Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

dexamethasone 700 micrograms intravitreal implant in applicator (Ozurdex®)

SMC No. (1046/15)

Allergan Ltd.

10 April 2015

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 full submission

dexamethasone intravitreal implant (Ozurdex®) is accepted for use within NHS Scotland.

Indication under review: 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.

Intravitreal dexamethasone improved visual acuity more than sham treatment in adult patients who were pseudophakic or had received prior treatment for diabetic macular oedema, based on subgroup analyses.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 May 2015

Indication

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.

Dosing Information

One dexamethasone 700 micrograms implant administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended. Patients treated with dexamethasone intravitreal implant 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 six months if the patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DMO. There is currently no experience of the efficacy or safety of repeat administrations in DMO beyond seven implants.

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

Product availability date

24 August 2014

Summary of evidence on comparative efficacy

Dexamethasone intravitreal implant is a biodegradable device that delivers a sustained dose of the corticosteroid through a solid polymer drug delivery system to the posterior segment of the eye over a period of up to six 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. Dexamethasone intravitreal implant has received marketing authorisation for the treatment of visual impairment due to diabetic macular oedema (DMO) in patients who are pseudophakic (i.e. with an artificial lens) or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy. Dexamethasone intravitreal implant is also licensed for the treatment of adult patients with macular oedema following retinal vein occlusion and has been accepted for restricted use by SMC for specified patient groups. It is also licensed for inflammation of the posterior segment of the eye presenting as non-infectious uveitis but has not been recommended by SMC for this indication due to non-submission.[2]

The evidence for this new indication is from two identically designed 3-year phase III randomised, masked, sham-controlled studies (MEAD-010 and MEAD-011)[3,4], an unpublished supportive 12-month phase IIIb randomised, open-label, ranibizumab-controlled study (206207-024)[5,6] and a supportive12-month phase II randomised, masked, sham-controlled study (PLACID).[7]

MEAD-010 and MEAD-011 studies recruited adults with a diagnosis of type 1 or 2 diabetes mellitus and fovea-involved macular oedema associated with diabetic retinopathy. Patients had either received prior treatment with medical or laser therapy or were not suitable for, or had declined, laser treatment. In the study eye, best-corrected visual acuity (BCVA) was ≥34 and ≤70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and central retinal thickness was ≥300 microns.[4] A total

of 1,048 patients were randomised equally to treatment with intravitreal dexamethasone 700 micrograms, intravitreal dexamethasone 350 micrograms or sham (a needleless applicator pressed against the conjunctiva of the study eye). Additional study treatment was permitted according to protocol specified criteria after at least six months. Only the licensed dose of dexamethasone (700 micrograms) will be discussed in this document. At baseline, over 70% of patients retained the natural lens in the study eye; approximately 60 to 75% of patients had received prior laser treatment for DMO and only 8.6% (90/1,048) of patients had previously received anti-VEGF treatment.[3,4]

The primary outcome of mean change in average BCVA from baseline during the 3-year study period using observed data in the study eye (area under the curve approach) was analysed in the intention to treat (ITT) population consisting of all randomised patients. In MEAD-010, there was a significant improvement for dexamethasone over sham (4.1 versus 1.9) of 2.1 letters (95% CI: 0.4 to 3.8, p=0.016). However, the difference in MEAD-011 was not significant (2.9 versus 2.0) difference of 0.8 letters (95% CI: -0.9 to 2.4, p=0.366). In the pooled analysis, the difference in primary outcome was significant: 3.5 versus 2.0 corresponding to a difference of 1.4 (95% CI: 0.2 to 2.6; p=0.023).[3]

