CRD and CHE Technology Assessment Group

Fingolimod for the treatment of relapsing remitting multiple sclerosis

16th September 2011

Response to Manufacturer's PAS Submission

The ERG was requested by the Institute to provide additional commentary and validity checks on the PAS submission provided by the manufacturer. It should be recognised that the work undertaken by the ERG does not constitute a full critique of the manufacturer's submission and does not accord with the procedures and templates applied to the original submission due to the limited time available to review the submission.

It is important to note that despite instructions in section 4.2 of the PAS template instructing the manufacturer to update the model to reflect the assumptions that the appraisal committee considered to be most plausible, the manufacturer has used exactly the same deterministic (not probabilistic) model as in the original submission, applied to the same population (population 1b) the same comparator (Avonex) with the only difference being the discount applied to the drug acquisition cost. Table 6 (below) – the probabilistic fully incremental analysis including BSC is the closest estimate in this analysis to what is required by section 4.2

a) Given the fact that the manufacturer has not corrected the model as suggested by the PAS template all the ERGs major concerns about the robustness of the model results still hold. In summary:

   The manufacturer does not appear to have used a systematic approach to identify and select appropriate data sources to inform the key parameters of the model – choices of data appear to be arbitrary and unjustified. Methods used for subsequently deriving the various model parameters from the selected data are not fully described and assumptions made in using these methods are not discussed or justified. There has been no attempt by the manufacturer to validate the predictions of the model either internally against the trial data or externally against other published studies or clinician opinion.

   To explore the impact of the values of key parameters and the assumptions used by the manufacturer, the ERG evaluated a number of scenarios using alternative sources of evidence referred to in the manufacturer's submission but not used in the model and using alternative modelling assumptions. This additional analysis demonstrated that cost-effectiveness results produced by the manufacturer's model are highly sensitive to changes in: the initial EDSS population distribution, interventions and comparators, natural history progression rates, waning of treatment effect, utility estimates, and the way effectiveness on relapse rates has been dealt with within the submission.

Refer to the ERG report section 6 for a full discussion of the implications of these concerns.

b) Given the fact that the manufacturer has presented results for population 1b the ERGs concerns about the use of this population in the analysis still hold. In summary:

The ERG considers the choice of the 1b population as being problematic, as it contains a mixture of RES and non-RES patients. These two subpopulations have different treatment options available to them and hence should be treated separately (as separate decision problems).

Refer to the ERG report section 3.1 for a full discussion of this issue.

c) Given the fact that the manufacturer has refused to produce a fully incremental analysis including BSC for the PAS the ERGs concerns on the choice of comparators still holds. In summary:

In addition to meeting the requirements of the NICE scope, the ERG deems a comparison against BSC to be important since the sub-population considered in this analysis is one where patients have failed to respond to a previous course of DMTs. The cost-effectiveness of continued use of beta-interferon (or switching to an alternative product) in this subpopulation has not been evaluated in previous NICE appraisals and hence it should not be assumed that continued use of a beta-interferon is, in itself, cost-effective.

For a full discussion of this issue refer to sections 3.3, 5.2.3 and 6.3 of the ERG report.

d) The manufacturer's cost effectiveness results reported in Table 1 and Table 2 of the PAS submission (reproduced below) are consistent with the changes that they state that they have made to the model and the ERG has been able to replicate these numbers. These are the deterministic results produced by the model and the equivalent probabilistic results are given in Table 3 and Table 4.

Table 1 Base-case results deterministic (without the PAS) ERG replicated manufacturer's results

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Avonex	271,647	3.98	—	—	—
Fingolimod	321,721	4.88	50,084	0.90	**55,634**

Table 2 Base-case results deterministic (with the PAS) ERG replicated manufacturer's results

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**

Avonex	271,647	3.98	—	—	—
Fingolimod	281,404	4.88	9,758	0.90	**10,839**

Table 3 Base-case results probabilistic (without the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Avonex	270,724	3.90	---	---	---
Fingolimod	321,897	4.64	51,173	0.74	**69,016**

Table 4 Base-case results probabilistic (with the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Avonex	271,089	3.91	---	---	---
Fingolimod	282,045	4.64	10,956	0.73	**14,997**

It is important to note that the probabilistic results in both cases are significantly different (higher) than the equivalent deterministic results, suggesting that the model is non-linear and therefore that the deterministic results are an unreliable estimate of the true ICER. Refer to section 6.1 of the ERG report for a full discussion of this issue.

e) In light of the requirement to consider all relevant comparators see c) above, the ERG has produced an incremental analysis including BSC as a comparator using the manufacturer's updated model including the PAS. Table 5 and Table 6 show the deterministic and probabilistic results from this analysis.

