Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for dexamethasone

Proprietary Product Name: Ozurdex

Sponsor: Allergan Australia Pty Ltd

October 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations 5

I. Introduction to product submission 7

Submission details 7

Product background 7

Regulatory status 8

Product Information 9

II. Quality findings 9

Introduction 9

Drug substance (active ingredient) 10

Drug product 10

Biopharmaceutics 12

Advisory committee considerations 12

Quality summary and conclusions 12

III. Nonclinical findings 13

Introduction 13

Pharmacology 13

Pharmacokinetics 14

Toxicology 16

Nonclinical summary and conclusions 19

IV. Clinical findings 24

Introduction 24

Pharmacokinetics 26

Pharmacodynamics 26

Dosage selection for the pivotal studies 26

Efficacy 26

Safety 28

First round benefit risk assessment 29

First round recommendation regarding authorisation 29

Clinical questions 30

Second round evaluation of clinical data submitted in response to questions 30

V. Pharmacovigilance findings 30

Risk management plan 30

VI. Overall conclusion and risk/benefit assessment 48

Quality 48

Nonclinical 48

Clinical 48
Risk management plan 52
Risk benefit analysis 53
Outcome 62
Attachment 1. Product Information 62
Attachment 2. Extract from the Clinical Evaluation Report 62

Common abbreviations

Abbreviation	Meaning
µm	micrometre
AAN	Australian approved name
ACPM	Advisory Committee on Prescription Medicines
ADRs	adverse drug reactions
AE	Adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
BCVA	best corrected visual acuity
BP	British Pharmacopoeia
BRVO	Branch Retinal Vein Occlusion
BSE	Better seeing eye
CRVO	Central Retinal Vein Occlusion
CSME	clinically significant macular oedema
DDS	drug delivery system
DEX PS DDS	Dexamethasone Posterior Segment Drug Delivery System
DME	diabetic macular oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HbA1c	glycosylated haemoglobin
IOP	intraocular pressure
ISE	integrated summary of efficacy
ISS	integrated summary of safety

Abbreviation	Meaning
ITT	Intention to treat
IVIVC	in vitro in vivo correlation
IVRS	interactive voice response system
IWRS	interactive web response system
LC MS/MS	liquid chromatography tandem mass spectrometry
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOEL	lowest observable effect level
ME	macular oedema
MedDRA	Medical Dictionary of Regulatory Activities
NOEL	No observable effect level
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
PLGA	poly [lactic glycolic] acid
PP	per protocol
PRP	panretinal photocoagulation
PSC	posterior subcapsular
SC	Subcutaneous
USP	United States Pharmacopeia
VAS	visual analogue scale
VEGF	vascular endothelial growth factor

I. Introduction to product submission

Submission details

Type of submission:	major variation; new dose form, new indication
Decision:	Approved
Date of decision:	29 May 2015
Date of entry onto ARTG	4 June 2015
Active ingredient:	Dexamethasone
Product name:	Ozurdex
Sponsor's name and address:	Allergan Australia Pty Ltd Locked Bag 1514 Pymble NSW 2073
Dose form:	Implant
Strength:	700 µg
Container:	Dispenser pack
Pack size:	One intravitreal implant
Approved therapeutic use:	*Ozurdex is indicated for the treatment of diabetic macular oedema (DME)*
Route(s) of administration:	Intravitreal – within the vitreous cavity of the eye
Dosage:	Ozurdex must be administered by a qualified ophthalmologist, experienced in intravitreal insertions. For further details regarding dosage please see the Product Information (PI)
ARTG number:	222392

Product background

This AusPAR describes the application by Allergan Australia Pty Ltd (the sponsor) to register Ozurdex dexamethasone 700 µg intravitreal implant for the following indication;

> *For the treatment of adult patients with visual impairment due to diabetic macular oedema, who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for, non-corticosteroid therapy.*

This submission is for new dose form of dexamethasone (sustained release intravitreal implant), new route of administration and new indication.

Ozurdex contains 700 µg of dexamethasone in an inactive biodegradable polymer matrix: this is named as a dexamethasone posterior segment drug delivery system (DEX PS DDS). Ozurdex implants provide sustained release of dexamethasone, thereby reducing the frequency of intravitreal injections.

Corticosteroids inhibit oedema, fibrin deposition and capillary leakage. They also prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema. The anti-inflammatory activity of the corticosteroid dexamethasone is well established, mediated by enhancement or inhibition of gene transcription leading to the up regulation or down regulation of multiple proteins. They have also been shown to inhibit the expression of vascular endothelial growth factor (VEGF); and have been hypothesised to antagonise VEGF mediated disease progression.

VEGF has been implicated as playing a pivotal role in diabetic macular oedema, along with roles for other cytokines/pathways.[1],[2] VEGF is already viewed as a viable therapeutic target for this disease, with treatment of visual impairment due to diabetic macular oedema included in the indications approved for ranibizumab (rbe) (Lucentis), a monoclonal antibody against VEGF administered by intravitreal injection.

Regulatory status

In March 2009, Allergan Australia submitted an application to register this product in Australia, for the treatment of adult patients with macular oedema due to either central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) [Submission No: PM-2009-00795-3-5]. The application was discussed at the 277th meeting (1 July 2011) of the Advisory Committee on Prescription Medicines (ACPM). The application was later withdrawn following a recommendation for rejection from the TGA's Delegate and the ACPM. The TGA's concerns were that the pivotal trials only showed marginal efficacy and that the optimal re-treatment period had not been well characterised.

For this application the indication will only be for diabetic macular oedema (DME).

This product has been approved by the FDA and EMA for 3 indications;

- macular oedema due to retinal vein occlusion (approved by FDA: 2009, EMA: 2010)
- non-infectious posterior segment uveitis (approved by FDA: 2010, EMA: 2011)
- diabetic macular oedema (approved by FDA: 2014, EMA: 2014).

At the time the TGA considered this application, a similar application had been approved in; (Argentina: 7 April 2011; Belgium: 1 September 2012; Brazil: April 2014; Bulgaria: 27 July 2012; Canada: 10 Feb 2011; Chile: 2 Jan 2012; Columba:* 22 March 2011; Cyprus: 27 July 2010; Ecuador: 31 August 2011; EU:* 27 July 2010; Hong Kong: 19 Jan 2011; India: 19 January 2010; Israel: 3 January 2012; Jordan: 21 April 2013; Korea:* 17 March 2011; Kuwait: 9 January 2013; Lebanon: 28 March 2013; Malaysia: 29 November 2012; Mexico: 25 January 2012; New Zealand: 17 December 2010; Peru: 30 July 2014; Philippines: 8 January 2014; Russian Federation: 23 November 2012; Serbia: 1 November 2011; Singapore: 23 November 2011; South Africa: 7 December 2012; Sri Lanka: 1 December 2011; Switzerland: 10 Jan 2011; Taiwan: 18 October 2012; Thailand: 5 February 2013; Turkey:* 28 February 2012; UAE: 10 June 2012; Ukraine: 2 July 2012; USA:* 17 June 2009; Vietnam: 22 March 2012). Note those marked with an asterisk* approved indications include for diabetic macular oedema.

For DME, the wording of the proposed Australian indication matches the wording of the EU indication:

> *adult patients with diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy.*

[1] Ehrlich R et al., Diabetic macular oedema: physical, physiological and molecular factors contribute to this pathological process. *Acta Ophthalmol.* 2010; 88: 279–291
[2] Owen LA and Hartnett ME. Soluble mediators of diabetic macular edema: the diagnostic role of aqueous VEGF and cytokine levels in diabetic macular edema. *Curr. Diab. Rep.* 2013; 13: 476–480

The EMA's CHMP considered that the benefit risk balance for Ozurdex for the originally proposed indication of "… *adult patients with diabetic macular oedema*" was negative. The concerns were:

> Only one of the two Phase III studies showed a statistically significant improvement on the pre specified primary endpoint (difference in mean best corrected visual acuity (BCVA) [area under the curve (AUC)] change from baseline) and this difference was small (1 to 2 letters over the 3 year study) and of questionable clinical significance (the minimal clinically important difference used in the sample size calculation was a 4 letter difference in the change).

As expected with corticosteroid injections, there was a high incidence of cataracts and raised intraocular pressure.

Based on subgroup analyses of the two Phase III trials, the CHMP considered that the benefit risk balance was favourable for the restricted patient population who were pseudophakic or insufficiently responsive or unsuitable for non-corticosteroid therapy.

The currently approved US indication is for *treatment of diabetic macular oedema*.

The indication initially approved by the FDA in the US was:

> *adult patients with diabetic macular oedema who have an artificial lens implant or who are scheduled for cataract surgery*

but, this was amended following a request from the FDA for a supplemental application.

This Australian application to the TGA initially proposed;

> *Treatment of diabetic macular oedema*

During the evaluation it was changed to that approved by the EMA:

> *adult patients with diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy*.

The final approved indication for this submission is:

> *Ozurdex is indicated for the treatment of diabetic macular oedema (DME).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product information pi>.

II. Quality findings

Introduction

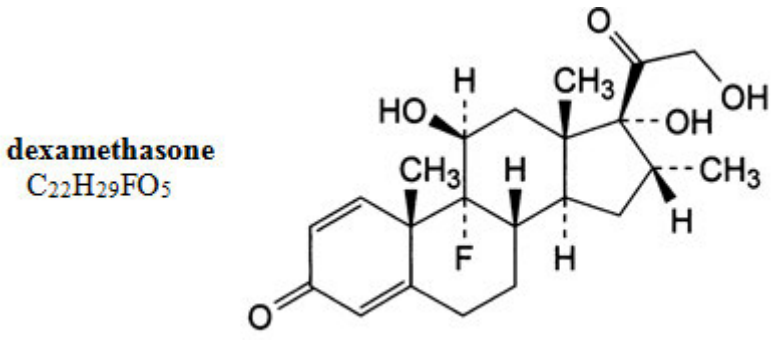
Ozurdex dexamethasone intravitreal implant is proposed for use in the treatment of diabetic macular oedema (DME). The implant is a solid rod of a biodegradable polymer matrix that will be implanted using an applicator into the posterior segment of the eye.

At the time of the ACPM for the previous submission (PM-2009-00795-3-5) all aspects of chemistry, manufacturing and quality had been resolved. However there are some differences between the previous submission and the current submission with regard to assays and limits.

Drug substance (active ingredient)

Ozurdex is formulated with dexamethasone, a synthetic steroid:

Figure 1 Structure of dexamethasone



Dexamethasone itself is currently registered in a number of products (frequently in combination with other drugs, not shown here):

- Maxidex 0.1% eye drops suspension [1 mg/mL]
- Dexmethsone 4 mg dexamethasone tablet
- Dexmethsone 0.5 mg dexamethasone tablet
- Sofradex Ear Drops dexamethasone 0.5 mg/mL
- Otodex Ear Drops dexamethasone 0.5 mg/mL
- Septodont Cresophene Application
- Buccal Solution dexamethasone 10,000 mg/g

There also dexamethasone derivatives:

- dexamethasone sodium phosphate; DBL Dexamethasone Sodium Phosphate Injections
- dexamethasone sodium phosphate Dexmethsone Injection

There are pharmacopoeial monographs for related steroid eye preparations (including Dexamethasone Suspension Eye Drops British Pharmacopoeia (BP), Dexamethasone Sodium Phosphate Solution Eye Drops BP, Dexamethasone Ophthalmic Suspension United States Pharmacopeia (USP), Dexamethasone Sodium Phosphate Ophthalmic Ointment USP and Dexamethasone Sodium Phosphate Ophthalmic Solution USP). However there is no monograph directly relevant to the proposed implant product.

The dexamethasone drug substance used in Ozurdex is the subject of BP and USP monographs. Micronised drug is used. Dexamethasone is practically insoluble in water (0.06 mg/mL). The drug substance manufacturer has provided adequate evidence to demonstrate that their production method leads only to polymorph Form B. Control of the drug substance is considered acceptable.

Drug product

Ozurdex delivers a biodegradable, extended release intravitreal implant. Two Ozurdex strengths were used in clinical trials: 350 µg and 700 µg, but it is only proposed to register the 700 µg implant in Australia.

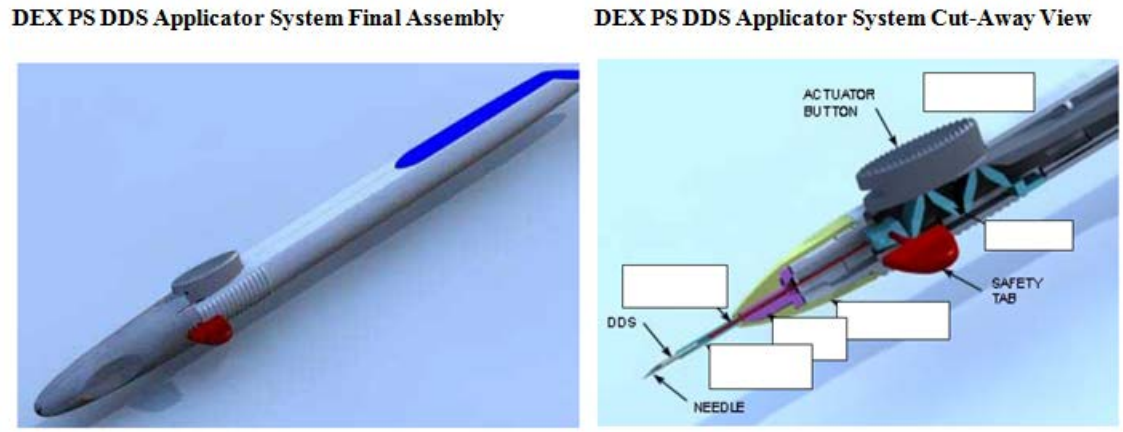
The dexamethasone is dispersed in a poly (D,L lactide co glycolide) polymer matrix and formed into a solid, rod shaped implant. The polymer matrix is a mixture of two different poly (D,L lactide co glycolide) polymers.

Both polymers are covered by the Australian approved name (AAN) 'polyglactin'.

The polymers slowly degrade in vivo by hydrolysis to lactic acid and glycolic acid. This erosion is an element in the controlled release of dexamethasone from the implant. Related polymers are used to make absorbable sutures (such as Dexon sutures used for ophthalmic surgery).

The implant is supplied pre-loaded in a single use, injector 'pen' as shown in Figure 2.

Figure 2. Diagram of implant injector pen



Pressing the button directly ejects the implant into the patient's eye (that is, it is not spring loaded). The implant is loaded close to the needle tip to minimise introduction of air into the eye. The 22 gauge needle projects 6 mm beyond the sleeve. Device aspects have been reviewed and are considered acceptable. There have been no significant changes to the device since the clinical trials.

