London Medicines Evaluation Network Review

Ozurdex® dexamethasone 700 microgram intravitreal implant for diabetic macular oedema
September 2014

Summary

<table>
<thead>
<tr>
<th>Background and licensed indication</th>
<th>Ozurdex® (dexamethasone 700 microgram intravitreal implant) has been available since 2010 with Marketing Authorisation for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion or Central Retinal Vein Occlusion and for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. In July 2014 the European Union’s Committee for Medicinal Products for Human Use (CHMP) recommended extending the Marketing Authorisation for Ozurdex® to treat adult patients with vision loss due to diabetic macular oedema (DMO) who are pseudophakic (have an artificial lens implant), or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. The SPC for Ozurdex® was updated in September 2014 to reflect the new indication.</th>
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<tbody>
<tr>
<td>Dosing</td>
<td>700 micrograms intravitreal implant every six months</td>
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<tr>
<td>Alternatives</td>
<td>Alternatives are dependent on pathways in place or being developed for DMO. They may include: Ranibizumab (Lucentis®) Laser photocoagulation Fluocinolone acetonide intravitreal implant (Iluvien®)</td>
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<tr>
<td>NICE</td>
<td>A NICE TA on dexamethasone intravitreal implant for DMO is due in April 2015. NICE (TA 274) recommends ranibizumab (Lucentis®) as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of ≥ 400 micrometres at the start of treatment. NICE (TA 301) recommends fluocinolone acetonide intravitreal implant (Iluvien®) for patients with DMO unresponsive to other treatment options. It should only be used in an eye with an artificial lens. Both ranibizumab and fluocinolone acetonide were approved by NICE on the condition that an approved but confidential patient access scheme is provided.</td>
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<td>Clinical studies</td>
<td>The MEAD study, published in June 2014, provided the evidence for the DMO licence extension. This three year phase 3 study (N=1,048) combined safety and efficacy results from two randomized, multicentre clinical trials using 2 strengths of dexamethasone intravitreal implant in adults with DMO. Dexamethasone intravitreal implant, 700 or 350 micrograms, was compared to sham intravitreal injections.</td>
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<td>Safety</td>
<td>Cataract related adverse events and rises in intraocular pressure.</td>
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<td>Convenience</td>
<td>Injections every six months compared with monthly injections of ranibizumab (Lucentis®)</td>
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<tr>
<td>Risk assessment</td>
<td>Not completed</td>
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<tr>
<td>Budget impact</td>
<td>Ozurdex® costs approximately £1,000 per injection. The manufacturer has provided a budget impact model based on two uptake assumptions based on a population of 100,000. Assumption 1 assumes that Ozurdex® and ranibizumab are each used to treat 38% of the patients who are not otherwise treated with laser or who are not treated at all. Assumption 2 assumes that Ozurdex® is used to treat 20% of patients and ranibizumab 55%, while keeping the other splits at 15% laser treatment and 10% no treatment. Both assumptions estimate a cost saving of £278,889 (assumption 1) and £152,969 (assumption 2) in the first year. This saving falls to £119,642 (assumption 1) and £67,912 (assumption 2) at year 3. However, these figures do not include the patient discount scheme for ranibizumab, which is commercial in confidence.</td>
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<tr>
<td>Funding</td>
<td>CCG funded</td>
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<tr>
<td>Suggested place in therapy</td>
<td>Ozurdex® is an option for patients unsuitable for non-corticosteroid therapy. They may be unable or unwilling to attend for monthly ranibizumab injections, or contraindicated for treatment with ranibizumab or partially responsive or unresponsive to non-corticosteroid therapy. Ozurdex® may be most suitable for pseudophakic patients, i.e. those patients with an artificial lens because of the high incidence of cataract related adverse events in phakic patients.</td>
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</table>
1. Background and introduction

Diabetic macular oedema is a common complication of diabetic retinopathy (DR) and can present at any stage of the disease. The vision loss associated with DR is most commonly the result of DMO and is estimated to affect 20% of patients with DR. (1) DR is the most common cause of visual impairment in diabetes mellitus and a leading cause of blindness and visual impairment in adults. (1, 2, 3) DMO can be defined as an abnormal collection of extravascular fluid in the macular caused by a breakdown of the blood-retinal barrier from various processes, such as increased production of inflammatory mediators. (3) Disruption of the blood-retinal barrier allows fluid to leak from blood vessels in the central part of the macular which can lead to severe visual impairment in the affected eye.

