NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal 271)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Alimera Sciences	We welcome and accept the Appraisal Committee's statement (ACD §1.1) that fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if: • the person has had their natural lens replaced with an intraocular (pseudophakic) lens; and • the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme Whilst we believe that ILUVIEN is also effective in other groups of DMO patients, we welcome the recommendation at this stage in order to give pseudophakic patients immediate access to fluocinolone acetonide. We request that the Committee's recommendation above is retained in full in the Final Appraisal Determination (FAD) to be published in August 2013.	Comment noted. Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens and the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme (see FAD section 1.1).
Alimera Sciences	The purpose of this response document is two-fold: first, to endorse the areas of agreement; and secondly, to clarify remaining doubts expressed by the Committee in the ACD. We set out areas where we take a different view from the Appraisal Committee, in order to lay the foundation for discussion in future technology appraisals.	Comment noted. Please see responses below.
Alimera Sciences	**Areas of agreement** We endorse the statement that "…on balance, the Committee concluded that fluocinolone acetonide intravitreal implant had been shown to be clinically effective in this subgroup of people." (ACD §4.18). The pseudophakic subgroup is of adequate sample size (225/536 or 42% of patients with chronic diabetic macular oedema). The treatment effect was clinically relevant and statistically significant (treatment difference = 14.2%, p = 0.043)	Comment noted. The Committee discussed the subgroup of people with chronic diabetic macular oedema who had treatment in an eye with a pseudophakic lens. The Committee concluded that fluocinolone acetonide intravitreal implant had been shown to be clinically effective in this subgroup of people (see FAD section 4.20).

Consultee	Comment	Response
Alimera Sciences	We welcome the Committee's approach in considering a range of ICERs based on different sources of utilities, namely Brown et al. (1999), Brown et al. (2000) and Czoski-Murray et al. (2009) (ACD §4.14 and §4.15). We note the Committee's comments that there were some uncertainties about the most appropriate utilities for this patient population, and that Czoski-Murray et al. (2009) had been considered for the appraisal of ranibizumab for the treatment of diabetic macular oedema. While the Committee has adopted an approach to apply a range to the calculation of ICERs, we maintain the view that Brown 2000 represents a more accurate source for assessment of DMO.	Comment noted. The Committee discussed the different utility values applied in the model. The Committee agreed to consider a range of ICERs based on utility values from Brown et al. (1999), Czoski-Murray et al. (2009) and Brown et al. (2000). (See FAD sections 4.16, 4.17).
Alimera Sciences	We note that the ERG has checked our submitted ICERs and found only minor differences in the values (ACD §3.50). We welcome this finding which underlines the robustness of our modelling. The convergence of our ICERs and those re-calculated by the ERG suggests that these ICERs were a good basis for decision making.	Comment noted. No actions requested.
Alimera Sciences	Accordingly, we welcome the Committee's acceptance of the ICERs presented by us under the patient access scheme, in particular the ICERs for the pseudophakic subgroup recommended in the ACD, namely £30,300 per QALY gained using the utilities from Brown et al. (1999), £19,900 per QALY gained with the utilities from Czoski-Murray et al. (2009) and £17,600 per QALY gained with the utilities from Brown et al. (2000) (ACD §4.19).	Comment noted. The Committee considered that the most plausible ICER with the patient access scheme for the pseudophakic subgroup would be in the upper end of £17,500 per QALY gained using utilities from Brown et al. (2000), £21,000 per QALY gained using utilities from Czoski – Murray et al (2009) and £30,000 per QALY gained using utilities from Brown et al. (1999) (see FAD section 4.21).

Consultee	Comment	Response
Alimera Sciences	**Areas of clarification:** **Proportion of patients with BSE treated** The proportion of patients with BSE treated, vis-à-vis the proportions with WSE treated and both eyes treated, has a significant impact on the ICERs. In keeping with recommendations of the ERG, our base case assumes that 20% of patients are unilaterally treated in the BSE, 40% of patients are unilaterally treated in the WSE, and the remaining 40% of patients receive bilateral treatment. In the FAME trials, higher proportion of patients had their WSE treated. This is due to ethical considerations inherent in a phase III clinical trial of an investigational product. We have been advised by eminent ophthalmologists in the UK that in routine clinical practice, it is mostly likely that a far larger number of patients would have their BSE treated first. This is because clinicians recognise the difference in the effect on quality of life when treating the BSE first, compared with treating the WSE first. As DMO is the result of a progressive, systemic disease, clinicians would want to protect the BSE first as this will give patients the greatest long-term chance of having functional vision. We will work with clinicians to audit data from clinical practice in the NHS after the FAD when the use of fluocinolone acetonide commences. Such audits will provide objective data on which eye is treated first in clinical practice.	Comment noted. The Committee noted the assumption in the model that 20% of the patients were treated in their best-seeing eye, 40% in their worse-seeing eye and 40% of patients were treated in both eyes. The Committee agreed that it could be the case that in clinical practice more patients would be treated in their best-seeing eye but considered that currently there is a lack of evidence and concluded that this assumption was reasonable (see FAD section 4.12).