The finished product is terminally sterilised by gamma irradiation. Manufacture causes minor degradation of dexamethasone to known impurities the levels of which have been toxicologically qualified.

Trials up to and including Phase IIa used 350 and 700 µg, compressed tablets with a different polymer composition. There were manufacturing difficulties with the tablets which led to development of the implant. Phase III trials used the proposed implant formulation.

Unlike some related products, recovered implants for this product cannot be usefully assayed to assess in vivo drug release. An in vitro drug release test was developed which is chiefly a quality control test of batch uniformity. This in vitro test was used in product development, with comparison to drug release into the vitreous humour of rabbit eyes. There appeared to be some in vitro in vivo correlation (IVIVC) between the 'real time' in vitro release and the in vivo release in rabbit eyes. However no formal IVIVC was calculated or validated.

Although there is no directly relevant EU guidance for what would be acceptable in vitro release limits for an intravitreal implant, many points in EU Guidance[3] which was adopted in Australia in April 2001 can be considered relevant. Thus in section 2.2 on oral products it is stated that;

> '*In general, a minimum of three points should be included in the specification on in vitro dissolution of an oral prolonged release product: an early time point to exclude dose dumping (typically 20 to 30% dissolved), at least one point to ensure*

[3] CPMP/QWP/604/96 (Note for Guidance on Quality of Modified Release Products: A: Oral Dosage Forms B: Transdermal Dosage Forms Section 1 (Quality)

> *compliance with the shape of the dissolution profile (around 50% dissolved) and one to ensure that the majority of the active has been released (generally more that 80% dissolved)'*

and

> *'The tolerance limits may be derived from the spread of the in vitro dissolution data of batches with demonstrated acceptable in vivo performance', but otherwise in the absence of a formal IVIVC (as here) 'the permitted variability in release at any given time point should not exceed a total numerical difference of ± 10% of the labelled content of the active substance'.*

As a result the sponsor was asked to provide the in vitro release results for the batches used in the clinical studies for the proposed indication.

The sponsor was also asked 'if any individual subjects did not show a positive clinical outcome and if this was the case analyse whether these subjects received a batch with low or high release rates'. The sponsor replied that no such analysis was possible, so in the absence of evidence to the contrary it was accepted that all clinical batches were efficacious.

Further the batch release data and stability data provided in the dossier indicate that these limits can be met.

All other quality control, stability and device aspects of the finished product are considered acceptable.

Biopharmaceutics

No bioavailability studies have been provided. The dose (700 μg) is relatively low and the product is locally acting. Plasma concentrations in patients were almost all below the lower limit of quantification (0.05 ng/mL). Systemic exposure is low.

Advisory committee considerations

There were no complicated issues with the chemistry, manufacturing and control aspects of this re submission and there were no bioavailability studies required as the product is for local action only. The details relating to this re submission were therefore not presented to PSC.

Quality summary and conclusions

Approval is not recommended from a pharmaceutical chemistry perspective as the proposed in vitro dissolution release limits have not been justified.[4]

EU Guidance [3] (albeit not specific for the proposed dosage form) only allows for a spread in the limits at any testing time based on the results observed for the clinical efficacy batches. In this case this allows for Level 1 limits of 40 to 70% at day 14, a maximum of 20% dissolved at 7 days and a minimum of 70% at day 21. The sponsor is proposing Level 1 limits which are not as tight as (wider than) these supported limits and has not justified the proposed limits on pharmaceutical chemistry (for example, with a IVIVC) or clinical grounds.

[4] In an email dated 12 February 2015 the sponsor agreed to adopt the above suggested in vitro release limits. Therefore approval can be recommended from a pharmaceutical chemistry and biopharmaceutics perspective.

Approval could be granted, however, if the sponsor were to amend the in vitro dissolution release limits at release and expiry to those described below or provide an acceptable clinical justification for why the currently proposed limits should be retained.

The quality evaluator suggested alternative in vitro release limits that could be met given the available data.

III. Nonclinical findings

Introduction

The nonclinical dossier contained data on primary pharmacology (nonclinical efficacy), pharmacokinetics (absorption, distribution and metabolism) and general toxicity after single and repeated intravitreal administration in animals. All of the toxicity studies were GLP compliant.

The nonclinical dossier of the current submission was the same as that submitted in Submission No. PM-2009-00795-3-5.

Pharmacology

Primary pharmacology

The anti-inflammatory activity of the corticosteroid dexamethasone is well established, mediated by enhancement or inhibition of gene transcription leading to the up regulation or down regulation of multiple proteins. With regard to efficacy for the proposed indication, VEGF has been implicated as playing a pivotal role in diabetic macular oedema, along with roles for other cytokines/pathways.[1,2] VEGF is already viewed as a viable therapeutic target for this disease, with treatment of visual impairment due to diabetic macular oedema included in the indications approved for ranibizumab (rbe)(Lucentis), a monoclonal antibody against VEGF administered by intravitreal injection.

Inhibition of VEGF expression by dexamethasone and other corticosteroids is reported in the literature.[5] Corticosteroids also inhibit prostaglandin release/synthesis, which has been implicated in the pathogenesis of cystoid macular oedema.[6] Intravitreal injection of VEGF in animals causes ocular changes that are characteristic of diabetic macular oedema: increased dilation and permeability of retinal blood vessels, and blood retinal barrier and blood aqueous barrier breakdown.[7],[8],[9];[10]

The sponsor investigated the effect of dexamethasone implants in a rabbit model of macular oedema. The intravitreal implants (350 and 700 µg/eye) produced dose dependent inhibition of blood retinal barrier breakdown, blood aqueous barrier

[5] Nauck Met al Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur. J. Pharmacol.* 1998; 341:309–315.
[6] Flach A.J. The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. *Trans. Am. Ophthalmol. Soc.* 1998; 96**:**557–634.
[7] Aiello L.P. et al. Vascular endothelial growth factor-induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective β-isoform-selective inhibitor. *Diabetes.* 1997; 46**:**1473–1480
[8] Ozaki H. et al. Intravitreal systained release of VEGF causes retinal neovascularisation in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. *Exp. Eye Res.* 1997; 64**:**505–517
[9] Tolentino M.J et al. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. *Am. J. Ophthalmol*. 2002; 133:373–385.
[10] Edelman J. et al. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp. Eye Res.* 2005; 80:249–258.

breakdown and retinal vasodilation/tortuosity induced by VEGF for up to 6 weeks post dose, returning to control levels by 10 weeks post dose. When adjusted for differences in the volume of vitreous humour across species (that is, 1.5 mL in rabbits compared with 4 mL in humans), the doses of dexamethasone used in the study are 1.3 to 2.7 times the proposed clinical dose. Similar findings were reported with another corticosteroid, triamcinolone (2 mg by intravitreal injection), as well as systemically administered dexamethasone (2 mg/kg/day, subcutaneous (SC)), but not with indomethacin (20 mg/kg/day, SC), ruling out the involvement of the cyclooxygenase pathway in VEGF induced blood ocular barrier breakdown.[10]

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamics or safety pharmacology data were submitted with this application. This is considered acceptable given the long history of clinical use of dexamethasone and the level of systemic exposure achieved.

Pharmacokinetics

Dexamethasone release from implants

In experiments in animals with the proposed commercial implants, 50% release of dexamethasone was observed approximately 2.5 weeks after implantation in rabbits and approximately 6 weeks after implantation in monkeys. Dexamethasone release from implants appeared to be highly variable in both species (see Figures 3 and 4), with standard deviations for percent release at particular time points of up to 37% seen in rabbits and 16% in monkeys. The majority (≥ 98%) of dexamethasone was generally released from implants in rabbit eyes in approximately 4 to 8 weeks, and complete release occurred within 13 weeks in monkeys. Implants were generally not visible in rabbit or monkey eyes 3 months post implantation. Fragmentation of the implant did not appear to alter the overall rate of dexamethasone release in rabbits.

Differences in the release profile were observed between early (used in two early single dose toxicity studies) and later forms of the implant (proposed commercial product; used in later toxicity studies) in comparative studies in rabbits. Release from the later implant was slower in the first two weeks following implantation, with approximately 2 to 3 times less dexamethasone released than from the tableted form.

Figure 3. Percent of dexamethasone released from DEX PS DDS over time for 350 µg and 700 µg DEX PS DDS in rabbits (n = 3 – 6)

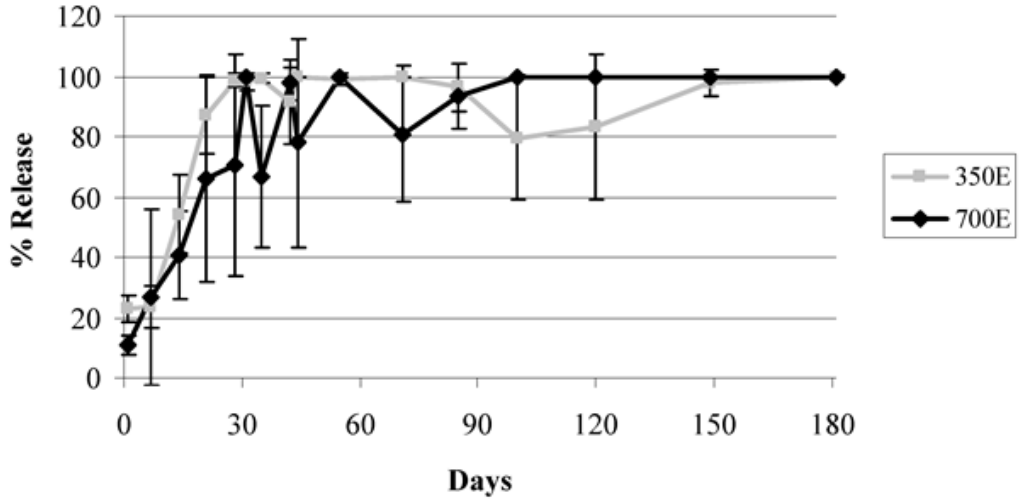
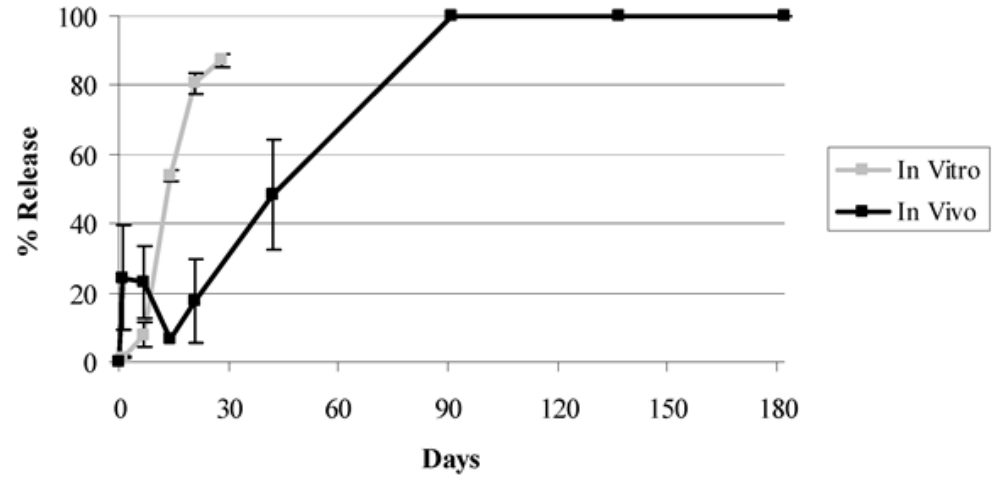


Figure 4. Percent of dexamethasone released from DEX PS DDS over time for 350 µg and 700 µg DEX PS DDS in monkeys (n = 1 – 4)



Absorption and distribution

Ocular and systemic exposure (based on AUC) to dexamethasone following single ocular implantation in rabbits (350 or 700 µg/eye) was approximately dose proportional. Distribution throughout the eye appeared to be extensive following intravitreal administration in rabbits and monkeys, with highest exposure seen in the retina in both species (approximately 1.4 to 3.9 times the AUC for vitreous humour). Peak dexamethasone concentrations were observed in the vitreous humour and most other ocular matrices 14 days after implantation of a single Ozurdex implant in rabbits and at 42 days post implantation in monkeys. In monkeys, the peak concentration of dexamethasone in the vitreous humour (the half distal to the 700 µg implant) was 100 ng/mL, and the apparent half-life was approximately 17 days. Dexamethasone remained detectable in the monkey vitreous to 3 months post injection.

Dexamethasone was detected in plasma of both animal species after intravitreal implantation, but only at very low levels. Systemic exposure (plasma AUC) to dexamethasone was substantially lower than that for vitreous humour (rabbit: approximately 2,300 times lower; monkey: approximately570 times lower) or

retina (rabbit: approximately3,750 times lower; monkey: approximately2,250 times lower).

Dexamethasone was shown to not bind to melanin in in vitro experiments.

Metabolism and excretion

To support the new route of administration, the ocular metabolism of dexamethasone was investigated in an in vitro study using human ocular tissue and in in vivo studies in rabbits and monkeys. No dexamethasone metabolites (only the unchanged drug) were detected in human cornea, iris, ciliary body, choroid, retina, vitreous humour or sclera following incubation for 18 hours, or in the aqueous and vitreous humour, retina, ciliary body, iris, choroid, cornea, lens or sclera from rabbits and monkeys for up to 24 hours post dose, apart from low levels of mono oxygenated dexamethasone in one monkey aqueous humour sample (accounting for less than 1% of sample radioactivity). Having already been adequately characterised, no further studies on the systemic metabolism of dexamethasone were conducted. The poly (D,L-lactide-co-glycolide) polymers used as excipients in the implant are degraded via backbone hydrolysis to lactic acid and glycolic acid, which are ultimately metabolised into carbon dioxide and water via normal metabolic pathways.

No conventional excretion studies were submitted for the dexamethasone implant, but systemic elimination is not expected to deviate from known pathways. Based on the distribution profile in rabbits and monkeys, clearance of dexamethasone from the vitreous humour is seen to be predominantly via diffusion into the retina/choroid/sclera membrane.

Toxicology

Three single dose toxicity studies (with observation periods of 4 to 24 weeks) were conducted in rabbits, and two repeat dose toxicity studies (two implantations, 3 months apart) of 12 months duration were conducted in rabbits and cynomolgus monkeys, by the intravitreal route. The single dose studies employed earlier forms of the implant and surgical implantation (sclerotomy), while the repeat dose studies used the clinical form of the implant, injected using the clinical (DEX PS DDS) applicator system. Animals in control groups received Sham treatment and/or placebo implants.

