Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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alemtuzumab, 12mg, concentrate for solution for infusion (Lemtrada®)

SMC No. (959/14)

Genzyme

04 April 2014 *(Issued 06 June 2014)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

alemtuzumab (Lemtrada®) is accepted for use within NHS Scotland.

Indication under review: For adult patients with relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Two phase III studies comparing alemtuzumab with interferon beta-1a in treatment-naive (CARE-MS I) and treatment-experienced (CARE-MS II) patients with relapsing remitting multiple sclerosis both showed a statistically significant relative decrease in relapse rate of 55% and 49% respectively in favour of alemtuzumab. There was a significant reduction in the risk of sustained accumulation of disability over 6 months of 42% in CARE-MS II, but for CARE-MS-I, this was not statistically significant.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 July 2014

Indication

For adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Dosing Information

The recommended dose of alemtuzumab is 12mg per day administered by intravenous infusion for two treatment courses[1]:

- Initial treatment course: 12mg per day for five consecutive days (60mg total dose).
- Second treatment course: 12mg per day for three consecutive days (36mg total dose) administered 12 months after the initial treatment course.

Patients should be pre-treated with corticosteroids immediately prior to alemtuzumab administration on each of the first three days of any treatment course. In clinical trials patients were pre-treated with 1000mg of methylprednisolone for the first three days of each alemtuzumab treatment course. Additionally, pretreatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered. Oral prophylaxis for herpes infection should be administered to all patients on the first day of each treatment course and continuing for a minimum of one month following treatment with alemtuzumab. In clinical trials, patients were administered aciclovir 200mg twice a day or equivalent.

Alemtuzumab should be initiated and supervised by a neurologist experienced in the treatment of patients with multiple sclerosis (MS)[1].

Product availability date

May 2014

Summary of evidence on comparative efficacy

Multiple sclerosis (MS) is a disease of the central nervous system where white matter within the brain or spinal cord becomes inflamed and then destroyed by the immune system. The relapsing remitting form (RRMS), occurring in 80% of people at presentation, is characterised by periods of good health or remission which are followed by sudden symptoms or relapses. The aim of treatment is to reduce the frequency and severity of relapses, reduce lesions, slow down physical disability and maintain and improve quality of life.

Alemtuzumab is a humanised monoclonal antibody directed against CD52, a surface antigen present at high levels on T- and B- lymphocytes. The mechanism of action of alemtuzumab in MS is not fully understood but treatment results in a rapid and long-lasting depletion of circulating T- and B-lymphocytes, with gradual repopulation over time. Repopulation of B-lymphocytes is usually complete within 6 months, but repopulation of T-lymphocytes occurs over a longer period and in most patients remain below baseline levels at 12 months after each treatment course.[1]

The clinical evidence in treatment-naive patients with RRMS was derived from one phase III randomised, rater-blinded study (CARE-MS I[2]) and one phase II, randomised, rater-blinded study (CAMMS223[3]). Both studies recruited patients aged 18 to 50 years with a diagnosis of RRMS according to McDonald criteria and a score of ≤3.0 on the Expanded Disability Status Scale (EDSS). Patients in CARE-MS I had a disease onset of 5 years or less and those in CAMMS223 had an onset of 3 years or less. In CARE-MS I, patients had to have had two or more relapses in the previous two years including one relapse in the previous year; and cranial abnormalities on magnetic resonance imaging (MRI) that were attributable to MS. In CAMMS223, patients had to have two clinical episodes in the previous two years and one or more enhancing lesions on cranial MRI. In both studies, previous treatment for MS apart from corticosteroids was not permitted.

