Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

ERG overview of manufacturer's additional analysis in response to the data requests made in the ACD

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Introduction

In the Appraisal Consultation Document (ACD) for alemtuzumab for treating relapsing-remitting multiple sclerosis (RRMS) NICE requested further clarification and analyses from the manufacturer.

The manufacturer outlined their response to these requests in an additional document and seven versions of the economic model.

In addition the manufacturer provided a document outlining their response to the ACD.

SHTAC was requested to provide an independent assessment of both of these documents and the associated changes in the economic model. This document provides the ERG critique of the first of these submissions, although for some analyses there is relevant information in both documents. The ERG indicate in this document where this is the case. This document refers to the original manufacturer's submission as the GMS, the analyses in response to the ACD requests as the 'additional submission' and the manufacturer's response to the ACD as the 'response to the ACD'.

ERG critique of Genzyme's response to NICE's request for additional information.

The ERG has checked the 14 data request analyses through running the manufacturer's model and checking results of the analyses, and checking the changes made to the model for correctness. Where possible data inputs have also been checked. The deterministic results presented in Table 1 of the additional submission were checked for alemtuzumab versus glatiramer acetate (GA) for all analyses and a small sample of probabilistic results was checked. Limited time and resources did not allow a complete re-running of all PSAs and so only those with the most impact on the model results were re-run (analysis 7 and analysis 15).

The manufacturer has presented incremental values (columns 4 and 5) in the cost effectiveness tables against the preceding row even when the previous row includes a dominated option. As a result many of the ICERs presented in the tables are unreliable.

Bottom line summary

The ERG considers that the manufacturer has responded appropriately to the NICE committee's requests for additional analyses in the majority of cases. The ERG have checked the modelled additional submission analyses and found these are presented correctly. Of the 14 analyses, the analyses that have the greatest impact on the model results are long term efficacy of alemtuzumab (analysis 7), lower health state costs (analysis 12) and changes to the natural history to allow improvement in patient EDSS states (analysis 5). For all analyses, the ICER for alemtuzumab against all comparators is less than £30,000 per QALY. For the combined analysis, including all

requested changes, the deterministic ICERs were less than £20,000 per QALY for alemtuzumab compared to all other treatments.

Data request 1: 6 month SAD as a primary outcome measure in the MTC and model.
The manufacturer amended the model to use relative estimates of disease progression for alemtuzumab, GA, and intra-muscular (IM) and sub-cutaneous (SC) interferon beta 1a (IFNβ-1a) (the latter only for 44µg dose) based on 6-month SAD. These data were included in the report of the mixed treatment comparison (MTC) in the original GMS – Table B6.7.8, Page 163 of GMS. The ERG previously noted that the original submission did not appear to have taken any account of the inclusion of multi-arm trials in the MTC (see pages 31 and 34 of ERG report), although including this adjustment had limited impact on the results (see Table 6 page 35 of ERG report). No adjustment for this has been applied to the data used by the manufacturer for this analysis. The values reported in the original table were correctly applied to the data input area on the "Defaults" worksheet (in cells A58:D77) and were selected for use in the model by placing an additional drop-down selection on the "Model Settings" worksheet (offering the option of estimates derived from comparisons using 3-month or 6-month SAD).

The ERG has rerun the model, after applying these changes, and obtained the same results for the deterministic analysis as reported by the manufacturer. The ERG notes that the results differ between the deterministic and probabilistic analysis, especially for lifetime QALY, which are about 1 QALY larger in the probabilistic than the deterministic analysis.

Overall, applying 6 month rather than 3 month SAD in the model, yields more QALYs at slightly lower cost (results using 6 month SAD can be found in Table B7.7.9 ("probabilistic base case results of alemtuzumab versus all comparators in active RRMS analysis ranked by cost", using 3 month SAD) in the original GMS). The relative increase in QALYs and reduction in total cost is particularly marked for GA, alemtuzumab and IM IFNβ-1a (QALY increase between 0.7 and 0.9, cost reduction between £14,750 and £19,500) in comparison with SC IFNβ-1a (QALY increase 0.25, cost reduction approximately £5,000). These are consistent with the results reported for the MTC in the GMS (see Table B6.7.7, Page 162 of GMS, for 3 month SAD and Table B6.7.8, Page 162 of GMS, for 6 month SAD) where the mean hazard ratios for alemtuzumab, GA and IM IFNβ-1a are broadly comparable (0.52 vs 0.49, 0.93 vs 0.89 and 0.91 vs 0.92 respectively) while there is a more noticeable difference for SC IFNβ-1a (0.79 vs 0.94). In all cases the 95% credible interval is much wider for 6 month SAD compared with 3 month SAD. The evidence networks for the two analyses are not the same, with the network for 6 month SAD being more sparse, which may give rise to some inconsistency between the two analyses. There is no direct evidence comparing SC IFNβ-1a with placebo (the contrast of interest in this analysis) in either network.