Significantly higher proportions of dexamethasone than sham patients achieved the following secondary outcomes after three years: proportions of patients with BCVA improvement ≥10 letters (39% versus 23% in MEAD-010, and 35% versus 25% in MEAD-011) and ≥15 letters (22% versus 13% in MEAD-010, 22% versus 11% in MEAD-011 and 22% versus 12% in the pooled analysis); p<0.05 for all analyses. The proportion with BCVA worsening of ≥15 letters after three years with dexamethasone versus sham was 9.2% versus 10% in MEAD-010 and 16% versus 12% in MEAD-011. In both studies, central retinal thickness was reduced significantly more with dexamethasone than sham.[3]

Health-related quality of life (HRQL) was measured using the visual functioning questionnaire 25 (VFQ-25). There was no statistically significant benefit with dexamethasone over sham.[3]

Pre-specified subgroup analyses of pooled MEAD-010 and MEAD-011 studies were conducted in pseudophakic patients and in patients with any prior treatment for DMO.[2]

Table 1. Efficacy in Pseudophakic Patients (Pooled Studies MEAD-010 and MEAD-011)[2]

Endpoint	Dexamethasone N = 86	Sham N = 101	p-value
Mean BCVA average change over 3 years, AUC approach (letters)	6.5	1.7	< 0.001
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	23.3	10.9	0.024
Mean BCVA change from baseline at year 3/Final visit	6.1	1.1	0.004
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (microns)	-131.8	-50.8	< 0.001

BCVA=best corrected visual acuity; AUC=area under the curve; OCT=ocular computer tomography

Table 2. Efficacy in Patients with Any Prior Treatment for DMO (Pooled Studies MEAD-010 and MEAD-011)[2]

Endpoint	Dexamethasone N = 247	Sham N = 261	p-value
Mean BCVA average change over 3 years, AUC approach (letters)	3.2	1.5	0.024
BCVA ≥ 15-letter improvement from baseline at Year 3/Final visit (%)	21.5	11.1	0.002
Mean BCVA change from baseline at year 3/Final visit	2.7	0.1	0.055
OCT retinal thickness at center subfield mean average change over 3 years, AUC approach (microns)	-126.1	-39.0	< 0.001

BCVA=best corrected visual acuity; AUC=area under the curve; OCT=ocular computer tomography

Study 206207-024 recruited adults with a diagnosis of type 1 or 2 diabetes mellitus and centre-involved macular oedema in the study eye with reduced BCVA (≥34 and ≤70 letters) attributable to macular oedema, and study eye central retinal thickness ≥300 microns.[5,6] A total of 363 patients were randomised in a 1:1 ratio to receive intravitreal treatment in the study eye: dexamethasone 700 micrograms implant on Day 1, Month 5, and Month 10, or ranibizumab 0.5mg injection on Day 1 with additional injections on a monthly basis as required for disease progression. Patients could receive deferred laser treatment any time during the study after month 2 if they met specific criteria.[5]

The primary outcome was mean BCVA average change from baseline through month 12 analysed in the ITT population consisting of all randomised patients. The results showed a gain of 4.34 letters for dexamethasone versus 7.60 letters for ranibizumab.[5,6]

PLACID recruited 253 adult diabetic patients with diffuse DMO, central retinal thickness ≥275mm, and reduced visual acuity BCVA (≥34 and ≤70 letters) in the study eye.[3,7] Patients were randomised to receive dexamethasone 700 micrograms plus laser photocoagulation or sham plus laser photocoagulation and could receive up to 3 additional laser treatments (at months 4, 7, and 10) and 1 additional dexamethasone implant or sham treatment (at month 6 or 9) during the study, according to pre-specified criteria.[3,7]

The primary outcome was not achieved. There was no significant difference between treatment groups in the proportions of patients that achieved ≥10 letter improvement in BCVA from baseline at month 12 in the ITT population (all randomised patients). At week 1 and at months 1 and 9, a significantly higher proportion of patients treated with dexamethasone plus laser achieved ≥10 letter improvement in BCVA from baseline compared with sham plus laser.[3,7]

