator must not be used.
Once the foil pouch is opened the applicator should be used immediately.

Administering OZURDEX

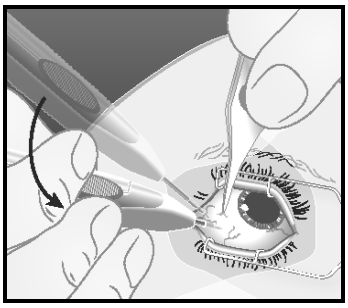
1) Hold the long axis of the applicator parallel to the limbus.



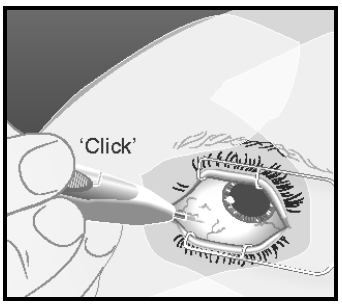
2) Allow the applicator to meet the sclera at an oblique angle with the bevel of the needle facing up, away from the sclera. Push the tip about 1 mm into the sclera, keeping it parallel to the limbus.



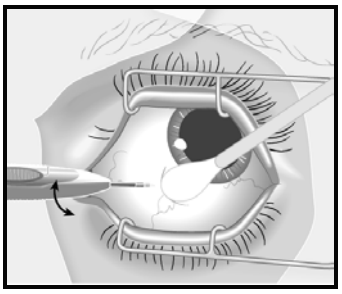
3) Redirect towards the centre of the eye into the vitreous cavity. This will create a shelved scleral path.
Advance the needle until you enter the vitreous cavity.
Do not advance the needle past the point where the sleeve of the applicator touches the conjunctiva.



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

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Co. Mayo
Westport
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/638/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27/07/2010
Date of latest renewal: 23/03/2015

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport, Co Mayo
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit:risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

If the dates for submission of a PSUR and the update of the RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where OZURDEX is marketed, at launch and after launch all ophthalmological clinics where OZURDEX is expected to be used are provided with an up-to-date patient information pack.

The patient information pack should be provided in both the form of patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for OZURDEX treatment
- What are the steps following treatment with OZURDEX
- Key signs and symptoms of serious adverse events including: worsening of vision after the injection; pain or discomfort in or around the eye, redness of the eye which continues to get worse; increase in floaters or spots in the vision; discharge from the eye
- When to seek urgent attention from their health care provider

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND POUCH EXTENDED LABEL

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator
dexamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One implant contains 700 micrograms of dexamethasone

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

One intravitreal implant in applicator.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
Intravitreal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH AND OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if foil pouch seal is damaged.

8. EXPIRY DATE

EXP
Once pouch opened, use applicator immediately.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/638/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

APPLICATOR LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OZURDEX 700 micrograms intravitreal implant in applicator
dexamethasone
Intravitreal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 implant

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

OZURDEX 700 micrograms intravitreal implant in applicator
dexamethasone

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor. See section 4.

What is in this leaflet

1. What OZURDEX is and what it is used for

The active substance in OZURDEX is dexamethasone. Dexamethasone belongs to a group of medicines called corticosteroids.

OZURDEX is used to treat adult patients with:

- Vision loss due to diabetic macular oedema (DME), if you have already had an operation for cataract, or if you have not previously responded to, or are not suitable for, other types of treatment. Diabetic macular oedema is a swelling of the light-sensitive layer at the back of the eye called the macula. DME is a condition that affects some people with diabetes.

- Vision loss caused by a blockage of veins in the eye. This blockage leads to a build up of fluid causing swelling in the area of the retina (the light-sensitive layer at the back of the eye) called the macula.

  Swelling of the macula may lead to damage which affects your central vision which is used for tasks like reading. OZURDEX works by reducing this swelling of the macular which helps to lessen or prevent more damage to the macula.

- Inflammation of the back of the eye. This inflammation leads to a decrease of vision and/or the presence of floaters in the eye, (black dots or wispy lines that move across the field of vision). OZURDEX works by reducing this inflammation.

