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 Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**teriflunomide (Aubagio®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of adults with relapsing remitting multiple sclerosis (MS).

**SMC restriction:** as an alternative to treatment with interferon beta or glatiramer acetate. Teriflunomide is not expected to be used for the treatment of patients with highly active disease.

In two phase III, randomised, double-blind, placebo-controlled, parallel-group studies in adult patients with relapsing MS, teriflunomide significantly reduced the annualised relapse rate. In a phase III, randomised, single-blind, parallel-group study, teriflunomide showed similar efficacy to interferon beta.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of teriflunomide. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,**  
**Scottish Medicines Consortium**
**Indication**
Treatment of adults with relapsing remitting multiple sclerosis (MS).

**Dosing Information**
14mg orally once daily. Treatment should be initiated and supervised by a physician experienced in the management of MS.

**Product availability date**
04 February 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 onset, 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. Treatments for RRMS include subcutaneous or intramuscular interferon beta (any type) or subcutaneous glatiramer acetate, available through a risk-sharing scheme established in 2002.

Teriflunomide is the main metabolite of the disease-modifying anti-rheumatic drug leflunomide. It acts on the immune system by inhibition of the enzyme dihydroorotate dehydrogenase, which is required for de novo pyrimidine synthesis. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of teriflunomide in its licensed indication as an alternative to interferon beta or glatiramer acetate.

The clinical evidence included two similarly designed, phase III, randomised, double-blind, placebo-controlled, parallel-group studies (TEMSO and TOWER), and one phase III, randomised, single-blind, parallel-group, study comparing teriflunomide with interferon beta-1a (TENERE). The TEMSO and TOWER studies evaluated the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing MS. Patients were eligible if they were aged between 18 years and 55 years and met the McDonald criteria for MS and had a relapsing clinical course with or without progression. They had to have had at least one relapse during the preceding year or two relapses within the previous two years and a score of ≤5.5 on the Expanded Disability Status Scale (EDSS) and no relapses in the 60 days (TEMSO study) or 30 days (TOWER study) before randomisation. Prior or concomitant use of immunosuppressive drugs including natalizumab, cladribine and mitoxantrone were not allowed and interferons, cytokines or glatiramer acetate must have been discontinued more than four and three months before participation in the respective study. Patients were randomised equally, with stratification by EDSS score and study site, to placebo, teriflunomide 7mg or teriflunomide 14mg once daily. Study duration was 108 weeks for the TEMSO study and the TOWER study had a duration of 48 weeks to 152 weeks depending on the time of enrolment. The primary outcome was annualised relapse rate (ARR), defined as the
number of confirmed relapses per patient-year. A relapse was defined as the appearance of a new clinical sign or symptom or worsening of a previously stable (for 30 days) sign or symptom that persisted for 24 hours in the absence of fever. Confirmed relapses required an increase of one point in each of two EDSS scores or of two points in one EDSS score (excluding bowel and bladder function and cerebral function). The main secondary outcome was the proportion of patients with disability sustained for ≥12 weeks (sustained accumulation of disability [SAD]), assessed by changes in the EDSS score. The table below shows the results for the primary and main secondary outcome in the TEMSO and TOWER studies. Results are shown for teriflunomide 14mg only, since this is the licensed dose.

Table: Results of the primary and main secondary outcomes of the TEMSO and TOWER studies

<table>
<thead>
<tr>
<th></th>
<th>TEMSO</th>
<th>TOWER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=363)</td>
<td>Teriflunomide 14mg (n=358)</td>
</tr>
<tr>
<td>ARR (95% CI)</td>
<td>0.54 (0.47 to 0.62)</td>
<td>0.37 (0.31 to 0.44)</td>
</tr>
<tr>
<td>ARR relative risk reduction versus placebo</td>
<td>-</td>
<td>32%*</td>
</tr>
<tr>
<td>SAD (%) (95% CI)</td>
<td>27 (22 to 32)</td>
<td>20 (16 to 25)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>-</td>
<td>0.70 (0.51 to 0.97), p=0.03</td>
</tr>
</tbody>
</table>

* p<0.001; ARR=annualised relapse rate; SAD=sustained accumulation of disability; CI=confidence interval.