Relative exposure

Relative ocular exposure in the toxicity studies is estimated based on comparisons of the dose administered per volume of vitreous humour. Relative systemic exposure in the toxicity studies is estimated based on dose adjusted for body surface area. Bilateral administration is assumed for patients for the purpose of the risk assessment. A plasma AUC could not be calculated for humans as plasma dexamethasone concentrations in patients after intravitreal implantation were mostly below the limit of quantitation (0.05 ng/mL) or otherwise very low (maximum observed concentration, 0.102 ng/mL). Significant multiples of the human exposure was achieved at the upper dose levels in rabbits, while low to modest multiples were obtained in monkeys.

Table 3. Relative exposure to dexamethasone in toxicity studies

Species	Study details	Dose#				Relative exposure	
		µg/eye	µg/mL vitreous	µg/kg	µg/m²	ocular [a]	systemic[b]
Rabbit (NZW)	single dose; unilateral; 4 to 24 weeks observation [Study P0701002]	700	467	233	2800	2.7	3
		1400	933	467	5600	5	6
		2100	1400	700	8400	8	9
	single dose; bilateral; 4 to 6/7 weeks observation [Study X7I062G, X81310G]	700	467	467	5600	2.7	6
		1400	933	933	11200	5	12
		2100	1400	1400	16800	8	18
	two doses, 3 months apart; unilateral; 12 months duration [Study TX05030]	700	467	233	2800	2.7	3
		1400	933	467	5600	5	6
Monkey (Cynomolgus)	two doses, 3 months apart; unilateral; 12 months duration [Study TX050329]	350	109	117	1400	0.6	1.5
		700	219	233	2800	1.3	3
Human	(assumed bilateral)	700	175	28	924	–	–

= calculated based on vitreous humour volumes of 1.5 mL in rabbits, 3.2 mL in cynomolgus monkeys and 4 mL in humans,[11] rabbit and monkey body weights of 3 kg, human adult body weight of 50 kg, and using µg/kg to µg/m² conversion factors of 12 for rabbits and monkeys and 33 for humans; a = animal :human dose per unit volume of vitreous humour; b = animal :human dose per m² body surface area

Ocular findings

Gross and microscopic examinations revealed effects on multiple structures of the eye, with findings present at high incidence in rabbits and monkeys at all doses of dexamethasone (after one or two implantations) and also in eyes treated with placebo implant(s). Findings were generally more pronounced in rabbits, consistent with their higher local exposure compared with monkeys.

[11]Short B.G. (2008) Safety evaluation of ocular drug delivery formulations: techniques and practical considerations. *Toxicol. Pathol*. 2008; 36: 49–62.

In rabbits, treatment with dexamethasone was associated with the development of small opacities in the central area of the posterior cortex of the lens. This was observed at both doses in the 12 month study (in 1 out of 8 animals treated at 700 µg/dose and 2 out of 8 animals treated at 1,400 µg/dose; estimated relative exposure, ≥ 2.7) from 5 months of treatment onwards, persisting until the end of the observation period, though showing some evidence of recovery. The prolonged use of glucocorticoids in identified as a significant risk factor for the development of cataracts in the literature. The development of inflammatory cysts appeared to be related to dexamethasone treatment in the single dose studies in rabbits, but this was not observed in the repeat dose study (relative exposure, ≤ 5). There were no dexamethasone related ocular findings in monkeys (relative exposure, ≤ 1.3), and no clear effect on intraocular pressure (IOP) in either species.

Most ocular findings in the two laboratory animal species appeared to be related to the implantation procedure or the implant itself, rather than dexamethasone treatment. Findings in rabbits included posterior capsular cataracts, focal inflammation, retinal disruption (including detachment and haemorrhage), vitreous opacity, haemorrhage, haziness and pannus in single dose studies, and mixed cell infiltration of the eyelid in the 12 month study. Conjunctival congestion, swelling and discharge and fibroplasia/fibrosis of the implant site were observed in both animal species. Ocular findings were fewer and less severe in the 12 month studies compared with the single dose studies, attributable to the use of the DEX PS DDS applicator system for the implantation rather than sclerotomy. Most of the minor findings in the studies, particularly those associated with inflammation, appeared to resolve within several weeks of implantation; fibrosis at the site of the implant insertion was not reversed within 9 months of implantation.

The degree of ocular toxicity in one single dose study in rabbits was markedly greater than in another single dose study with the same treatment regimen. This was attributable to post-operative infection; steps were subsequently taken by the study investigators to ensure the sterility of the surgical suite.

Systemic toxicity

Systemic toxicity was investigated in both species, although the analysis was limited in most of the studies in rabbits (the exception being single dose study P0701002). Dexamethasone was well tolerated in monkeys, with not clear systemic treatment related effects up to an estimated relative exposure level of 3. Evidence of systemic toxicity was observed at all doses in all single dose studies in rabbits (relative exposure, 3 to 18). The findings were generally consistent with corticosteroid treatment, and included reduced body weight gain, lymphoid depletion (reduced white blood cell counts and lymphoid atrophy of the thymus, spleen and lymph nodes) and liver changes (fatty change predominantly in females, elevated liver enzymes and cloudy swelling and hydropic degeneration). Reversibility was demonstrated for most systemic findings. In the 12 month rabbit study, there was suppression of body weight gain at the high dose level (relative exposure, 6); non-ocular tissues were not subjected to microscopic examination in this study.

Genotoxicity, carcinogenicity and reproductive toxicity

The sponsor did not submit any studies on genotoxicity, carcinogenicity or reproductive toxicity. This is considered acceptable in view of the long history of clinical use of dexamethasone, existing nonclinical data, and the limited systemic exposure in patients.

Pregnancy classification

The sponsor proposed Pregnancy Category B3[12] for Ozurdex. This is consistent with the category for an existing ocular dexamethasone product, Maxidex eye drops, and is supported.

It is noted that there are other dexamethasone products that are in Category A (Dexmethsone tablets) or C (Dexmethsone and DBL, Dexamethasone sodium phosphate injection). The previously published TGA/ADEC Prescribing Medicines in Pregnancy booklet has given Category A[13] and C[14] for systemic dexamethasone in different editions. The available data support Category B3 as the appropriate category: there remains an outstanding concern for a risk of malformations (particularly cleft palate and cleft lip) with dexamethasone and other corticosteroids from human epidemiological studies[15],[16],[17],[18]; a finding consistent with teratogenicity observed with the drug (and other corticosteroids) in multiple laboratory animal species, recognised to be associated with drug induced disruption of cell proliferation and survival and protein signalling in developing tissues (for example, Hu et al.[19]).

Phototoxicity

No study investigating phototoxicity was submitted. This is acceptable given that dexamethasone does not absorb light within the range of natural sunlight (290 to 700 nm), consistent with the applicable guideline.[20]

The proposed specification for the drug substance/product is considered to be acceptable from a nonclinical perspective.

Paediatric use

Ozurdex is not proposed for paediatric use; no studies in juvenile animals were submitted.

Nonclinical summary and conclusions

Summary

- The nonclinical dossier contained data on primary pharmacology (nonclinical efficacy), pharmacokinetics (absorption, distribution and metabolism), and general

[12] Pregnancy Category B3 is defined as *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus have been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*
[13] Pregnancy Category A is defined as *Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.*
[14] Pregnancy Category C is defined as *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*
[15] Carmichael S.L., et al National Birth Defects Prevention Study Maternal corticosteroid use an orofacial clefts. *Am. J. Obstet. Gynaecol.* 2007; 197**:** 585.e1–585.e7.
[16] Källén B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac. J.* 2003; 40: 624–628
[17] Carmichael S.L. and Shaw G.M. Maternal corticosteroid use and risk of selected congenital anomalies. *Am. J. Med. Genet.* 1999; 86**:** 242–244.
[18] Rodríguez-Pinilla E. and Martínez-Frías M.L. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology.* 1998; 58**:** 2–5
[19] Hu Xet al Dexamethasone alters epithelium proliferation and survival and suppresses Wnt/β-catenin signaling in developing cleft palate. *Food Chem. Toxicol.* 2013; 56: 67–74.
[20] ICH S10 Photosafety evaluation of pharmaceuticals

toxicity after single and repeated intravitreal administration in animals. The nonclinical dossier was the same as that submitted in an earlier application to register this product for macular oedema due to central retinal vein occlusion or branch retinal vein occlusion, which was withdrawn by the sponsor following negative recommendations by the Clinical Evaluator and ACPM, and proposed rejection by the Delegate. The nonclinical studies were of adequate quality; all toxicity studies were conducted according to GLP.

- Of relevance to the proposed indication, intravitreal dexamethasone implants were shown to reduce vascular endothelial growth factor (VEGF) induced blood retinal barrier breakdown, blood aqueous barrier breakdown and retinal vasodilation/tortuosity in a rabbit model of macula oedema. The effect lasted for up to 6 weeks post dose. Adjusted for differences in vitreous humour volume across species, the doses used in the nonclinical efficacy study are 1.3 to 2.7 times the proposed clinical dose.
- The time course for dexamethasone release from the implants appeared to be highly variable in animals (assessed in rabbits and monkeys). Mean peak dexamethasone concentrations were observed in the vitreous humour 14 days after implantation in rabbits and at 42 days post implantation in monkeys. Dexamethasone remained detectable in the monkey vitreous to 3 months post injection. No metabolism of dexamethasone was apparent in vitro in human ocular tissues or in vivo in the rabbit eye; negligible ocular metabolism of dexamethasone was observed in vivo in monkeys.
- Plasma levels of dexamethasone after intravitreal implantation in rabbits and monkeys were very low. Systemic exposure (plasma AUC) in animals was approximately570 to 2,300 times lower than that for vitreous humour and approximately 2,250 to 3,750 times lower than for retina.
- Three single dose toxicity studies (with observation periods of 4 to 24 weeks) were conducted in rabbits, and repeat dose studies of 12 months duration (involving two implantations, 3 months apart) were conducted in rabbits and cynomolgus monkeys. The single dose studies involved surgical (sclerotomy) implantation of earlier forms of the implant, while the repeat dose studies used the clinical form of the implant, administered using the clinical applicator system.
- Dexamethasone related ocular findings in rabbits comprised inflammatory cysts in single dose studies and the development of small opacities in the central area of the posterior cortex of the lens in the 12 month study (estimated relative exposure, ≥ 2.7 [based on dose adjusted for vitreous humour volume]). No dexamethasone related ocular toxicity was observed in monkeys (relative exposure, ≤ 1.3). Other ocular findings related to the implantation procedure or the physical presence of the implant itself. These included posterior capsular cataracts, focal inflammation, retinal disruption (including detachment and haemorrhage), vitreous opacity, haemorrhage, haziness, and pannus in the single dose studies in rabbits, and mixed cell infiltration of the eyelid in the repeat dose rabbit study; conjunctival congestion, swelling and discharge and fibroplasia/fibrosis of the implant site were observed in both species. There were no clear effects on intraocular pressure in either species.
- Systemic toxicity was evident in rabbits at estimated relative exposure levels ≥ 3 (based on dose adjusted for body surface area and assuming bilateral clinical administration). Findings were generally consistent with corticosteroid administration (reduced body weight gain, lymphoid depletion and liver findings [fatty change, elevated liver enzymes, cloudy swelling and hydropic degeneration]), and reversible upon cessation of dexamethasone exposure. There was no evidence of systemic toxicity in monkeys at doses estimated to yield up to 3 times the maximum clinical exposure.

Conclusions and recommendation

- A nonclinical efficacy study in rabbits offers support for the use of the intravitreal implant in diabetic macular oedema.
- The major findings in the toxicity studies were ocular, and mostly related to the implantation procedure or the implant itself. A no observable effect level (NOEL) was not established for posterior lens opacities in rabbits (attributable to dexamethasone; relative exposure at the lowest observable effect level (LOEL), ≥ 2.7), although this was not seen in monkeys (relative exposure, ≤ 1.3). Ocular findings in the repeat dose studies are considered to be of potential significance in humans. Systemic toxicity in rabbits (relative exposure, ≥ 3) was consistent with corticosteroid administration. Ozurdex was well tolerated systemically in monkeys (relative exposure, 1.5 to 3).
- No safety pharmacology, reproductive toxicity, genotoxicity or carcinogenicity studies were submitted by the sponsor, which is acceptable given the long history of clinical use of dexamethasone, existing nonclinical data and the limited systemic exposure achieved in patients.
- No study on phototoxicity was submitted, but this is acceptable given the absence of absorption of relevant wavelengths of light by dexamethasone and that the drug does not bind to melanin.
- There are no nonclinical objections to the registration of Ozurdex provided that the ocular safety of the product is satisfactorily addressed by clinical data.
- The nonclinical evaluator also made recommendations with regard to the draft Product Information and the Risk Management Plan but these are beyond the scope of the AusPAR.

Additional nonclinical assessment

Allergan Australia Pty Ltd provided an updated draft PI document with their response to the TGA request for information. All changes to the PI that were requested by the nonclinical evaluator in the first round report have been adopted by the sponsor with one exception.

Pharmacokinetics

Absorption and distribution

The evaluator recommended that, in the absence of analogous ocular data for humans, information on vitreous concentrations of dexamethasone recorded in treated monkeys should be included in this section. The following text was recommended to be added:

> "In monkeys, single intravitreal implantation of Ozurdex 700 µg resulted in a peak concentration of dexamethasone in the vitreous humour (the half distal to the implant) of 100 ng/mL, observed 42 days post-injection. Dexamethasone remained detectable in the monkey vitreous to 3 months post-injection."

The sponsor proposed the following alternative text for the PI:

> "In monkeys, following single bilateral intravitreal implantation of Ozurdex 700 µg, peak concentration of dexamethasone was observed in the retina 60 days post injection. Dexamethasone remained detectable in the monkey retina for up to 7 months post injection."

and responded that:

> "Using the drug product that was used in the Phase III clinical studies, dexamethasone was detected in monkey eyes for 6 months (Report PK-07-095). The dexamethasone concentrations in vitreous humour were highest over Days 1

to 42 post intravitreal injection, declined relatively rapidly from days 43 to 90, and then declined gradually from days 91 to 180. At day 180, dexamethasone was still detectable at approximately 10 ng/mL. The results in this study are also in general agreement with another study reported in the literature,[21] where peak concentration was observed in the retina at 60 days post injection, and dexamethasone was found to be detectable in monkey retina at up to 7 months post injection. Therefore, Allergan believes that the proposed amended statement more accurately reflects the preclinical data."

The statement proposed by the evaluator is based on pharmacokinetic data reported in Study PK-06-113 (a sub-report of Study PK-06-115), involving single unilateral administration of implant (700 µg clinical form) in cynomolgus monkeys. Data are summarised in Table 4.