Consultee	Comment	Response
Alimera Sciences	**"Insufficiently responsive"** We note the Committee's comment that "the data from the FAME trials did not reflect a group of patients who had disease that was insufficiently responsive to other therapies because people in the FAME trials did not necessarily have disease that was unresponsive to treatment with anti-VEGF or laser photocoagulation before randomisation", and that "the data from the trials may not be representative of the group of people who would be receiving fluocinolone acetonide intravitreal implant in UK clinical practice,…" (ACD §4.6). We wish to point out that at the commencement of the FAME trials in 2005, anti-VEGF therapies were not available. Anti-VEGF therapies became available during the course of the FAME trials. Although not licensed for use in diabetic macular oedema, clinicians began to use anti-VEGF in the FAME trials, which were double-masked and randomised. In clinical practice, a Best Corrected Visual Acuity (BCVA) of 20/80 is generally considered poor and insufficiently responsive to treatment. In the FAME trials, 59% of the patients with chronic diabetic macular oedema had vision of 20/80 or worse at baseline (ACD §3.44). In the FAME trials, the inclusion criteria required that all patients had at least one prior macular laser photocoagulation to be eligible for enrolment. There was no stipulation that only one prior laser could be administered. Given the long duration of DMO in the chronic population, if a clinician had believed that the patient would respond to laser, such treatment would certainly have been administered. Therefore, these 59% of patients were clearly insufficiently responsive to laser photocoagulation. As we previously reported, a highly significant treatment effect was seen in this group: 42.7% of the fluocinolone-treated group achieved 15-letter gain at month 36, compared with 12.7% of the control group ($p < 0.001$). This addresses the Committee's view, referencing laser photocoagulation in ACD §4.6 that "…FAME trials did not necessarily have disease that was unresponsive to treatment with anti-VEGF or laser photocoagulation before randomisation".	Comment noted. After considering the manufacturer's submission and comments on the Appraisal Consultation Document, the Committee remained concerned that the data from the trials may not be fully representative of the group of people who would be receiving fluocinolone acetonide intravitreal implant in UK clinical practice. However, it concluded that although there is uncertainty about the generalisability of the trial data to UK clinical practice, fluocinolone acetonide intravitreal implant is likely to be clinically effective in this population (see FAD section 4.6).

Consultee	Comment	Response
	The rationale for the indication “insufficiently responsive” has been presented in our patient access scheme submission (§3.4M and 3.4N). We believe this goes some way to addressing the Committee’s comments, and is re-stated briefly below. When rescue laser and off-protocol anti-VEGF treatments administered to the control population are compared, it is clear that patients with chronic DMO (≥ 3 years) received more such treatments compared with patients with non-chronic DMO. Despite this, control patients with chronic DMO responded significantly less well (13.4% achieved 15-letter gain) compared with control patients with non-chronic DMO (< 3 years) (27.8% achieved 15-letter gain) ($p = 0.012$). The chronic DMO patients were therefore insufficiently responsive to such off-protocol anti-VEGF treatments. When fluocinolone acetonide was added to these two populations, chronic and non-chronic DMO, a very different treatment effect profile was seen. In the non-chronic population, there was no additive benefit to the short acting anti-VEGF therapies and laser photocoagulation which these patients were receiving. In the chronic population, a highly statistically significant and clinically relevant treatment effect was seen. The significant treatment effect seen with fluocinolone acetonide in the chronic population clearly shows that they were insufficiently responsive to the available therapies. Based on the above rationale, seven regulatory authorities in Europe including the Medicines and Healthcare products Regulatory Agency (MHRA) granted the marketing authorisation for fluocinolone acetonide to be used in patients with chronic diabetic macular oedema (DMO) “considered insufficiently responsive to available therapies”. In clinical practice in the UK, the standard therapy for diabetic macular oedema is laser photocoagulation. Ranibizumab became an option recently following NICE guidance issued in April 2013 (TA274, rapid review of TA237). As pointed out by eminent ophthalmologists, fluocinolone acetonide is unlikely to be used if patients are sufficiently responsive to these therapies. Furthermore, according to the TA274 Toolkit adopted by NICE, it is estimated that 90% of patients treated with ranibizumab “are expected to respond positively”. In other words, 10% are expected to have insufficient response. This is a group of patients in whom there is currently no approved treatment option. As stated in the ACD, “The Committee understood that there are currently no standard treatments for people with chronic diabetic macular oedema after other therapies have failed.” (ACD §4.3).	