2. What you need to know before you are given OZURDEX

You must not be given OZURDEX

- if you are allergic to dexamethasone or any of the other ingredients of this medicine (listed in section 6)
- if you have an infection of any kind in or around your eye (bacterial, viral or fungal)
- if you have glaucoma or high pressure inside your eye which is not controlled properly with the medicines you may be using
- if the eye to be treated does not have a lens and the back of the lens capsule (“the bag”) has been ruptured

- if the eye to be treated has undergone cataract surgery and has a man-made lens, which was implanted in the front compartment of the eye (anterior chamber intraocular lens) or was fixed to the white portion of the eye (sclera) or to the coloured part of the eye (iris), and the back of the lens capsule ("the bag") has been ruptured

Warnings and precautions

Before your OZURDEX injection tell your doctor if:
- You have had cataract surgery, iris surgery (the coloured part of the eye that controls the amount of light that enters into the eye) or surgery to remove the gel (called the vitreous) from within the eye
- You are taking any medicines to thin the blood
- You are taking any steroid or non-steroidal anti-inflammatory medicines by mouth or applied to the eye
- You have had a herpes simplex infection in your eye in the past (an ulcer on the eye that has been there a long time, or sores on the eye)

Occasionally the injection of OZURDEX may cause an infection inside the eye, pain or redness in the eye, or a detachment or tear of the retina. It is important to identify and treat these as soon as possible. Please tell your doctor immediately if you develop increased eye pain or increased discomfort, worsening redness of your eye, flashing lights and sudden increase in floaters, partially blocked vision, decreased vision or increased sensitivity to light after your injection.

In some patients the eye pressure may increase with the possible development of glaucoma. This is something you may not notice so your doctor will monitor you regularly and, if necessary provide treatment to lower the eye pressure.

In the majority of patients who have not yet had an operation for cataract, a clouding of the eye's natural lens (a cataract) may occur after repeated treatment with OZURDEX. If this occurs your vision will decrease, and you are likely to need an operation to remove the cataract. Your doctor will help you to decide when is the most appropriate time to perform this operation, but you should be aware that until you are ready for your operation your vision may be as bad or worse than it was before you started receiving your OZURDEX injections.

The implant can move from the back to the front of the eye in patients with a tear in the back of the lens capsule and/or those who have an opening in the iris. This can lead to swelling of the clear layer in the front of the eye and cause blurred vision. If this continues for a long time and is left untreated, it may require tissue transplantation.

The injection of OZURDEX into both eyes at the same time has not been studied and is not recommended. Your doctor should not inject OZURDEX into both eyes at the same time.

Children and adolescent (below 18 years of age)
The use of OZURDEX in children and adolescents has not been studied and is therefore not recommended.

Other medicines and OZURDEX
Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There is no experience of using OZURDEX in pregnant women or during breast-feeding. OZURDEX should not be used during pregnancy or breast-feeding unless your doctor thinks it is clearly necessary. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, discuss this with your doctor before OZURDEX treatment. Ask your doctor for advice before taking any medicine.

Driving and using machines

After OZURDEX treatment you may experience some reduced vision for a short time. If this happens, do not drive or use any tools or machines until your vision improves.

3. How OZURDEX is used

All OZURDEX injections will be given by an appropriately qualified eye doctor.

The recommended dose is one implant to be given by injection into your eye. If the effect of this injection wears off and your doctor recommends it, another implant may then be injected into your eye.

Your doctor will ask you to use antibiotic eye drops daily for 3 days before and after each injection to prevent any eye infection. Please follow these instructions carefully.

On the day of the injection, your doctor may use antibiotic eye drops to prevent infection. Before the injection, your doctor will clean your eye and eyelid. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection. You may hear a 'click' during the injection of OZURDEX; this is normal.