There was no significant difference in measures of fatigue or quality of life in the placebo-controlled TEMSO and TOWER studies. The TEMSO extension study included 742 patients who completed the initial phase. An interim analysis performed five years after initial randomisation indicated that the treatment effect of teriflunomide was maintained over this period.

The TENERE study compared teriflunomide with interferon beta-1a in patients aged >18 years with relapsing MS. Eligibility criteria were the same as for the TOWER study. Patients were randomised equally to oral teriflunomide 7mg (n=109) or 14mg (n=111) once daily (double-blind) or subcutaneous interferon beta-1a 44µg (open-label) (n=104) three times a week, with stratification by geographical region and baseline EDSS score. The primary composite outcome was time to failure, defined as first occurrence of confirmed relapse or permanent discontinuation for any cause. There was no significant difference in the time to treatment failure between either dose of teriflunomide and interferon beta-1a. At week 48 the cumulative percentage of estimated treatment failures was 37% in the interferon beta-1a group, compared with 33% in the teriflunomide 14mg group (p=0.60). ARR was a secondary outcome in TENERE; adjusted ARR for interferon beta-1a was 0.22 (95% CI: 0.11 to 0.42) compared with 0.26 (95% CI: 0.15 to 0.44) for teriflunomide 14mg (p=0.59). The adverse impact on fatigue was numerically but not significantly greater for interferon beta-1a than teriflunomide 14mg. Treatment satisfaction for medication was significantly improved for teriflunomide compared with interferon beta-1a for the domains of Global Satisfaction, Side-effects and Convenience.
Summary of evidence on comparative safety

In the TENERE study, the proportion of patients experiencing any adverse event was similar in all three treatment groups (96% for interferon beta-1a; 94% for teriflunomide 7mg and 93% for teriflunomide 14mg) and there were more serious adverse events reported for teriflunomide 7mg (n=12; 11%) than for interferon beta-1a (n=7; 6.9%) or teriflunomide 14mg (n=6; 5.5%).

Adverse events that occurred at a frequency of ≥10% and more frequently for teriflunomide 14mg than interferon beta-1a included nasopharyngitis (20% [n=22] for teriflunomide versus 18% [n=18] for interferon beta-1a), diarrhoea (21% [n=23] versus 8% [n=8] respectively), hair thinning (20% [n=22] versus 1% [n=1]), paraesthesia (10% [n=11] versus 8% [n=8]), and back pain (10% [n=11] versus 7% [n=7]). Adverse events that occurred less frequently for teriflunomide 14mg than interferon beta-1a included headache (16% [n=17] for teriflunomide versus 26% [n=26] for interferon beta-1a), influenza-like illness (2.7% [n=3] versus 54% [n=54] ) and alanine aminotransferase (ALT) increased (10% [n=11] versus 31% [n=31]).

The pooled safety population from placebo-controlled studies (phase II and phase III) of teriflunomide included 1,265 patients (n=421 for placebo; n=429 for teriflunomide 7mg; n=415 for teriflunomide 14mg) who were treated for up to two years. The most commonly reported adverse events in the teriflunomide 14mg group versus placebo were: diarrhoea (17.3% versus 8.3%); alopecia (14.7% versus 4.3%); nausea (14.2% versus 6.9%); ALT increased (14.0% versus 7.1%); influenza (11.8% versus 9.3%), upper respiratory tract infection (10.8% versus 9.0%); paraesthesia (10.6% versus 7.8%) and urinary tract infection (10.6% versus 9.5%).

Elevations of liver enzymes have been observed in patients receiving teriflunomide. In the pooled safety population, ALT increased up to ≤3 times the upper limit of normal (ULN) were reported in 50% (205/413) of patients in the teriflunomide 14mg group compared with 30% (124/240) of the placebo group. ALT elevations of >3 ULN and ≤5 ULN were reported in 3.9% (16/413) of patients in the teriflunomide 14mg groups compared with 3.6% (15/420) of patients in the placebo group. The summary of product characteristics (SPC) recommends that liver enzymes should be assessed before initiation of treatment, every two weeks for the first six months and every eight weeks thereafter or as indicated by symptoms and signs.

