Public Summary Document

Product: Teriflunomide, tablet, 14 mg, Aubagio ®
Sponsor: Genzyme (Sanofi-Aventis Australia Pty Ltd)
Date of PBAC Consideration: July 2013

1. Purpose of Application

The re-submission requested an Authority required listing for the initial and continuing treatment of relapsing-remitting multiple sclerosis (RRMS) in ambulatory patients who meet certain criteria.

2. Background

This was the second consideration by the PBAC.

The PBAC rejected a major submission in November 2012 due to unclear clinical benefit, lack of formal economic analysis and undetermined uptake and therefore unclear costs to the Pharmaceutical Benefits Scheme (PBS).

3. Registration Status

Teriflunomide was TGA registered on 14 November 2012 for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the progression of physical disability.

4. Listing Requested and PBAC's View

Authority required

Initial treatment, as monotherapy, of clinically definite relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients who have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years. The diagnosis must be confirmed by magnetic resonance imaging of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient. The authority will be limited to the maximum quantity and number of repeats indicated in the schedule;

Continuing treatment, as monotherapy, of clinically definite relapsing-remitting multiple sclerosis in patients previously issued with an authority prescription for this drug who do not show continuing progression of disability while on treatment with this drug and who have demonstrated compliance with, and an ability to tolerate, this therapy. Authorities will be limited to the maximum quantity and number of repeats indicated in the schedule.

Caution

Teriflunomide is a category X drug and must not be given to pregnant women or women of childbearing potential who are not currently taking reliable contraception.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The re-submission proposed that teriflunomide 14 mg tablets will provide an additional treatment option for patients with relapsing remitting multiple sclerosis (RRMS). The PBS currently lists six disease modifying treatment options. The submission placed interferon beta 1a (IFNβ-1a) intramuscular or subcutaneous injection (I.M or S.C), interferon beta 1b (IFNβ-1b) (S.C) and glatiramer (S.C) as first-line therapy in its clinical algorithm.

6. Comparator

The re-submission nominated IFNβ-1a and IFNβ-1b as comparators. The PBAC recalled that is had previously accepted that these were the appropriate comparators.

7. Clinical Trials

The submission presented the following clinical trials:

TRIALS	DESIGN (N)	COMPARATOR
TENERE teriflunomide 7 mg, 14 mg	Head to head randomised (324)	IFNβ-1a
TEMSO Teriflunomide 7 mg, 14 mg	Randomised, direct comparison (1,088)	Placebo
TOWER Teriflunomide 7 mg, 14 mg	Randomised, direct comparison trial (1,169)	placebo
MSCRG	Indirect comparison, phase III trial (301)	IFNβ-1b, placebo
PRISMS	Indirect, randomised study,4 year extension study (560)	IFNβ-1a, placebo
IFNBMSSG	Indirect comparison, 2 year core study and 5 year extension study (372)	IFNβ-1b, placebo

The re-submission included updated indirect comparisons, an additional trial (TOWER), and post-hoc analyses for TENERE, TEMSO and TOWER trials, which included RRMS patients who have had at least two relapses within the last two years. The re-submission also updated annualised relapse rate (ARR) as the primary clinical outcome.

The PBAC recalled from its November 2012 consideration of teriflunomide that it had noted exchangeability issues between TEMSO and INFβ trials regarding inclusion/exclusion criteria, baseline clinical characteristics of patients and the placebo response rates for the outcomes reported varied between the trials. The PBAC noted that the re-submission provided sub-group analyses for the teriflunomide trials including only those patients with RRMS and had at least 2 relapses in the last two years in order to address these concerns. Meta-analyses of the TEMSO and TOWER trials were used for the indirect comparison. The PBAC noted that there were still differences in baseline characteristics and placebo response rates between the subgroup of the teriflunomide trials and the INFβ trials, and considered that this diminished the reliability of the results of the indirect comparison.

