

Resubmission:

dexamethasone 700 microgram intravitreal implant (Ozurdex®)

SMC No. (652/10)

Allergan Ltd

04 November 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

dexamethasone intravitreal implant (Ozurdex®) is not recommended for use within NHS Scotland.

Indication under review: treatment of adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

In two phase III studies dexamethasone 700 microgram intravitreal implant was superior to sham administration at day 90 for the proportion of patients with a best corrected visual acuity improvement of ≥ 15 letters. Longer-term effectiveness of treatment is uncertain.

The submitting company did not provide a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of adult patients with macular oedema following either branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Dosing Information

One dexamethasone 700 microgram implant administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended.

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from re-treatment without being exposed to significant risk. There is only very limited information on repeat dosing intervals. There is currently no experience of repeat administrations beyond two implants in retinal vein occlusion (RVO).

Patients who experience and retain improved vision should not be retreated. Patients who experience deterioration in vision, which is not slowed by dexamethasone intravitreal implant, should not be retreated.

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

Product availability date

27 July 2010

Summary of evidence on comparative efficacy

Retinal vein occlusion is a leading cause of visual impairment and is the second most common form of retinal vascular disorder after diabetic retinopathy with a prevalence of between 0.7 and 1.6%. RVO can occur in the branch veins or the central vein as a result of thrombus formation or venous blockage due to compression of the venous wall by an arteriole. It is classified into two main types: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Macular oedema is a common complication of BRVO or CRVO; it is the primary cause of visual loss in patients with BRVO and one of the leading causes of visual loss in patients with CRVO.

Dexamethasone intravitreal implant is a biodegradable implant that delivers a sustained dose of dexamethasone (a corticosteroid) through a solid polymer drug delivery system to the posterior segment of the eye over a period of up to 6 months. Dexamethasone suppresses inflammation in the eye by inhibiting oedema, fibrin deposition, capillary leakage and phagocytic migration. Corticosteroids inhibit the expression of vascular endothelial growth factor (VEGF), a cytokine that is a potent promoter of vascular permeability and expressed at increased concentrations in macular oedema.

Two phase III randomised, sham-controlled, three arm parallel-group multicentre studies of identical design except for the timing of the primary endpoint analysis have been conducted in adult patients with vision loss due to macular oedema associated with RVO. Approximately two thirds of patients had BRVO (duration 6 weeks to 12 months) and one third had CRVO (duration

6 weeks to 9 months).^{1,2,3} Patients were randomised equally to treatment with dexamethasone 700 microgram (licensed dose), dexamethasone 350 microgram administered intravitreally or sham procedure (needleless applicator placed against the conjunctiva), all administered once with patients followed up for 6 months. All patients received a topical ophthalmic antibiotic for 3 days before and for 3 days after study drug administration.

Patients were also required to have a best corrected visual acuity (BCVA) score between 34 and 68 letters by the Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria in the study eye, with a score of better than 34 in the non-study eye, and retinal thickness ≥ 300 micrometres by optical coherence tomography (OCT) in the study eye. The ETDRS provides a score of 0 to 100 which represents the number of letters read correctly.

The primary endpoint for the submission to the European Medicines Agency (EMA) was the same for both studies but measured at different times: the proportion of patients with a BCVA improvement of ≥ 15 letters from baseline at day 180 (in the first study) and day 90 (in the second study) using the ETDRS method analysed in the intention-to-treat (ITT) population which included all randomised patients. Dexamethasone 700 microgram was superior to sham administration at 90 days in both studies, but this was the primary endpoint only in the second study (see table).

Table: Primary endpoint: percentage of patients with a BCVA improvement ≥ 15 letter increase from baseline to day 180 (study 1) and day 90 (study 2) in ITT population

Visit	Study 1				Study 2			
	DEX700 n=226	DEX350 n=218	Sham n=224	p-value*	DEX700 n=201	DEX350 N=196	Sham n=202	p-value*
Day 30	22.6%	20.6%	7.6%	<0.001	19.9%	14.8%	7.4%	<0.001
Day 60	29.6%	31.2%	12.1%	<0.001	28.9%	25.5%	10.4%	<0.001
Day 90	21.2%	25.7%	13.8%	0.039	22.4%	20.9%	12.4%	0.008
Day 180	23.5%	22.0%	17.0%	0.087	19.4%	16.3%	18.3%	0.780

DEX= dexamethasone intravitreal implant. *for dexamethasone 700 microgram versus sham. Primary endpoint results in bold.

Secondary endpoints included subgroup analysis of the proportion of patients with a BCVA improvement of ≥ 15 letters from baseline in the groups of patients with either BRVO or CRVO. Although generally both subgroups responded to treatment with dexamethasone in a qualitatively similar way to the overall population, the response in the sham group was greater in patients with BRVO than CRVO. Mean BCVA slowly improved throughout the duration of the study among BRVO eyes treated with sham, but gradually deteriorated to below baseline levels in CRVO eyes treated with sham.

