MANUFACTURER'S RESPONSE TO

APPRAISAL CONSULTATION DOCUMENT

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

SUMMARY

1. 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

2. 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.

3. We request that the Committee's recommendation above is retained in full in the Final Appraisal Determination (FAD) to be published in August 2013.

4. 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.

Areas of agreement

5. 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).

6. 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.

7. 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.

8. 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).

Areas of clarification

9. There are three areas which we wish to provide further clarification, namely the proportion of patients who were treated unilaterally in their worse-seeing eye (WSE) compared with better-seeing eye (BSE), the Committee's comments on "insufficiently responsive", and the Committee's view on the most plausible ICERs for the pseudophakic subgroup under the patient access scheme.

Proportion of patients with BSE treated

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

"Insufficiently responsive"

15. 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).

16. 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.

17. 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".

18. 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.

19. When rescue laser and off-protocol anti-VEGF treatments administered to the <u>control population</u> 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.

20. 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.

21. 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".

22. 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.

23. 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).

24. 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.

The most plausible ICER in the pseudophakic subgroup

25. 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).

26. 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.

27. 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)).

Conclusion

28. 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."

29. 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".

30. 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.