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

Summary of evidence on comparative safety

In pooled analysis of MEAD-010 and MEAD-011 studies, adverse events were reported in 96% of dexamethasone patients and 80% of sham patients.[2,4] Treatment-related ocular adverse events were reported in 70% and 25% of patients in the dexamethasone and sham groups, respectively. Cataract formation (in patients with a natural lens in the study eye at baseline) occurred in 68% (178/262) versus 20% (50/250) of patients receiving dexamethasone and sham, and lead to cataract surgery during the study in 59% and 7.2% of patients in the respective groups.[3] Raised intraocular pressure (IOP) adverse events occurred in 36% (125/347) and 5.1% (18/350) patients in the dexamethasone and sham groups, and IOP-lowering medication was used in 42% (144/347) versus 9.1% (32/350) of

the respective groups, and surgical intervention in four patients in the dexamethasone group.[2,3] Eight patients in the dexamethasone group (and none in the sham group) discontinued from the study due to treatment-related adverse events: cataract (two patients), endophthalmitis, lens dislocation, necrotising retinitis, open angle glaucoma, retinal detachment, and vitreous adhesions (one patient each).[3]

Serious adverse events were reported in 22% (40/181) of patients in the dexamethasone group and in 23% (41/182) of patients in the ranibizumab group; the most frequent were: acute renal failure (4 versus 3); basal cell carcinoma (3 versus 0) and congestive cardiac failure (4 versus 1), respectively.[5] Ten (5.5%) patients in the dexamethasone group and five (2.7%) patients in the ranibizumab group discontinued the study due to adverse events.[5]

The European Public Assessment Report (EPAR) noted that in the subgroups of pseudophakic patients and patients with previously treated DMO, the safety of dexamethasone was comparable to that of the overall population except for the risk of cataract in phakic patients. The duration of dexamethasone treatment in DMO may be longer than in patients with retinal vascular occlusion or uveitis, with an associated increase in these adverse events. The EPAR also noted a range of other ocular adverse events that seemed more prevalent in patients receiving dexamethasone, either as a result of the active substance or the injection procedure, including retinal tear/detachment and endophthalmitis. In addition, there is some uncertainty concerning the increased incidence of certain non-ocular serious adverse events in patients receiving dexamethasone, (cellulitis, pneumonia, gastroenteritis, and urinary tract infection). These events were of particular concern in diabetic patients and were considered to require close monitoring.[3]

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

Summary of clinical effectiveness issues

Diabetic retinopathy affects up to 80% of all patients who have had diabetes for 10 years or more. DMO is a consequence of diabetic retinopathy and it develops in approximately one third of patients who have had diabetes for more than 20 years.[1] DMO is characterised by increasing vasopermeability and damage to retinal capillaries, and can lead to visual impairment. Dexamethasone intravitreal implant is the second intravitreal corticosteroid to be licensed for the treatment of visual impairment in DMO in the UK. Fluocinolone acetonide intravitreal implant (Iluvien®), and the anti-VEGF intravitreal injections ranibizumab and aflibercept, have all been accepted for restricted use in DMO by SMC. The advice for aflibercept was published recently (in November 2014) and was not considered a comparator in this submission. Dexamethasone intravitreal implant is currently available for use in NHS Scotland for specified patients with macular oedema following retinal vein occlusion. Clinical experts consulted by SMC considered that there is unmet need in diabetic macular oedema, namely in patients who have failed anti-VEGF treatment.

