Evidence Review Group Report

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

Addendum

In the original manufacturer's submission, the clinical outcome for three months sustained disability in the mixed treatment comparison was measured as a relative risk; although the term hazard ratio and relative risk appeared to be used interchangeably. In the points for clarification raised by the ERG, we requested clarification about the outcome measure adopted and an explanation for the choice of that measure. It was clarified that the original submission incorporated relative risks. The manufacturer explained that the most consistent reporting of outcomes in the trials was the proportion of patients with sustained disability progression, so to maximise the number of trials included in the analysis a relative risk outcome was chosen. However, the manufacturer acknowledged the potential limitations of using relative risk for sustained disability progression and submitted a revised mixed treatment comparison using hazard ratio as the outcome.

In the new network based on three months sustained progression using hazard ratios, one glatiramer acetate trial (Bornstein 1987) was lost and one fingolimod trial (FREEDOMS II) was gained. In the six months network, one extra fingolimod trial (FREEDOMS II) was gained. The manufacturer also responded by producing revised results for a decision model incorporating hazard ratios; although this decision model was not submitted.

On receipt of these new data it was not clear to the ERG from the SAS code and accompanying text that the output was indeed hazard ratios. Rather it was interpreted as rate ratios, which the ERG considered less appropriate then the original relative risk outcome. Further, the new analysis appeared to rely on the same data that would be used when conducting an analysis based on relative risks (the number of events and the total number of patients) with the addition of the trial duration, and it was not clearly explained why, therefore, changes to the trials included in the networks for the mixed treatment comparisons were required. As a consequence the ERG chose to present results based on the original submission.

In the manufacturer's factual error report, the manufacturer further clarified the SAS code used for the mixed treatment comparison and the output of the analysis is hazard ratios. The analysis conducted took the summary outcome data at 2 years, which would also be used in calculating relative risks at 2 years, and assumed an exponential distribution for the survival function. This approach in calculating hazard ratios is consistent with that taken in other technology appraisals

where the appropriate relative hazard ratio data were absent such as, “The clinical effectiveness and cost-effectiveness of interferon-beta and glatiramer acetate in the management of relapsing/remitting and secondary-progressive multiple sclerosis”. (Tappenden et al. 2006) Relative risks were used in submission TA127 (natalizumab) and TA254 (fingolimod). Both the assumptions of a constant relative risk and an exponential distribution are subject to uncertainty over a long period of time. Due to this uncertainty, no amendment has been made to the ERG report to incorporate results based on the hazard ratio analysis. Rather comparative results are presented here. The relative risk and hazard ratio results for both the three months and six months sustained disability outcomes are reported in Table 1. In the decision model, as there was no result for Avonex, the manufacturer made the Avonex estimate for 3 months sustained progression the average of Rebif 22µg and Rebif 44µg.

Table 1: Comparative relative risk and hazard ratio MTC results of each comparator compared to dimethyl fumarate

	EDSS progression confirmed at three months: relative risk (95% CI)	EDSS progression confirmed at three months: hazard ratio (95% CI)	EDSS progression confirmed at six months: relative risk (95% CI)	EDSS progression confirmed at six months: hazard ratio (95% CI)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]
Avonex	[redacted]	[redacted]	[redacted]	[redacted]
Betaferon	[redacted]	[redacted]	[redacted]	[redacted]
Rebif 22µg	[redacted]	[redacted]	[redacted]	[redacted]
Rebif 44µg	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 7 mg	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide 14 mg	[redacted]	[redacted]	[redacted]	[redacted]

Comparative cost-effectiveness results based on these two different outcomes follow. To obtain these results the hazard ratios presented in the points for clarification have been incorporated into the decision model which was received as part of the original submission. In addition, the ERG sensitivity analyses have been undertaken using this same model. The manufacturer presented cost-effectiveness results in the error report, but as previously stated the ERG only received one model so have opted to incorporate hazard ratios into that model to ensure consistency and comparability of the two sets of results.

For the comparators against which dimethyl fumarate has a positive ICER and is more expensive, the pairwise probabilistic results produced by the ERG are within £600 of those reported by the

manufacturer. This applies to the comparators: Rebif 22µg, Rebif 44µg, Avonex and glatiramer acetate.

The deterministic pairwise cost-effectiveness results are presented in Table 2 for dimethyl fumarate versus each comparator using relative risks or hazard ratios as the outcome measure.

Table 2: The deterministic pairwise cost-effectiveness results using the discounted prices (where possible) for all drugs for both relative risk and hazard ratio outcomes

	ICER of DF versus comparator (Discounted prices)	
	RR (as in ERG report)	HR
Rebif 22 µg	26,026	21,377
Rebif 44 µg	7,289	15,971
Avonex	DF dominates	DF dominates
Glatiramer acetate	36,511	19,746
Fingolimod (35% red)	DF dominates	DF dominates
Fingolimod (53% red)	DF dominates	DF dominates
Natalizumab†	(534,04)	(448,632)
Betaferon	DF dominates	DF dominates

†: There is no discounted price for natalizumab; ‡: brackets indicate the ICER reflects the reverse comparison, i.e. natalizumab versus dimethyl fumarate

The probabilistic pairwise cost-effectiveness results are presented in Table 3 for dimethyl fumarate versus each comparator using relative risks or hazard ratios as the outcome measure.