Table 4. Summary data of Study PK-06-113

Matrix		C_{max}	T_{max}	$t_{½}$	C_{last}	T_{last}
Vitreous humour	(half distal to implant)	100 ng/mL	day 42	17.4 days	5.57 ng/mL	day 91
Retina	(half proximal to implant)	180 µg/g	day 21	6.13 days	39.5 ng/g	day 91
	(half distal to implant)	399 ng/g	day 42	18.1 days	27.3 ng/g	day 91

Sampling at 1, 7, 14, 21, 42, 91, 137 and 182 Days post-dose; lower limit of quantitation (LLoQ): 0.5 ng/mL for vitreous humour and 0.1 ng/g for retina.

The sponsor refers to pharmacokinetic data reported in Study PK-07-095 (another sub-report of Study PK-06-115). This study included data for the quantification of dexamethasone in the half of the vitreous humour proximal to the implant; distal samples from the same animals were analysed in the study above. These data are summarised in Table 5.

Table 5. Pharmacokinetic data reported from Study PK-07-095

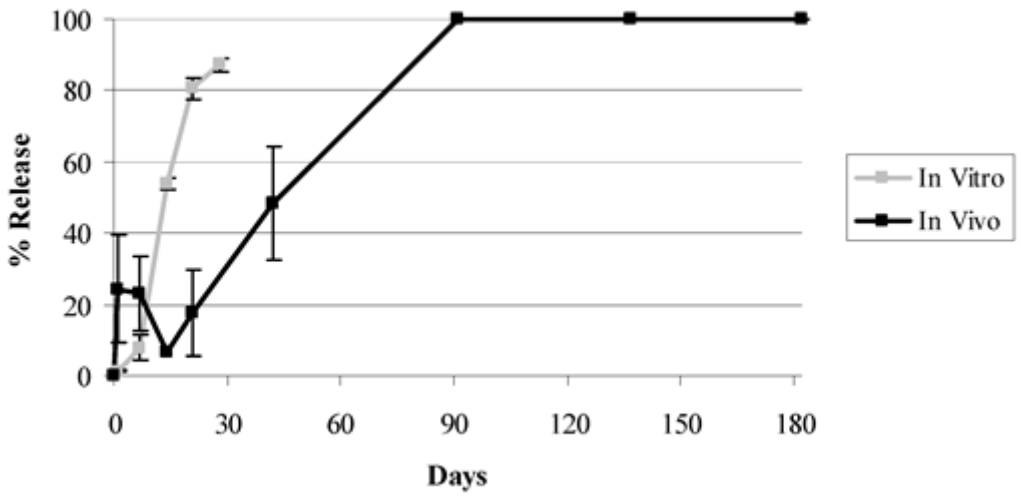
Matrix		C_{max}	T_{max}	$t_{½}$	C_{last}	T_{last}
Vitreous humour	(half proximal to implant)	536 µg/mL	day 1	–	12.6 ng/mL	182 days

Sampling at 1, 7, 14, 21, 42, 91, 137 and 182 Days post-dose; – = not reported; LLoQ: 0.5 ng/mL for vitreous humour

Study PK-07-095 states that single unilateral intravitreal implantation (700 µg dexamethasone) in cynomolgus monkey resulted in vitreous humour drug concentrations that "declined exponentially from 536,000 ng/mL (24.2% released) at 1 Day post dose to 330,000 ng/mL (48.4% dose released) by 42 Days post dose to 37.6 ng/mL (100% dose released) by 91 Days post dose". A figure (Figure5) showing the in vivo release profile is reproduced below. The study authors concluded that "dexamethasone was released from [the implant] in monkeys up to approximately 3 months with low dexamethasone concentration in the vitreous up to 6 months."

[21] Chang-Lin J.E. et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest. Ophthalmol. Vis. Sci.* 2011; 52:80–86

Figure 5. Percent of dexamethasone released for DEX PS DDS over time for 700 µg DEX PS DDS in monkeys



The paper cited by the sponsor[21] was not included in the dossier at the time of submission, but was provided with sponsor's response (as unsolicited data). Dexamethasone was quantified in the vitreous humour and retina of male Cynomolgus monkeys after bilateral administration of the Ozurdex implant (700 µg) using a much more sensitive analytical technique (lower limits of quantification, 1 pg/mL for vitreous humour and 1 pg/retina [that is, 100 to 500 times lower than in the studies above]). Data are summarised in the Table 6.

Table 6. Summary data from study by Chang-Lin J.E. et al

Matrix		C_{max}	T_{max}	t½	C_{last}	T_{last}
Vitreous humour	(half without implant)	213 ng/mL	day 60	–	1.31 pg/mL	day 180
Retina	(total)	1110 ng/g	day 60	–	16.7 pg/g	day 210

Sampling at 7, 30, 60, 90, 120, 150, 180, 210, 240 and 270 Days post-dose; – = not reported; LLoQ: 0.5 ng/mL for vitreous humour and 0.1 ng/g for retina

The last detectable concentrations are more than 160,000 (vitreous humour) or 66,000 (retina) times lower than the peak concentrations. A figure from the paper illustrating the concentration-time profile is shown (Figure 6) (note, log scale). Increased CYP3A8 expression in the retina was used as a biomarker for dexamethasone activity in the study, and showed pharmacological activity in retina samples collected at 7 to 60 days and 90 to 210 days post-dose, but not at 240 to 270 days post-dose. The authors described the results as showing "delivery of [dexamethasone] in the retina and vitreous with two phases of drug release after implant administration. The first phase [2 months duration] provided high concentrations of [dexamethasone] followed by a second phase in which low concentrations of [dexamethasone] were released, extending the therapeutic period to 6 months. The sustained delivery of [dexamethasone] was supported by the increased expression of CYP3A8 (a marker of [dexamethasone] biological activity) in the retina, which was maintained for 6 months"

Figure 6. Concentration time profile from Chang-Lin J.E. et al

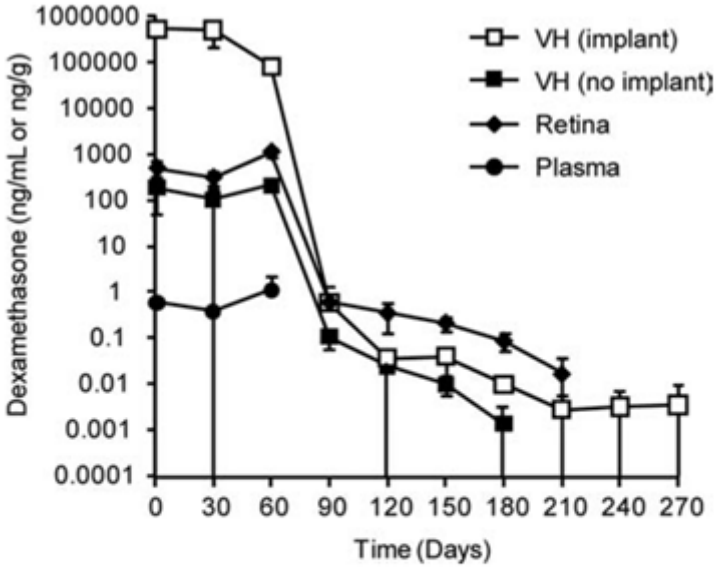


FIGURE 2. DEX concentrations in the vitreous humor (VH), with and without the implant (nanograms/milliliter); retina (nanograms/gram); and plasma (nanograms/milliliter) after intravitreal administration of the 0.7-mg DEX implant (semilogarithmic scale). Data points and error bars represent the mean concentration ± SD in three to six animals. The limit of detection for the DEX assay was 0.001 ng/mL for the vitreous humor, 0.001 ng/retina for the retina, and 0.200 ng/mL for plasma.

It has become apparent that the long detection period is more a function of the assay than the implant. Simply reporting the last time point of detection is considered to no longer provide adequate information on the pharmacokinetic profile in the eye. The two phases of drug delivery should be described, and the last time point cited should only be that to which therapeutically relevant concentrations of dexamethasone were maintained.

The following statement should be used in the PI in place of the one proposed by the sponsor:

> "In monkeys, following single bilateral intravitreal implantation of Ozurdex 700 µg, dexamethasone was released in two phases. The first phase provided high concentrations of dexamethasone, with peak concentrations of dexamethasone observed in the vitreous humour and retina at 60 days post-injection. This was followed by a second phase in which low concentrations of dexamethasone were released, extending the therapeutic period to 6 months."

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Diabetic macular oedema (DME) is the most common cause of moderate vision loss in developed countries. Its onset is usually insidious with loss of central visual acuity. It is

caused by a breakdown of the capillary endothelium of the blood retina barrier resulting in leakage into adjacent retinal tissues. Fluid accumulation and macular thickening may be reversible in the short term but it may cause irreversible damage leading to permanent visual loss. Laser photocoagulation has been the treatment of choice for many years. Deterioration is often slowed but normal vision is not usually restored. In recent years, VEGF inhibitors have been developed which are effective but require monthly injections. Corticosteroids have been shown to suppress inflammation by inhibiting inflammatory mediators, oedema, fibrin deposition, capillary leakage and phagocytic migration, at least in part by inhibiting VEGF expression. Systemic corticosteroids are associated with serious side effects, including the exacerbation of diabetes mellitus, and topical formulations are unable to penetrate the posterior segment. Intraocular steroid injections such as triamcinolone acetonide have proved effective but duration of effect has now been extended using biodegradable depot steroid formulations. It is proposed that direct injection of a slow release formulation of dexamethasone will provide a sustained therapeutic response without the risk of systemic side effects in patients with DME.

Guidance

Regulatory guidance from the US FDA was provided in 2003, 2011 and in a pre-NDA briefing in 2012. Advice from the UK MHRA was provided in 2011. Issues addressed included the use of Sham implantations rather than active controls, the nature of DME compared with other acute forms of ME, and the choice of primary study endpoints. No record of any guidance provided by the TGA has been provided.

Contents of the clinical dossier

The submission contained the following clinical information:

- Two pivotal Phase III efficacy/safety Studies (206207 010 and 206207 011). Pooled efficacy and safety data from these two studies were analysed in an Integrated Summary of Efficacy (ISE), and an Integrated Summary of Safety (ISS).
- Two limited population pharmacokinetic analyses performed in selected patients from the pivotal Phase III studies.
- One dose finding study in patients with persistent ME (206207 06).
- Two Phase II studies assessing Ozurdex as an adjunct to laser photocoagulation in patients with DME (206207 012); and in patients who had a pars plana vitrectomy in the study eye (206207 018).
- Nonclinical Overview, Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include evaluable paediatric data and usage in children is not proposed.

Good clinical practice

All studies were conducted in accordance with the principles of ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Serial blood samples for the measurement of plasma dexamethasone concentrations were collected from selected patients in the pivotal Studies 206207 010 (also referred to as '010') and 206207 011 (also referred to as '011'). Summaries of these limited population pharmacokinetic studies are provided in Attachment 2.

Evaluator's conclusions on pharmacokinetics

The dose of dexamethasone in each implant is low and less than a daily physiological replacement dose (approximately 0.75 mg). This already low dose is released for up to 6 months into the eye from where little systemic absorption would be predicted. As expected, the population PK studies demonstrated negligible systemic exposure to dexamethasone at any time point within the first 3 months after administration. No pharmaceutical studies were conducted to assess the drug release characteristics or to support the claim for full biodegradability. Such studies in man would be unacceptably invasive but the performance of the implant has been extensively studied in animal models.

Pharmacodynamics

Studies providing pharmacodynamic data

No new data submitted.

Dosage selection for the pivotal studies

Dose selection was based on multiple preclinical studies, conducted mainly in a rabbit model of VEGF induced vascular retinopathy. No testing in human eyes was conducted because of the invasive nature of these experiments. The final dose selection was based on two studies in rabbits which evaluated two dose forms each at two dose levels (350 µg and 700 µg) with analyses performed at 72 hours or 84 days after implantation. These and other studies showed that the dexamethasone release profiles were similar and the mean intraocular dexamethasone concentrations were consistent with the dose levels administered. Peak dexamethasone concentrations were achieved within the first 24 hours and they remained detectable for 35 days after implantation. Necropsy samples confirmed complete degradation of the biodegradable polymer matrix. Ocular adverse effects including cataract were observed at these doses.

Based on these findings, the same two 700 µg and 350 µg doses were selected for the dose ranging Study 06 in patients with macular oedema (ME) of any cause. Only 53.9% of the study population had DME. An analysis of the DME subgroup showed similar efficacy rates compared with the overall population, with a dose response effect in favour of the higher dose. However, there was no analysis of the adverse event (AE) profile reported for the subgroup of patients with DME.

Efficacy

Studies providing efficacy data

There were two Phase III pivotal efficacy studies:

Study 206207 010 (010) and Study 206207 011 (011)

Other studies which provided efficacy date included;

- Study DC103 06 (06) (a Phase II study)
- Study 206207 012 (012) (a Phase II study)
- Study 206207 018 (018) (a Phase II study)

A pooled efficacy analysis of Studies 206207 010 and 206207 011 was also provided.

For details of these studies and their results please see Attachment 2.

Evaluator's conclusions on efficacy

Evaluator's conclusions on clinical efficacy for the treatment of diabetic macular oedema (DME):

Statistically significant efficacy has been demonstrated for the use of Ozurdex 700 µg and 350 µg in both pivotal studies; although improved best corrected visual acuity (BCVA) using the AUC approach was not confirmed in Study 011. Improved visual acuity occurred within the first month of treatment and was sustained with repeat dosing over a 3 year observation period. The BCVA clinical endpoints and the 3 year observation period were appropriate using design and methodologies agreed by the EU and US FDA. In both studies the positive BCVA findings were supported by the optical coherence tomography (OCT) findings which clearly demonstrated reductions in retinal thickening due to macular oedema. Both DEX PS DDS doses were effective with a modest benefit in favour of the 700 µg dose. Dose selection was based on preclinical studies in a rabbit model of VEGF induced vasculopathy as the characterisation of intraocular pharmacokinetics (PK) is invasive. The studies confirmed the release of effective dexamethasone concentrations. However, the implant has a 35 day release profile (in rabbits) and the rationale for a 6 month dose interval is not clear. The dose ranging clinical Study 06 showed that both doses were effective with an acceptable safety profile.

No active comparator group was included in the pivotal studies. At the time the studies were designed, there were no approved medications for DME although triamcinolone injections have been used off label for some years. VEGF inhibitors are now widely used but laser therapy remains the most widely used intervention. It is not clear why a laser therapy control group was not included, or why the study population was restricted to patients unsuitable for laser therapy.[22] Sham injections are an accepted masking methodology in ocular studies. This is largely due to ethical concerns about potential damage, including infection, in eyes given placebo injections.