Consultee	Comment	Response
	Therefore the guidance proposed in the ACD that fluocinolone acetonide is an option for chronic diabetic macular oedema that is insufficiently responsive to available therapies is both sound and pragmatic.	
Alimera Sciences	**The most plausible ICER in the pseudophakic subgroup** We note the Committee's recognition that under the patient access scheme, the ICERs for the pseudophakic subgroup were £30,300 per QALY gained using the utilities from Brown et al. (1999), £19,900 per QALY gained with the utilities from Czoski-Murray et al. (2009) and £17,600 per QALY gained with the utilities from Brown et al. (2000). The Committee considered that the most plausible estimates of cost effectiveness would be in the upper end of this range, and that there was significant uncertainty around this estimate (ACD §4.19). We maintain our view that Brown et al. (2000) is a more appropriate source of utilities compared with Brown et al. (1999), because it has a larger, more homogenous group with patients who suffered from visual impairment due to macular oedema. Further, the Committee previously relied on Czoski-Murray et al. (2009) in its appraisal of ranibizumab for diabetic macular oedema.	Comment noted. The Committee discussed the different utility values applied in the model. The Committee noted that Brown et al. (2000) includes more people with age-related macular oedema. However, the Committee does not consider that this outweighed the benefits of the larger sample size and the associated finer delineation of utilities across different levels of visual acuity possible with larger patient numbers in Brown et al. (1999). The Committee noted that utility values from Czoski-Murray (2009) had been considered in NICE technology appraisal guidance 274 and agreed to consider it as another source of utility values for this appraisal. Because there are uncertainties about the most appropriate source of utility values the Committee agreed to consider a range of ICERs based on utility values from Brown et al. (1999), Czoski-Murray et al. (2009) and Brown et al. (2000) (see FAD sections 4.16, 4.17).
Alimera Sciences	We therefore take the view that the most plausible estimates of cost-effectiveness lie in the middle, and not the upper end, of the range from £17,600 per QALY gained (Brown et al. (2000)), £19,900 per QALY gained (Czoski-Murray et al. (2009)) to £30,300 per QALY gained (Brown et al. (1999))	Comment noted. The Committee considered that the most plausible ICER with the patient access scheme for the pseudophakic subgroup would be in the upper end of £17,500 per QALY gained using utilities from Brown et al. (2000), £21,000 per QALY gained using utilities from Czoski – Murray et al (2009) and £30,000 per QALY gained using utilities from Brown et al. (1999) (see FAD section 4.21).

Consultee	Comment	Response
Alimera Sciences	**Conclusion** To conclude, we wish to quote the statement of the Royal College of Ophthalmologists dated 10th May 2013 "It is hoped that NICE will be able to approve the use of fluocinolone acetonide for the growing numbers of patients with visual loss due to diabetic macular oedema. The availability of a treatment option which does not require frequent intravitreal injections would be greatly welcomed by patients and by service providers." Finally, as Mr. Winfried Amoaku, associate professor and consultant ophthalmologist of Nottingham University Hospitals NHS Trust said in a recent press release dated 14th June 2013, "Chronic DME patients who are pseudophakic are now one step closer to receiving this crucial sight-saving treatment from the National Health Service. We cannot put a price on eyesight. Anything we can do to treat or prevent vision loss is essential. I welcome the Appraisal Committee's recommendation on the pseudophakic subgroup. It is hoped that NICE will update its recommendation in the fullness of time to allow access for a wider population of people with chronic DME". We urge the Committee to implement in the forthcoming FAD its initial recommendation in the ACD in full, to give immediate access to pseudophakic patients with chronic DMO to fluocinolone acetonide on the NHS.	Comment noted. Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens and the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme (see FAD section 1.1).
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document (ACD) for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted. No actions requested.
Royal College of Ophthalmologists	**Has all of the relevant evidence been taken into account?** All the relevant evidence from FAME trials have been used. Primary endpoint data as well as subgroup analysis and also patient reported outcome data analyses were used to evaluate cost effectiveness.	Comment noted. No actions requested.