The primary outcome was not achieved in one of the key phase III MEAD studies comparing dexamethasone with sham. In the pooled analysis, the difference between dexamethasone and sham after three years was statistically significant but small: 1.4 letters, (95% CI: 0.2 to 2.6). The treatment effect was not consistent over the lifespan of the implant and its clinical relevance is unclear. The study population included phakic and pseudophakic patients, as well as treatment-naïve and previously treated patients. Therefore evidence supporting the licensed population was derived from pre-specified subgroup analyses. Cataract formation, in patients with a natural lens in the study eye at baseline, reduced visual acuity in these patients. Improvement in visual acuity over sham was demonstrated in the subgroup of pseudophakic patients. In the subgroup of patients with prior DMO treatment, the effect size was small (<2 letters) and of uncertain clinical relevance.[3]

The only direct evidence comparing dexamethasone with an active drug is the phase IIIb study, 207206-024, in which dexamethasone resulted in a mean loss of 3.3 letters compared with ranibizumab.[5]

In the phase II PLACID study, the primary outcome of ≥10 letter improvement in BCVA, was not significantly different with dexamethasone plus laser than with sham plus laser[3,7] and in the post-hoc pseudophakic subgroup analysis, it was significantly worse: 17% (6/35) versus 38% (12/32); difference -20.9% (95% CI: -42.4 to 0.50), p=0.047.[8]

The evidence had several limitations. The high incidence of cataract formation in patients with phakic study eyes confounded the results. The use of post hoc subgroups to test the comparative efficacy of dexamethasone in patients who had prior treatment for DMO limits the robustness of these results. The only direct comparative study evidence is from a phase II study (206207-024) that has not been published. This study lasted for 12 months which is a short follow-up time for a medicine that is licensed to be administered no more frequently than every six months. The dosage schedule in the 206207-024 study was more frequent than the licensed schedule.[5,6] In addition, in the MEAD studies a total of 24% of sham patients discontinued due to lack of efficacy and the EMA noted this as a concern in the EPAR since no imputation methods were applied for missing data in the primary efficacy analysis.[3] Furthermore, 28% of patients in the MEAD studies were treatment-naive and may not reflect the licensed indication. Two thirds of the pooled MEAD study population (698/1,048) had previously received laser treatment; however, because anti-VEGF drugs were not available during much of the duration of these studies, only 8.6% of study patients had previously received anti-VEGF treatment.[4] Therefore, the level of previous treatment in study patients does not reflect current practice. The EMA was critical of the failure to use laser as a control in the MEAD studies and noted that this would probably have further reduced the size of the treatment effect. The reason for not using laser treatment as a comparator was to minimise bias from complications of laser.[3]

Clinical experts consulted by SMC advised that current treatment in pseudophakic patients is anti-VEGF treatment or laser photocoagulation therapy, with some use of fluocinolone in pseudophakic patients unresponsive to anti-VEGF treatment. There is no currently available treatment for phakic patients who are insufficiently responsive to non-corticosteroid therapy or for the very few patients unsuitable for non-corticosteroid therapy.

Clinical experts considered that dexamethasone intravitreal is a therapeutic advancement due to its benefit in some patients who have failed on anti-VEGF treatment and that its place in therapy would be for third-line use, after failure on laser/anti-VEGF treatment, in pseudophakic patients who do not have glaucoma. They considered that the introduction of dexamethasone intravitreal may impact on the patient and/or service delivery as administration is complex and requires controlled aseptic conditions; IOP monitoring is necessary.

Intravitreal dexamethasone has a less frequent administration schedule than ranibizumab which could be advantageous to the patient and the service. Fluocinolone acetonide intravitreal implant releases drug over a three year period. It is licensed for use in patients who have chronic DMO insufficiently responsive to available therapies. In the event of IOP increases that do not respond to IOP-lowering medications or IOP-lowering procedures, the fluocinolone acetonide implant can be removed by vitrectomy.

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

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing dexamethasone with a range of comparators for the treatment of patients with visual impairment due to DMO. In line with the licensed indication, the analysis focused on three subgroups:

- Patients who are pseudophakic, where the comparator was ranibizumab. Scenario analyses were also presented versus laser and watch and wait.
- Patients who are insufficiently responsive to non-corticosteroid therapy, where the comparator was watch and wait. A scenario analysis was also presented versus fluocinolone.
- Patients who are unsuitable for non-corticosteroid therapy, where the comparator was watch and wait.