The time to achieve ≥ 15 letters improvement from baseline in BCVA was analysed using a Kaplan-Meier survival analysis with the log-rank test for treatment differences. Response curves were significantly different for dexamethasone 700 microgram compared with sham and the rates were consistently higher from day 30 onwards.

A pooled analysis of the pivotal studies demonstrating the superior effect of dexamethasone intravitreal implant on visual functioning measured by the National Eye Institute Visual Function Questionnaire-25 (VFQ-25) has been published as a conference presentation abstract. Analysis of 91% of enrolled patients 6 months after a single treatment showed statistically significant differences between the dexamethasone 700 microgram group and sham group for the subscales of near vision, distance vision, general vision, role difficulties, mental health and for the composite score.⁴

Summary of evidence on comparative safety

Pooled analysis of the pivotal studies found that the use of intraocular pressure lowering medication increased four-fold from baseline (approximately 6%) to day 180 (approximately 24%) in the dexamethasone group, with no change in the sham group.

Adverse events (AE) that occurred significantly more frequently with dexamethasone 700 microgram than sham included eye pain (7.4% versus 3.8%), ocular hypertension (4.0% versus 0.7%) and the presence of anterior chamber cells, indicative of a mild inflammatory response, (1.2% versus 0%). Cataracts in the study eye were reported in 7.3% patients in the dexamethasone 700 microgram group versus 4.5% patients in the sham group.^{1,2,3}

Summary of clinical effectiveness issues

The pivotal studies compared the licensed dose of dexamethasone intravitreal implant to sham administration. The potential for macular oedema to improve spontaneously without treatment was one reason for the use of sham as a comparator as it allowed tracking of changes due to the natural course of the disease. Laser treatment is effective only in macular oedema caused by BRVO not CRVO and was therefore unsuitable as a comparator. The efficacy of dexamethasone intravitreal implant relative to alternative treatment strategies is not known.

Statistical significance was not achieved for the licensed dose of dexamethasone versus sham in one of two registration studies in which the primary outcome was measured at day 180. Pooled analysis of the primary outcome at day 180 was not statistically significant. However, when the analysis excluded patients whose last assessment (scheduled for day 180) was actually performed later than day 180 because of delays in performing the study visit (approximately 50% of patients), the proportion of patients with ≥ 15 letter improvement in BCVA from baseline was 26% (55/208) versus 17% (39/229) respectively and was statistically significant ($p=0.017$). This was a post hoc analysis. There remains some uncertainty around how long benefits are sustained beyond day 90.

There are issues in relation to the submitting company's choice of comparator. The company stated that observation is current standard practice in Scotland but in response to requests from SMC also presented secondary analyses with ranibizumab and bevacizumab intravitreal injection. Ranibizumab received marketing authorisation in May 2011 for the treatment of visual impairment due to macular oedema secondary to BRVO or CRVO in adults and has recently been accepted by SMC for restricted use in patients with CRVO. The naïve indirect comparison with ranibizumab provided included patients with macular oedema associated with CRVO only. It concluded that dexamethasone was less effective than ranibizumab. However, the analysis

lacked transparency and robustness. A mixed treatment comparison (MTC) versus intravitreal bevacizumab was also presented but, as there is no licensed preparation of bevacizumab for treatment in the eye, this was not considered to be an appropriate comparator and the MTC was not assessed.

Summary of comparative health economic evidence

For the main comparison of dexamethasone with observation the submitting company presented a lifetime cost-utility Markov model of the effects of dexamethasone intravitreal implant compared to no treatment. Additional analyses were also provided using ranibizumab or bevacizumab as the comparator treatment; the cost effectiveness estimate for dexamethasone compared to ranibizumab was not considered further due to the limited current use of ranibizumab; and, the analysis comparing to bevacizumab was not considered further given that it is unlicensed for this indication.

The model had six main health states ranging from a visual acuity of 20/40 in the treated eye, to less than 20/200. The modelling was restricted to the subset of patients who were not suitable for laser photocoagulation therapy, and was undertaken for three subgroups:

- CRVO patients
- BRVO patients with macular haemorrhage
- BRVO patients not responsive to photocoagulation

Most of these patients were assumed to require treatment in their worse seeing eye, but 10% were assumed to require treatment for their better seeing eye in contrast to the pivotal studies in which only 3% of patients received treatment in their better seeing eye.

Rates of dexamethasone treatment were taken from the studies for the first two 6-monthly injections, with an assumption supported by expert opinion that retreatment could occur up to a possible maximum of six treatments. Among those patients discontinuing treatment a constant proportion were assumed to have resolved, as observed in the initial 6 months study data.

Transition probabilities for the first 6 months were drawn from patient-level pooled randomised controlled trial (RCT) data for the relevant subgroups. For dexamethasone the subsequent 6 months' transition probabilities were drawn from the pooled open-label study data. For the no treatment arm the transitions from the last 3 months of the RCT data were applied, suitably adjusted for the 6-month cycle period. These were re-applied for an additional five 6-monthly cycles for CRVO patients, and four for BRVO patients. Thereafter, treatment stopped and visual acuity was assumed to have stabilised for the remaining patient lifetime.

