Response to Appraisal Consultation Document (1)

Allergan March 2011

In addition to the specific new analyses provided at the request of the Appraisal Committee, please find below a consideration of the following questions:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- 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?
- Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

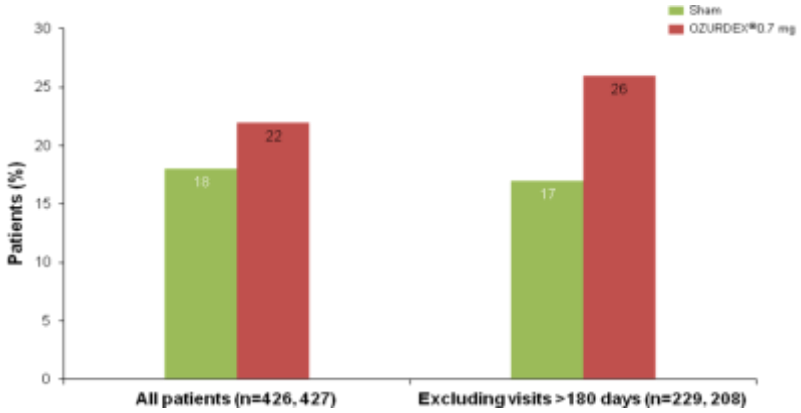
Has all the relevant evidence been taken into account?

Statement: Section 3.3, 4.21 – ***At day 180, there is no statistical significance between the sham and dexamethasone groups.***

Response: The clinical results discussed in section 3.3 only relate to one clinical measure of the efficacy of Ozurdex, specifically the proportion of patients achieving a ≥15 letter gain in BCVA in their study eye. Statistical significance was achieved for this measure at days 30, 60, and 90 and a similar trend was observed at day 180; however the window for scheduled post-implant visits varied, and many patients were assessed for efficacy considerably later than day 180 (197 patients treated with Ozurdex and 219 patients in the Sham group were assessed after day 180 of the ITT period). This is an important point, as we know from the pharmacokinetic profile of Ozurdex that after day 180 there are not therapeutic levels of dexamethasone in the eye.

The exclusion of these patients in a post-hoc analysis resulted in a statistically significantly higher proportion of patients with an improvement of ≥ 15 letters BCVA at all time points, including day 180 (for 180 day visits up to and including day 180: 136-180), with Ozurdex (26%) versus Sham (17%) ($P \leq 0.017$) (Figure 1).

Figure 1: Effect of excluding visits beyond 180 days: BCVA improvement ≥15 letters



Additionally both individual and pooled data from the GENEVA studies demonstrated that the proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (a level which would be considered clinically significant) was statistically significantly higher at days 30, 60 and 90 (P ≤ 0.010); and additionally in GENEVA 009 and the pooled analysis at day 180 (P ≤ 0.037) with Ozurdex versus Sham (Table 1). Significant between-group differences in the pooled analysis were 26.2% [95% CI: 20.3%, 32.1%] at day 30, 25.0% [95% CI: 18.7%, 31.3%] at day 60, 15.2% [95% CI: 8.8%, 21.5%] at day 90, and 6.7% [95% CI: 0.4%, 13.0%] at day 180.

Table 1: Proportion of patients with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit	GENEVA 008		GENEVA 008		Pooled	
	Ozurdex (n = 201)	Sham (n = 202)	Ozurdex (n = 226)	Sham (n = 224)	Ozurdex (n = 427)	Sham (n = 426)
Day 30	41.3%†	18.3%	45.6%†	16.5%	43.6%†	17.4%
Day 60	49.3%†	25.7%	52.7%†	26.3%	51.1%†	26.1%
Day 90	39.3%‡	27.2%	47.3%†	29.5%	43.6%†	28.4%
Day 180	32.3%	29.7%	40.3%§	29.9%	36.5%¶	29.8%

† (P < 0.001); ‡ (P = 0.010), § (P = 0.021); ¶ (P = 0.037)

Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

Statement: 3.7 – *Anterior chamber cells and retinal neovascularisation were also reported*

Response: While this statement is correct, it does not provide information regarding the extent to which these adverse events are experienced by the Ozurdex and Sham groups. Additionally, there were statistically significant differences between the groups for both events; therefore, it is important to be accurately report the results for each treatment group. Anterior chamber cells occurred in <2% of the

patient population with 5 (1.2%) of patients affected in the Ozurdex group vs. no occurrences in the Sham arm (p=0.031). Conversely, Retinal neovascularisation occurred more frequently in the Sham group than the Ozurdex group, 2.6% versus 0.7% (P = 0.032), respectively.