Teriflunomide has been shown to be teratogenic in animal tests. Treatment during pregnancy is contra-indicated and treatment is not recommended if a patient is planning a pregnancy. Teriflunomide has a long elimination half-life and an accelerated elimination procedure may be required, as described in the SPC.

Since teriflunomide is a metabolite of leflunomide, the safety profile of leflunomide may be pertinent when prescribing teriflunomide for MS.

Summary of clinical effectiveness issues

Teriflunomide is an immunomodulatory agent licensed for relapsing remitting MS in adult patients. The submitting company has requested that SMC considers teriflunomide as an alternative to treatment with interferon beta or glatiramer acetate including, but not exclusively, as a first-line option. Teriflunomide is administered orally once daily, in contrast to interferon or
glatiramer acetate, which are administered by subcutaneous or intramuscular injection with frequencies ranging from once daily to once weekly, depending on the product used.

The clinical evidence included two similarly-designed placebo-controlled randomised studies (TEMSO and TOWER) and one active comparator study (TENERE) in adult patients with relapsing MS. The results of the TEMSO and TOWER studies were consistent for both the primary and main secondary outcomes; teriflunomide significantly reduced ARR by 32% and 36% respectively and the proportion of patients with progression of disability was lower in patients who received teriflunomide 14mg than placebo (HR 0.70 for both studies). In the TENERE study comparing teriflunomide with interferon beta-1a, there was no significant difference in the primary outcome of time to treatment failure or in the secondary outcome of ARR between the treatment groups.

Although both placebo-controlled studies showed a relative risk reduction for the primary outcome of ARR of >30%, the adjusted ARR in both the placebo and active treatment groups was low in both studies, so that the absolute risk reduction in ARR was small (<0.2). There was no significant difference compared with placebo in measures of fatigue or quality of life, which may be of greater importance to patients living with MS. In the TENERE study, the adverse impact on fatigue was numerically but not significantly greater for interferon beta-1a than teriflunomide 14mg. Treatment satisfaction for medication was significantly improved for teriflunomide compared with interferon beta-1a in TENERE.

The TEMSO and TOWER studies only included patients up to age 55 years, so the results may not be generalisable to older patients. In the TENERE study, median age was 35 years (range 18 to 65 years). The SPC states that teriflunomide should be used with caution in patients aged ≥65 years due to insufficient data on safety and efficacy. The TEMSO study recruited patients from 2004 and 2008, so may not reflect current practice in the management of MS.

There are no studies directly comparing teriflunomide with glatiramer acetate.

There is a requirement for monitoring of liver enzymes before starting treatment and every two weeks for the first six months of treatment, which is a potential disadvantage for the patient in terms of increased clinic visits and for the service in terms of resources required for increased monitoring.

To support the economic case, the company performed a mixed treatment comparison (MTC) of teriflunomide with other disease-modifying treatments used in MS (beta-interferons and glatiramer acetate) for the outcomes of 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 relapsing remitting MS. A sensitivity analysis including all relevant studies from 1980 onwards was performed. The results of the MTC showed that there was no significant difference in efficacy between teriflunomide, the beta interferons or glatiramer acetate for ARR. For 3-month SAD, the comparison with interferon beta-1b 250μg gave the lowest hazard ratio, although none was statistically significant. Teriflunomide was superior to interferon beta-1b 250μg and glatiramer acetate for discontinuations, although the results for discontinuations were less consistent than for the other outcomes, with interferon beta-1a 44 μg appearing better than teriflunomide for discontinuations (although not statistically significant). Limitations of the MTC included heterogeneity between the studies in terms of the patient populations, baseline characteristics and outcomes. The three key outcomes of the MTC were not always well-defined in the constituent studies; in some studies these were secondary
outcomes or were inferred from other reported outcomes. In particular, the outcome of
treatment discontinuations was not well defined.

Clinical experts highlighted an unmet need for oral treatments in the management of multiple
sclerosis as alternatives used at this point in the treatment pathway are administered by
injection.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing teriflunomide, 14mg once daily
oral treatment, with a range of comparators including beta interferon 1a (Rebif® 44µg), beta
interferon 1a (Rebif® 22µg), beta-interferon 1a (Avonex® 30µg), beta interferon 1b 250µg and
glatiramer acetate 20mg over both a 1 and 2 year time horizon. The analysis focuses on the
use of teriflunomide for patients with RRMS as an alternative to treatment with beta-interferon or
Glatiramer acetate.

