Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

ERG additional analyses

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Emma Loveman

Jeremy Jones

Jackie Bryant

Keith Cooper

Correspondence to Emma Loveman

Senior Research Fellow

Southampton Health Technology Assessments Centre (SHTAC)

University of Southampton

First Floor, Epsilon House

Enterprise Road, Southampton Science Park

Southampton SO16 7NS

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Following the pre-meeting teleconference SHTAC were requested to undertake two additional exploratory analyses.

1) For the highly active RRMS and the RES RRMS subgroups, SHTAC were asked to rerun the model to investigate what happens when the technologies have the same efficacy. For this we have applied the same hazard ratios for alemtuzumab and fingolimod, and also used a midpoint between the alemtuzumab and fingolimod hazard ratios. The results for these changes are presented below for the HA RRMS (analysis 1a) and RES RRMS (analysis 1b) subgroups respectively.

2) SHTAC were asked to explore the impact of an error identified in the 'Long term' sheet of the manufacturer's model #7 where changes to the waning effect of fingolimod alter the results between alemtuzumab and non-HA RRMS treatments.

1a) Alemtuzumab vs. fingolimod for HA RRMS

Table 1 shows the hazard ratios (versus placebo) for fingolimod and alemtuzumab derived in the manufacturer's MTC - HA RRMS sub-group.

Table 1 Hazard ratios from the MTC sub-group analysis

HA	3 month SAD (hazard ratio)	ARR (hazard ratio)	Relative risk of relapse hospitalisation
Fingolimod	[redacted]	[redacted]	0.6
Alemtuzumab	[redacted]	[redacted]	0.22
Halfway point	[redacted]	[redacted]	0.41

3 month SAD from Table B6.7.13, page 171 of GMS. Also Table A2.2.1.1, page 9, of ACD response
ARR from Table B6.7.14, page 171 of GMS. Also Table A2.2.2.1, page 11, of ACD response
Relative risks of relapses resulting in hospitalisation are not specific to the patient sub-group

The results for alemtuzumab vs. fingolimod for HA RRMS, which applies changes made to the hazard ratios for disease progression (3 month SAD), ARR and hospitalisation, so that equal hazard ratios for alemtuzumab and fingolimod are used can be seen in Table 2.

Table 2 Results for almetuzumab vs fingolimod for HA RRMS with changes to hazard ratios

	Alemtuzumab		Fingolimod		Incremental		ICER (£ per QALY gained)
	Costs (£)	QALYS	Costs (£)	QALYs	Costs (£)	QALYs	
Base case	£492,374	4.33	£501,581	3.15	-£9,207	1.176	-£7,828 (Dominates)
HR Alemtuzumab	£492,374	4.33	£493,291	3.61	-£917	0.713	-£1,286 (Dominates)
HR Fingolimod	£513,008	3.47	£501,581	3.15	£11,426	0.318	£35,975
HR half way between each	£503,427	3.86	£497,623	3.37	£5,804	0.493	£11,765

Base case results from Table B7.9.4, page 355 of the GMS

Altering the hazard ratios applied in the model has a large impact on the model results, with ICERs varying between -£1286 (alemtuzumab dominates fingolimod) and £35,975 / QALY gained, using the hazard ratios for alemtuzumab and fingolimod respectively. Using a HR halfway between those for alemtuzumab and fingolimod for both treatments gives an ICER of £11,765 / QALY. The model results for HA RRMS for alemtuzumab vs. fingolimod are largely driven by the superior clinical results for alemtuzumab, particularly for disease progression. In the case, where alemtuzumab and fingolimod have equal efficacy, alemtuzumab has higher QALYs than fingolimod, and this is due to the superior length of effect of alemtuzumab. Patients receiving fingolimod withdraw from treatment over time and transfer to best supportive care which has a worse long term outcome than alemtuzumab.

1b) Alemtuzumab vs. natalizumab for RES RRMS

Table 3 shows the hazard ratios (versus placebo) for natalizumab and alemtuzumab derived in the manufacturer's MTC - RES RRMS sub-group.

Table 3 Hazard ratios from the MTC sub-group analysis

RES	3 month SAD (hazard ratio)	ARR (hazard ratio)	Relative risk of relapse hospitalisation
Natalizumab	[redacted]	[redacted]	0.6
Alemtuzumab	[redacted]	[redacted]	0.22
Halfway point	[redacted]	[redacted]	0.41

3 month SAD from Table B6.7.16, page 174 of GMS. Also Table A3.2.1.1, page 29, of ACD response
ARR from Table B6.7.17, page 174 of GMS. Also Table A3.2.3.1, page 32, of ACD response
Relative risks of relapses resulting in hospitalisation are not specific to the patient sub-group

Table 4 shows the results for alemtuzumab vs. natalizumab for RES RRMS with changes made to the hazard ratios for disease progression, ARR and hospitalisation, so that equal hazard ratios for alemtuzumab and natalizumab are used.

Table 4 Results for almemtuzumab vs natalizumab for RES RRMS with changes to hazard ratios

	Alemtuzumab		Natalizumab		Incremental		ICER (£ per QALY gained)
	Costs (£)	QALYS	Costs (£)	QALYs	Costs (£)	QALYs	
Base case	£490,016	4.42	£536,379	3.75	-£46,363	0.67	-£69,309 (Dominates)
HR Alemtuzumab	£490,016	4.42	£535,115	3.86	-£45,099	0.56	-£81,200 (Dominates)
HR Natalizumab	£494,726	4.24	£536,379	3.75	-£41,653	0.49	-£85,042 (Dominates)
HR half way between each	£492,368	4.33	£535,729	3.81	-£43,361	0.52	-£83,078 (Dominates)

Base case results from Table B7.9.8, page 359-360 of the GMS

Changes to the hazard ratios for natalizumab, so that the hazard ratios are equal to those of alemtuzumab have a small large effect on the model results, with ICERs varying between -£81,200 and -£85,042 per QALY gained, using the hazard ratios for alemtuzumab and natalizumab respectively. There is only a small difference in the hazard ratios, especially for disease progression. In the base case the treatment cost of alemtuzumab was less (£73,039) than natalizumab (£98,258). In addition, there are further differences in costs between the two treatments due to the lower disease costs for alemtuzumab. In the case of natalizumab, the model results for RES RRMS for alemtuzumab vs. natalizumab are largely driven by the superior length of effect of alemtuzumab. Patients receiving natalizumab withdraw from treatment over time and transfer to best supportive care which has a worse long term outcome than alemtuzumab.

2) Exploration of the impact of the identified error

The results change when altering the waning effect for fingolimod, for example base case results for alemtuzumab vs. GA change from £8924 to £10,318 if the waning effect is 50% for fingolimod for years 3+.

The model error changes the number of relapses per patient for the alemtuzumab arm. When long term effectiveness (waning of efficacy) of fingolimod is set to 50% from year 3

onwards it causes the total number of relapses per patient for intervention (alemtuzumab) to increase from 20.734 to 22.757. The effect of this is to increase relapse cost for alemtuzumab from £20,972 to £22,614 (hence increasing total disease cost from £428,186 to £429,829 and total cost per patient to increase from £499,347 to £500,989). This also causes relapse disutility to decrease from -0.1477 QALYs to -0.1627 QALYs (thus reducing total QALYs per patient from 4.034 to 4.019). Life years for both intervention and comparator are unchanged.

The error has no effect on results for the comparator arm (when the comparator is not fingolimod) and does not affect any of the results submitted by the manufacturer.