Data request 2: an 'all years' MTC adjusted for baseline relapse rates.

The manufacturer amended the model to use relative estimates of annualised relapse rate (ARR) and disease progression for alemtuzumab, GA, IM and SC IFNβ-1a from an amended MTC including all trial data, and adjusted for baseline ARR. The values reported in Appendix 1 to the additional submission (Table A.1.1 for ARR and Table A.1.2 3 month SAD) were correctly applied to the input table area on the "Defaults" worksheet (in cells Z46:AC56 for ARR and cells F47:I56 for 3 month SAD) and were selected for use in the model by including an additional option in the "Choose MTC" drop-down selection on the "Model Settings" worksheet (offering the option of "Adjusted all years 80% RRMS"). Applying these changes gives the indicated deterministic ICER of £11,959 for alemtuzumab compared with GA.

The ERG has rerun the model, after applying these changes, and obtained the same results for the deterministic analysis as reported by the manufacturer.

The ERG previously noted that the original submission did not appear to have taken any account of the inclusion of multi-arm trials in the MTC. While the MTC has been updated to include all trials, and to adjust for baseline ARR by use of meta-regression, the analysis does not appear to have been amended to take account of multi-arm trials used by the manufacturer for this analysis.

Data request 3: the ITT analyses for the included trials adjusted for baseline EDSS only (unadjusted for country or region).

The manufacturer provided ITT data for the three outcomes of 3-month SAD, 6-month SAD and ARR from the three trials. This was adjusted for baseline EDSS score using a covariate of EDSS <2 or ≥2. The proportions of participants in these two categories across the three trials were broadly similar in two trials. In the third trial, the proportion of participants in the EDSS <2 category was lower than in the other two trials. This was by the nature of the trial inclusion criteria which allowed a wider group of participants to be included. However, the ERG believes that the approach to categorise the data is reasonable. As discussed by the manufacturer the data for the three outcomes are very similar to the original trial data, both in the trial data and the MTC.

In Table 7 of the manufacturer's document there is an error where the QALY results for alemtuzumab and IFNβ-1a are transposed.

The ERG has rerun the model results for the deterministic analysis and found a minor error in the ICER which should be £10,338 (rather than £10,388).

Data request 4: EQ-5D data from the CARE-MS I and CARE-MS II trials.

The manufacturer has amended the model to use, where possible, utility data from the three included RCTs and has applied utility in the model by intervention and EDSS state. This approach differs from the original approach which applied utility data according to EDSS state and SPMS state.

In the CARE MS I and II trials, EQ-5DL was collected at baseline and at six month intervals up to 24 months. For alemtuzumab and IFNβ-1a, utility scores were taken from the 24 month data from the trials, whilst for BSC utility scores were taken from IFNβ-1a baseline scores, for EDSS states zero to six. There were small sample sizes for EDSS states seven to nine and so for these states, the decrements seen in the Orme et al data, and used in the original GMS, are applied. IFNβ-1a is assumed to be comparable to all beta-interferons and GA and the IFNβ-1a data was used for these comparators. Adverse event disutilities are set to zero as this is captured within the trial utilities, and disutility from relapse is zero in the treatment arms while patients are receiving treatment. Once patients switch to BSC, disutilities for relapse are the same as the original GMS. The manufacturer reports that adverse events make a small contribution to differences in utility. The AE disutility for the treatments in the original version of the model is low, less than -0.1 QALY. The relapse disutility for alemtuzumab was -0.15 QALYs in the original model.

