Dear National Institute for Health and Care Excellence

RE: Appraisal consultation document for 'dexamethasone intravitreal implant (DEX) for treating diabetic macular oedema' (reference ID653)

Alimera Sciences Limited is the marketing authorisation holder of ILUVIEN® (fluocinolone acetonide 190µg intravitreal [FAc] implant) which is indicated for the treatment of vision impairment associated with chronic DMO, considered insufficiently responsive to available therapies.[1] This was approved by NICE in November 2013 in technology appraisal guidance TA301, which stipulated that ILUVIEN should be used in patients with a pseudophakic lens, and under the agreed patient access scheme. This effectively positions ILUVIEN as a second line treatment.

The appraisal committee requested feedback for DEX for treating diabetic macular oedema and Alimera Sciences would like to raise key considerations relating to the interpretations of the clinical and effectiveness data.

The economic evaluation was based on a number of assumptions which included the use of DEX in a pseudophakic lens as a first (i.e., unsuitable for non-corticosteroid treatment) or second-line treatment (i.e., not responsive to non-corticosteroid treatment; see pp. 15, point 3.30).[2] There are a number of assumptions that need to be considered and these are detailed below.

Clinical interpretations

1. The first issue relates to the 'watch-and-wait' therapy (i.e., no active treatment received). We would like to highlight that 'watch and wait' is not a standard of care (SOC) for patients with DMO. It is also potentially detrimental to the patient's outcome, with nearly half of the patients developing DMO losing two or more lines of visual acuity within 2 years.[4] Furthermore, watch-and-wait therapy is not a position supported by clinical practice as physicians using FAc implants in patients with DMO do so according to the recommendations of the NICE technology appraisal TA301[4] and this is when the patient shows an insufficient response to first-line therapy. Since November 2013, the usage of ILUVIEN in clinical practice has been growing with 141 hospitals registered to receive ILUVIEN and 65% of all UK hospitals having treated at least one patient with ILUVIEN. This usage is reflected in the increasing number of published case reports.[6-11]

2. The second objection relates to the appropriate comparator for DMO patients with a pseudophakic lens. In current practice, NICE recommends the use of the FAc implant in patients as "…an option for the treatment of chronic diabetic macular

oedema considered insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens." [4] Hence the SOC and the logical comparator to DEX is the FAc implant, given that this is approved for use in DMO patients with a pseudophakic lens and in patients that do not respond to non-corticosteroid treatment. Current practice is also reflected by the views of the ERG. Indeed, they expressed concern that FAc implant was not included in the base case analysis for patients who had a pseudophakic lens and for patients with disease that has not had an adequate response to non-corticosteroid therapy. (pp. 31, point 3.74).[2]

3. The third point relates to the uncertainty of the clinical efficacy of DEX. The clinical studies included patients that were naïve to DMO therapy in addition to patients that were insufficiently responsive to non-corticosteroid therapy.[12] The CHMP states that "While one of the two pivotal studies (study 206207-010) achieved statistically significant improvement in the primary endpoint, the other study (206207-011) failed to show superiority of DEX. In this study, the difference in mean BCVA average change from baseline compared to Sham was not significant for either dose of dexamethasone. Furthermore, the clinical relevance of an average increase of 1 to 2 letters over the 3 year study period (1.4 in the pooled analysis compared to Sham) was considered questionable by the CHMP." (pp. 68).[12] Pivotal trials were therefore inconclusive, showing an average benefit of a mere 1.4 letters in BCVA over 3 years.

4. The fourth point relates to the appraisal committee's preliminary recommendations for DEX. The CHMP showed that in patients that had already received treatments for DMO (i.e., laser, steroid or anti-VEGF treatment; non-corticosteroid treatments) prior to the start of the study there was an overall gain in letters that was similar to the overall population (a mean gain of +1.4 letters; see point 3 above). This then led the CHMP to question the clinical relevance of this data by stating "…this population may have had more stubborn disease than treatment naïve patients, hence contributing to the limited treatment benefits observed." (pp. 68).[12] Available data therefore questions the relevance of the appraisal committee's preliminary recommendations for the use of DEX.