In CARE-MS I, patients were randomised 2:1, stratified by study site, to receive alemtuzumab 12mg intravenous infusion once daily for five days at baseline and for three days at 12 months; or interferon beta-1a 44µg subcutaneously three times per week after titration. Patients and treating physicians were aware of the treatment allocation, but blinded reviewers assessed EDSS every three months and when a relapse was suspected. The co-primary outcomes were relapse rate and time to sustained accumulation of disability for 6 months (6-month SAD). Relapse was defined as new or worsening neurological symptoms attributed to MS, lasting at least 48 hours without pyrexia, occurring after at least 30 days of clinical stability, with an objective change in neurological examination assessed by a blinded reviewer. Six-month SAD was defined as an increase from baseline of at least one EDSS point (or ≥1.5 points if baseline EDSS score was 0) confirmed over six months. After 24 months, 22% (82/376) of patients in the alemtuzumab group had a relapse, compared with 40% (75/187) of patients in the interferon beta-1a group; rate ratio: 0.45 (95% confidence interval [CI] 0.32 to 0.63), p<0.0001. There was no significant difference in 6-month SAD between the two treatment groups: 8% (30/376) of patients in the alemtuzumab group had 6-month SAD, compared with 11% (20/187) of patients in the interferon beta-1a group: hazard ratio [HR] 0.7 (95% CI: 0.40 to 1.23), p=0.22.[2]

In the phase II study, CAMMS223, patients were randomised equally to alemtuzumab 12mg per day per cycle; alemtuzumab 24mg per day per cycle; or interferon beta-1a 44µg subcutaneously three times per week after dose escalation. Alemtuzumab was administered on five consecutive days during the first month and on three consecutive days at months 12 and 24 (the latter at the treating physician's discretion if the CD4+ T-cell count was ≥100x10^6 cells per litre). The co-primary outcomes were time to 6-month SAD and rate of relapse. Over the 36 month study period, 21% (24/112) of patients in the alemtuzumab 12mg group had a total of 34 relapses, compared with 41% (45/111) of patients in the interferon beta group (total number of relapses: 89); hazard ratio 0.31 (95% CI: 0.18 to 0.52), p<0.001. 8.5% (8/112) of patients in the alemtuzumab 12mg group had 6-month SAD compared with 26% (24/111) in the interferon beta-1a group; HR: 0.25; 95% CI: 0.11 to 0.57).[3]

The clinical evidence in treatment-experienced patients derives from one phase III randomised, rater-blinded study (CARE-MS II[4]) in adult patients with RRMS who had relapsed despite first-line treatment with interferon beta or glatiramer acetate. Eligible patients were aged 18 to 55 years with RRMS according to McDonald criteria, an EDSS score of ≤5.0, and a disease duration of ≤10 years, with at least two relapses in the previous two years and one relapse in the previous year; at least one relapse had to have occurred while on interferon beta or glatiramer acetate after at least six months of treatment.[4] Patients were randomised in a ratio of 2:2:1, stratified by study site, to receive alemtuzumab 12mg per day per cycle, alemtuzumab 24mg per day per cycle (administered in the same schedule as in CARE-MS I) or interferon beta-1a 44µg subcutaneously three times per week after dose titration. The co-primary outcomes were relapse rate and time to 6-month SAD, defined as for CARE-MS I. Over the 24-month study period, 35% (147/426) of patients in the alemtuzumab 12mg group had a relapse, compared with 51% (104/202) of patients in the interferon beta-1a group; a risk reduction of 49% (HR: 0.51; 95% CI: 0.39 to 0.65).[4] The proportion of patients with 6-month SAD was 13% (54/426) for the alemtuzumab 12mg group and 20% (40/202) for the interferon beta-1a group, a risk reduction of 42% (HR: 0.58; 95% CI: 0.38 to 0.87).[4]

An open-label extension study (CAMMS03409[5]) is ongoing to examine the long term safety and efficacy of alemtuzumab in patients who participated in one of the three studies described above. The study began in August 2009 and is due to complete in February 2016. Results for patients entered into the extension study from CARE-MS I and CARE-MS II have been published in abstract form and provide data up to three years of follow-up.[6] The annualised relapse rate (ARR) after 3 years was 0.24 for patients who were previously treated with alemtuzumab 12mg in CARE-MS I and 0.25 for patients previously treated with alemtuzumab 12mg in CARE-MS II; these results are consistent with the ARR that was reported for alemtuzumab 12mg in CARE-MS II at 2 years (0.26)[4] and slightly greater than that for alemtuzumab 12mg at 2 years in CARE-MS I (0.18).[2]

