NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Review of TA301; Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy

Final recommendation post consultation
The consultees and commentators agreed with the proposal to part-review via appraisal and partially re-issue the TA301 guidance. The recommendation has not changed after the consultation.

1. Background

The TA301 guidance was issued in November 2013

At the Guidance Executive meeting of 9 January 2018 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

A part-review and part re-issue of the guidance should be planned into the appraisal work programme. For those people within the marketing authorisation with phakic lenses, for whom fluocinolone is not recommended in TA301, a part-review will be conducted through the STA process.

For those people with pseudophakic lenses where fluocinolone is already recommended in TA301, a re-issue of these, unchanged, positive recommendations, accounting for the new PAS is suggested.

3. Rationale for selecting this proposal

The company in its response to the review proposal indicated that there is new evidence supporting the clinical and cost effectiveness of fluocinolone acetonide for the full licenced population. Currently, fluocinolone acetonide is only recommended by NICE for people who have implanted intraocular lenses. The new evidence would support the use of fluocinolone acetonide in people with phakic lenses. [redacted] will impact on the cost-effectiveness of groups of people for which fluocinolone acetonide is not currently recommended and for which fluocinolone acetonide is currently recommended. A part STA review of TA301 for people within the marketing authorisation with phakic lenses where fluocinolone acetonide is not recommended in TA301 was considered. For people with pseudophakic lenses where fluocinolone is already recommended a re-issue of the

positive recommendations in TA301 was suggested. The positive recommendations remain unchanged, [redacted].

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: The Royal College of Ophthalmologists **Response to proposal:** Agree Thank you for asking The Royal College of Ophthalmologists to comment on the proposal to do a part-review and part re-issue of the guidance. The Royal College of Ophthalmologists supports a review looking at whether this technology can be used in phakic patients. Its long acting nature would be very useful for some patients who find the frequent anti-VGF injections that can be needed very difficult and so do not maintain ongoing treatment. Wider use of this could help access to DMO treatment. Raised intraocular pressure post injection has been found not to be a big concern, see paper below. Eye (Lond). 2017 Dec;31(12):1707-1715. doi: 10.1038/eye.2017.125. Epub 2017 Jul 24. **Real-world experience with 0.2 µg/day fluocinolone acetonide intravitreal implant (ILUVIEN) in the United Kingdom.** Bailey C1, Chakravarthy U2, Lotery A3, Menon G4, Talks J5; Medisoft Audit Group. Cataract surgery in a diabetic patient can induce macular oedema or exacerbate oedema but this is less likely with steroid in the eye and steroid is used to treat post-operative oedema so if a phakic patient has a fluocinolone acetonide intravitreal implant and later gets worsening of cataract the fluocinolone acetonide intravitreal implant may actually help the outcome of surgery. Cataracts are also more common in diabetics.	**Comment from Technology Appraisals** Comments noted. The new evidence will be considered during the appraisal.

Respondent: Novartis Pharmaceuticals UK Limited **Response to proposal:** Please could we clarify the review is for those people within the marketing authorisation with phakic lenses, for whom fluocinolone is not recommended in TA301? We were confused with the wording on page 2 of the 'Appendix B – GE proposal paper' which refers to 'both' subgroups. Which is the other subgroup? «... *will impact on the cost-effectiveness of both the subgroups for which fluocinolone actonide is not currently recommended and that for which fluocinolone acetonide is currently recommended, a part STA review of TA301 for those groups not recommended in TA301 should be considered »* We have a few comments regarding the Yang et al 2015 FLAME subanalyis: 1. As the authors themselves have mentioned in the discussion, the study has limitations; i) It is a post hoc analysis. Retrospective studies have several limitations including poor control over the exposure factor, covariates and potential confounders [1]. As the study was not designed for this subanalysis, the results were not powered to detect differences between patients receiving the sham and those treated with 0.2µg/day FAc. ii) There was a significant difference in the age of participants in the CAI and CBI groups that could have affected the results. 2. The authors have suggested caution in the use of 0.2µg/day FAc intravitreal implant in younger patients who still have natural accommodative power and no cataract formation until it is clear that an adequate response with anti-VEGF therapy cannot be achieved. We ask that this point is considered by NICE before any recommmendations are made on FAc's use in the full licensed population. 3. Please consider the published comment by B Takkar & S Asad on the subanalysis, which queries whether FAc can be credited for better visual results in the CAI group. They have suggested that in the CAI group, the favourable change in visual acuity may have been partly contributed by removal	**Comment from Technology Appraisals** Comments noted. It is proposed to re-issue the current positive recommendation i.e. in an eye with an intraocular (pseudophakic) lens. The use of fluocinolone acetonide in phakic lense will be appraised through the single technology appraisal. All available and relevant evidence will be taken into account during the appraisal.