In the overall Phase III study population there was a statistically significant treatment benefit in favour of DEX 700 compared with Sham. Approximately 20 to 25% of patients had a meaningful increase in visual acuity with DEX 700 compared with 10 to 15% in the Sham population. However, the average improvements in measures of BCVA were modest and not clinically meaningful. In the integrated summary of efficacy (ISE), two paragraphs have been devoted to efficacy in subpopulations, with reference only to patients with pseudophakic eyes and/or severe non-proliferative diabetic retinopathy (NPDR) (in

[22] Clarification: The inclusion criteria associated with diabetic macular edema for Studies 010 and 011 were as follows: Diabetic macular edema in the study eye defined as clinically observable macular edema involving the center of the macula (fovea) associated with diabetic retinopathy with any of the following characteristics: a) prior medical therapy for diabetic macular edema; b) prior macular laser(s) for diabetic macular edema with the most recent laser at least 3 months prior to Baseline/ Qualification where, in the opinion of the investigator, the patient will be able improve 15 or more letters in BCVA from baseline with the resolution of the macular edema despite the presence of macular laser scars; c) in the investigator's opinion the patient would not benefit from macular laser treatment; d) the patient refuses laser treatment.

whom efficacy appeared most favourable). Only scant subgroup data have been provided in the clinical study reports but it appears that efficacy is significantly less or non-existent in other subgroups. A more thorough analysis of efficacy in all subgroups should be provided. BCVA improvement in phakic eyes appears to be ill sustained due to the almost inevitable development of cataract. The sponsor's argument that cataract formation masks the positive effects of DEX in patients with phakic eyes is reasonably made. OCT data appear similar in pseudophakic and phakic study eyes and BCVA improvement is restored following cataract surgery in phakic eyes. However, the data suggest that treatment of phakic eyes is largely ineffective, unless or until the patient has a lens replacement.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Two pivotal 3 year Phase III Studies (010 and 011). The data were presented as individual studies and as a pooled Integrated Summary of Safety (ISS).

Three Phase II Studies. These data could not be pooled due to differences in patient groups, and study design and duration.

Patient exposure

In the ISS, 1,040 patients with DME received at least one dose of study drug (347 patients in the DEX 700 group, 343 patients in the DEX 350 group, and 350 patients in the Sham group). Cumulative exposure was 22% less in the Sham group than in the DEX groups due to more patient discontinuations (See Table 7 Attachment 2). A total of 3,037 retreatments were administered during the 3 year study period. Approximately 80% of them were administered between 5 to 7 months after the initial treatment.

In Study 06, 101 patients received a single DEX 700 dose, 100 patients received a single DEX 350 dose, and 105 patients were followed with Observation only. In Study 012, the mean duration of exposure to DEX 700 was 348.0 days in the Combination Therapy group and 339.1 days in the Laser Alone group.

Post-marketing data

Since the initial marketing approval in the US in 2009, there have been an estimated 45,018 patient-years of exposure to Ozurdex. The safety profile in the DME study program are consistent with the overall experience when used in patients with other causes of ME, and consistent with events typically associated with the use of injected ophthalmic steroids. However, there is no post-marketing experience in patients with DME.

For the complete evaluation of the clinical safety data please see Attachment 2.

Evaluator's conclusions on safety

The incidence of non-ocular AEs and SAEs was higher in the DEX groups compared with Sham. However, the rates were similar when the data were adjusted for exposure, and the pattern was consistent with the diabetic study population. Ocular AEs and adverse drug reactions (ADRs) in the study eye were similar in the DEX 700 and DEX 350 groups and higher compared with the Sham group. However, with the exception of cataract, the incidence of AEs remained stable throughout the 3 year study. Most AEs related to cataract, intraocular pressure (IOP) increased, conjunctival haemorrhage, reduced visual acuity, and vitreous haemorrhage. In phakic eyes, approximately 2 out of 3 of patients had

cataract AEs and 57% required cataract surgery within the study period. IOP was consistently increased in the DEX groups. The elevations were generally reversible with time but approximately 40% of patients in the DEX groups required medical intervention to lower IOP. Only eight patients required surgical intervention for raised IOP and endophthalmitis was reported in only two patients. In the pooled studies, 37 patients had severe visual loss of which approximately 90% were due to cataract. The pattern of AEs was consistent with the known effects of ocular steroids. The incidence of AEs in phakic eyes was unacceptable due to the risk of cataract and/or raised IOP.

First round benefit risk assessment

First round assessment of benefits

The benefits of Ozurdex in the proposed usage are:

- Improved visual acuity
- Rapid onset of action
- Long duration of effect with sustained benefits for up to 3 years following repeated doses
- Low frequency of injections and risk of procedure related AEs
- Proven reduction of macular oedema measured by OCT.

First round assessment of risks

The risks of Ozurdex in the proposed usage are:

- A high risk of steroid related ocular AEs in the treated eye
- A high risk of cataract formation in phakic eyes
- A high risk of raised IOP
- A low risk of ocular infection
- A low risk of complications following surgery for cataract or raised IOP.

First round assessment of benefit risk balance

The benefit-risk balance of Ozurdex is unfavourable given the proposed usage, but would become favourable if the changes recommended in the first round recommendation regarding authorisation are adopted.

First round recommendation regarding authorisation

Approval is not recommended for the proposed indication:

> *'Ozurdex is indicated for the treatment of diabetic macular oedema (DME)'.*

Approval is recommended for the indication:

> *Ozurdex is indicated for adults with diabetic macular oedema who have an artificial lens implant or who are scheduled for cataract surgery.*

This recommendation is in line with the indication approved by the FDA but it is subject to satisfactory responses from the sponsor to the clinical questions.

Clinical questions

Pharmacokinetics

1. In preclinical studies, the in situ release characteristics from the implant suggest that peak intravitreal dexamethasone concentrations are achieved within 24 hours and remain detectable for 35 days. Based on OCT measurements, efficacy benefits are significantly attenuated from Months 3 to 6. Please confirm the release characteristics of the implant and explain why 6 monthly repeat injections were recommended in the clinical trial program.

Pharmacodynamics

No questions.

Efficacy

1. In Studies 010 and 011, analyses of efficacy in the study eye by subgroups are summarised as shown in Table 4 and Table 6 (of Attachment 2). Please provide an analysis of the pooled data to identify subgroups with the best and least responses to treatment. For example, is there a rationale for treating diabetics with poor glycaemic control?
2. Please explain why a triamcinolone or laser alone control arm was not used in the pivotal studies.
3. A key inclusion criterion for the pivotal study was patients unsuitable for laser therapy, or patients who had refused it. It could be argued that the indication for Ozurdex should be restricted to second line therapy for this patient population. Please discuss.

Safety

1. Please provide a brief summary of ocular AEs in the study eye based on subgroups in the ISS. The analysis should be combined with the subgroup analysis of efficacy to permit a risk/benefit assessment in each subgroup.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

The analysis of the response to the questions was presented in the Delegates overview.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan 'Ozurdex Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System Risk Management Plan (RMP) EU RMP Version 4.0' (dated 18 March 2014) with an Australian Specific Annex (ASA) Version 1.0 (dated 20 March 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 7.

Table 7. Summary of ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Increased intraocular pressure, Glaucoma, Ocular Hypertension Cataract formation Vitreous detachment, haemorrhage Endophthalmitis (infectious, non-infectious) Retinal tear/ detachment Significant vitreous leak or hypotony Device dislocation Implant misplacement Retinitis secondary to reactivation of latent viral or other ophthalmic infections
Missing information	Paediatric use Pregnancy and lactation Long term safety, repeat dosing data Concurrent use of anticoagulants Patients with significant retinal ischemia

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns and missing information. Copies of the targeted questionnaires for the important identified risks: 'Endophthalmitis (infectious/ non-infectious)', 'Significant vitreous leak or hypotony', 'Device Dislocation', 'Implant misplacement' and 'Retinitis secondary to reactivation of latent viral or other ophthalmic infections' have been provided in Annex 7 of the EU RMP. However, it is not clear if these targeted questionnaires are proposed for use in Australia as part of routine pharmacovigilance.

Additional pharmacovigilance in the form of an ongoing EU observational study (PASS) – Study 206207 025: 'Post Authorization Safety Study of Ozurdex (Dexamethasone Intravitreal Implant): A Prospective Observational Study to Evaluate Long Term Safety in Real World Clinical Practice' is also proposed to further characterise all the specified ongoing safety concerns, except for the missing information: 'Paediatric Use', 'Pregnancy and lactation', 'Concurrent use of anticoagulants' and 'Patients with significant retinal ischemia'. The EU RMP reports that the first patient enrolment occurred in March 2012. A total of 18 sites have been initiated (9 in Germany, 7 in the UK, and 2 in France). As of 24 January 2014, 783 patients have been enrolled. The final study report is anticipated to be submitted in the EU as of 28 March 2016. A number of progress reports for this study have been provided in Annex 9 of the EU RMP. However, reference to this ongoing study is found in Section 3: 'Risk Minimisation Plan' of the ASA rather than the section related to pharmacovigilance, which refers to the completed Phase III studies 206207 010 and 206207 011, evaluating safety and efficacy of Dexamethasone Posterior Segment Drug

Delivery System (DEX PS DDS) Applicator System for the treatment of diabetic macular oedema (DME).

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns and missing information are sufficient. Additional risk minimisation in the form of prescriber educational material is proposed for all the specified important identified risks and patient educational material is proposed for the important identified risks: 'increased intraocular pressure, glaucoma, ocular hypertension' and 'endophthalmitis (infectious/ non-infectious)'.

Comment: At this time the sponsor's conclusion in regard to the need for risk minimisation activities is considered acceptable.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Table 8 reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
The sponsor has advised that the data set package for Australia is essentially the same as submitted in the EU. Nevertheless it is drawn to the Delegate's attention that the indications foreshadowed for approval in the EU are more restrictive than those sought for in Australia. Consequently Sub section 1.2.1: 'Differences in indication between the European Union (EU) and Australia' of the ASA should also be updated with this information.	The sponsor states: "As described elsewhere in the response to the Consolidated Section 31 request for information and in the Australian Specific Annex v 2.0 (supplemented with EU RMP v 7.0), Allergan is proposing the following revised indication for Ozurdex to be registered in Australia: 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. The proposed indication is	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	the same as the indication approved in EU on 26 August 2014 for DME patients."	
Both sub sections: 'Australian specific epidemiological information on the population to be treated' and 'Differences in indication between the EU and Australia' of the ASA have been labelled: '1.2.1'. This discrepancy should be corrected and subsequent sub section numbering amended.	The sponsor states: "The discrepancy in numbering of Sub section 1.2.2 has been corrected and subsequent numbering has been amended in the ASA v2.0."	This is acceptable.
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor states: In order to address the comments received in the clinical evaluation report, Allergan has revised the proposed indication and is seeking the approval of Ozurdex for the following: *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*. It was concluded that in view of changes in the proposed indication for Ozurdex in Australia, there is no added safety consideration that needs to be added to the current RMP v 7.0. As the patient population, for the current proposed indication,	This is acceptable. Nevertheless the sponsor should explain the discrepancy observed in the Nonclinical Safety Specification of the draft RMP (Module SII) by the nonclinical evaluator.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	may require multiple injections and need a long term treatment, the important potential risk of 'Systemic corticosteroid effect' (infection, hypertension and impaired healing) has already been included in the EU RMP v 7.0. Allergan believes that current EU RMP v 7.0 (along with the ASA v2.0) adequately addresses any safety concern(s) arising out of use of Ozurdex in Australia.	
It is recommended that the important potential risk: 'Off label use' be included as a new ongoing safety concern given the sponsor is not seeking to register the EU approved indications (that is the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) and for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis). Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for this new ongoing safety concern and only the ASA need be revised accordingly.	The sponsor agrees that post approval of Ozurdex in Australia for the proposed indication there is a potential for off label use for the remaining approved indications in the EU and the US (macular oedema following BRVO or CRVO and non-infectious uveitis). However, the sponsor argues that safety concerns (if any) associated with the use of Ozurdex in adult patients with macular oedema following BRVO or CRVO and non-infectious posterior uveitis will be similar, if not, less than those expected with its usage in diabetic macular oedema patients. On this basis	It is agreed that routine pharmacovigilance and risk minimisation are appropriate for this new ongoing safety concern specific to Australia. Nevertheless to ensure that it is appropriately monitored by routine pharmacovigilance it is reiterated that 'Off label use' should be included as an important potential risk, which need only be reflected in a revised ASA preferably before this application is approved.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	the sponsor refuses to amend Section 2 of the ASA as recommended.	
The EU RMP states the following for Version 3.0 dated May 2013: "Systemic corticosteroid effects and Mechanical failure are proposed to be removed as important potential risks." However, the current UK SmPC for this medicine still states: "*The safety and efficacy of Ozurdex administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended*", which was the routine risk minimisation activity related to the former ongoing safety concern: 'Systemic corticosteroid effects'. The sponsor should provide an explanation for the removal of these former ongoing safety concerns. If this removal was accepted by the EMA the sponsor should then explain why the routine risk minimisation activity related to the former ongoing safety concern: 'Systemic corticosteroid effects' is still present in the UK SmPC.	The sponsor states: "While in EU RMP v4.0, Allergan proposed to remove 'Systemic corticosteroid effect' as an important potential risk, it was later agreed to keep it as an important potential risk for Ozurdex. This risk was therefore included in EU RMP v7.0. As requested by EMA, the potential risk of "Systemic corticosteroid effect" will continue to be assessed by monitoring the events of infections, impaired healing and hypertension."	This is acceptable.
The sponsor should definitively state in a revised ASA whether the targeted questionnaires for the important identified risks: 'Endophthalmitis (infectious/ non-infectious)', 'Significant vitreous leak or hypotony', 'Device Dislocation', 'Implant misplacement' and 'Retinitis secondary to reactivation of latent viral or other	The sponsor states: "The targeted questionnaires for the important identified risks, 'Endophthalmitis (infectious/ non-infectious)', 'Significant vitreous leak or hypotony', 'Device Dislocation', 'Implant	Table 2–1: 'Pharmacovigilance activities for safety concerns and missing information' of the updated ASA also indicates that targeted questionnaires are also used to further