The EQ-5DL data presented is pooled from the three trials. The manufacturer acknowledges that the data show some inconsistencies because of small samples sizes and as such there is no consistent evidence of a decreased utility across EDSS states.

The ERG notes that the trial data concern the less severe EDSS states with the biggest sample sizes (1-1.5, 2-2.5, 3-3.5) and these represent more reliable data. The manufacturer has assumed that the utility values for EDSS states seven to nine are related to EDSS state six by an adjustment with the decrements from Orme et al. However the EDSS state six data are based upon only a small sample, and the ERG considers that the EDSS utility estimates for the more severe EDSS states should be treated with caution. The ERG notes that there is a large difference between the utility values in these states between treatments, for example EDSS state 7 utility scores are [redacted] and [redacted] for alemtuzumab and IFNβ-1a, but the EDSS state utility scores are similar between BSC and alemtuzumab (BSC EDSS state 7 utility score [redacted]).

The use of these data has the effect of lowering the QALYs,
[redacted].

The manufacturer has also presented an additional analysis that applies utility from EQ-5DL values from the TEMSO (teriflunomide) trial data for EDSS states zero to six and utility decrements seen in Orme et al for EDSS states seven to nine as these were higher than those in the alemtuzumab trials (CARE MS I/II). Results of the analysis using these data can be seen in Table 12 where alemtuzumab remains cost effective. There is no discussion from the manufacturer as to why the EQ-5DL scores in these trial participants is higher than those seen in the alemtuzumab trials, or how homogenous these populations are.

The ERG has rerun the model results for the deterministic analysis and obtained the same results.

Data request 5: an amendment to the model to allow improvements in patients' EDSS states.
The ERG has rerun the model results for the deterministic analysis for the first analysis with the TEMSO and TOWER trials and obtained the same results. This was provided as an option in the drop down menu in work sheet 'Clinical Data'. The ERG was not able to replicate the second analysis as this option was not available.

In the response to the ACD document the manufacturer considered that modelling disease progression using the TEMSO / TOWER placebo arms data for EDSS states 6 - 9 is inappropriate (section A.4, p42), because the inclusion criteria of the trials was EDSS score 0 to 5, and the trial duration is up to 2 years. It states that the short time duration makes it inappropriate to use for a life time health economic model and that the London Ontario data with follow up data over a longer time period seems more appropriate (mean 22 years follow-up).

The ERG notes that the committee had concluded that the number of lifetime QALYs generated by the model was implausibly low (ACD p34) and that this may be in part due to choosing the London Ontario dataset for the transition probabilities between EDSS health states. The effect of incorporating TEMSO and TOWER trials increases the QALYs for alemtuzumab from 4.296 to 8.643, whilst the second scenario using London Ontario data has a lifetime QALY of 6.68. In the original ERG report, we noted that the manufacturer had not fully explored the uncertainty around the natural history of MS and that alternative data sources should have been explored more extensively and validated against trial data. As the manufacturer has not provided these analyses, it is still unclear how well the manufacturer's model predicts the natural progression of multiple sclerosis.

Data request 6: an amendment to the model incorporating the observed deaths from the trial data.
The manufacturer provided an amendment to the model which incorporated the observed deaths from the trial data. The number of QALYs were adjusted for the number of the deaths in the trials,

i.e. reduced by 3/1485 = 0.20%. Deterministic cost effectiveness results give an ICER of £8,979 for alemtuzumab versus GA (probabilistic £7,063).

The ERG considers the assumptions used to estimate data request 6 to be appropriate and similar to those used by the ERG in their analyses for the 1st Appraisal Committee Meeting. The ERG has rerun the model results for the deterministic analysis and obtained the same results. However there is a minor error in Table 15, where the results for alemtuzumab and IM IFNβ-1a have been transposed.

Data request 7: a reduction in efficacy for alemtuzumab starting at 3 or 5 years.