Ozurdex® is an intravitreal implant containing dexamethasone, a potent corticosteroid, which suppresses inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. (4) Vascular endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of oedema. (2,4) Ozurdex® is available as a biodegradable drug delivery device and is administered via injection into the vitreous cavity of the eye (intravitreal) and it delivers dexamethasone to the posterior segment of the eye for up to 6 months. (2) Current standard treatment options for DMO include focal grid laser photocoagulation and ranibizumab (Lucentis®). NICE guidance TA 274 recommends ranibizumab as an option for treating visual impairment due to DMO if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment. (5)

Fluocinolone acetonide intravitreal implant is the only other intravitreal steroid implant licensed for DMO (6). Its licence is restricted to patients with DMO unable to use alternative treatments. NICE further restricts its use to those patients who already have an artificial lens. (7)

2. Proposed place in therapy

This review outlines the clinical and cost effectiveness evidence for dexamethasone intravitreal implant (Ozurdex®) in the treatment of DMO. The licence extension for Ozurdex® was approved in September 2014. (4) Ozurdex® has been available since 2010 with marketing authorisation for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion or Central Retinal Vein Occlusion and for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. (4) The manufacturer submitted a licence extension application to both the EMA and the FDA. In July 2014 the EMA adopted a positive opinion recommending a variation to the terms of the marketing authorisation for Ozurdex®. The CHMP recommended the following new indication “Ozurdex® is indicated for the treatment of adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy”. (8) The SPC was updated in September 2014.

Ozurdex® has been developed for patients who are unsuitable for non-corticosteroid therapy (i.e. unable to receive frequent intracocular injections) or unresponsive, or only partially responsive, to non-corticosteroid therapy. (1) The alternative corticosteroid implant, fluocinolone, is given every 3 years and has a high incidence of cataracts associate with its use in phakic patients. The reported safety profile of Ozurdex® in the Boyer study (1) was better than the reported safety profiles of other intravitreal corticosteroids in patients with DMO. Boyer et al included evidence from a systematic review, that dexamethasone implant has been associated with a lesser incidence of increases in IOP compared with intravitreal fluocinolone implant. (1)

3. Evidence selected for inclusion

In previous studies, dexamethasone implant has demonstrated efficacy in the treatment of DMO, DMO resistant to anti-VEGF treatment and DMO in difficult to treat vitrectomised eyes. (1) The evidence supplied to the EMA for this licence extension came from the MEAD study (1) which consisted of 2 identical clinical trials whose results were pooled for analysis. The aim of MEAD was to evaluate the safety and efficacy of 2 strengths of dexamethasone intravitreal implant in adults with DMO, best corrected visual acuity (BCVA) of 20/50 to 20/200 Snellen equivalent, and a central retinal thickness (CRT) of ≥300 micrometers by optical coherence tomography. Patients were randomised 1:1:1 to dexamethasone intravitreal implant (700 micrograms N=347) or sham (N=350) intravitreal injections. They were followed for 3 years (or 39 months for those patients not treated at month 36). Patients who met retreatment eligibility could be retreated no more often than every 6 months.

Outcome measures

The predefined (FDA for the USA) primary efficacy endpoint was the percentage of patients with best corrected visual acuity (BCVA) improvement of 15 letters or more, from baseline, in the study eye at the end of the study, with missing observations inputted using last observations carried forward. Secondary outcomes for the study eye included average change in BCVA from baseline during the study determined with the area under the curve method (the EMA primary endpoint), mean change in BCVA from baseline at each study visit, time to 15 letters or more improvement in BCVA from baseline, percentage of patients with BCVA of ≥20/60 at each study visit, and average change in central retinal thickness (CRT) from baseline during the study by optical coherence tomography (OCT) (area under the curve approach). Safety measures included adverse events, intra-ocular pressure (IOP) measurements, biomicroscopic and ophthalmoscopic findings and measures of diabetic control (HbA1c and glomerular filtration rate).

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4. Critical evaluation

The study had 2 key end points. This was because the FDA in the US required one and the EMA another. The FDA end point was percentage of patients with improvement at a fixed time point. The EMA end point was the mean average change in visual acuity at three years. Both these outcomes were achieved.