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
ophthalmic infections' are proposed for use in Australia, and if so reference the copies located in the EU RMP.	misplacement' and 'Retinitis secondary to reactivation of latent viral or other ophthalmic infections' are applicable to, and will be used for the Australian population. Copies are provided as Annex 7 in the EU RMP v7.0 and are appropriately referenced in Section 2.1 of ASA v2.0."	characterise the important identified risks: 'Increased IOP, Glaucoma, Ocular Hypertension', 'Cataract formation and associated visual acuity reduced', 'Vitreous Haemorrhage/detachment' and 'Retinal detachment/tear' without providing copies of such documentation. In addition the missing information: 'Long term safety, Repeat dosing data' appears to be missing from this table. The sponsor should explain and if required correct these apparent discrepancies preferably before this application is approved.
The sponsor should provide the details of the Qualified Person for Pharmacovigilance, who will be responsible for the implementation of the RMP activities within Australia, in a revised ASA.	The sponsor states: "The Qualified Person for Pharmacovigilance, responsible for the implementation of the RMP activities in Australia is: [information redacted] The details of the	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	Qualified Person for Pharmacovigilance are appropriately mentioned in Section 4.0 of the Australian Specific Annex v2.0."	
The ongoing EU observational PASS (Study 206207 025) is not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study documentation has not been reviewed. Nevertheless this study will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. Consequently information related to this ongoing study in Section 3: 'RMP' of the ASA should be relocated to Section 2.2: 'Studies referenced in RMP' of the ASA.	The sponsor states: "The EU observational PASS (Study 206207 025) is now discussed in Section 2.2 "Studies referenced in RMP" of the ASA v2.0 based on the EMA approved EU RMP v7.0."	This is acceptable.
At this time the sponsor's handling of this matter using routine pharmacovigilance and risk minimisation activities and additional risk minimisation activities is considered to be acceptable. Nevertheless the ASA should provide Australian information on the potential for medication errors.	The sponsor states: "Ozurdex is a highly specialised drug, which will be dispensed by pharmacists directly to the treating physician. Therefore as it will not be dispensed to patients, the likelihood of a medication error occurring at the pharmacy and not being identified prior to administration is extremely limited. Furthermore, Ozurdex is only available in one	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	strength, 700 µg; which further reduces the risk of a medication error. As part of the review of the initial Ozurdex marketing applications, the EMA and FDA evaluated the potential for medication errors resulting from the proposed brand name and packaging design. Both agencies approved the Ozurdex brand name. Allergan believes that the conclusions also apply to Australia, and the risk of medication errors resulting from the Ozurdex brand name is minimal."	
The RMP Questions and Answers (Version 1.3, October 2012) as found on the TGA website state: "The ASA should identify any differences between the EU RMP and the local implementation of risk management activities, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI, and the reasons for the difference." Consequently the ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed	The sponsor states: "The assessor's observation has been addressed and a table listing risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI for all of the specified ongoing safety concerns and missing information has now been included in Section 3.0 of ASA v2.0 based on the EMA approved EU RMP v7.0."	Table 3–1: 'Differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI' of the ASA does not specifically identify and provide reasons for any observed differences. For example for the important identified risk: 'Increased IOP, Glaucoma, Ocular Hypertension', Section 4.4 of

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences; particularly where it appears the EU SmPC is more restrictive. Upon receipt of such information recommendations to the Delegate in regard to the proposed routine risk minimisation activities can then be made. Such a table should also definitively indicate whether additional risk minimisation in the form of prescriber educational material is proposed for all the specified important identified risks and patient educational material is proposed for the important identified risks: 'Increased intraocular pressure, Glaucoma, Ocular Hypertension' and 'Endophthalmitis (infectious/ non-infectious)' in Australia, as some inconsistency is observed in the EU RMP on this matter (for example the tables included in Part V.1: 'Risk minimization measures by safety concern', Table 9 16: 'Summary Table of Risk Minimization Measures' and Table 9 19: 'Summary Table of Risk Minimization Measures').		the SmPC states that patients should be monitored following the injection to permit early treatment if an infection or increased IOP occurs and such 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. The proposed Australian PI provides no such detail. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved.
The current UK SmPC states: "The safety and efficacy of Ozurdex administered to both eyes concurrently have not	The sponsor states: "The assessor's observation is addressed in the	It is observed that this information is in fact now

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
been studied. Therefore administration to both eyes concurrently is not recommended". This precautionary statement is cross referenced to the 'Posology and method of administration' section of the UK SmPC and was related to the former ongoing safety concern: 'Systemic corticosteroid effects'. However, a similar precautionary statement does not appear to be included in the proposed Australian PI, but is included in the proposed Australian CMI. The sponsor should correct this oversight and amend the proposed Australian PI accordingly.	updated Australian PI, and the following sentence has been added to the draft PI under Dosage and Administration: "The safety and efficacy of Ozurdex administered to both eyes concurrently have not been studied. Therefore, administration to both eyes concurrently is not recommended."	included in the Precautions section, not in the dosage and administration section, of the proposed Australian PI. This is not entirely satisfactory and it is reiterated that these precautionary statements should also be cross referenced to the dosage and administration section of the proposed Australian PI. Furthermore Table 3–1: 'Differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI' of the ASA contrarily indicates that no routine risk minimisation is proposed for the important potential risk: 'Systemic corticosteroid effects (infections, impaired healing and hypertension)'.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		The sponsor should correct this inconsistency preferably before this application is approved. It is noted that Table 9–22: 'Summary Table of Risk Minimization Measures' and Table 9–25: 'Summary Table of Risk Minimization Measures' of the updated EU RMP are also inconsistent on this matter.
Given the sponsor is not seeking to register the EU approved indications (that is the treatment of adult patients with macular oedema following either BRVO or CRVO and for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis), the prescriber and patient educational materials provided in Annex 11 of the EU RMP will need to be amended to be consistent with Australian registration details. Revised draft prescriber and patient educational materials should be attached to the ASA.	The sponsor states: "The current ASA v2.0 is based on EMA approved EU RMP v7.0. This version contains educational materials that were revised to enhance the clarity and focus on essential information. These revised educational materials as presented in EU RMP v7.0 are currently proposed to be provided in Australia as well. The revised educational material are not specific to a particular indication and are intended to provide treating physicians with information on the recommended injection technique	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	and the important risks related to the intravitreal injection of Ozurdex. The patient guide provides information on what the patient needs to do before their treatment, what they should expect during the treatment and what they should look out for, after the treatment. Allergan believes these materials are sufficient and succinct and can be used in the Australian population and therefore an amendment is not necessary. The only minor change made to Annex 11 Educational Material is to remove the reference to the SmPC on page 5; this is replaced by the 26 November 2014 68 reference to the Australian PI (these 'updated' educational materials are attached as Appendix 1 to the ASA v2.0)."	
Given these differences in registration details it would also be expected that the sponsor will conduct a physician survey in Australia to assess the effectiveness of the prescriber educational materials as a measure to reduce all the specified important identified risks. Consequently the sponsor should provide to the TGA for review the details of the nature (quantitative) and	The sponsor states: "The overall AE reporting rate, as well as the injection procedure related adverse event rate, will be used as a measure of effectiveness of these educational materials. A decrease in overall reporting rate, as well as frequency and severity of injection	This approach is reliant upon data from spontaneous AE reports which are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
content of the survey testing to be conducted in Australia, including the specific review period, the criteria used to verify success and how the results of this testing will be reported to the TGA. Section 3: 'RMP' of the ASA should be revised accordingly.	procedure related adverse events, will be considered as verification of the success of the educational materials."	reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved.
It would appear that no information detailing how the patient educational materials as a measure to reduce the important identified risks: 'Increased IOP, glaucoma, ocular hypertension' and 'endophthalmitis (infectious/ non-infectious)' has been provided. Consequently the sponsor should state how the effectiveness of this additional risk minimisation measure for these ongoing safety concerns will be measured, the criteria used to verify success and how the results of such testing will be reported to the TGA. Section 3: 'RMP' of the ASA should be revised accordingly.	The sponsor "proposes capturing data on identified risks through the targeted questionnaire and spontaneous AE reporting to Allergan's pharmacovigilance department. Data collected via these channels will be reported to the TGA through established reporting mechanisms if required." The updated ASA states: "Allergan diligently monitors AEs (related	This approach is reliant upon data from spontaneous AE reports which are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under reporting and the lack of reliable exposure (usage) data associated with spontaneous

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	to injection procedure). The overall AE profile, reporting rate, as well as the type and frequency of injection procedure related adverse events will all be used as a measure of effectiveness of these educational materials."	reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved. In addition the sponsor stated that educational materials were attached as Appendix 1 to the updated ASA. However, it appears that the patient educational materials have not been so attached. The sponsor should correct this oversight.
A table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia should be included in the revised ASA.	The sponsor states: "A table listing all proposed Pharmacovigilance activities (Table 2 1) and risk minimisation activities (Table 3 1) is incorporated in the ASA v2.0 to address this observation."	This is acceptable.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The sponsor had advised that the data set package for Australia is essentially the same as submitted in the EU. Nevertheless it was drawn to the Delegate's attention that the indications foreshadowed for approval in the EU are more restrictive than those sought for in Australia. In addition the sponsor was asked to respond to safety considerations raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports respectively, in the context of relevance to the RMP. The sponsor states that in order to address the comments received in the clinical evaluation report; it has revised the proposed indication to be the same as the indication approved in EU on 26 August 2014 for DME patients. Nevertheless the sponsor should explain the discrepancy observed in the nonclinical safety specification of the draft RMP by the nonclinical evaluator.

It was recommended that the important potential risk: 'off label use' be included as a new ongoing safety concern given the sponsor is not seeking to register the EU approved indications (that is the treatment of adult patients with macular oedema following either BRVO or CRVO and for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis). Consideration must also be given as to what pharmacovigilance and risk minimisation activities will be proposed for this new ongoing safety concern and only the ASA need be revised accordingly. The sponsor agrees that post approval of Ozurdex in Australia for the proposed indication there is a potential for off label use for the remaining approved indications in the EU and the US (macular oedema following BRVO or CRVO and non-infectious uveitis). However, the sponsor argues that safety concerns (if any) associated with the use of Ozurdex in adult patients with macular oedema following BRVO or CRVO and non-infectious posterior uveitis will be similar, if not, less than those expected with its usage in diabetic macular oedema patients. On this basis it refuses to amend Section 2 of the ASA as recommended. It is agreed that routine pharmacovigilance and risk minimisation are appropriate for this new ongoing safety concern specific to Australia. Nevertheless to ensure that it is appropriately monitored by routine pharmacovigilance it is reiterated that 'off label use' should be included as an important potential risk, which need only be reflected in a revised ASA preferably before this application is approved.

The sponsor was asked to definitively state in a revised ASA whether the targeted questionnaires for the important identified risks: 'endophthalmitis (infectious/ non-infectious)', 'significant vitreous leak or hypotony', 'device dislocation', 'implant misplacement' and 'retinitis secondary to reactivation of latent viral or other ophthalmic infections' are proposed for use in Australia, and if so it should reference the copies located in the EU RMP. The sponsor has stated: "The targeted questionnaires for the important identified risks, 'endophthalmitis (infectious/ non-infectious)', 'Significant vitreous leak or hypotony', 'device dislocation', 'implant misplacement' and 'retinitis secondary to reactivation of latent viral or other ophthalmic infections' are applicable to, and will be used for the Australian population. Copies are provided as Annex 7 in the EU RMP v7.0 and are appropriately referenced in Section 2.1 of ASA v2.0." However, Table 2–1: 'pharmacovigilance activities for safety concerns and missing information' of the updated ASA also indicates that targeted questionnaires are also used to further characterise the important identified risks: 'Increased IOP, glaucoma, ocular hypertension', 'cataract formation and associated visual acuity reduced', 'vitreous haemorrhage/detachment' and 'retinal detachment/tear' without providing copies of such documentation. In addition the missing information: 'long term safety, repeat dosing data' appears to be missing from this table. the sponsor should explain and if required correct these apparent discrepancies preferably before this application is approved.

The sponsor was asked to revise the ASA to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive. The sponsor states: "*The assessor's observation has been addressed and a table listing risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI for all of the specified ongoing safety concerns and missing information has now been included in Section 3.0 of ASA v2.0 based on the EMA approved EU RMP v7.0*." However, Table 3–1: 'differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI' of the ASA does not specifically identify and provide reasons for any observed differences. For example for the important identified risk: 'increased IOP, glaucoma, ocular hypertension', Section 4.4 of the SmPC states that patients should be monitored following the injection to permit early treatment if an infection or increased IOP occurs and such 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. The proposed Australian PI provides no such detail. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved.

The sponsor was advised that the current UK SmPC states: "*The safety and efficacy of Ozurdex administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended*." This precautionary statement is cross referenced to the 'posology and method of administration' section of the UK SmPC and was related to the former ongoing safety concern: 'systemic corticosteroid effects'. However, a similar precautionary statement does not appear to be included in the proposed Australian PI, but is included in the proposed Australian CMI. The sponsor was asked to correct this oversight and amend the proposed Australian PI accordingly. The sponsor states: "The assessor's observation is addressed in the updated Australian PI, and the following sentence has been added to the draft PI under dosage and administration: "The safety and efficacy of Ozurdex administered to both eyes concurrently have not been studied. Therefore, administration to both eyes concurrently is not recommended." However, it is observed that this information is in fact now included in the precautions section, not in the dosage and administration section, of the proposed Australian PI. This is not entirely satisfactory and it is reiterated that these precautionary statements should also be cross referenced to the dosage and administration section of the proposed Australian PI. Furthermore Table 3–1: 'Differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI' of the ASA contrarily indicates that no routine risk minimisation is proposed for the important potential risk: 'systemic corticosteroid effects (infections, impaired healing and hypertension)'. The sponsor should correct this inconsistency preferably before this application is approved. It is noted that Table 9–22: 'summary table of risk minimization measures' and Table 9–25: 'summary table of risk minimization measures' of the updated EU RMP are also inconsistent on this matter.

The sponsor was advised that it would be expected to conduct a physician survey in Australia (similar to that conducted in the EU) to assess the effectiveness of the prescriber educational materials as a measure to reduce all the specified important identified risks. Consequently the sponsor was asked to provide details of the nature (quantitative) and content of the survey testing to be conducted in Australia, including the specific review period, the criteria used to verify success and how the results of this testing will be reported to the TGA. Subsequently Section 3: 'RMP' of the ASA should be revised accordingly. The sponsor states: "The overall AE reporting rate, as well as the injection

procedure related adverse event rate, will be used as a measure of effectiveness of these educational materials. A decrease in overall reporting rate, as well as frequency and severity of injection procedure related adverse events, will be considered as verification of the success of the educational materials." However, this approach is reliant upon data from spontaneous AE reports which are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved.