of lenticular aberrations expected in diabetic patients having early lens opacities or even lenticular swelling [2]. References 1. Suchmacher, M. and M. Geller, Chapter 1 - Study Type Determination, in Practical Biostatistics. 2012, Academic Press: San Diego. p. 3-15. 2. Takkar, B. and S. Azad, Comments on; Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants&#39. Eye, 2016. 30: p. 1023.	

Respondent: Alimera Sciences **Response to proposal:** Agree **Feedback on 'APPENDIX B. GUIDANCE EXECUTIVE'** Alimera Sciences welcomes the intention to keep the current guidance in place in respect of patients with chronic diabetic macular oedema (DMO) affecting pseudophakic eyes. We also welcome the consideration given to changing the recommendation for patients with chronic DMO affecting phakic eyes and the intention to review new cost effectiveness and clinical evidence. A change to the NICE guidance to include use in phakic eyes will align ILUVIEN usage with its current licensed indication in the United Kingdom and other countries in Europe. During any reappraisal of ILUVIEN, in addition to data pertaining to use in phakic eyes, Alimera Sciences would also like to share data that answer some areas for further research highlighted by NICE during the review of TA301. This includes data specific to patients with a pseudophakic eye that insufficiently responded, defined as a change in visual acuity of <5 letters by Gonzalez *et al*.1, to the current standard of care (i.e. intravitreal injections of anti-VEGF). Such data were not available at the time of TA301. Alimera Sciences would like to bring the following key points to the attention of NICE: **1. Recommendation** "A part-review and part re-issue of the guidance should be planned into the appraisal work programme. For those people within the marketing authorisation with phakic lenses, for whom fluocinolone is not recommended in TA301. The part-review will be conducted through the STA process." *Request from Alimera Sciences: Alimera Sciences would welcome the opportunity to present the increasing body of evidence that supports the use of ILUVIEN in phakic eyes. This is a group of patients where it is medically acceptable to treat with ILUVIEN when there is a risk of vision loss due to DMO provided the patient*	**Comment from Technology Appraisals** Comments noted. The process route of the part-review (STA or FTA) will be discussed and agreed when the appraisal is in the final scoping and early development stages. The committee will consider the newest evidence submitted during the appraisal process.

has insufficiently responded to intravitreal anti-VEGF injections. Based on current real-world experience (Appendix 2), Alimera Sciences anticipates that uptake in phakic eyes would reflect those patients most in need of treatment of their visual impairment. *We believe there is sufficient evidence (cost-effectiveness, cost-savings and clinical) to widen the current NICE guidance for TA301 to permit use in eyes with either a natural lens (phakic eye) or an intraocular (pseudophakic eye) lens, in line with the marketing authorisation for the product. Moreover, Alimera Sciences also believes that ILUVIEN fulfils the pre-defined criteria for the Fast-Technology Re-Appraisal (FTA) route, as opposed to STA, and would like ask NICE to consider the route for re-appraisal. Applying a fast track approach is particularly important in this case because the data Alimera will present a significant financial saving to the NHS versus the use of alternative treatments that are currently use in these patients.* **4. Rationale** **"…**will impact on the cost-effectiveness of both the subgroups for which fluocinolone acetonide is not currently recommended and that for which fluocinolone acetonide is currently recommended, a part STA review of TA301 for those groups not recommended in TA301 should be considered. For those groups with pseudophakic lenses where fluocinolone is already recommended a re-issue of the positive recommendations is suggested. The positive recommendations remain unchanged." *Request from Alimera Sciences: At the time that TA301 was approved there were little data describing the use of the FAc implant following prior treatment with intravitreal injections of ranibizumab. This led NICE to recommend further research in this area and as a consequence Alimera Sciences has developed a new cost-effectiveness model to explore the value of ILUVIEN in this situation, utilising real-world data following the prior use of anti-VEGF. We can now demonstrate that ILUVIEN is cost-effective in*	