Detailed instructions for your doctor on how to carry out the OZURDEX injection are provided in the medicine carton.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may be seen with OZURDEX:

Very common (may affect more than 1 in 10 people):

Increased pressure in the eye, clouding of the lens (cataract), bleeding on the surface of the eye*

Common (may affect up to 1 in 10 people):

High pressure in the eye, clouding at the back of the lens, bleeding into the inside of the eye*, worsening of vision*, difficulties in seeing clearly, detachment of the jelly inside the eye from the light-sensitive layer at the back of the eye (vitreous detachment)*, a feeling of spots in front of the eye (including 'floaters')*, a feeling of looking through mist or fog*, inflammation of the eyelid, eye pain*, seeing flashes of light*, swelling of the layer over the white part of the eye*, redness of the eye*, headache

Uncommon (may affect up to 1 in 100 people):

A severe inflammation at the back of the eye (usually due to viral infection), serious infection or inflammation inside the eye*, glaucoma (an eye disease in which increased pressure in the eye is associated with damage to the optic nerve), detachment of the light-sensitive layer from the back of the eye* (retinal detachment), tear of the light-sensitive layer at the back of the eye (retinal tear)*, a decrease in the eye pressure which is associated with leakage of the jelly (vitreous) from inside the eye*, inflammation inside the front part of the eye*, increased protein and cells in the front of the eye due to inflammation*,

abnormal feeling in the eye * itchiness of the eyelid, redness of the white of the eye*, migration of the OZURDEX implant from the back to the front of the eye causing blurred or decreased vision and which may or may not cause swelling of the clear part of the eye (cornea)*, accidental incorrect placement of the OZURDEX implant*, migraine

**These side effects may be caused by the injection procedure and not the OZURDEX implant itself. The more injections you have the more these effects can occur.*

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store OZURDEX

Keep this medicine out of the sight and reach of children.

Do not use OZURDEX after the expiry date which is stated on the carton and the pouch after EXP:. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What OZURDEX contains

- The active substance is dexamethasone.
- Each implant contains 700 micrograms of dexamethasone.
- The other ingredients are: Ester terminated 50:50 poly D,L-lactide-co-glycolide and Acid terminated 50:50 poly D,L-lactide-co-glycolide.

What OZURDEX looks like and contents of the pack

OZURDEX is a rod-shaped implant which is stored inside the needle of an applicator. The applicator and a packet of drying material are sealed in a foil pouch which is inside a carton. One carton contains one applicator with one implant which will be used once and thrown away.

Marketing Authorisation Holder and Manufacturer

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien/
Luxembourg/Luxemburg/ Nederland
Allergan n.v
Tél/Tel: +32 (0)2 351 24 24

Latvija
Allergan Baltics UAB
Tel: +371 676 60 831

България
Алерган България ЕООД
Тел.: +359 (0) 800 20 280

Česká republika
Allergan CZ s.r.o.
Tel: +420 800 188 818

Danmark
Allergan Norden AB
Tlf: + 4580884560

Deutschland
Pharm-Allergan GmbH
Tel: +49 69 92038 1050

Eesti
Allergan Baltics UAB
Tel: + 37 2634 6109

Ελλάδα/Κύπρος
Allergan Hellas Pharmaceuticals S.A.
Τηλ: +30 210 74 73 300

España
Allergan S.A.
Tel: + 34 91 807 6130

France
Allergan France SAS
Tél: +33 (0)1 49 07 83 00

Hrvatska
Ewopharma d.o.o.
Tel: +385 1 6646 563

Ireland/Malta
Allergan Pharmaceuticals Ireland
Tel: 1800 931 787 (IE)
+356 27780331 (MT)

Ísland
Actavis Pharmaceuticals Iceland ehf.
Sími: +354 550 3300

Italia
Allergan S.p.A
Tel: + 39 06 509 562 90

Lietuva
Allergan Baltics UAB
Tel: +37052 072 777

Magyarország
Allergan Hungary Kft.
Tel.: +36 80 100 101

Norge
Allergan Norden AB
Tlf: +47 80 01 04 97

Österreich
Pharm-Allergan GmbH
Tel: +43 1 99460 6355

Polska
Allergan Sp. z o.o.
Tel.: +48 22 256 3700

Portugal
Profarin Lda.
Tel: + 351 21 425 3242

România
Allergan S.R.L.
Tel: +40 21 301 53 02

Slovenija
Ewopharma d.o.o.
Tel: + 386 (0) 590 848 40

Slovenská republika
Allergan SK s.r.o.
Tel: +421 800 221 223

Suomi/Finland
Allergan Norden AB
Puh/Tel: + 358 800 115 003

Sverige
Allergan Norden AB
Tel: + 46859410000

United Kingdom
Allergan Ltd
Tel: +44 (0) 1628 494026

This leaflet was last revised in MM/YYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

[To be provided in the carton]

The following information is intended for medical or healthcare professionals only, and includes the numbered sections of the SmPC which provide practical information for use of the medicinal product. Please refer to the SmPC for full product information.

