
DATA SHEET

NAME OF MEDICINE

OZURDEX[®] (dexamethasone) 700 µg implant

Presentation

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

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

Uses

Actions

Pharmacotherapeutic group: Corticosteroid

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

Pharmacokinetics

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month efficacy studies prior to dosing and on days 7, 30, 60, and 90 following the intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/mL). The highest plasma concentration value of 0.094 ng/mL was observed in one subject from the 700 µg group.

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

In a 6 month monkey study following a single intravitreal injection of OZURDEX[®] the concentration of dexamethasone in vitreous humor (the half distal to the implant) peaked at

100 ng/mL at day 42 post-injection and was 5.57ng/mL at day 91. Dexamethasone remained detectable in the vitreous to 3 months post-injection, at which time release from the implant was complete. The rank order of dexamethasone exposure (AUC and C_{max}) was ciliary body > iris > retina > aqueous humor > vitreous humor > plasma.

In an *in vitro* metabolism study, following the incubation of [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, and then further degrades into carbon dioxide and water.

Indications

OZURDEX[®] is indicated for the treatment of macular oedema due to Retinal Vein Occlusion (RVO).

Clinical Studies

The efficacy of OZURDEX[®] was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies which together comprised 1,267 patients who were randomised to receive treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to OZURDEX[®], 414 to dexamethasone 350 µg and 426 patients to sham.

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

The proportion of patients achieving the primary efficacy measure of ≥ 15 letter improvement from baseline in BCVA following injection of a single implant is shown in Table 1. 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 1. Proportion of Patients with ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

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

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

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

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

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

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

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

Dosage and Administration

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

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

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

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk. Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX[®] should not be retreated.

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

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure. The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad-spectrum topical

microbicide should be administered prior to the injection and following the intravitreal injection, patients may be treated with antibiotics and should be monitored. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between 2 and 7 days following the injection.

Aseptic technique should be maintained at all times prior to and during the injection procedure.

Remove the foil pouch from the carton and examine for damage. Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab.

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

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

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

Following the intravitreal injection, patients should be monitored for elevation in IOP and for endophthalmitis. 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.

Paediatric Use

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

Use in Elderly

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

Contraindications

OZURDEX[®] is contraindicated in:

- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma (disease that cannot be adequately controlled by medications alone)
- Hypersensitivity to the active substance or to any of the excipients.

Warnings and Precautions

General:

Any intravitreal injection can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure (IOP) and retinal detachment. Proper aseptic injection techniques must always be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased IOP should occur. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma, and may result in secondary ocular infections due to bacteria, fungi, or viruses.

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

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

Preclinical Findings:

Carcinogenicity and Genotoxicity:

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

Effects on Fertility:

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

Use in Pregnancy and Lactation: Category B3

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

Safety for use in lactation has not been established. OZURDEX[®] should not be used by breastfeeding women unless clearly necessary.

Effects on ability to drive and use machines:

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

Information for patients:

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

Adverse Effects

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

A total of 47.3% of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX[®] were increased 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.

- b) The following undesirable effects, considered related to OZURDEX[®] treatment were reported during these two Phase III clinical trials

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

Table 1.

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

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

- c) Increased IOP with OZURDEX[®] peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medications. During the initial treatment period, 0.7% (3/421) of the patients who received OZURDEX[®] required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2% (1/423) with sham.

The adverse event profile of 100 patients analysed following a second injection of OZURDEX[®], was similar to that following the first injection. The incidence of increased IOP was similar to that seen following the first injection and likewise returned to baseline

by open-label day 180. As expected, the overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

Interactions

No interaction studies have been performed.

Overdosage

No case of overdose has been reported

Pharmaceutical Precautions

OZURDEX® has a shelf life of 3 years.

Store below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

1 pack contains:

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

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

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

Further Information

List of excipients

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

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

Name and Address

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