The clinical evidence used in the analysis was taken from both a direct study (TENERE) and a
MTC. The results of the TENERE study showed comparable efficacy between teriflunomide
and Rebif® 44µg. The MTC was used to support the assumption of comparable efficacy
between teriflunomide and both glatiramer acetate and the other interferon treatments. These
data sources supported the assumption of comparable efficacy which underpins the cost-
minimisation analysis.

The analysis included drug acquisition costs, administration costs, monitoring costs and adverse
event costs.

The submitting company estimated the following base case results:

<table>
<thead>
<tr>
<th></th>
<th>Acquisition costs</th>
<th>Total costs</th>
<th>Incremental cost teriflunomide versus comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 1</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>£13,529</td>
<td>£13,529</td>
<td>£13,979</td>
</tr>
<tr>
<td>Rebif 44µg</td>
<td>£10,572</td>
<td>£10,572</td>
<td>£11,155</td>
</tr>
<tr>
<td>Rebif 22µg</td>
<td>£7,513</td>
<td>£7,513</td>
<td>£8,095</td>
</tr>
<tr>
<td>Aggregated Rebif</td>
<td>£9,445</td>
<td>£9,445</td>
<td>£10,027</td>
</tr>
<tr>
<td>Avonex</td>
<td>£8,502</td>
<td>£8,502</td>
<td>£9,073</td>
</tr>
<tr>
<td>Betaferon</td>
<td>£7,239</td>
<td>£7,239</td>
<td>£7,812</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>£6,681</td>
<td>£6,681</td>
<td>£7,234</td>
</tr>
</tbody>
</table>

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the
Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS
Scotland. Under the PAS a simple discount was applied which reduced the cost of
teriflunomide. With the PAS, teriflunomide became a cost-effective treatment option.
The following issues were identified:

- Only one direct head to head trial was available. There was a lack of direct comparative trial data comparing teriflunomide against the other active comparators. However, the MTC was used to support the assumption of comparable efficacy.
- Adverse event costs were included in the analysis. As this is a cost minimisation analysis, adverse event costs are not expected to be included as comparable efficacy and safety is assumed. The company has subsequently provided additional sensitivity analysis excluding these costs and this had only a minor impact on the results.
- Sensitivity analysis was only provided for the comparisons with Rebif® 44µg and glatiramer acetate.

Despite these weaknesses, the economic case has been demonstrated.

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

Summary of patient and public involvement

Patient Interest Group Submissions were made from:

- The MS Society
- The MS Trust

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.

NICE published clinical guideline 8: Multiple sclerosis: management of multiple sclerosis in primary and secondary care in 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.

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.

**Additional information: comparators**

Interferon beta-1a, interferon beta-1b, glatiramer acetate. Fingolimod and natalizumab are licensed for use only in highly active disease.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide</td>
<td>14mg orally once per day</td>
<td>13,529</td>
</tr>
<tr>
<td>Interferon beta-1a (Rebif®)</td>
<td>44 micrograms (12 million units) by subcutaneous injection three times a week</td>
<td>10,572</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex®)</td>
<td>30 micrograms (6 million units) by intramuscular injection once a week</td>
<td>8,502</td>
</tr>
<tr>
<td>Interferon beta-1b (Betaferon®)</td>
<td>250 micrograms (8million units) by subcutaneous injection every other day</td>
<td>7,239</td>
</tr>
<tr>
<td>Interferon beta-1b (Extavia®)</td>
<td>250 micrograms (8million units) by subcutaneous injection every other day</td>
<td>7,239</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20mg by subcutaneous injection every day</td>
<td>6,683</td>
</tr>
</tbody>
</table>

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 01/11/2013; cost for glatiramer acetate from MIMS on 05/11/13; cost for teriflunomide from the company submission document (cost without PAS).

**Additional information: budget impact**

The submitting company estimated the population eligible for treatment to be 2,176 in year 1 rising to 2,195 in year 5.

Without PAS: The gross impact on the medicines budget was expected to be £497k in year 1 and £4m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is expected to be £220k in year 1 and £1.8m in year 5.
References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 13 December 2013.

*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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.
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.