The manufacturer presents results for a reduction in efficacy for alemtuzumab and the alternative disease modifying treatments (DMTs) for the following scenarios:

- Scenario 1: 50% for year 5 and onwards,
- Scenario 2: 75% efficacy at 3-5 years followed by 50% efficacy for year 6 and onwards

The manufacturer notes that in the assessment of fingolimod by NICE a waning of efficacy of 50% from 5 years onwards was applied, as in scenario 1. The manufacturer states scenario 2 would be consistent with the NICE assessment of teriflunomide,. Furthermore it notes that data exists from the CAMMS 223 extension study which shows superior maintenance of efficacy data (both ARR RR and 6 month's SAD HRs) for alemtuzumab than for the fingolimod assessment, i.e. 5 years data against an active comparator (see GMS Tables B6.5.2 – B6.5.4, p120-122).

The manufacturer maintains that the effects of alemtuzumab on SAD appeared to be durable since the difference between the alemtuzumab groups and the SC IFNβ-1a group was maintained at 5 years of follow-up (GMS p274). The ERG is unclear whether the evidence presented indicates a waning effect in treatment efficacy, as the treatment effect in CAMMS 223 is better than for the other CARE-MS trials (Tables B6.6.1- B6.6.6, p132). The ERG considers that the waning effect over the long term is unknown.

The ERG considers that the manufacturer has produced the required analysis requested by NICE and that the modifications made to the model have been completed correctly. The ERG has rerun the model results for the deterministic and probabilistic analyses and obtained the same results.

In addition, the manufacturer produces the above two analyses for the situation where the DMT comparators' efficacy do not wane over time (discussed in more detail in A.6, p45 of the manufacturer's response to the ACD document). The manufacturer has submitted these analyses based upon their interpretation of the wording in NICE's request for additional analyses. It does not

agree with the need for the analysis for assuming a divergent approach for waning between alemtuzumab and its comparators. The ERG is unclear on the interpretation of NICE's request and whether they intended for this to imply a different waning effect between alemtuzumab and its comparators. The ERG is unclear of the long term waning effect beyond the trial data but consider that the data presented by the manufacturer do not imply different waning effects between alemtuzumab and its comparators.

Data request 8: additional costs of other licensed RRMS treatments after alemtuzumab treatment failure.

The manufacturer based their estimate of the additional treatment cost following alemtuzumab treatment failure on the proportion of patients reported as receiving additional treatments in one year of CARE-MS extension studies. These additional costs are applied cumulatively from year 3 over the remaining model horizon, assuming a constant proportion of alemtuzumab-treated patients requiring additional treatment. Including these additional costs in the analysis increases total cost for alemtuzumab by approximately £4650 and increases the ICER versus the next best (non-dominated) option from approximately £5,400 per QALY gained to approximately £9100 per QALY gained (at the means values reported for the probabilistic analyses).

The additional costs are applied in the model by adding a column to the "Treatment costs" worksheet with values for alemtuzumab in cells A125:A172. The additional costs are included in the model using an additional drop-down selection on the "Cost Data" worksheet (offering a Yes/No option to include additional DMTs after failure).

The ERG has rerun the model, after applying these changes, and obtained the same results for the deterministic analysis as reported by the manufacturer.

The additional costs enter the model as deterministic values – there is no functionality to consider uncertainty in the calculation of the weightings used to estimate the annual cost per patient receiving additional treatment, nor of the proportion of alemtuzumab-treated patients requiring additional treatment. There is also no consideration of uncertainty around the structural assumption of a constant proportion of alemtuzumab-treated patients requiring additional treatment.

Data request 9: a time-dependent re-treatment rate for alemtuzumab.

The manufacturer amended the model to include probability of re-treatment based on alemtuzumab re-treatment observed between years 3 and 5 in CAMMS 223 and in the CARE MS extension studies. Longer term re-treatment is stated as being based on an unpublished observational study – although the values used from year 6 onward appear to be based on assumption (year 6 probability

is half that for year 5, while values beyond year 6 are based on an assumption of a 10% annual reduction from the re-treatment probability in the previous year). These assumptions are broadly consistent with the observational study, although this appears to involve a small number of patients (not reported by manufacturer, but estimated by ERG_[redacted]), with the extrapolated rate of decrease (10%) largely based on data beyond the mean follow-up (median not reported). There is a slight error in the text of the manufacturer's response which states incorrectly that Table 18 reports values used in the model (should read Table 19) – the tables are correctly labelled. The values reported in Table 19 were correctly transferred to the model and are found on the "Cost Data" worksheet (in cells AO25:AQ73). The revised electronic model includes a drop-down selection on the "Cost Data" worksheet to choose between re-treatment based on CAMMS 223 (base case) or CARE MS extension studies (higher value for scenario analysis).