Consultee	Comment	Response
Royal College of Ophthalmologists	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** • It is beyond my remit to comment in detail on the summary of cost effectiveness. • Regarding clinical effectiveness, (section 4.6) the committee felt that subgroup of patients who were unresponsive to other therapies were somewhat different to the population with chronic DMO as defined by the subgroup analysis from the FAME studies because study eyes did not have prior therapy with Anti-VEGF, only laser photocoagulation. As corticosteroids are believed to have an antiVEGF effect, the committee felt that the level of response to Iluvien could be less if used in patients who have not been responsive to ranibizumab. • I feel that although this is a logical assumption, there is little evidence to support the hypothesis that patients who are unresponsive to antiVEGF would also be unresponsive to corticosteroids. Indeed there are numerous clinical studies using off-label therapies showing that intravitreal corticosteroid such as triamcinolone had a strong effect on resolution of macular oedema in cases where avastin have not been efective. Several basic science studies showing that in one third of eyes with DMO, VEGF levels are not elevated compared to controls and antiVEGF therapy may be futile in those cases. Furthermore, the effect of corticosteroid on suppressing VEGF is very weak as patients with ischaemic retinal vein occlusion still develop iris neovascularisation and neovascular glaucoma(VEGF driven complications which respond well to anti VEGF).	Comment noted. The Committee discussed this comment that studies of other intravitreal corticosteroids have shown a beneficial effect on macular oedema when used after anti-VEGF treatments. The Committee remained concerned that the data from the trials may not be fully representative of the group of people who would be receiving fluocinolone acetonide intravitreal implant in UK clinical practice. However, it concluded that although there is uncertainty about the generalisability of the trial data to UK clinical practice, fluocinolone acetonide intravitreal implant is likely to be clinically effective in this population (see FAD section 4.6).
Royal College of Ophthalmologists	In my opinion, current evidence is tending to suggest that there will be a significant proportion of eyes with DMO that will be unresponsive to anti VEGF and switching to a long acting corticosteroid with a better safety profile than triamcinolone can be expected to give additional treatment response. It is reasonable to consider switching to intravitreal fluocinolone especially if there is minimal response to antiVEGF, rather than continuing with multiple antivegf therapy which is futile.	Comment noted. The Committee concluded that although there is uncertainty about the generalisability of the trial data to UK clinical practice, fluocinolone acetonide intravitreal implant is likely to be clinically effective in this population (see FAD section 4.6).
Royal College of Ophthalmologists	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes – it is very sensible to target those patients who are pseudophakic in the first instance.	Comment noted. No actions requested.

Consultee	Comment	Response
Royal College of Ophthalmologists	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** No	Comment noted. No actions requested.
Royal College of Nursing	**Has the relevant evidence been taken into account?** Yes this seems a comprehensive review of the current evidence base	Comment noted. No actions requested.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries of cost effectiveness seem reasonable interpretations of the evidence. The review seems to have taken into account the chronic nature of this debilitating disease in the estimate	Comment noted. No actions requested.
Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes, we agree with the recommendations. We welcome the opportunity to have access to this pharmacological agent for those patients that are not responding to other treatment modalities and have chronic macular oedema. The slow release and sustained duration effect of the drug has the additional benefit for the elderly patients that may find it difficult to attend monthly clinics. Restricting it to patients that have already had cataract surgery will also minimize the impact for phakic patients that have a high risk of requiring surgical intervention due to cataract formation associated with steroid therapy. The RCN would welcome guidance to the NHS on the use of this health technology	Comment noted. Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens and the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme (see FAD section 1.1).
Royal College of Nursing	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** We are not aware of any at this stage.	Comment noted. No actions requested.

Consultee	Comment	Response
Royal College of Nursing	**Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate	Comment noted. No actions requested.