# Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

## SHTAC ERG additional analyses

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## Introduction

SHTAC conducted the following analyses following discussions at the pre-meeting teleconference on 10th October. The analyses have been applied to the manufacturer base case and/or the ERG preferred base case as outlined below.

## Monitoring

Increasing the monitoring for alemtuzumab to 4 neurology visits in first year and 2 neurology visits thereafter (from 2 neurology visits in first year and 1 neurology visit thereafter), and increasing the number of MRI to 1 per year for alemtuzumab, increases the ICER for the manufacturer's base case from £8445 to £11,131 per QALY.

For the corrected ERG preferred base case these changes increase the ICER to £1376 per QALY gained (from the ERG preferred base case of £852 per QALY).

## Mid cycle correction

Across the three trials there were 55 discontinuations (6% over 2-3 years) in the alemtuzumab 12mg arms. The manufacturer uses a mid cycle correction, and so treatment costs are estimated at this time point. However, treatment costs should be applied at the start of the cycle. Changing this in the model requires restructuring the model. In the model, in the first two years of the manufacturer's base case, there are 4% more patients at the start of the year compared to the mid point. We can estimate the effect of treatment costs being applied at the start of the cycle by using a crude adjustment, increasing the treatment cost by 4% for alemtuzumab, and this increases the ICER to £10,591 per QALY. This crude correction is an overestimation to the change to the ICER as we have not estimated the difference to the cost for SC IFNβ-1a 44µg.

Using a similar crude adjustment for the ERG preferred base case, in the first two years, 2% more patients are at the start of the year compared to the mid-point. Increasing the treatment cost by 2% for alemtuzumab, and this increases the ICER to -£30 per QALY.

## Trial mortality

The manufacturer model does not incorporate the deaths seen in the trials. There were three related deaths in the trials, two in CAMMS223 (1 in the 24mg group, 1 two months after the

3rd cycle) and one during the extension study (occurred 19 months after the 2nd cycle). It is not straight forward to include this in the model. However, in the manufacturer's base case a typical patient would have 4.034 discounted QALYs. Therefore, we can adjust the number of QALYs for the number of deaths in the trials i.e. 3/1200 * 4.034 = 0.01. Thus the adjusted total discounted QALYs would be 4.034 – 0.01 = 4.024, and the ICER would increase to £8517 per QALY.

In the ERG's preferred base case a typical patient would have 7.147 discounted QALYs. Adjusting in a similar way, for the number of deaths in the trials i.e. 3/1200 * 7.147 = 0.018, the adjusted total discounted QALYs would be 7.147 – 0.018 = 7.129, and alemtuzumab continues to dominate SC IFNβ-1a 44µg (ICER = -£860 per QALY).

The combined effect of the changing monitoring, mid cycle correction and trial mortality as above is an ICER of £13,390 per QALY for the manufacturer's base case.

The combined effect of the changing monitoring, mid cycle correction and trial mortality as above is an ICER of £2218 per QALY for the ERG's preferred base case.

**Worst case scenario**

The analyses that have most impact on model results are:

- disease health state costs from Biogen et al. 2007;
- waning effect years 6-9 75%, 10+ 50%;
- % patients receiving alumtuzumab, year 3 60%, year 5+ 20%.

Combining these analyses for the worst case scenario (all three analyses) gives an ICER of £20,822 per QALY for alemtuzumab versus SC IFNβ-1a 44µg for the ERG's preferred base case. For the worst case scenario and the increased monitoring, adjustment for the mid cycle correction and including trial mortality, the ICER increases to £25,329 per QALY.

**Table 1. Cost effectiveness of alemtuzumab compared to SC IFNβ-1a 44µg for the ERG preferred base case for a worst case scenario**

| | SC IFNβ-1a 44µg | | Alemtuzumab | | | | |
|---|---|---|---|---|---|---|---|
| **Technologies** | **Total costs (£)** | **Total QALYs** | **Total costs (£)** | **Total QALYs** | **Inc costs (£)** | **Inc QALYs** | **ICER (£) inc (QALYs)** |
| ERG preferred base case | 431,896 | 5.205 | 430,241 | 7.147 | -1655 | 1.942 | -852[a] |
| Disease health states costs from Biogen et al.2007 | 248,579 | 5.205 | 257,617 | 7.147 | 9038 | 1.942 | 4,654 |
| Waning effect, years 6-9 75%, 10+ 50% | 432,843 | 5.162 | 443,079 | 6.560 | 10236 | 1.399 | 7,319 |
| % patients receiving alumtuzumab, year 3 60%, year 5+ 20% | 431,896 | 5.205 | 446,160 | 6.917 | 14263 | 1.711 | 8,336 |
| Worst case scenario (all three above) | 249,294 | 5.162 | 278,416 | 6.560 | 29122 | 1.399 | 20,822 |
| Worst case scenario (all three above) with additional monitoring, adjustment for mid cycle and trial mortality | 249,294 | 5.162 | 284,304 | 6.544 | 35010 | 1.382 | 25,329 |

**Time spent in EDSS health states**

The increased acquisition costs of alemtuzumab compared to SC IFNβ-1a 44µg are offset by the reduced disease costs, due to the reduced time spent in the more severe health states by a typical patient. We conducted several scenario analyses to demonstrate the effect of these on the time spent in the less severe health states (EDSS < 6), as shown in Table 2. In the baseline case, patients spent on average 2.38 years longer in the less severe states for alemtuzumab than SC IFNβ-1a 44µg. Changing the treatment effect duration, using a waning effect, reduces the additional years in the less severe states to 1.67 years. Using the same treatment withdrawal rate for alemtuzumab and SC IFNβ-1a 44µg, reduces the additional years in the less severe states to 1.22 years. Changing the transition probability transition matrix shows a difference of 2.43 years (no difference from previous estimates) in the additional years in the less severe states. Using the same reduction in SAD for alemtuzumab as for SC IFNβ-1a 44µg, reduces the additional years in the less severe state to 0.54 years.

These analyses show that the duration spent in the more severe health states (EDSS states ≥6) are most dependent upon the treatment effect in terms of SAD values used in the model.

**Table 2. Time spent in the EDSS states < 6 for different model scenarios**

| | **Time spent in EDSS states < 6** | | | **Disease costs, £** | | | | |
|---|---|---|---|---|---|---|---|---|
| | **SC IFNβ-1a 44µg** | **Alem-tuzumab** | **Diff** | **SC IFNβ-1a 44µg** | **Alem-tuzumab** | **Inc costs (£)** | **Inc QALYs** | **ICER (£) inc (QALYs)** |
| ERG preferred base | 7.5587 | 9.9445 | 2.3858 | 394,913 | 340,459 | -1655 | 1.942 | -852 |
| Treatment effect duration[a] | 7.5062 | 9.1924 | 1.6862 | 396,181 | 355,870 | 10236 | 1.399 | 7,319 |
| Treatment Withdrawal [b] | 7.5587 | 8.7824 | 1.2237 | 394,913 | 367,707 | 2328 | 1.020 | 2,283 |
| Transition probability[c] | 8.2889 | 10.7175 | 2.4286 | 369,922 | 316,338 | -784 | 1.909 | -411 |
| SAD as for SC IFNβ-1a 44µg | 7.5587 | 8.0910 | 0.5323 | 394,913 | 375,730 | 27471 | 0.552 | 49,794 |

[a] using waning effect of years 6-9 75%, 10+ 50%
[b] using treatment withdrawal for alemtuzumab equal to that for SC IFNβ-1a 44µg
[c] using 50% reduced transition probabilities
[d] using SAD for alemtuzumab equal to that for SC IFNβ-1a 44µg