The sponsor was advised that no information detailing how the patient educational materials as a measure to reduce the important identified risks: 'Increased IOP, glaucoma, ocular hypertension' and 'endophthalmitis (infectious/ non-infectious)' appeared to have been provided. Consequently the sponsor was asked to state how the effectiveness of this additional risk minimisation measure for these ongoing safety concerns will be measured, the criteria used to verify success and how the results of such testing will be reported to the TGA. Subsequently Section 3: 'risk minimisation plan' of the ASA should be revised accordingly. The sponsor "proposes capturing data on identified risks through the targeted questionnaire and spontaneous AE reporting to Allergan's pharmacovigilance department. Data collected via these channels will be reported to the TGA through established reporting mechanisms if required." The updated ASA states: "Allergan diligently monitors AEs (related to injection procedure). The overall AE profile, reporting rate, as well as the type and frequency of injection procedure related adverse events will all be used as a measure of effectiveness of these educational materials." However, this approach is reliant upon data from spontaneous AE reports which are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. Consequently this recommendation remains outstanding and should be adequately addressed preferably before this application is approved. In addition the sponsor stated that educational materials were attached as Appendix 1 to the updated ASA. However, it appears that the patient educational materials have not been so attached. The sponsor should correct this oversight.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA requests for information the sponsor provided an updated EU RMP (Version 7.0, dated 5 August 2014) with an updated ASA (Version 2.0, dated 10 December 2014). Key changes from the versions evaluated at Round 1 are summarised in Table 9

Table 9. Key changes to the updated RMP

Key changes to the updated RMP	
EU RMP	'Systemic corticosteroid effects' is added as an important potential risk.
ASA	The proposed indication has been amended to be the same as the indication approved in EU on 26 August 2014 for DME patients.

Key changes to the updated RMP	
	Section 1.2.2: 'Differences in indication between the European Union (EU) and Australia' has been updated. Section 1.2.3: 'Australian information on potential for medication errors or other risks' has been updated. Section 2.1: 'Routine pharmacovigilance system in Australia' has been updated and Table 2–1: 'Pharmacovigilance activities for safety concerns and missing information' is added. Section 2.2: 'Studies referenced in RMP' has been updated. Section 3: 'Risk Minimisation Plan' has been updated and Table 3–1: 'Differences between the risk minimisation activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed Australian Product Information (PI)' is added. Appendix 1: 'Mock-up of Proposed Additional Risk Minimisation Measure in Australia (prescriber and patient educational materials)' is added.

Suggested wording for conditions of registration

RMP; at this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator did not recommend approval because the proposed in vitro dissolution release limits have not been justified.

The sponsor will need to resolve this to the satisfaction of the quality evaluator before registration can be finalised.[4,23]

Nonclinical

There were no nonclinical objections to the registration of Ozurdex.

Clinical

Evidence of clinical efficacy from the pivotal Phase III studies

There were two twin Phase III studies, which had the same design; and differed only in the location of the study centres. Both studies recruited patients between 2005 and 2012.

[23] This matter was resolved to the satisfaction of the TGA prior to approval.

There were centres in Australia, US, Canada, Europe, South Africa, and Asia. A brief description of the studies is in Table 10.

Table 10. Description of the Phase III studies

Description of studies	
Participants	Type1 diabetic (approximately10%) or Type 2 diabetic DME of a severity that would be amenable to treatment: macular thickness 300+ µm, BCVA 20/50 to 20/200 (34 68 early treatment diabetic retinopathy study (ETDRS) letters) Most patients had prior treatment (roughly three quarters)
Intervention	700 µg implant 350 µg implant
Comparator	Sham; needleless applicator Laser was not used as a comparator and this resulted in a large number of withdrawals from the Sham arm (lack of efficacy, necessitating rescue treatment).
Endpoint	Primary Difference in the mean [AUC] change in BCVA Secondary (various)
Duration	3 years

Minimal clinically important difference used in sample size calculation

Four letter difference in change in mean (AUC) BCVA.

Timing of treatments

Patients received dexamethasone 700 µg, 350 µg or Sham at Day 0. They could have received another 6 treatments (that is, 7 in all). Patients were assessed for retreatment eligibility every 3 months (from Month 6 to Month 36), but retreatment was not given more frequently than approximately every 6 months. Following a protocol amendment, the final possible treatment was moved from Month 33 to Month 36 and the last visit/assessment was moved from Month 36 to Month 39.

Discontinuations

Discontinuation rates were high in both studies: 700µg (36%), 350 µg (34%), Sham (57%). Most discontinuation occurred due to lack of efficacy, most by the end of 12 months. For the primary endpoint, no imputation was performed for missing values. BCVA assessments after escape therapy were set to missing.

Results, ITT

Primary endpoint: BCVA (letters) mean change from baseline (AUC) are shown in Table 11.

Table 11. Primary endpoint: BCVA (letters) mean change from baseline (AUC)

Study	700 µg	350 µg	Sham
010			
N mean change difference from Sham (95% CI)	163 4.1 2.1 (0.4, 3.8)	166 4.3 2.3 (0.5, 4.0)	165 1.9
011			
N mean change difference from Sham (95% CI)	188 2.9 0.8 (0.9, 2.4)	181 2.9 0.7 (0.9, 2.4)	185 2.0

Pooled: 700 µg difference from Sham: 1.4 letters, 95% CI (0.2, 2.6)

Selected secondary endpoint: Percentage of patients with 15+ letter improvement in BCVA are shown in Table 12.

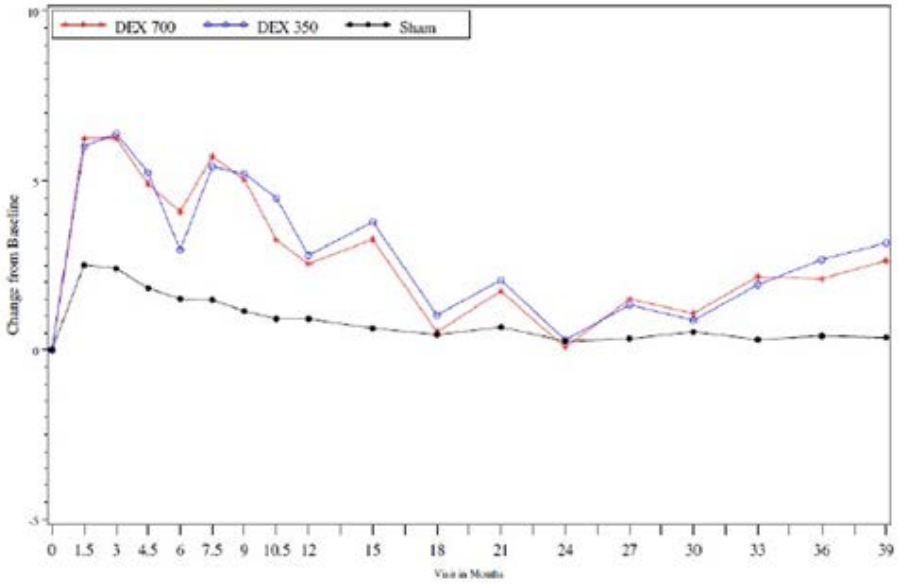
Table 12. Selected secondary endpoint: Percentage of patients with 15+ letter improvement in BCVA

Study	700 µg	350 µg	Sham
010			
N n (%)	163 36 (22)*	166 31 (19)	165 22 (13)
011			
N n (%)	188 42 (22)*	181 33 (18)*	185 20 (11)

"*" statistically significantly different from Sham

The mean change from baseline, pooled data from Studies 010 and 011 is show in in Figure 7.

Figure 7. Mean change from baseline, pooled data from Studies 010 and 011



Results, selected pre specified subgroup analyses

Difference from Sham, BCVA (letters) mean change from baseline (AUC) are shown in Table 13.

Table 13. Difference from Sham, BCVA (letters) mean change from baseline (AUC)

Study / pre specified subgroup	700 µg	350 µg
010		
Any prior treatment N (Sham N=127) difference from Sham (p value)	 123 2.6 (0.011)	 126 3.2 (0.002)
Pseudophakic eye at baseline N (Sham N=50) difference from Sham (p value)	 44 5.9 (<0.001)	 47 4.1 (0.007)
011		
Any prior treatment N (Sham N=134) difference from Sham (p value)	 124 0.7 (0.495)	 123 0.8 (0.409)
Pseudophakic eye at baseline N (Sham N=51) difference from Sham (p value)	 42 3.6 (0.018)	 41 4.3 (0.005)

Percentage of patients with 15+ letter improvement in BCVA, difference from Sham are shown in Table 14.

Table 14. Percentage of patients with 15+ letter improvement in BCVA, difference from Sham

	700 µg versus Sham	350 µg versus Sham
010		
Any prior treatment N (Sham N=127) difference from Sham (p value)	 123 11% (0.020)	 126 10% (0.036)
Pseudophakic eye at baseline N (Sham N=50) difference from Sham (p value)	 44 18% (0.042)	 47 -1% (0.880)
011		
Any prior treatment N (Sham N=134) difference from Sham (p value)	 124 10% (0.032)	 123 3% (0.410)
Pseudophakic eye at baseline N (Sham N=51) difference from Sham (p value)	 42 6% (0.461)	 41 11% (0.104)

Safety

The most common adverse drug reactions from the two Phase III trials were cataract, raised intra ocular pressure, and injection related events. These were not unexpected, given the pre-approval and post approval data available for the other two indications, for which Ozurdex is registered overseas (macular oedema secondary to retinal vein occlusion, non-infectious posterior uveitis); and experience with the use of other intra ocular corticosteroids (for example, triamcinolone).

Raised IOP was reported for 36% of patients treated with the 700 µg dose compared to 5% of patients in the Sham group. The rise in IOP was generally manageable with medication; a handful of patients required a surgical or laser procedure.

Cataract occurred in 68% of patients with a phakic study eye who were treated with the 700 µg dose (59% had cataract surgery during the study) compared to 7% of patients in the Sham group. This was also manageable in most patients.

The frequency of adverse events was similar for the 700 µg versus the 350 µg dose.

Risk management plan

Table 15 presents the summary of safety concerns.

Table 15. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Increased intra ocular pressure , glaucoma, ocular hypertension Cataract formation and associated reduced visual acuity Vitreous detachment, haemorrhage Endophthalmitis (infectious, non-infectious) Retinal tear, detachment Significant vitreous leak or hypotony Device dislocation Implant misplacement Retinitis secondary to reactivation of latent viral or other ophthalmic infections
Important potential risks	Systemic corticosteroid effects (infections, hypertension, impaired healing) Off label use
Missing information	Paediatric use Pregnancy and lactation Long term safety Repeat dosing data Concurrent use of anti-coagulants Use in the presence of significant retinal ischemia

Risk benefit analysis

This brief summary is based both on the TGA's clinical evaluation report and the EMA's Assessment Report (24 July 2014, Procedure No. EMEA/H/C/001140/II/0015).

Delegate's considerations

Benefit/harm balance

The improvement, compared to Sham, in the pre specified primary endpoint (change in BCVA from baseline) was small (Study 010: 2.1 letters, Study 011: 0.8 letters, pooled: 1.4 letters). By way of indirect comparison, the improvement, compared to laser treatment, for ranibizumab is about 5 letters.

The lack of a laser as control is a weakness in the study designs for Ozudex, unless it is argued that the patients in the trials were unsuitable for laser, which does not seem to be the case, based on the amount of rescue treatment [of course, not all rescue treatment was laser]. It could also be argued that lack of a VEGF inhibitor arm is a weakness, but at the time the studies were designed and initiated, VEGF inhibitors were not on the market. There are unanswered questions about the role of corticosteroids in combination with

VEGF inhibitors and laser. However, in terms of a simple sequence of treatments, indirect comparisons of treatment effect (that is, a 2.6 letter gain versus a 5 letter gain), (and the high incidence of cataract and raised IOP), suggest that corticosteroids are last line treatment.

It is reasonable to argue that the high incidence of the adverse drug reaction of cataract (approximately 70%, for the phakic subgroup) influenced the BCVA results. A subgroup analysis of pseudophakic patients showed larger improvements, compared to Sham (Study 010: 5.9 letters; Study 011: 3.6 letters).

The EMA considered that the benefit harm balance was not favourable for all patients with DME, but was favourable for pseudophakic patients (no risk of cataract), or for patients were unsuitable for or insufficiently responsive to non-corticosteroid treatment (that is, last line).

The incidence of cataracts and raised IOP is high, but these are manageable in the clinical context of a patient who is going blind; and who has no other option. The treatment effect, averaged across all patients, is only moderate, but for some selected patients, there might be material benefits. There is currently no way of predicting which patients will benefit; although the benefit harm balance might be more favourable for pseudophakic patients because there is no risk of cataract.

There is an unmet clinical need for treatments for patients who do not respond to VEGF inhibitors or who are unsuitable for monthly VEGF inhibitor injections. A trial of steroids is probably reasonable in these patients.

Dosing instructions

Visual response peaked at 1 3 months after implant and then declined. There seemed to be no effect 6 months after implant.

These results suggest that more frequent implants could improve the treatment effect, but [in the absence of other evidence] EMA considered that posology recommendations should be based on the regimen used in the trials. The EMA has requested a post approval study to investigate the optimal interval for re treatment.

Proposed Australian PI:

> Retreatment of Ozudex is recommended when the patient reports a loss of visual acuity or there are anatomical signs of recurrent or worsening diabetic macular oedema. In clinical trials, the majority of retreatments were administered between 5 and 7 months after a prior treatment.

EU SmPC:

> 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 or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema.
>
> There is currently no experience of the efficacy and safety of repeat administrations in diabetic macular oedema beyond 7 implants.

FDA PI

> The dosage sub section is silent on the retreatment interval. The clinical trials section states that patients in the Ozurdex arm of the pivotal RCTs received an average of 4 implants over 3 years.

Bilateral use

Concurrent administration has not been studied. In response to the RMP evaluator, the sponsor has added a statement to the precautions section saying that "administration to both eyes is not recommended." This is in the EMAs SmPC, but not in the FDAs PI.

Question: It seems reasonable that the PI state that concurrent use has not been studied. Should it also state that concurrent use is not recommended?

350 µg versus 700 µg

Although there was no dose ordering for efficacy, the 350 µg dose did not have a lower frequency of adverse events. The sponsor has explained the decision to only register and market the 700 µg dose in Australia, because the 700 µg dose is the only dose marketed overseas, where there are also two additional indications (macular oedema secondary to retinal vein occlusion and non-infectious posterior uveitis). Given there is no safety advantage from the lower 350 µg dose, does the decision to only register and market the 700 µg dose seem reasonable?

Conditions of registration

Implement EU RMP Version 4.0 (dated 18 March 2013) with the latest version of the Australian Specific Annex (ASA) to the satisfaction of Post Marketing and Safety Branch.

Notify the TGA of the results of any relevant studies as soon as they are available.

Summary of Issues

This product was registered by the EMA and FDA in 2014 for diabetic macular oedema (the indication for this current submission to the TGA). It has been registered for macular oedema due to retinal vein occlusion and non-infectious posterior segment uveitis in the US and EU for about 4 to 5 years. It is not registered for these indications in Australia.

There is an unmet clinical need for treatments for patients with DME who do not respond to VEGF inhibitors. A trial of this product is probably reasonable in these patients.