A 15-year Markov model was used with a 3-month cycle length. The model included six BCVA health states based on 10-letter changes in BCVA based on the ETDRS chart. Patients treated in their better-seeing eye (BSE) or worse-seeing eye (WSE) were modelled separately and bilateral treatment was also included. The distribution of patients by health state and by DMO status (i.e. BSE, WSE or bilateral treatment) at the start of the model was based on the dexamethasone pooled pivotal studies.

The clinical data inputs for the dexamethasone arm of the model were taken from the MEAD studies. Transition probabilities for the unsuitable and insufficiently responsive subgroups were estimated using patient-level data from 3-monthly follow-up periods for the whole population. Pre-specified subgroup data in pseudophakic patients were available for the pseudophakic subgroup analysis. The efficacy of watch and wait, ranibizumab, laser and fluocinolone were estimated based on the results of the MTC by applying relative treatment effects to the dexamethasone transition probabilities. Patients were assumed to receive treatment for a maximum of three years, after which their vision was assumed to decline according to disease natural history. The transition probabilities from year 4 onwards were taken from a published study and applied to all treatment arms. The 3-month probability of gaining or losing at least 10 letters of BCVA was estimated to be 3.5% and 4.5% respectively based on the published study.

Quality of life data were collected in the MEAD studies using two generic HRQL instruments (SF-36 and EQ-5D) and one disease specific instrument (VFQ-25). The company noted that as the SF-36 and EQ-5D were only issued at baseline they were less relevant for estimating utility values to use in the model. However, a published study was identified which used a subset of six items from the VFQ-25 to produce the VFQ- utility index (VFQ-UI). The utility values used in the model were then estimated using the VFQ-UI scores (and EQ-5D in a scenario analysis) mapped onto the BCVA health states using a published algorithm. The values used were consistent with previously accepted utility values for different visual acuity levels.

The drug acquisition and administration costs of dexamethasone, ranibizumab and fluocinolone were included. Patient Access Schemes (PAS) are in place for both ranibizumab and fluocinolone and the analysis used estimates of the relevant PAS prices of these treatments. In terms of administration costs, all intravitreal injections and laser administrations were assumed to be performed in the outpatient setting. Scenario analysis was conducted to test this assumption by varying the proportion administered as a day case and outpatient visit. Following discontinuation, no other treatment costs were included. Costs of treating adverse events were also included. Adverse events included cataracts, raised intra-ocular pressure, retinal detachment, endophthalmitis and vitreous haemorrhage. Other costs included routine monitoring, tests and the cost of severe vision loss.

For patients who are pseudophakic, dexamethasone was estimated to be cost-saving but also less effective, such that the incremental cost-effectiveness ratio (ICER) shows ranibizumab would be considered the cost-effective treatment. Scenario analyses were presented comparing dexamethasone with laser, and watch and wait. For the comparison with laser, dexamethasone is dominated by laser with an estimated incremental cost of £7,141 and a QALY loss of 0.0451. For the comparison with watch and wait, dexamethasone is the dominant treatment with estimated savings of £5,234 and a QALY gain of 0.0993. Expert responses indicate ranibizumab is the key comparator for this patient subgroup.

For patients unsuitable for or insufficiently responsive to non-corticosteroid therapy, the company estimated dexamethasone would dominate watch and wait (i.e. less costly and more effective) based on savings of £1,046 and a QALY gain of 0.0626. For patients insufficiently responsive to non-corticosteroid treatments and who are pseudophakic, a scenario analysis was also provided comparing dexamethasone with fluocinolone.