Table 5 Fully incremental results deterministic (with the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
BSC	224,311	3.81	---	---	---
Avonex	271,647	3.98	47,335	0.17	ED (279,107)
Fingolimod	281,404	4.88	9,758	0.90	**53,366**

Table 6 Fully incremental results probabilistic (with the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**

BSC	224,245	3.65	---	---	---
Avonex	271,089	3.91	46,844	0.27	ED (176,357)
Fingolimod	282,045	4.64	10,956	0.73	**58,024**

The results in the above tables show the weakness of using Avonex as a comparator in this population. Avonex is extendedly dominated by fingolimod and has an ICER of £279,107 or £176,357 derived from the deterministic and probabilistic analyses respectively. We also note that the ICER for fingolimod with the discount applied as specified in the PAS when considering BSC as a comparator is £53,366 or £58,024 derived from the deterministic and probabilistic analyses respectively. The differences between the deterministic and probabilistic results provide further evidence that it is necessary to look at the probabilistic results from this model.

f) As noted in a) the model used by the manufacturer to evaluate the PAS is unchanged from the original submission and has not been modified to account for the shortcomings highlighted in the ERG report. Here we show that despite the discounted drug cost (PAS) the remaining uncertainty in the model still cause significant swings in the ICER. As an illustrative example, reducing the progression rates in the model by half (reflecting the lower progression rates observed in the trials than predicted by the model) gives the following cost-effectiveness results.

Table 7 Reduced (50%) progression results deterministic (with the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
BSC	170,084	6.91	---	---	---
Avonex	227,919	6.81	57,834	-0.10	D
Fingolimod	241,608	7.45	13,689	0.64	**131,663**

Table 8 Reduced (50%) progression results probabilistic (with the PAS) ERG generated results from manufacturer's model

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
BSC	170,140	6.69	---	---	---
Avonex	230,410	6.44	60,270	-0.25	D
Fingolimod	242,527	7.17	12,118	0.73	**151,388**

The results show that Avonex is dominated as a treatment by BSC and again show the divergence between the deterministic and probabilistic results. The probabilistic ICER for fingolimod, incorporating the PAS discount, under this scenario using a lower rate of progression than the manufacturer's base case is £151,388.

g) It is interesting to note that results in the PAS submission presented in Table 8 (reproduced below) showing the Avonex is the worst performing interferon from all those compared in the PAS. The cost-effectiveness of fingolimod when compared with the other interferons, even when applied at significantly reduced efficacy levels from those reported in the MTC , are only at best borderline cost-effective. The model used for this analysis was not provided to the ERG hence we have not been able to validate these numbers, they are reproduced as is from the manufacturer's PAS submission and all the noted caveats around the reliability of the model results discussed above are assumed to apply.

Table 9: Exploratory comparison with Betaferon and Rebif-22 (with the PAS) reproduced Table 8 from PAS

	Fingolimod	**Rebif-22**	**Rebif-22**	**Betaferon**	**Betaferon**
Efficacy adjustment	N/A	MTC unscaled	**MTC -13.25%**	MTC unscaled	**MTC -13.25%**
Total costs (£)	284,332	254,456	**258,177**	248,670	251,942
Difference in total costs (£)	N/A	29,876	**26,155**	35,662	32,390
QALYs	4.94	4.08	**3.83**	3.98	3.77
QALY difference	N/A	0.857	**1.109**	0.959	1.171
ICER (£)	N/A	**34,877**	**23,587**	**37,200**	**27,660**

The table above incorporates estimates of relative effectiveness scaled to account for differences in trial populations. These were derived by the manufacturer using extrapolations from the indirect comparison between Avonex and placebo (based on population 1b) employed in the economic model presented in the original submission. These have been used to adjust the estimated efficacy generated by the MTC for Rebif-22 and Betaferon (trials included general, but primarily interferon-naïve, RRMS population), but not for Rebif-44. However the EVIDENCE trial used in the Rebif-44 analysis also used an interferon-naïve RRMS population rather than patients with suboptimal response. Given the level of heterogeneity noted between trials in the MTC it is unclear how appropriate this extrapolation can be considered. The ERG is also concerned that there is a high degree of uncertainty surrounding the level of adjustment that would be required to incorporate the differences in populations between the existing trials and the licensed population.

In conclusion the ERG feels that the manufacturer has not addressed many of the key uncertainties identified with the original submission. The robustness of the model, the arbitrary nature of the input parameters, the choice of comparators and the target population are still of major concern. The analysis here shows that even after incorporating the discount specified in the PAS, accounting for these uncertainties can still push the ICER for fingolimod well beyond usual NICE cost-effectiveness thresholds.