The ERG has rerun the model, after applying these changes, and obtained the same results for the deterministic analysis as reported by the manufacturer.

The re-treatment probabilities enter the model as deterministic values – there is no functionality to consider uncertainty in the calculation of year 3 to 5 re-treatment probabilities nor of the assumptions that probability reduces by half in year 6 and declines by ten percent each subsequent year.

Data request 10: removing the mid-cycle correction for the costs of alemtuzumab.
The manufacturer has amended the model so that drug treatment costs are incurred at the start of the year, rather than at the mid-year point. The ERG has checked the amendments to the model and considers these changes have been made correctly. The ERG has rerun the model results for the deterministic analysis and obtained the same results.

Data request 11: increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab treatment.
The manufacturer presents an analysis for the impact on the model results of increasing the number of monitoring and neurology visits for patients treated with alemtuzumab and additional monitoring after re-starting alemtuzumab. The monitoring for alemtuzumab was increased to 4 neurology visits in first year and 2 neurology visits thereafter and the number of MRIs has increased to 1 per year.

The manufacturer has made a change to the calculation of the monitoring cost after year 1, to take account of patients receiving re-treatment with alemtuzumab. The cost of year 2 onwards is now the sum of the year 1 monitoring costs for all patients receiving re-treatment and the year 2 monitoring costs for all patients not receiving re-treatment.

The ERG has checked the changes the manufacturer made and considers these changes have been made correctly. The ERG has rerun the model results for the deterministic analysis and obtained the same results.

Data request 12: higher [lower] health state costs used in the Evidence Review Group's analyses.

The manufacturer has conducted an analysis using alternative health state costs from the Biogen manufacturer submission. These health state costs use only direct medical costs; no direct non-medical costs are included. The impact of using alternative health state costs from the Biogen manufacturer submission is to substantially reduce the total costs for all treatments by about £200,000.

The ERG has rerun the model results for the deterministic analysis and obtained the same results.

In the response to the ACD the manufacturer states that it disagrees with excluding the direct non health care costs from the model (section A.5, p43), arguing that substantial social care costs are paid for by the government for MS patients and that these costs are supported by results of the MS Survey and a report from the Work foundation. Furthermore it argues that the non-medical costs reported in Karampampa et al. are similar to those from Tyas et al. Finally it notes that in the NICE appraisal of teriflunomide, the most plausible ICER was likely to lie between the ICERs estimated with and without non-health care costs, given the uncertainty about how much of the non-health costs from the cited sources were within the NICE reference case.

The ERG considers that direct non health care costs are likely to be incurred through the payment of social care for MS patients, especially for those patients with higher rates of dependency (EDSS six and above). Whilst these costs are unclear, the ERG considers that although problems have been identified for the values from Biogen and Tyas et al, these may provide upper and lower limits to the costs.

Data request 13: costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death.

The manufacturer based their estimate of the cost of renal failure, renal transplant, dialysis and associated with alemtuzumab on the proportion (0.41%) of the trial population experiencing nephropathies "over the trial duration" (trial ID not specified). This proportion is higher than the value used for modelling the costs of treating all nephropathies in the original submission ([redacted] [sourced directly from the model, discussed

briefly on page 261 of the GMS]) – the model originally assumed all nephropathies occurred in the first year. All patients experiencing nephropathy had an annual cost of £1822.93 (based on NHS Reference Costs for chronic renal disease with/ without intervention). It appears that this cost was applied in addition to the £338.96 already included in the model for patients experiencing nephropathy. The differences (or any relationship) between the original assumptions and those adopted for the additional analyses are not discussed in the manufacturer's response.

The manufacturer estimated the proportion of nephropathies that would progress to end-stage renal failure (ESRF) using data from a study of patients with chronic renal failure, stating that no progression probability for nephropathy could be sourced (but did not describe or discuss the search process). Using the identified study the progression probability was estimated at 2.2% per year. The manufacturer further assumed that half patients with ESRF would incur one-off cost of kidney transplant, while the remainder would incur recurrent costs of dialysis, citing limited evidence to support this assumption. The appropriateness of assuming a one-off cost for renal transplantation is not discussed. Unit costs for kidney transplant and dialysis were based on activity-weighted NHS Reference Costs and seem reasonable. However there appears to be a slight discrepancy between the annual cost of dialysis estimated in Table 28 (£24,773) and that applied in the calculations applied in the model which are reported in Table 29 (£24,470).