The following limitations were noted:

- The results of the base case analysis show dexamethasone is not cost-effective in the pseudophakic subgroup when compared with ranibizumab. Although dexamethasone is estimated to be cost-saving, it is also less effective such that ranibizumab would be considered the cost-effective treatment. The QALY loss in this analysis is based on non-significant differences and when these are removed and equal efficacy assumed, dexamethasone was estimated to be cost-saving. However, given the limitations with the MTC, the assumption of comparable efficacy between dexamethasone and ranibizumab is uncertain.
- It is not clear if the comparator of watch and wait is appropriate for all patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapies. Some SMC clinical experts noted fluocinolone could be a treatment option for some of these patients. The company highlighted there are limitations with this analysis due to the differences in study designs and patient populations used to estimate comparative efficacy of the treatments. An additional analysis was provided which assumed equal efficacy between the treatments and this showed dexamethasone to be cost-saving. However, as noted above, the limitations of the MTC are such that an assumption of comparable efficacy between these treatments may not be robust.
- The MTC results also showed there were no significant differences in efficacy between dexamethasone and watch and wait, but non-significant differences were included in the analysis. The pooled MEAD studies did show dexamethasone was superior to sham injection for the primary outcome measure and the result was statistically significant. To explore this further, the company was asked to provide the results using the pooled MEAD data only. However, this analysis showed dexamethasone was not cost-effective when only the pooled MEAD data were used. The company noted there were a number of reasons for preferring the analysis based on the MTC results, such as the number of discontinuations in the sham arm of the MEAD studies resulting in an underestimation of visual acuity decline in the watch and wait arm of the model.
- The results were also sensitive to the cost of blindness, which was assumed to be £17k per annum in the base case analysis. This cost, although based on the same data source, is higher than accepted in previous submissions due to the inclusion of higher residential care costs. Previous submissions have used a cost of around £12k per annum and using this cost increased the ICERs to around £15k and £23k per QALY for the comparisons with watch and wait and ranibizumab respectively (note again the comparison with ranibizumab in this scenario is still based on dexamethasone being less effective but lower cost). A threshold analysis was also provided by the company to test the efficacy data for the comparison with watch and wait, and using the lower cost of blindness. This showed that the ICER increased to £30k when the relative risk of improving vision in the dexamethsone arm was increased to 0.78 (from a base case of 0.71).

- A key assumption of the analysis was that the results in the total DMO population of the MEAD studies were assumed to generalise to patients who are unsuitable for or insufficiently responsive to non-corticosteroid therapy, but the appropriateness of this assumption is not clear. Only a small proportion of patients in the studies had received prior anti-VEGF treatment, but the company noted that for patients who had received prior laser there was no difference in outcomes compared with the whole trial population.

Despite the limitations outlined above, the economic case has been demonstrated.

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

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- A joint submission was received from the Royal National Institute of Blind people (RNIB) and the Macular Society, both registered charities.

- The RNIB has received pharmaceutical company funding in the past two years including funding from the submitting company. The Macular Society does not receive any pharmaceutical company funding.

- Diabetic macular oedema (DMO) has a huge impact on patients as it affects central vision. Early symptoms include straight lines appearing wavy and later symptoms include gaps or loss of central vision. If left untreated, or if patients are not treated optimally, they are at risk of forced early retirement, giving up driving, increased falls, social isolation and difficulty in daily living tasks. These can all have a significant financial and emotional impact on themselves, their families and carers.

- Not all patients respond to currently available therapies. In addition, some may not be able to take them due to being at a high risk of stroke and/or heart attacks.

- The long acting nature of the implant means that it involves six monthly injections with fewer clinic visits than many current therapies.

- Dexamethsone is a convenient, well tolerated, effective treatment for DMO that gives patients who cannot use other currently available therapies a further option.

Additional information: guidelines and protocols

The Royal College of Ophthalmologists Diabetic Retinopathy Guidelines were updated in July 2013. Focal and focal/grid laser photocoagulation was previously the standard treatment for diabetic macular oedema. Growing evidence suggests that intravitreal VEGF-inhibitors (with or without laser photocoagulation) are superior to laser photocoagulation alone with better visual outcomes and the potential to improve visual acuity. They are therefore now considered the gold standard for patients with centre-involving diabetic macular oedema and reduced vision.[9]

These guidelines predate the marketing authorisation of dexamethasone intravitreal implant for the treatment of DMO.