As dexamethasone intravitreal implant has been licensed since 2010, there is an increasing body of evidence of its use both licensed and off-label. In the trials submitted for this licence extension, the use of dexamethasone intravitreal implant was permitted only every 6 months. There is anecdotal evidence that in clinical practice (3), administration of the implant may be more frequent than this, for example every 4–5 months. If this becomes the norm, not only is there no evidence from the MEAD study (1) to support this frequency of use, but the safety data would not have been fully established for this frequency in this indication i.e. there may be more or different adverse events. There would also be an impact on any proposed budget impact and projected costs savings. It is reassuring that in the Geneva study of 1,256 patients included in the current SPC (4), of the patients who were treated with the open label phase, 98% received an Ozurdex® injection between 5 and 7 months after the initial treatment and the safety profile was similar for the 6 month and 12 month data.

The MEAD study completed in 2012 and only compared dexamethasone intravitreal implant with sham injections. To date there is no published randomised controlled trial vs a comparator drug in DMO. However, COMRADE B, a trial sponsored by the manufacturers of ranibizumab (Novartis) completed in early 2014. The results are still being evaluated and are therefore neither published nor peer reviewed with no measure therefore of statistical or clinical significance. In addition this trial is not for the indication under review in this document. That said, preliminary data suggests ranibizumab demonstrated an advantage over dexamethasone intravitreal implant in the treatment of macular oedema as a result of branch retinal vein occlusion (BRVO). In COMRADE B the visual acuity was measured at 6 months. In the MEAD study, a noted imitation was that the dexamethasone implant may have been more beneficial if given more frequently. Clearly if that were the case then a 6 month evaluation of both drugs might favour ranibizumab. In addition to the Novartis trial, there is also an ongoing 12 month Allergan sponsored head to head study (MAGGIORE) comparing Ozurdex® with ranibizumab in DMO, however as with COMRADE B this data is neither published nor peer reviewed and no assessment of statistical or clinical significance is available. (3)

The licence extension study (1) began in 2005 and there are limitations in comparing older studies, as the guidelines surrounding study design have changed. In the MEAD study, no rescue medication was allowed and as a result many patients dropped out of the study in order to receive rescue medication. This was particularly the case in the sham group. Newer studies, for example the RISE/RIDE studies, completed in 2009, for ranibizumab, allowed rescue medication and as such, some of the patients in those studies were allowed to receive treatment with macular laser treatment. In the RISE study 74% of the sham group and 35.2% of the ranibizumab treatment group received macular laser treatment. In the RIDE study, 70% in the sham group and 19.7% in the ranibizumab group received macular laser treatment. These patients would have been removed from the MEAD study. (3) Also, during the MEAD study, anti-VEGF treatment became available, giving patients a ‘good escape’. (1)

The main safety concerns surrounding the use of intravitreal steroids are that they can cause cataract related adverse events and rises in IOP. In the MEAD study, the data was also analysed according to which patients had and had not had cataract surgery prior to the trial. In the patients who have already had cataract extraction surgery (the pseudophakic patients) the improvement in visual acuity continued. In phakic eyes the mean average BCVA improvement from baseline with dexamethasone implant 700 micrograms was substantial until the time of a cataract adverse event report. In phakic patients, the visual acuity of the study eyes reduced as cataracts formed, although not all of the phakic eyes (766 eyes) developed cataracts. Improvement in visual acuity from baseline was restored after cataract surgery. The percentage of patients who gained 15 letters or more from baseline at study end was similar in the phakic and pseudophakic subgroups.

There are study limitations. There is no information regarding the use of dexamethasone implant in combination with laser or
other treatment. The fixed dosing schedule used may have limited efficacy and more frequent dosing may have improved results.

4.1. Clinical application
For patients who do not respond, or respond inadequately to ranibizumab a switch to Ozurdex® may be an option if aligned with an agreed pathway for the treatment of DMO. The main safety concern with dexamethasone intravitreal implant is that it can increase the incidence of cataracts. Clearly this group of diabetic patients is predisposed to cataract formation; however their formation is likely to be accelerated by the use of this agent. In pseudophakic patients this is not a concern and the improvement in visual acuity in those patients continues. Ranibizumab has already received its licence for DMO and is recommended by NICE for this indication subject to a patient access scheme. The NICE TA for dexamethasone intravitreal implant is due in April 2015.