Utility values were based upon values drawn from members of the UK, US, Canadian and Australian general public using the time trade off technique; these showed a much greater patient impact if the BCVA in the better seeing eye improved compared to an improvement in BCVA in the worse seeing eye.

For patients who were initially treated in the worse seeing eye, the submitting company also modelled the incidence of RVO in the fellow better seeing eye. Where this occurred, the same modelling approach and costs were applied, with the fellow eye also receiving four or five dexamethasone treatments.

The submitting company estimated rates of intervention for raised intraocular pressure and cataracts based on trial data. An annual £6k cost of blindness was also applied among patients with their worse seeing eye affected at baseline, if fellow eye involvement occurred and the better seeing eye fell below 20/200. If the patient initially had their better seeing eye affected and this fell below 20/200, since fellow eye involvement was not modelled for these patients an adjustment was made to the annual cost of blindness.

The results of the analysis for each patient group versus the no treatment comparator are shown below:

Patient group	Incremental costs	Incremental quality adjusted life years (QALYs)	Incremental effectiveness (ICER) cost ratio
CRVO	£4,602	0.28	£16,694
BRVO with macular haemorrhage	£3,025	0.17	£17,968
BRVO not responsive to laser	£1,874	0.28	£6,684

Results were sensitive to the costs of blindness assumed, whether the eye requiring treatment at baseline was the better seeing eye or the worse seeing eye, the assumed duration of treatment, the proportion of dexamethasone patients requiring retreatment, the resolution rate among those assumed to discontinue treatment, the mortality multiplier for blindness and the proportion of RVO in the fellow eye that would lead to macular oedema that was suitable for dexamethasone treatment. One way sensitivity analysis indicated that the results were most sensitive to the assumptions made regarding re-treatment rates and transition probabilities for dexamethasone patients who did not receive re-treatment. If re-treatment rates were based on the proportion re-treated in the trial, the ICERs were £22,731, £41,940 and £14,551 for CRVO, BRVO with macular haemorrhage and BRVO not responsive to laser respectively. Applying the transition probabilities of the observation group to all patients who were not re-treated increased the ICERs to £30,445, £45,215 and £15,468 respectively.

The main weaknesses with this analysis were:

- assuming that all fellow eye RVO involvement would lead to macular oedema suitable for treatment with dexamethasone;
- not modelling fellow eye involvement for those initially affected in their better seeing eye; and
- uncertainty in extrapolation of resolution rates.

In the light of these weaknesses, the manufacturer did not present a sufficiently robust economic case to gain acceptance by the SMC.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was received from the Royal National Institute for the Blind (RNIB).

Additional information: guidelines and protocols

The Royal College of Ophthalmologists published updated Retinal Vein Occlusion (RVO) Interim Guidelines in December 2010. These recommend the use of dexamethasone intravitreal implant or intravitreal ranibizumab for non-ischaemic BRVO or CRVO.

Additional information: comparators

Ranibizumab has recently been licensed for the treatment of visual impairment due to macular oedema secondary to BRVO or CRVO in adults and has recently been accepted by SMC for restricted use in patients with CRVO. Experts consulted by SMC report that there is some use of unlicensed preparations of triamcinolone and the anti-vascular endothelial growth factor (anti-VEGF) agent bevacizumab administered by intravitreal injection. Laser treatment is used for macular oedema following BRVO.

Cost of relevant comparators

Drug	Dose Regimen	Cost per six months (£)
Dexamethasone intravitreal implant	700 microgram intravitreally	870
Ranibizumab	0.5mg intravitreally once monthly until maximum visual acuity is achieved	up to 4,567

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMs August 2011. Costs do not include topical antimicrobial treatment. Cost of dexamethasone intravitreal implant based a single treatment. Cost of ranibizumab based on up to six doses.

Additional information: budget impact

The submitting company estimated that 214 patients would be treated in year 1, based on a predicted market share of 2%, with a gross budget impact of £562k. This was estimated to rise to 633 patients treated in year 5, based on a market share of 5%, with a corresponding gross budget impact of £1.7m.

The relatively low market share assumed by the manufacturer was based on an assumption that only new incident cases would be treated.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

1. Haller J, Bandello F, Belfort R et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology*. 2010; 117; 1134-46
2. Haller J, Bandello F, Belfort R et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion - Twelve-Month Study Results Ozurdex GENEVA Study Group. Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion Twelve-Month Study Results; *Ophthalmology* (Jul 2011)
3. European Medicines Agency. CHMP Assessment Report for Ozurdex® (dexamethasone) Procedure No. EMEA/H/C/001140. www.ema.europa.eu
4. Kowalski J, Rentz A, Revicki D et al. Effect of dexamethasone intravitreal implant on patient-reported visual functioning for the treatment of macular edema following retinal vein occlusion The Association for Research in Vision and Ophthalmology Conference May 2 to 6 2010 presentation abstract

This assessment is based on data submitted by the applicant company up to and including 17 October 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.