The manufacturer estimates end of life costs from organ failure based on a calculation (source not referenced) that gives a probability of death from organ failure of 0.08%. It is unclear from the text whether this is intended to refer only to death from organ failure in patients with ESRF. However Table 29 states that this is the value adopted in the model for "death due to ESRF". This value appears to have been adopted as an annual probability of death due to ESRF. However its calculation is unconnected to the estimated incidence of ESRF in patients experiencing nephropathy and does not seem appropriate as it is almost ten times the incidence of ESRF.

The manufacturer states that the end of life costs associated with deaths due to adverse events has been included in the model based on the proportion (0.2%) observed in the alemtuzumab clinical trials, although the row in Table 29 relating to these costs is blank.

These additional costs were included by adding a column to the "Treatment costs" worksheet with values for alemtuzumab in cells A792:A841 and can be activated using an additional drop-down selection on the "Cost Data" worksheet (offering a Yes/No option to include costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis, and death).

The additional costs enter the model as deterministic values – there is no functionality to consider uncertainty in the calculation of proportions of patients experiencing nephropathy, progression to ESRF or experiencing death nor in the weightings used to estimate the annual cost of dialysis. There is also no consideration of uncertainty around the structural assumption to apply only one-off costs for renal transplant or discussion whether the proportion of patients experiencing nephropathy in clinical trials (of varying durations) can be used directly as an annual probability.

The ERG has rerun the model, after applying these changes, and obtained the same results for the deterministic analysis as reported by the manufacturer. Inclusion of these additional adverse event costs has little impact on the ICER. However the ERG urges caution in interpreting these results, given the uncertainty over the proportion of patients experiencing nephropathies, inconsistencies in the application of adverse event costs, and uncertainty over the estimation of end of life costs and the extent to which they have been included in the analysis.

Data request 14: baseline characteristics from patients in the alemtuzumab trials instead of from the UK Risk Sharing Scheme, and rates of disease progression incorporating the characteristics of the placebo group from the TOWER and TEMSO trials instead of data from the London Ontario data set.

The manufacturer provided an amendment to the model to incorporate the natural history transition matrix from the placebo arms of the TEMSO and TOWER trials to allow for improvement in EDSS (See Analysis 5) with baseline characteristics from the CARE MS I and II trials (for initial EDSS distribution, age and male to female ratio) as a more relevant population. Results show alemtuzumab dominates all comparators (Table 31).

The analysis was repeated using the initial EDSS distribution and baseline characteristics from alemtuzumab trials and natural history transition matrix with TEMSO and TOWER for EDSS 0-5 and London Ontario otherwise and results give an ICER of £1473 (in summary Table 1) and £364 for alemtuzumab versus GA (deterministic and probabilistic respectively) and that alemtuzumab dominates all other comparators (Table 32).

The ERG has rerun the model results for the deterministic analysis and obtained the same results. The ERG has rerun the probabilistic analyses for the first analysis, which appears to be reported in Table 32, rather than Table 31.

Data request 15: Combined analyses to provide overall updated ICERs

The ERG has rerun the model results for the deterministic and probabilistic analysis and obtained the same results. It checked that the changes from all analyses 1-14 had been implemented in the

combination model correctly. The ERG discovered that the combination analysis differed slightly from the individual analysis in two instances: for the waning effect (analysis 7), in the combination analysis the deterministic results are presented for years 6 onwards (rather than years 5 onwards); for observed deaths the analysis uses a trial population of 1208 (rather than 1485).

In the combination analysis, the PSA is highly unstable. This is because there are large ranges in the HR confidence intervals, particularly for GA. For example for disease progression the HR confidence interval is 0.29 - 2.31. When sampling from this distribution, the model gives some infeasible results, for example some of the total lifetime QALYs are negative. So the ERG has less confidence in these PSA results than for the other data requests.