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in 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) (see SmPC section 5.1)
- 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 (see SmPC section 4.4).

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

Special populations
Elderly (≥65 years old)
No dose adjustment is required for elderly patients.

Method of administration
OZURDEX is a 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).

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 (see SmPC section 6.6). 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients as listed in SmPC 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), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.
- Aphakic eyes with ruptured posterior lens capsule.
- Eyes with Anterior Chamber Intraocular Lens (ACIOL), iris or transscleral fixated intraocular lens and ruptured posterior lens capsule.

4.4 Special warnings and precautions for use

Intravitreous injections, including those with OZURDEX, can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure 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 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 above mentioned events without delay, e.g. eye pain, blurred vision etc. (see SmPC section 4.8).

All patients with posterior capsule tear, such as 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 for corneal transplantation. Other than those patients contraindicated (see SmPC section 4.3) where OZURDEX should not be used, 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 of device migration.

Use of corticosteroids, including 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, 59% of patients with a phakic study eye treated with OZURDEX underwent cataract surgery in the study eye (see SmPC 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 SmPC section 4.8). Only 1 patient out of 368 required cataract surgery during the first treatment and 3 patients out of 302 during the second treatment. In the non-infectious uveitis study, 1 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.

As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. The rise in IOP is normally 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 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 herpes simplex 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.

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

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

In RVO, anti-coagulant therapy was used in 2% 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 events was similar in the OZURDEX and sham groups (29% vs 32%). Among patients who did not use anti-coagulant therapy, 27% of OZURDEX treated patients reported haemorrhagic adverse events compared to 20% in the sham group. Vitreous haemorrhage was reported in a higher proportion of patients treated with OZURDEX who received anti-coagulant therapy (11%) compared with those not receiving anticoagulant therapy (6%).

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

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

<u>Visual disturbance</u>

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 medicinal products and other forms of interaction

No interaction studies have been performed.
Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown teratogenic effects following topical ophthalmic administration (see SmPC 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 newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment**.** OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding
Dexamethasone is excreted in breast milk No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive and use machines

OZURDEX may have a moderate influence on the ability to drive and use machines. Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection (see SmPC section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

Summary of the safety profile
The most commonly-reported adverse events reported following treatment with OZURDEX are those frequently observed with ophthalmic steroid treatment or intravitreal injections (elevated IOP, cataract formation and conjunctival or vitreal haemorrhage respectively).

Less frequently reported, but more serious, adverse reactions include endophthalmitis, necrotizing retinitis, retinal detachment and retinal tear.

With the exception of headache and migraine, no systemic adverse drug reactions were identified with the use of OZURDEX.

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 Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous system disorders	Common	Headache
	Uncommon	Migraine
Eye disorders	Very common	Intraocular pressure increased**, cataract**, conjunctival haemorrhage*
	Common	Ocular hypertension, cataract subcapsular, vitreous haemorrhage**, visual acuity reduced*, visual impairment/ disturbance, vitreous detachment*, vitreous floaters*, vitreous opacities*, blepharitis, eye pain*, photopsia*, conjunctival oedema* conjunctival hyperaemia*
	Uncommon	Necrotizing retinitis, endophthalmitis*, glaucoma, retinal detachment*, retinal tear*, hypotony of the eye*, anterior chamber inflammation*, anterior chamber cells/ flares*, abnormal sensation in eye*, eyelids pruritus, scleral hyperaemia*
General disorders and administration site conditions	Uncommon	Device dislocation* (migration of implant) with or without corneal oedema (see also section 4.4), 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).
** in a 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 these adverse events were reported more frequently among patients who received >2 injections vs patients who received ≤2 injections; cataract formation (24.7% vs 17.7%), cataract progression (32.0% vs 13.1%), vitreous haemorrhage (6.0% vs 2.0%), and increased IOP (24.0% vs 16.6%).