Summary of evidence on comparative safety

Safety data were pooled from the three active comparator studies CAMMS223, CARE-MS I and CARE-MS II and from the extension study CAMMS03409. Overall, 919 patients received alemtuzumab 12mg and 496 patients received interferon beta 1a.[7] The proportion of patients who had any adverse event was 98% for alemtuzumab 12mg and 95% for interferon beta-1a.[7]

The most important adverse reactions for alemtuzumab are autoimmunity (including thyroid disorders, immune thrombocytopenic purpura (ITP), nephropathies and cytopenias), infusion-associated reactions (IARs) and infections.[1]

In the pooled studies, thyroid disorders were reported more frequently for alemtuzumab 12mg than for interferon beta-1a (17% versus 5.2%).[7] Over 48 months of follow-up from initial exposure to alemtuzumab 12mg, the estimated incidence of thyroid disorders was 36%. The most commonly reported thyroid disorders were hypothyroidism, hyperthyroidism and thyroiditis. Most thyroid events were managed with conventional medical therapy, although a few patients required surgical intervention.[7]

ITP was reported more frequently in alemtuzumab- treated patients than interferon beta-1a. In patients receiving alemtuzumab, ITP occurred in two patients (1.9%), three patients (0.8%) and three patients (0.7%) respectively for CAMMS223[3], CARE-MS I[2] and CARE-MS II[4], compared with one patient (0.9%) receiving interferon beta-1a in CAMSMS223 and none in CARE-MS I or CARE-MS II. One patient receiving alemtuzumab in CAMMS223 died as a result of ITP. In CARE-MS I, agranulocytosis occurred in two patients (0.5%) who received alemtuzumab 12mg (none for interferon beta-1a). Pooled safety data showed that nephropathies were reported in five (0.4%) patients who received alemtuzumab 12mg.[7]

Due to the potential for autoimmune adverse reactions, the summary of product characteristics (SPC) for alemtuzumab recommends that thyroid function tests should be obtained before starting treatment, and then monitored every three months afterwards until 48 months after the last infusion. Complete blood count with differentials, and serum creatinine and urinalysis with microscopy should be obtained before starting treatment, and then monitored monthly until 48 months after the last infusion.[1]

IARs were defined as any event occurring within 24 hours of infusion, and these occurred in 98% of patients in CAMMS223 and 90% of patients in CARE-MS I and CARE-MS II who received alemtuzumab 12mg, of which 1.9% and 3% respectively were serious[2,3,4]. The majority of IARs may be due to cytokine release during infusion.[1] IARs most frequently involved headache, rash, pyrexia and nausea.[2,4] The SPC recommends that patients should be pre-treated with corticosteroids immediately before alemtuzumab administration for the first three days of each treatment course. Antihistamines and/or antipyretics may also be considered for pre-treatment.[1]

In pooled data infections were reported more frequently in alemtuzumab 12mg-treated patients than those who received interferon beta-1a (71% versus 53%), of which the majority were non-serious (for the alemtuzumab 12mg groups, 1.9% and 3.7% of infections were serious in CARE-MS I and CARE-MS II respectively). The most commonly reported infections in CARE-MS I and CARE-MS II were nasopharyngitis, urinary tract infections, upper respiratory tract infections and herpes virus infections.[2,4] The SPC recommends that oral prophylaxis for herpes infection should be administered to all patients on the first day of each treatment course and continued for at least one month.[1]

The SPC states that, as with other immunomodulatory therapies, caution should be exercised in initiating alemtuzumab in patients with pre-existing and/or ongoing malignancy.[1] In CARE-MS 1, two patients in the alemtuzumab group developed thyroid cancer (none in interferon beta-1a group).[2] In CARE MS-II, two patients (one in the alemtuzumab 12mg group and one in the interferon beta-1a group) developed basal cell carcinoma; one patient in the alemtuzumab 12mg group developed thyroid cancer and one patient in the interferon beta-1a group developed acute myeloid leukaemia.[4]

Summary of clinical effectiveness issues

Alemtuzumab is a humanised monoclonal antibody acting against lymphocytes that causes long-term immunomodulation. It is licensed for the treatment of adult patients with RRMS with active disease defined by clinical or imaging features.[1] The submitting company has requested that SMC considers alemtuzumab in line with its licensed indication and has suggested that initially, most use will be in patients with more highly active RRMS, including as an alternative to natalizumab or fingolimod; but has also stated that alemtuzumab may be used in place of interferons or glatiramer acetate, including first-line use. Current first-line treatments for RRMS include subcutaneous or intramuscular interferon beta (any type), subcutaneous glatiramer acetate or oral teriflunomide. Natalizumab has been accepted for use within NHS Scotland for rapidly evolving severe disease and fingolimod has been accepted for use in patients with highly active disease despite treatment with interferon beta.