Table 3: The pairwise probabilistic cost-effectiveness results using discounted prices (where possible) for each drug for both relative risk and hazard ratio outcomes

	ICER of DF versus comparator (Discounted prices)	
	RR	HR
Rebif 22	34,065	31,248
Rebif 44	11,963	23,213
Avonex	114	2,100.25
Glatiramer acetate	49,687	29,516
Fingolimod (35% reduction)	DF dominates	DF dominates
Fingolimod (53% reduction)	DF dominates	DF dominates
Natalizumab	(691,373)	(564,187)
Betaferon	DF dominates	DF dominates

Brackets indicate that the ICER is for the reverse comparison, i.e. natalizumab versus dimethyl fumarate

The full incremental cost-effectiveness results based on discounted prices where appropriate are presented in Table 4. The results are slightly different to those in Table 2 as costs were rounded to the nearest pound and the QALYs were rounded to three decimal places and these rounded values were used to calculate the ICERs in Table 4. The differences are minimal. The price of fingolimod has been reduced by 35% and by 53% in different analyses. As stated in the main ERG report, when using relative risk outcomes, glatiramer acetate was the next most cost-effective comparator. However, using hazard ratios, Rebif 22µg is now the next most cost-effective comparator. This is due to the fact that the hazard ratio for dimethyl fumarate compared to glatiramer acetate is more favourable for dimethyl fumarate than the relative risk. This is not the case when dimethyl fumarate is compared to Rebif 22µg. See Table 1.

Table 4: Deterministic full incremental cost-effectiveness analysis based on discounted prices (where applicable)

	Cost (£)	QALY	ICER (£/QALY)
Glatiramer acetate	231455	5.453	-
Rebif 22 µg	231878	5.498	9,400
Rebif 44 µg	235380	5.621	Dominated by extension
Dimethyl fumarate	237981	5.783	21,414
Avonex	238228	5.584	Dominated
Betaferon	240805	5.398	Dominated
Fingolimod (53% reduction)	243468	5.519	Dominated
Fingolimod (35% reduction)	256154	5.519	Dominated
Natalizumab	284227	5.887	(444,673)

Brackets indicate that the ICER is for the reverse comparison, i.e. natalizumab versus dimethyl fumarate

The probabilistic full incremental cost-effectiveness results are presented in Table 5. The ICER for dimethyl fumarate is £31,244 per QALY. The manufacurer's model produces incremental results from the probabilistic sensitivity analyses, so the deterministic values for glatiramer acetate were taken as the baseline for the purpose of conducting the full incremental cost-effectiveness analysis.

Table 5: Probabilistic full incremental cost-effectiveness analysis based on discounted prices (where applicable)

	Cost (£)	QALY	ICER (£/QALY)
Glatiramer acetate	231,455	5.453	
Rebif 22 µg	232,164	5.490	19,008
Rebif 44 µg	236,171	5.584	Dominated by extension
Avonex	238,920	5.550	Dominated
Dimethyl fumarate	239,272	5.718	31,244
Betaferon	240,694	5.393	Dominated
Fingolimod (53% reduction)	243,328	5.513	Dominated
Fingolimod (35% reduction)	256,031	5.513	Dominated
Natalizumab	285,407	5.800	(563,998)

Brackets indicate that the ICER is for the reverse comparison, i.e. natalizumab versus dimethyl fumarate

The relevant comparators (which are the next most cost-effective comparators), and the probabilistic and deterministic base case results for analyses using hazard ratios and relative risks are presented in Table 6.

Table 6: The comparators, and probabilistic and deterministic base case ICERs for both analyses with relative risk and hazard ratio outcomes

	ICER ranges (£/QALY)	
	Relative risk	Hazard ratio
Comparator (the next most cost-effective)	Glatiramer acetate	Rebif 22 µg
Probabilistic base case ICER	49,687	31,244
Deterministic base case ICER	36,511	21,414

A summary of the ICER ranges for different sensitivity analyses conducted by the ERG using hazard ratios is compared with those using relative risks in Table 7. Although the probabilistic results are the appropriate results, for pragmatic computation reasons, the ERG sensitivity analyses were conducted with deterministic analyses. The significance of the change in result from the deterministic base case result should be considered, and this should roughly reflect the change that would be observed from the probabilistic base case result had probabilistic results been produced.

Table 7: Deterministic ICERs from ERG sensitivity analyses based on discounted prices (where appropriate) for all drugs for analyses with relative risks and hazard ratios

Sensitivity analysis	ICER ranges (£/QALY)	
	Relative risk	Hazard ratio
Alternative treatment monitoring resource assumptions	37,477 to 43,874	21,419 to 28,973
Discontinuation rate after two years is 50% of 0% of the trial duration discontinuation rate for dimethyl fumarate and the comparator	40,633 to 48,436	23,278 to 23,292
Using the 95% lower and upper limits of the confidence interval for the relative discontinuation risks for dimethyl fumarate versus glatiramer acetate	31,367 to 40,546	Dimethyl fumarate dominates to 32,302
Transition rates to SPMS for each EDSS state increased or decreased by 50%	34,345 to 39,568	18,079 to 25,142
Alternative utility estimates for EDSS states using other publications	34,427 to 37,952	18,700 to 22,144
Alternative cost estimates for EDSS states using other publications	32,157 to 39,248	17,239 to 21,377
Natural history relapse rates from MS survey	38,356	24,530
Alternative relapse cost estimates from other publications	35,116 to 38,923	18,660 to 26,074
No adverse events assumed	37,818	24,869
Adverse events derived from MTC	37,176	26,683
Alternative utility estimates for flu-like symptoms and influenza	36,504	21,377