Statement: 3.8 – ***Health effects were assumed to last 2.5 years in BRVO and 3 years in CRVO; thereafter, visual acuity was assumed to be stable.***

Response: The duration of treatment was assumed to be 2.5 years in BRVO and 3 years in CRVO. As stated above, it was assumed that visual acuity stabilised after this treatment period. However, as the health effects of treatment would be carried forward through the model (maintained as seen at the end of treatment) it is not accurate to state that health effects lasted only during the treatment period.

Statement: 3.14 – ***Although there was a statistically significant increase in BCVA based on the mean letter score with the dexamethasone implant, the ERG did not consider this to be clinically significant because most patients did not achieve a 15-letter improvement from baseline.***

Response: It is important to note that a 15 letter improvement in BCVA (measured by the ETDRS method) is a regulatory endpoint and the gold standard for assessing treatments for registration purposes. A 15-letter change in BCVA using the ETDRS method considerably exceeds the amount required to have a high degree of certainty that the observed alteration is a valid change in VA and not attributable to random chance (Beck, 2007). The primary goal of treating BRVO and CRVO is to improve or prevent further loss of visual acuity (VA) and to reduce Macular Oedema (Hansen, 2007; Hoerauf,2007). In the GENEVA study, statistically significantly more Ozurdex patients achieved a ≥15 letter gain when compared to observation at all time points except day 180. Additionally, Ozurdex patients demonstrated significantly greater clinical effects in terms of mean change in BCVA and fewer patients losing letters of vision, as was described in the initial submission. Furthermore, the Appraisal Committee's clinical experts have stated that a 10 letter gain in BCVA would be considered clinically significant. Again, a statistically significantly greater proportion of Ozurdex patients achieved a 10 letter gain at all time points in the pooled analysis (Table 1).

Based on the full body of evidence submitted to the ERG and evaluated by the Appraisal Committee we do not consider it the statement shown above to be accurate.

Statement: 3.15 – ***The ERG also expressed concern over the size of implantation needle which is larger than those for other treatment.***

[redacted]

Statement: 3.21; 4.31, p37 – *The ERG and Appraisal Committee question the use of 6-12 month data and 3-6 month data to calculate transition probabilities for patients in the Ozurdex and observation after 1 year of treatment.*

This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document.

Statement: 4.5; 4.11 – *Bevacizumab is widely used in the NHS*

This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document. a formal survey commissioned from the School or Health and Related Research at the University of Sheffield (ScHARR) suggests that the majority of centres surveyed regard bevacizumab as an occasional or exceptional treatment for this condition. In the majority of cases, individual funding requests are sent to primary care trusts for exceptional approval in order to fund the use of bevacizumab in this indication. This is in accordance with guidelines provided by the Royal College of Ophthalmologists (RCO) and guidance provided by the MHRA on the unlicensed nature of bevacizumab when used in the eye.

Statement: 4.7 – *The ERG had identified a number of clinical trials evaluating the effectiveness of bevacizumab and an indirect comparison could have been performed.*

This is explored thoroughly in the detailed submission provided in response to analyses requested in the Appraisal Consultation Document.

In summary, in addressing the appraisal committee's questions around bevacizumab, it is important to recognise that the absence of robust controlled trials to quantify the efficacy and safety of bevacizumab in this indication hamper attempts to conduct a rigorous comparative analysis by usual means which would be considered scientifically valid.

Therefore, it has been necessary to use exploratory techniques to i) illustrate the feasibility of a network model approach to effect a mixed treatment comparison ii) consider a cost minimisation evaluation of OZURDEX relative to bevacizumab and iii) use data from another anti-VEGF (ranibizumab) to provide a proxy of the "best" possible efficacy and safety profile anticipated for bevacizumab

Are the provisional recommendations sound and suitable basis for guidance to the NHS?

The Appraisal Committee have requested additional information to inform a final recommendation regarding the use of OZURDEX (dexamethasone intravitreal implant) within the UK NHS. Allergan have made every attempt to provide detailed analyses to support a final decision that will enable patients to have access to the first licensed treatment for macular oedema following retinal vein occlusion.

Allergan believe that OZURDEX represents a significant advance for the preservation and improvement of vision in patients with macular oedema following RVO. The analyses provided demonstrate that OZURDEX is a cost (and capacity) saving strategy compared to the experimental use of anti-VEGF treatments in UK practice, and is cost effective compared to standard of care (observation).

Are there any aspects of the ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

No