The incidence of cataracts and raised intra ocular pressure is high, but these are arguably manageable in the clinical context of a patient who is going blind and who has no other options. The treatment effect, averaged across all patients, is only moderate, but for some selected patients, there might be material benefits. There is currently no way of predicting which patients will benefit.

The pharmaceutical chemistry evaluator did not recommend approval because the proposed in vitro dissolution release limits have not been justified. The sponsor needed to resolve this to the satisfaction of pharmaceutical chemistry before registration can be finalised.[23]

Proposed action

The Delegate had no reason to say, at that time, that the application for Ozurdex should not be approved for registration.

Request for ACPM advice

Question 1

Wording of the indication

Current treatment algorithms clearly position corticosteroids as last line treatment. Is there any benefit, in terms of informing ophthalmologists (that is, the potential

prescribers), of adding this to the indication, as per the EMA? Put another way, is the FDA indication sufficient?

EMA indication:

> "*adult patients with diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy*."

FDA indication:

> "*adult patients with diabetic macular edema".*

Question 2

Wording about re treatment in the dosage and administration section of the PI

The protocol in pivotal randomised clinical trials was for a 6 monthly dosing interval, but there is some evidence that more frequent dosing might be beneficial. The EMA has requested a post approval study to clarify the dosing interval. Generally speaking, the dosing instructions in the Australian PI should align with one of the major overseas regulators (for example, EMA, FDA). Please comment on the EMA versus the FDA wording.

EU SmPC

> 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 or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema.
>
> There is currently no experience of the efficacy and safety of repeat administrations in diabetic macular oedema beyond 7 implants.

FDA PI

> The dosage sub section is silent on the retreatment interval. The clinical trials section states that patients in the Ozurdex arm of the pivotal RCTs received an average of 4 implants over 3 years.

Question 3

Bilateral use: It seems reasonable that the PI state that concurrent bilateral use has not been studied. Should it also state that concurrent use is not recommended?

Response from sponsor

Allergan Australia Pty Ltd. refers to the Delegate's overview and request for ACPM's advice and concurs with the Delegate's preliminary assessment that there is "no reason to say, at this time, that the application for Ozurdex should not be approved for registration". We note the Delegate's questions to the ACPM regarding the indication and dosage and administration sections of the PI and Allergan's response to the questions and additional comments raised by the Delegate (in italics) are provided below.

Allergan also acknowledges the Delegate's comments that most clinical practices now recommend intravitreal vascular endothelial growth factor (VEGF) inhibitors as initial therapy, but that there is an unmet clinical need for treatments for patients who do not respond to VEGF inhibitors, or who are unsuitable for monthly VEGF inhibitor injections.

General comments on study design

The Delegate makes 2 comments on the study design, namely how data was treated after patients received escape medication, and use of Sham as the comparator rather than laser.

With regard to the treatment of data from patients who received escape medication, per the study protocol, patients who received escape medication were to be discontinued from the study. No best corrected visual acuity (BCVA) or other efficacy assessments were to be collected afterwards. However, if assessments were recorded in the case report forms after use of escape medications, those assessments were set as missing data. Last observation carried forward (LOCF) was the method used for missing value imputation.

With regard to the comparator, while laser was the standard of care at the time the studies were initiated, a laser control group would not have been appropriate for all patients (for example those with oedema near the central subfield or patients who had failed prior laser). Also, as noted by the Delegate, anti VEGF products were not on the market at the time of study initiation and therefore were not considered as a comparator. The use of an inactive control (and a second dose of dexamethasone to reduce bias), allowed a clear assessment of the benefits and risks of Ozurdex, and ensured that the add-on effect from other therapies did not confound the results against a pure control group (Sham).

Overseas regulatory history

The Delegate comments, in relation to the regulatory history in the USA, that the initial indication for diabetic macular oedema (DME) approved by the US FDA was amended following a request from the FDA for a supplemental application. Allergan would like to clarify that no additional information or rationale was requested by the FDA, or provided by Allergan, to support the reconsideration of the indication. Approval of the indication 'treatment of diabetic macular oedema' was based on the same clinical dataset that has been submitted to TGA.

Delegate's questions to the ACPM

Question 1. Wording of the indication:

> *Current treatment algorithms clearly position corticosteroids as last line treatment. Is there any benefit, in terms of informing ophthalmologists (that is, the potential prescribers), of adding this to the indication, as per the EMA? Put another way, is the FDA indication sufficient?*

Sponsor's response

The efficacy and safety of Ozurdex in patients with DME was demonstrated in 2 masked, randomised, controlled Phase III studies 206207 010 and 206207 011. Patients were randomised to treatment with Ozurdex 700 µg or 350 µg compared to Sham (needleless applicator). Patients received up to 7 treatments during the 3 year study period.

The long term benefit of Ozurdex in the general DME population was demonstrated using a number of clinically relevant and complementary endpoints. There was a clinically meaningful improvement of 15 or more letters in BCVA from baseline with Ozurdex 700 µg compared to Sham at the Year 3/final visit. Furthermore, the BCVA average change from baseline during the study (AUC approach) was significantly greater with Ozurdex compared to Sham. As noted by the Delegate, the high incidence of cataract reduced the clinical meaningfulness of the results during the second year of the trial; however, following cataract surgery, vision improvement with Ozurdex was re-established.

The benefits of treatment with Ozurdex were observed following the first injection with an early onset of action, and long duration of effect. Following retreatment, patients achieved clinically relevant and statistically significant increases in visual acuity. This was further supported by rapid and sustained anatomical improvement as measured by optical coherence tomography (OCT).

Allergan believes that a positive benefit-risk profile for Ozurdex was established for all patients with DME in the pivotal registration studies, but also recognises that the benefit-risk profile is more favourable in particular patient subgroups.

Compared to the general DME population, there are 2 subpopulations in which Ozurdex demonstrates a more robust benefit-risk profile. Firstly, the benefit of treatment is higher in pseudophakic patients because of the absence of cataract and its corresponding impact on vision, and the risk of treatment is reduced because cataract does not apply to such patients.

Secondly, based on entry criteria patients in the pivotal studies represented a population that was considered unsuitable for or inadequately responsive to therapies that were available at the time the study began, including laser or other off label pharmacological treatments (that is, anti VEGF, intravitreal triamcinolone). For these patients, the relative risk of cataracts and IOP elevation is justifiable compared to the far more serious risk of irreversible vision loss in this population.

Therefore, Allergan proposed to include these subpopulations in the following revised indication:

> *Ozurdex is indicated for the treatment of adult patients with diabetic macular oedema who are pseudophakic, or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy*

However, as the Delegate points out, current treatment algorithms would indicate that clinicians would already be aware of the relevant DME patient subgroups that would be appropriate for treatment. Retina specialists understand the seriousness of sight threatening DME, and where Ozurdex 700 µg lies within the armamentarium. Allergan believes the treating physician is in the best position to determine the benefit-risk balance for the patient, based on their individual history and condition. Therefore there may be limited value in adding these subpopulations specifically to the indication. As such, Allergan is supportive of revising the indication to remove reference to these specific subpopulations (that is, equivalent to the FDA indication). The indication therefore would be the following:

> *Ozurdex is indicated for the treatment of adult patients with diabetic macular oedema*

Question 2. Wording about re treatment in the dosage and administration section of the PI.

The protocol in pivotal RCTs was for a 6 monthly dosing interval, but there is some evidence that more frequent dosing might be beneficial. The EMA has requested a post approval study to clarify the dosing interval. Generally speaking, the dosing instructions in the Australian PI should align with one of the major overseas regulators (for example, EMA, FDA). Please comment on the EMA versus the FDA wording

Sponsor's response

Starting from the month 6 visit in the Phase III studies (206207 010 and 206207 011), patients were evaluated for retreatment eligibility every 3 months. Patients were eligible for retreatment if retinal thickness in the 1 mm central macular subfield by OCT was > 175 µm or upon investigator interpretation of the OCT for any evidence of residual retinal oedema consisting of intra retinal cysts or any regions of increased retinal thickening (within or outside of the centre subfield). In the pooled Phase III studies, during the course of the 3 year study period, a total of 1,080 study retreatments for Ozurdex were administered.

Approximately 80% of the retreatments were administered between 5 to 7 months after the prior treatment Allergan acknowledges that more frequent (than 6 monthly) dosing may be beneficial, and does not believe that restriction of retreatment to strictly 6 months is warranted. Allergan proposes that the current statement in the dosage and administration section of the PI document should be modified to the following:

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 with Ozurdex is recommended if the patient experiences decreased vision and/or an increase in retinal thickness, secondary or worsening DME. In clinical trials, the majority of retreatments were administered between 5 and 7 months after a prior treatment.

The proposed language is largely consistent with the concepts in the USPI and the EU SmPC.

Currently, a post authorisation study is planned to better understand the use of Ozurdex in real world clinical practice for the treatment of DME, ie, real world effectiveness and safety data for treatment with Ozurdex as both monotherapy and combination therapy in both treatment naïve and previously treated DME patients. Allergan will review the findings from this study once available, and propose changes to the dosing section of the PI if necessary.

Question 3. Bilateral use

It seems reasonable that the PI state that concurrent bilateral use has not been studied. Should it also state that concurrent use is not recommended?

Sponsor's response

Allergan agrees to accept the committee's advice on whether to keep the statement "administration to both eyes is not recommended" or remove it. However if the ACPM recommends keeping the statement, then Allergan would request that the statement be further clarified as "administration to both eyes at the same time is not recommended".

Delegate's comment on dose strength 350 µg versus 700 µg

Given there is no safety advantage from the lower 350 µg dose, does the decision to only register and market the 700 µg dose seem reasonable?

Sponsor's response

In each of the Phase III studies (206207 010 and 206207 011) and the pooled analysis, both the 350 µg and 700 µg doses were shown to be effective in treating macular oedema associated with diabetes. The 700 µg dose however generally showed a greater and more consistent response than 350 µg compared to Sham. Ozurdex was well tolerated with up to 7 treatments over 3 years. Ocular adverse events were consistent with ophthalmic steroid therapy, and the overall safety profiles were similar between the 700 µg and 350 µg doses.

Overall, a numerical trend of better efficacy with Ozurdex 700 µg compared to 350 µg was observed across the spectrum of efficacy endpoints, which in the absence of dose dependent clinically relevant side effects suggests the use of Ozurdex 700 µg in this population to maximise the treatment benefit. Allergan, therefore, is seeking only approval of the 700 µg dose.

Quality evaluation

The pharmaceutical chemistry evaluator did not recommend approval because the proposed in vitro dissolution release limits have not been justified.

In an email to the TGA dated 12 February 2015, Allergan agreed to adopt the evaluator's suggested in vitro dissolution release limits in full. Consequently, the TGA issued an updated round 2 quality evaluation report and an updated quality ACPM summary on 13 February 2015, in which the evaluator recommended approval.

Conclusion

Intravitreal dexamethasone, in the form of Ozurdex, targets multiple pro inflammatory factors associated with DME, with a slow release profile from the biodegradable implant.

A flexible retreatment paradigm with defined minimum dosing intervals avoids overtreatment and reduces the treatment burden compared to other available therapies. Ozurdex has been shown to be effective in treating DME in the overall study population as well as multiple patient subgroups, and has a well-defined safety profile with 111,561 patient years of use and no systemic drug reactions.

Allergan therefore:

- Agrees with the Delegate's conclusion that Ozurdex should be approved for the treatment of DME.
- Notes the Delegate's comments regarding the place of corticosteroid treatment in the treatment algorithm and believes that there may be limited benefit in specifying those subpopulations in the indications
- Notes the Delegate's comment that more frequent dosing might be beneficial, and have proposed wording for the Dosage and Administration section accordingly.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Ozurdex implant containing 700 µg of dexamethasone to have an overall positive benefit–risk profile for the indication;

Treatment of adult patients with diabetic macular oedema

In making this recommendation the ACPM

- Noted the treatment interval should not be less than 3 months as data are only available for approximately 6 month intervals over 3 years
- Noted there was no evidence on bilateral simultaneous treatment
- Noted there was no evidence for use in children

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically with the need for post marketing study reports to be submitted to the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM advised on the proposed amendments to the PI and CMI in the specific questions below.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

Question 1

Wording of the indication.

Current treatment algorithms clearly position corticosteroids as last line treatment. Is there any benefit, in terms of informing ophthalmologists (that is, the potential prescribers), of adding this to the indication, as per the EMA? Put another way, is the FDA indication sufficient?

EMA indication:

> *adult patients with diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.*

FDA indication:

> *Adult patients with diabetic macular edema.*

The ACPM advised that in clinical practice, the EMA and FDA indications amounted to the same information for prescribers; however, the ACPM practice of preferring simpler indications suggests an indication similar to that of the FDA would be preferable.

Question 2

Wording about re treatment in the dosage and administration section of the PI

The protocol in pivotal RCTs was for a 6 monthly dosing interval, but there is some evidence that more frequent dosing might be beneficial. The EMA has requested a post approval study to clarify the dosing interval. Generally speaking, the dosing instructions in the Australian PI should align with one of the major overseas regulators (for example, EMA, FDA). Please comment on the EMA versus the FDA wording.

EU SmPC

> *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 or an increase in retinal thickness, secondary to recurrent or worsening diabetic macular oedema.*
>
> *There is currently no experience of the efficacy and safety of repeat administrations in diabetic macular oedema beyond 7 implants.*

FDA PI

> *The dosage sub section is silent on the retreatment interval. The clinical trials section states that patients in the Ozurdex arm of the pivotal RCTs received an average of 4 implants over 3 years.*

The ACPM advised that statement in dosage and administration section of the PI in relation to re treatment should be modified to the following;

> *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. In clinical trials, the majority of retreatments were administered between 5 and 7 months after a prior treatment. Patients in the Ozurdex arm of the pivotal RCTs received an average of 4 implants over 3 years. The protocol in the pivotal RCTs specified a 6 monthly dosing interval. There is currently no experience of the efficacy and safety of repeat administrations in diabetic macular oedema beyond 7 implants.*

Question 3

Bilateral use:

It seems reasonable that the PI state that concurrent bilateral use has not been studied. Should it also state that concurrent use is not recommended?

The ACPM advised that PI and the relevant section of the CMI should state that concurrent bilateral use has not been studied and is not recommended. Perhaps the word "simultaneous" should be used instead of "concurrent".

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ozurdex dexamethasone 700 microgram intravitreal implant indicated for:

Ozurdex is indicated for the treatment of diabetic macular oedema (DME).

Specific conditions of registration applying to these goods

- The Ozurdex dexamethasone EU Risk Management Plan (RMP), Version 7.0, dated 5 August 2014, revised as specified by the Australian Specific Annex, Revision 4.0, dated 22 May 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia
- Notify the TGA of the results of any relevant studies as soon as they are available

Attachment 1. Product Information

The PI for Ozurdex approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product information pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au