Additional information: comparators

Intravitreal ranibizumab, intravitreal fluocinolone acetonide, laser photocoagulation. SMC advice for aflibercept was published in November 2014 and it was not considered a comparator in this submission

Cost of relevant comparators

Drug	Dose Regimen	Cost in first year (£)
Dexamethasone	**700 microgram implant to be administered intravitreally. Retreatment may be performed after approximately 6 months**	**870 to 1,740**
Aflibercept	2mg intravitreal injection once a month for five consecutive doses, followed by one injection every two months. After the first 12 months the treatment interval may be extended based on visual and anatomical outcomes.	6,528
Fluocinolone acetonide	190 micrograms intravitreal implant as a single dose.	5,500*
Ranibizumab**	0.5mg intravitreal injection once a month until maximumvisual acuity is achieved. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to DMO.	5,194

Doses are for general comparison and do not imply therapeutic equivalence. Costs do not take any patient access schemes into consideration. Costs from eMIMS on 01 February 2015. *An additional implant may be administered after 12 months if there is worsening. **Annual cost for ranibizumab based on mean of seven injections used in RESTORE study over the first 12 months. Data reporting follow up to 2 years suggest that the number of injections in the second 12 months is approximately three to four injections.

Additional information: budget impact

Pseudophakic patients:

The company estimated there would be 3,028 patients eligible for treatment in year 1, rising to 3,309 in year 5, with a discontinuation rate of 11% and 31% in years 1 and 5 respectively. The market share was estimated to be 1% in year 1 and 12% in year 5.

The gross impact on the medicines budget was estimated to be £58k in year 1, rising to £445k in year 5. The net medicines budget impact assuming displacement of ranibizumab was estimated to be £56k in year 1 and £353k in year 5.

Patients who are insufficiently responsive to non-corticosteroid therapy:

The company estimated there would be 1,135 patients eligible for treatment in year 1, rising to 1,275 in year 5, with a discontinuation rate of 9% and 30% in years 1 and 5 respectively. The market share was estimated to be 3% in year 1 and 30% in year 5.

The gross impact on the medicines budget was estimated to be £177k in year 1, rising to £1.27m in year 5. No displaced treatments were included as the company assumed there are no existing treatments for this patient group.

Patients who are unsuitable for non-corticosteroid therapy:

The company estimated there would be 3,028 patients eligible for treatment in year 1, rising to 3,399 in year 5, with a discontinuation rate of 9% and 30% in years 1 and 5 respectively. The market share was estimated to be 3% in year 1 and 25% in year 5.

The gross impact on the medicines budget was estimated to be £66k in year 1, rising to £396k in year 5. No displaced treatments were included as the company assumed there are no existing treatments for this patient group.

References

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

1. National Health Service (NHS). Patient information Laser treatment for diabetic macular oedema. 2013.

2. Summary of product characteristics for dexamethasone 700 micrograms intravitreal implant in applicator (Ozurdex®) Last Updated on eMC 12-Sep-2014.

3. European Medicines Agency Committee for Medicinal Products for Human Use Assessment report for dexamethasone (Ozurdex®) Procedure No. EMEA/H/C/001140/II/001524 July 2014.

4. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014.

5. NCT01492400; Allergan 206207-024 Clinicaltrials.gov

6. *Commercial in Confidence**

7. Callanan DG, Gupta S, Boyer DS, et al. Dexamethasone intravitreal implant in combination with laser photocoagulation for the treatment of diffuse diabetic macular edema. *Ophthalmology*. 2013; 120(9):1843-51.

8. *Commercial in Confidence**

9. Royal College of Ophthalmologists Diabetic Retinopathy Guidelines December 2012 (update to section 14.3.4 in July 2013)

This assessment is based on data submitted by the applicant company up to and including 12 March 2015.

**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. 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.