The clinical evidence included two phase III active comparator studies in patients with RRMS, one in treatment-naive patients (CARE-MS I) and one in patients who had experienced relapse despite treatment with interferon beta or glatiramer acetate (CARE-MS II). Both studies compared alemtuzumab with interferon beta-1a over a study period of 24 months for the co-primary endpoints of relapse rate and time to 6-month SAD. In both studies, alemtuzumab significantly improved the rate of relapse by 55% and 49% respectively. There was a statistically significant reduction in the risk of 6-month SAD in CARE-MS II of 42%, but for CARE-MS I the reduction in the risk of 6-month SAD was not statistically significant. A phase II study in treatment-naive patents (CAMMS 223), which was similar in design to CARE-MS I showed a 69% reduction in the risk of relapse for alemtuzumab 12mg compared with interferon beta-1a, over a 36-month study period, and a reduction in the risk of 6-month SAD of 75%, which was statistically significant.

The submitting company performed a meta-analysis of the three studies discussed above and presented the results in their submission. However, as acknowledged by the company, there were differences in the patient populations between the studies in terms of previous treatment and length of time since diagnosis of MS, so the validity of this approach is uncertain.

Due to unfeasibility of masking the treatments, all three studies were “rater-blinded”, with both patients and treating physicians aware of the treatment allocations. This is a potential source of bias and it is notable that in all three studies there was a higher drop-out rate in the interferon beta groups than the alemtuzumab groups. Another potential source of bias in the CARE-MS II study is that a large proportion of patients had previously received treatment with interferon beta, the comparator treatment.[4]

The submitting company has asked SMC to consider the use of alemtuzumab both as an alternative to fingolimod or natalizumab, and for first-line treatment as an alternative to interferon beta or glatiramer acetate. Interferon beta is an appropriate comparator to support first-line use, but not for the company's proposed positioning as an alternative to fingolimod or natalizumab. There are no direct comparative data with glatiramer acetate.

A mixed treatment comparison (MTC) of alemtuzumab with other disease-modifying treatments (DMTs) used for RRMS for the outcomes of annualized relapse rate (ARR), 3-month SAD and hazard ratio for treatment discontinuations. The base-case MTC included 30 studies from 2000 onwards with ≥80% of the patient population having RRMS. The MTC was generally well-conducted, but the outcome of discontinuations showed greater heterogeneity between studies than the other outcomes, so the conclusion for treatment discontinuations is less certain. However, due to the short treatment course and sustained treatment effect of alemtuzumab, the validity of comparing discontinuations for alemtuzumab with other DMTs is uncertain.

There are no studies directly comparing alemtuzumab with either fingolimod or natalizumab. To support the proposed positioning as an alternative to fingolimod or natalizumab, the company presented sub-group analyses of the base case MTC in patients who would be eligible for fingolimod or natalizumab in NHS Scotland. However, there were a number of important limitations in the subgroup analyses. Specifically, there was no description of the selection criteria for the studies included in the subgroup analyses, and the relevant subgroups could not be accurately defined in all the constituent studies due to variations in the reporting of baseline criteria (e.g. MRI data), so different criteria were used to select the sub-populations from the constituent studies and the sample size of the subgroups was not known for all the included studies. The credible intervals for the results of the subgroup analyses were very wide, so comparisons with the base case results is of uncertain validity. Due to the limitations in identifying the relevant sub-groups and the uncertainty in the estimate of the results, the effectiveness of alemtuzumab in patients who would be eligible for treatment with fingolimod or natalizumab is unknown.