Description of selected adverse reactions
Diabetic Macular Oedema

The clinical safety of OZURDEX in patients with diabetic macular oedema was assessed in two phase 3 randomized, double-masked, sham-controlled studies. In both studies, a total of 347 patients were randomized 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.

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

28% of patients treated with OZURDEX had a ≥ 10 mm Hg IOP increase from baseline at one or more visits during the study. At baseline 3% of patients required IOP-lowering medication(s). Overall, 42% of patients required IOP-lowering medications in the study eye at some stage during the 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 4 patients (1%) treated with OZURDEX had procedures in the study eye for the treatment of IOP elevation. One patient treated with OZURDEX required incisional surgery (trabeculectomy) to manage the steroid-induced IOP elevation, 1 patient had a trabeculectomy owing to anterior chamber fibrin blocking the aqueous outflow leading to increased IOP, 1 patient had an iridotomy for narrow angle glaucoma and 1 patient had iridectomy due to cataract surgery. No patient required removal of the implant by vitrectomy to control IOP.

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. A total of 427 patients were randomised to receive OZURDEX and 426 to receive 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 intraocular pressure (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.

Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. 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.

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%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

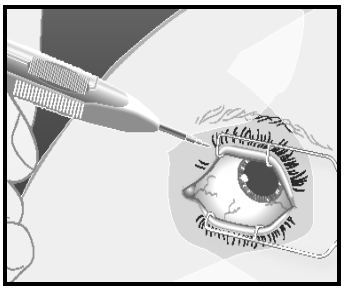
6.6 Special precautions for disposal and other handling

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

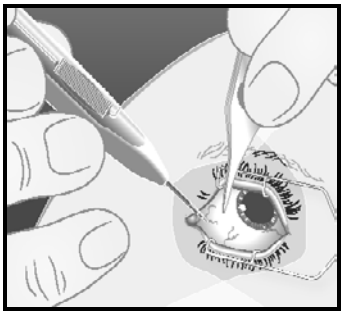
If the seal of the foil pouch containing the applicator is damaged, the applicator must not be used.
Once the foil pouch is opened the applicator should be used immediately.

Administering OZURDEX

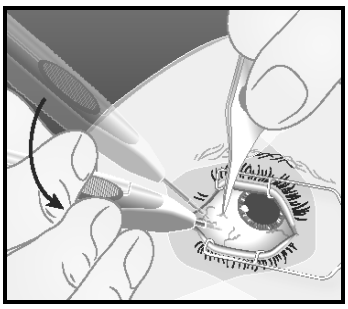
1) Hold the long axis of the applicator parallel to the limbus.



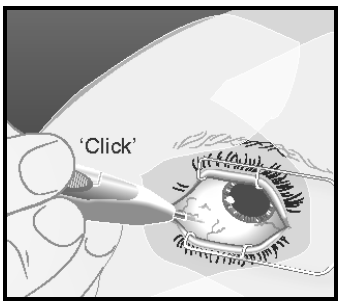
2) Allow the applicator to meet the sclera at an oblique angle with the bevel of the needle facing up, away from the sclera. Push the tip about 1 mm into the sclera, keeping it parallel to the limbus.



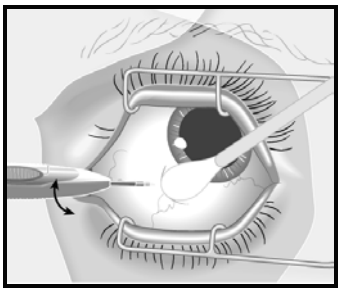
3) Redirect towards the centre of the eye into the vitreous cavity.
This will create a shelved scleral path.
Advance the needle until you enter the vitreous cavity.
Do not advance the needle past the point where the sleeve of the applicator touches the conjunctiva.



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