4.2. Safety
4.2.1. Key adverse events
The overall incidence of AEs at any time during the study was 96.0% with dexamethasone 700 micrograms, 97.4% with dexamethasone 350 micrograms and 80.3% with sham. The overall incidence of AEs adjusted for treatment exposure was similar between the groups. This was because more of the sham patient discontinued the study due to lack of efficacy in this group of patients and so did not take the treatment for as long as the dexamethasone treated patients. Rates of cataract-related adverse events were greater in phakic eyes with dexamethasone 700 micrograms (67.9%) and 350 micrograms (64.1%) compared with sham (20.4%). IOP elevation was typically managed with topical IOP lowering medication and only 2 patient’s required glaucoma incisional surgery (one in the dexamethasone 700 microgram group and one in the dexamethasone 350 microgram group).

There was no cumulative effect of the dexamethasone implants on IOP over the three years.

4.2.2. Risk assessment.
No formal risk assessment is available.

4.3. Potential advantages and disadvantages over existing technologies
4.3.1. Convenience
Reduced frequency on intravitreal injection; Ozurdex® is given via a biodegradable intraocular implant every 6 months. The NICE approved alternative ranibizumab is given via intraocular injection on a monthly basis.

4.3.2. Healthcare resource utilisation
Dexamethasone intravitreal implant could reduce the frequency of attendance for intraocular injections compared with the current alternative monthly ranibizumab injections.

4.3.3. Suitability for shared care:
None required.

4.3.4. Drug cost and likely budgetary impact
Ozurdex® costs £870 plus VAT, i.e. around £1000 per injection.

The manufacturer has provided a budget impact model based on two uptake assumptions. Assumption 1 assumes that Ozurdex® and ranibizumab are each used to treat 38% of the patients who are not otherwise treated with laser or who are not treated at all. Assumption 2 assumes that Ozurdex is used to treat 20% of patients and ranibizumab 55%, while keeping the other splits at 15% laser treatment and 10% no treatment. Both options predict a saving (indicated by the negative number). However, this projection does not include the patient discount scheme for ranibizumab and is therefore rather optimistic.

For a comprehensive budget impact model for your local health economy contact the manufacturer (Allergan).

<table>
<thead>
<tr>
<th>Total Budget impact per 100,000</th>
<th>Assumption 1</th>
<th>Assumption 2</th>
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</thead>
<tbody>
<tr>
<td>Total costs at year 1</td>
<td>-£278,889</td>
<td>-£152,969</td>
</tr>
<tr>
<td>Total costs at year 2</td>
<td>-£169,185</td>
<td>-£94,230</td>
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<tr>
<td>Total costs at year 3</td>
<td>-£119,462</td>
<td>-£67,912</td>
</tr>
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5. Likely Health Economics
Health economic analyses are not available.

6. Likely commissioning and funding pathway
CCGs

7. Suggested place in therapy
- Intravitreal dexamethasone implant may be a treatment option in pseudophakic patients, i.e. those who have already had cataract surgery and have an artificial lens.
- Intravitreal dexamethasone implant may be a treatment option for DMO in patients who, either do not respond to, or do not respond adequately to the alternatives or who are not suitable or contraindicated to anti-VEGF treatment.
- Intravitreal dexamethasone implant may be an alternative for patients unwilling or unable to present for monthly intravitreal injections.
- Intravitreal dexamethasone implant needs to be considered as part of an overall DMO pathway.

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References


3. Personal communication with Allergan 04/06/2014 and 22/07/2014


5. NICE TA 274 Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237) Published April 2013

6. Iluvien Summary of Product Characteristics available via www.medicines.org.uk date last revised 18/02/2014

7. NICE TA 301 Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271) Published: November 2013


Search terms used
Medline: dexamethasone exp. and intravitreal injections exp and macular edema
Embase: dexamethasone exp. and intravitreal drug administration exp. and diabetic macular edema

Written by Sarah Cavanagh, East Anglia Medicines Information Service, Ipswich Hospital, Ipswich, IP4 5PD. Sarah.cavanagh@ipswichhospital.nhs.uk Allergan has had the opportunity to carry out a factual check on this review. LMEN would like to thank Rachael Yoon, Clinical Trials Pharmacist, Moorfields Hospital, London for her comments on this review.