It is not clear where alemtuzumab would fit in the current treatment pathway for MS. The clinical evidence demonstrated superior efficacy of alemtuzumab compared with interferon beta-1a in treatment-naive patients in terms of relapse rate, but the result for accumulation of disability was not statistically significant in the phase III study in these patients. The Committee for Medicinal Products for Human Use (CHMP) noted this may have been due to a lower than expected disability progression in the interferon-beta group.[7] The evidence in treatment-experienced patients is limited in terms of the appropriateness of the comparator, and the fact that the majority of the patients in the phase III study had previously received interferon beta-1a. Clinical experts consulted by SMC have indicated that alemtuzumab is likely to be used as a second or third line treatment, or in patients with highly active disease.

There are a number of potentially serious safety concerns with this medicine, so risk/benefit considerations are important for patients and physicians before starting treatment. Although the treatment course is short, patients must be monitored for a period of four years after the last infusion. Patients treated with alemtuzumab must be given the Patient Alert Card and Patient Guide and be informed about the risks of alemtuzumab. Due to the long-lasting effects of the medicine, adverse events would require active management. There are resource and planning implications for the service in terms of monthly clinic visits and monitoring, and the management of adverse events.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted a cost utility analysis over a 50 year time horizon comparing alemtuzumab to interferon-beta1a 44µg for the treatment of adult patients with RRMS with active disease defined by clinical or imaging features. Subgroup analyses were also provided comparing alemtuzumab with fingolimod (in patients with highly active RRMS) and natalizumab (in rapidly evolving severe MS). There is some uncertainty surrounding the positioning of alemtuzumab in the treatment pathway. SMC clinical experts have indicated that natalizumab or fingolimod may be the treatments most likely to be displaced.

A Markov model which consisted of 20 health states was used in the analysis. In each annual cycle, patients were capable of remaining in the same EDSS health state, progressing to a higher or lower EDSS state or converting to secondary progressive multiple sclerosis. In terms of relapse, patients in the model may relapse throughout progression from EDSS 0 to 10; therefore each EDSS state is associated with a different relapse rate. The model differentiates between relapses which lead to hospitalisation and those that do not in order to account for the difference in cost and quality of life loss.

The clinical evidence used in the economics came from the pooled results of the phase II CAMMS 223 and phase III CARE MS I and CARE MS II studies described above. Transition probabilities were derived from the pooled results and then extrapolated in the model while patients were on active disease modifying treatment (until EDSS health state 7). A MTC was carried out to compare alemtuzumab with other disease modifying treatments used for RRMS; this included other interferon treatments, glatiramer acetate, fingolimod and natalizumab. Two subgroup analyses were also conducted comparing alemtuzumab to fingolimod in patients with highly active RRMS and alemtuzumab to natalizumab in patients with RES.

A range of costs were included such as drug acquisition costs, monitoring costs, administration costs and adverse event costs. The monitoring costs consisted of various biochemistry tests, as well as full blood count and neurology visits. Disease management costs by EDSS state were also included in the analysis and were based on the estimates used in a UK published study. The cost of retreatment with alemtuzumab was included. A retreatment rate of 19.2% was applied in year 3 with lower rates applied in subsequent years.

The company combined utility values from two sources. Utility values from a randomised controlled trial comparing teriflunomide to interferon were used up to EDSS 6. Values for higher EDSS states were supplemented using utility values from another published UK study, which was a cross-sectional study in people with MS, to estimate the utility associated with disease, functional status and relapse. Disutilities due to adverse events were also included.

The base case cost per quality-adjusted life year (QALY) was estimated to be £209 based on an incremental cost of £320 and an incremental QALY gain of 1.536. Based on the results of the subgroup analysis, the company estimated alemtuzumab to be the dominant treatment when compared with fingolimod (i.e. less costly and more effective). Treatment with alemtuzumab resulted in savings of £30,697 and a QALY gain of 0.922. A patient access scheme (PAS) is in place in NHS Scotland for fingolimod and analysis was also provided which incorporated the relevant PAS price for fingolimod. For the comparison with natalizumab the results indicated alemtuzumab to be dominant with savings of £62,461 and an incremental QALY gain of 1.791.