Cost-effectiveness interpretations

1. The models comparing the cost-effectiveness of therapies for patients with DMO that have not responded adequately to non-corticosteroid therapy clearly show that for all comparisons, except at a discount of 10%, FAc implant dominated dexamethasone intravitreal implant. This was based on a list price of £5,500 for FAc implant which

the manufacturer makes available to the NHS under the terms agreed with the Department of Health as part of a patient access scheme (pp. 23, point 3.52).[2]

2. Using the models comparing the cost-effectiveness of therapies for patients with DMO that have a pseudophakic lens and disease that does not respond adequately to non-corticosteroid therapy, or such treatment is not suitable for them, the ERG stated that with a 40% and 50% discount in the price of FAc implant, it dominated DEX (pp. 38, point 3.91).[2]

Alimera Sciences would very much like the appraisal committee to comment on these important considerations at the Appraisal Committee on 24th March 2015.

Yours sincerely

Alimera Sciences Limited.
Royal Pavillion, Wellesley Road, Aldershot, Hampshire, GU11 1PZ, UK.
Registered in England: 08018355.
Date of preparation: March 2015; Job code: UK-UNB-MMM-0002

References

1. Summary of Product Characteristics (SmPC) for ILUVIEN 190 micrograms intravitreal implant in applicator. Source: https://www.medicines.org.uk/emc/medicine/27636 Published 18th February 2015.
2. National Institute for Health and Care Excellence Appraisal consultation document for Dexamethasone intravitreal implant for treating diabetic macular oedema [ID653].
3. Ciulla TA et al. Treatment of diabetic macular edema with sustained-release glucocorticoids: intravitreal triamcinolone acetonide, dexamethasone implant, and fluocinolone acetonide implant. Expert Opinion on Pharmacotherapy 2014; 15 (7): 953-959. Source: http://informahealthcare.com/doi/abs/10.1517/14656566.2014.896899).
4. NICE technology appraisal guidance [TA301] published November 2013. Appraisal 301. Source: http://www.nice.org.uk/guidance/ta301/documents
5. Quhill F. The Treatment of Diabetic Macular Oedema with ILUVIEN® Intravitreal Implant Following Prior Anti-VEGF Therapy – Case Study. European Ophthalmic Review, 2014; 8 (2): 140–144. Source: http://www.touchophthalmology.com/articles/treatment-diabetic-macular-oedema-iluvien-intravitreal-implant-following-prior-anti-vegf.
6. Cudrnak T. Early Clinical Experience with ILUVIEN in the UK. In 'Managing Insufficiently Responsive DMO Patients Post-NICE Guidance' by Chakravarthy U. European Ophthalmic Review, 2014; 8 (1): 61–66. Source: http://webcache.googleusercontent.com/search?q=cache:Ir4mSlf42EQJ:www.touchophthalmology.com/articles/managing-insufficiently-responsive-dmo-patients-post-nice-guidance+&cd=1&hl=en&ct=clnk&gl=uk
7. Tsaloumas M. ILUVIEN in diabetic macular odema. Presentation at BARS conference 2014. Source: http://www.eyescreening.org.uk/userFiles/File/Conference%202014/presentations/iluvin%20BARS_%20MDT%204small.pdf.
8. Quhill F. Session 1: Clinical case experience with ILUVIEN. DMO Grand Round Webinar on 25th November 2014. Source: http://www.events4healthcare.com/alimera_sciences/Webinars.html
9. Tsaloumas M. Session 2: Clinical case experience with ILUVIEN. DMO Grand Round Webinar on 25th November 2014. Source: http://www.events4healthcare.com/alimera_sciences/Webinars.html
10. El-Ghrably I. Session 3: Clinical case experience with ILUVIEN. DMO Grand Round Webinar on 25th November 2014. Source: http://www.events4healthcare.com/alimera_sciences/Webinars.html

11. Ahfat F. Session 4: Clinical case experience with ILUVIEN. DMO Grand Round Webinar on 25th November 2014. Source: http://www.events4healthcare.com/alimera_sciences/Webinars.html
12. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency. Assessment report for Ozurdex. Report number EMA/492068/2014. Published 24th July 2014.