current UK clinical practice in DMO patients following prior treatment with anti-VEGF irrespective of lens status. *This new model was developed using the FAME trial outcomes and other real-world source of data (i.e.ICE-UK*3 *[see Appendix 2]) and based on the model, and utilities, used in TA346 ('Aflibercept for treating diabetic macular oedema'), which was submitted to the NICE by Bayer in 2014. This model includes anti-VEGFs, the dexamethasone implant and laser as comparators and is based over a 15 year timeframe and utilises real-world outcomes as opposed to the outcomes of randomised controlled trials. Since TA301 guidance was issued, the availability of treatments for the treatment of DMO has increased and Alimera Sciences believes the new model provides a useful update.* *The model developed by Alimera Sciences has previously been presented (i.e. The International Society for Pharmacoeconomics and Outcomes Research, Glasgow, November 4-8, 2017)*4 *and shows that:* *a. The FAc implant is cost-effective in DMO patients with a pseudophakic eye and thus supporting the findings of the rapid review for TA301* *b. The FAc implant is cost-effective in DMO patients with a pseudophakic eye versus other NICE approved DMO therapies (i.e. ranibizumab, aflibercept and dominates the dexamethasone implant).* *c. The FAc may provide gains in QALYs related to anti-VEGFs because of the relatively low persistence on anti-VEGFs in these patients.* *d. Incremental costs and QALYs between the FAc implant and aflibercept / ranibizumab are generally small.* *e. Results are sensitive to the method used for estimation of transition probabilities.* *Alimera Sciences would like to present the new model*4 *and cost-effectiveness data*5 *to highlight how the positive recommendation for pseudophakic eyes also translates to DMO patients with a natural lens (phakic eyes).*	

6. New evidence

"The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2013 to the present day were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below.

Request from Alimera Sciences: We would like the literature strategy to be updated to reflect the most recent peer-reviewed content relating to ILUVIEN. The above search strategy has failed to identify a number of ILUVIEN (fluocinolone acetonide) articles which have been published since January 2013 and now appear on Medline, Embase or other databases citing newly published peer reviewed materials. In March 2017 Alimera Sciences provided a list of peer-reviewed articles to NICE. This list has been updated since and seems to be missing key papers that are important to this re-appraisal process. Alimera Sciences would recommend including the most recent literature.

***7.* Summary of evidence and implications for review**

"There are no changes to the current marketing authorisation and none are expected in the next 3 years. Nor have there been any changes in the marketing authorisation for its comparators."

General comment from Alimera Sciences (confidential):

[redacted]

"There is one retrospective long-term study of outcomes in people with diabetic macular oedema treated with intravitreal fluocinolone acetonide implants whose lenses are phakic (Yang 2015). This study analysed the phase 3 FAME safety and efficacy data of

fluocinolone acetonide implants in patients who underwent cataract extraction before implant or cataract extraction after implant. The results suggest that best corrected visual acuity after 36 months was comparable in both groups."

*General comment from Alimera Sciences: As mentioned already, there are a number of articles not captured in the current literature search. Furthermore, cataract formation and development are a well-known side effect of corticosteroids, but not the only known risk factor. Indeed, a recent UK cohort study*6*, based on the Clinical Practice Research Datalink and involving 56,510 newly-diagnosed patients with diabetes aged 40 and above, found that the incidence rate ratio was highest in diabetes patients of the age group of 45–54 years with more than 6-fold increased risk of cataract compared to a random matched sample of the general population. This study also found a positive relationship between the increasing risk of cataract and the duration of diabetes (adjusted odds ratio 5.14, 95% CI 4.19–6.30 diabetes for ≥10 years vs. diabetes <2 years) and duration of DMO.*

8. Adoption and Impact

"A submission from the Adoption and Impact team is included in Appendix 3. The implementation report suggests that the use of fluocinolone acetonide is only prescribed in secondary care and steadily increased since NICE technology appraisal 301 was published. However, the since NICE technology appraisal 349 (Dexamethasone intravitreal implant for treating diabetic macular oedema) and 346 (Aflibercept for treating diabetic macular oedema) were given positive recommendations, the uptake of fluocinolone acetonide has decreased by one-third (from approximately £1.2 million in quarter 1 of 2015 to £850,000 in quarter 3 of that same year." *General comment from Alimera Sciences (confidential):*

[redacted]

[redacted]	

Respondent: Department for Health and Social Care **Response to proposal:** No Comment	**Comment from Technology Appraisals** -

Paper signed off by: Frances Sutcliffe, 06/04/2018

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Confidential information has been removed