The main issues were:

- The company has presented the economic case versus beta-interferon 1a 44µg, as direct clinical evidence exists for this comparison. However, SMC clinical experts indicate natalizumab or fingolimod may be the more relevant comparators. Therefore there may be a mismatch between the direct clinical data and where clinicians consider alemtuzumab will be used in practice.

- There were a number of issues with the way the clinical evidence was used in the economic analysis, primarily related to the pooling of the trial data. It could be argued that including the results of the phase II study in the economic model may overestimate the benefits of alemtuzumab. In addition, for the comparison with interferon it would be more appropriate to base this analysis on data from treatment naive patients only. Using only CARE MS I data resulted in an incremental cost-effectiveness ratio (ICER) of £3,576 per QALY.

- A key assumption in the model is that patients continue to receive benefit with alemtuzumab over the model time horizon while on active treatment. However, it was also assumed that only a small proportion of patients would require retreatment in order to maintain the same level of efficacy. Sensitivity analysis indicated the results were sensitive to this assumption. Reducing the time horizon to 20 years increased the ICER to £9,292 per QALY and when the treatment effect was reduced by 25% after 2 years and 50% after 5 years the ICER increased to £10,827 per QALY.

- Base case results were sensitive to retreatment rates so SMC clinical experts were asked to comment on the appropriateness of the retreatment rates used in the analysis. Overall responses were mixed, which indicates there is some uncertainty about the proportion of patients who would be retreated with alemtuzumab (or another disease modifying therapy) in practice. Alternative retreatment rates were examined in the sensitivity analysis. Assuming a retreatment rate of 19.2% in years 3+, increased the ICER to £8,526 per QALY.

- The disease management costs appear high in comparison with other MS submissions. This may bias the analysis in favour of alemtuzumab, as the cost offsets from patients moving to worse health states may be overestimated. When disease costs were reduced by 40% the ICER increased to £8,194 per QALY.

- As noted above, there were weaknesses with the subgroup analysis on which the comparisons with natalizumab and fingolimod are based. Alemtuzumab was associated with a QALY gain versus fingolimod and natalizumab despite equal outcomes for both SAD and ARR. The company clarified that the QALY gain was due to continuation of the treatment effect, even when patients receiving alemtuzumab stopped treatment. This is due to the way in which alemtuzumab treatment is delivered compared with fingolimod and natalizimab which are on-going treatments. However, there is some uncertainty regarding the assumption of continued benefit.

In order to determine a more plausible ICER, the company was asked to provide a revised base case analysis versus beta-interferon1a 44µg, which incorporated the key uncertainties outlined above. This was subsequently provided and showed that the ICER remained below £30k per QALY when more conservative assumptions were used.

In relation to the analyses versus fingolimod and natalizumab, the company was asked to provide additional sensitivity analyses to test the assumption of continued benefit and also assume a higher retreatment rate. For the comparison with natalizumab, alemtuzumab remained the dominant

treatment when the time horizon was reduced to 30 years, treatment benefit was assumed to reduce by 50% after year 5, and the retreatment rate was assumed to be 20%. For the comparison with fingolimod the results were more uncertain, but the ICER remained below £30k per QALY in the majority of scenarios except when more extreme assumptions were used.

The Committee considered that the additional sensitivity analysis provided by the submitting company helped to address a number of the weaknesses identified with the analysis. Therefore, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A submission has been received from the MS Society Scotland, which is a registered charity.
- The MS Society has received funding from several pharmaceutical companies in the last two years.
- The submission notes that MS is an incurable progressive disease with devastating effects on the lives of patients, carers, and families, as evidenced by patients' experience. Symptoms are often distressing and debilitating and can include intense pain, problems with mobility and coordination, severe depression, deadening fatigue, incontinence and loss of vision.
- MS can also have a significant emotional and financial impact on patients, carers and family members.
- Most currently available disease modifying agents are administered by injection, which can be a severe drawback because of practical problems with repeated injections and the resulting side effects. Even with these treatments, the capacity of patients to continue a near normal life and to remain in work is severely impaired.
- Alemtuzumab offers an innovative alternative to current practice in reducing the frequency and visibility of treatment, enabling patients to have more freedom and potentially remain in work.

Additional information: guidelines and protocols

The Association of British Neurologists published consensus guideline: Revised (2009) Guidelines for Prescribing in Multiple Sclerosis. These guidelines recommend treatment with interferon beta or glatiramer acetate in patients with relapsing remitting MS.[8]

NICE published clinical guideline 8: Multiple sclerosis: management of multiple sclerosis in primary and secondary care in November 2003, which recommends that patients with relapsing remitting MS should be offered interferon beta (any type) or glatiramer acetate within the 'risk sharing' scheme if the following criteria are met: can walk 100m or more without assistance; have had at least two clinically significant relapses in the last two years; are aged 18 years or older; and do not have any contra-indications to treatment.[9]

The Health Technology Board for Scotland (HTBS) published the following statement in January 2002: The Health Technology Board for Scotland welcomes the Risk Sharing Scheme for beta interferons and glatiramer acetate, announced by the Scottish Executive. We are pleased that this is based on the National Institute for Clinical Excellence (NICE) recommendation to work with manufacturers to secure these medicines for patients in a cost effective manner. In light of the exceptional circumstances created by the Risk Sharing Scheme, HTBS and the Scottish Executive have agreed that HTBS will not provide a Comment on the NICE Technology Appraisal Guidance No 32: Beta interferons and glatiramer acetate for the treatment of multiple sclerosis. This decision was taken after careful consideration of the needs of patients and health professionals in Scotland. As the Health Department Letter detailing the Risk Sharing Scheme addresses the implications for Scotland, we believe further authoritative advice in the form of an HTBS Comment is not only unnecessary, but may cause unhelpful confusion at this time. HTBS will work to ensure that the Scottish data from the Risk Sharing Scheme is taken into account in future advice to NHS Scotland on these treatments.[10]

Additional information: comparators

Interferon beta, glatiramer acetate, teriflunomide, fingolimod, natalizumab.

Cost of relevant comparators

Drug	**Dose Regimen**	**Cost per year (£)** **Cost per course (£)**
Alemtuzumab	Initial course: 12mg iv infusion for 5 days; second course one year later: 12mg iv infusion for 3 days.	35,225 in year 1 21,135 in year 2
Fingolimod	0.5mg orally once daily	19,110
Natalizumab	300mg iv infusion once every 4 weeks	14,690
Teriflunomide	14mg orally once per day	13,492
Interferon beta-1a (Rebif®)	44 micrograms (12 million units) by subcutaneous injection three times a week	10,572
Interferon beta-1a (Avonex®)	30 micrograms (6 million units) by intramuscular injection once a week	8,502
Interferon beta-1b (Betaferon®)	250 micrograms (8million units) by subcutaneous injection every other day	7,239
Interferon beta-1b (Extavia®)	250 micrograms (8million units) by subcutaneous injection every other day	7,239
Glatiramer acetate	20mg by subcutaneous injection every day	6,681

Doses are for general comparison and do not imply therapeutic equivalence. Costs for Rebif, Betaferon and Extavia assume a fixed dose per year and do not take into account the initial dose titration. Costs for interferons from eVadis on 24/01/2014; cost for glatiramer acetate and teriflunomide from MIMS on 06/02/14; costs for alemtuzumab from the company submission document.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 3,678 in year 1 and 4,129 in year 5. The uptake rate was estimated to be 0.4% in year 1, rising to 13% in year 5.

The gross impact on the medicines budget was estimated to be £518k in year 1 and £10.8m in year 5. As other drugs were assumed to be displaced, the net drug budget impact was estimated to be £296k in year 1 rising to £2.4m in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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9. National Institute for Health and Care Excellence, Clinical Guideline 8. Management of multiple sclerosis in primary and secondary care, 2003.Multiple sclerosis

10. Healthcare Improvement Scotland, NICE Technology Appraisal Guidance No.32. Beta interferons and glatiramir acetate for the treatment of multiple sclerosis; HTBS statement on risk sharing scheme. Appraisal Guidance No 32: Beta interferons and glatiramer acetate for the treatment of multiple sclerosis

This assessment is based on data submitted by the applicant company up to and including 19 March 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.