The PBAC noted that the eligibility of patients in trials for INFβ and natalizumab (IFNBMSSG, MSCRG PRISMS and Co1MSSG*)* was determined by Poser criteria. McDonald criteria were subsequently adopted and were used in trials for natalizumab (AFFIRM), fingolimod (FREEDOMS), cladribine (CLARITY) and teriflunomide (TEMSO and TOWER). The PBAC considered that the different diagnostic criteria for the earlier INFβ trials made the indirect comparison with those trials difficult to interpret.

The details of the published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Indirect comparison common reference Placebo		
Teriflunomide		
TEMSO O'Connor et al.	Randomised trial of oral teriflunomide for relapsing multiple sclerosis.	N Engl J Med. 2011; 365(14):1293-1303.
Wolinsky et al.	Magnetic resonance imaging outcomes from a phase III trial of teriflunomide	Mult Scler 2013 Sep; 19(10): 1310-9
Miller et al.	Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis	Mult Scler 2012 Nov ; 18(11): 1625-32
Interferon beta-1b		
IFNBMSSG Duquette et al.	Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial	Neurology 1993; 43(4 I):655-661.
Sibley et al.	Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomised controlled trial. (5 years extension trial report)	Neurology 1995; 45(7):1277-1285
Sibley et al.	Interferon beta treatment of multiple sclerosis [reply to letters].	Neurology 1994; 44:188-190
MSCRG Jacobs et al.	A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: design and conduct of study and baseline characteristics of patients. Multiple Sclerosis Collaborative Research Group.	Multiple sclerosis (Houndmills, Basingstoke, England) 1995; 1(2):118-135.

Interferon beta-1a		
PRISMS Ebers et al.	Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/ remitting multiple sclerosis.	Lancet 1998; 352(9139):1498-1504.
The PRISMS study group.	PRISMS-4: Long-term efficacy of interferon-β-1a in relapsing MS (4 years extension trial report)	Neurology 2001;56:1628-1636
Meta-analysis		
He et al 2012	Teriflunomide for multiple sclerosis	Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD009882.

8. Results of Trials

The PBAC noted the small number of participants in the teriflunomide arm (N=111) in the ITT population of the key study, TENERE. The PBAC also noted that as in the previous submission, the ITT analysis favoured IFNβ, with a higher adjusted annualised relapse rate and more patients experiencing relapse in the teriflunomide treatment arm, though this was not statistically significant. The PBAC noted also the wide confidence intervals (RR: 1.20, 95%CI: 0.62, 2.30). The relative risk for the post-hoc subgroup (patients who experienced two or more relapses in the preceding 2 years) was 0.98 (95%CI: 0.45, 2.14). No non-inferiority margin was specified.

The PBAC considered the subgroup analyses in the PBS population i.e., patients with more than 2 relapses, and the post hoc subgroup analysis appeared to favour IFNβ. The PBAC considered it reasonable to conclude that the absolute difference in annualised relapse rate of 0.04 observed in the ITT analysis and 0.01 in the post-hoc subgroup was not clinically relevant, and that therefore the ITT analysis indicated non-inferiority of teriflunomide to INFβ.

Considering the small number of patients with 2 or more relapses in the last 2 years in the trial, the PBAC agreed that the analysis within these groups had limited statistical power.

The results of the indirect comparisons for the post-hoc subgroup of RRMS patients with at least two relapses in the last two years showed no significant differences in annualised relapse rates between teriflunomide (TEMSO and TOWER) and each of the IFNβ trials.

Substantial differences in the post-hoc subgroup annualised relapse rates were noted between the placebo arms in each of the trials. The PBAC considered that the populations in the trials were not comparable, and that the validity of the indirect comparisons was questionable.

The PBAC noted that the time to disability outcomes were reported inconsistently. The IFNβ-1b (IFNBMSSG) trial reported the proportion of patients with 3 months sustained disability progression (SDP) at the 3 year trial end point, whilst all other trials applied Kaplan-Meier analysis for time to 3 or 6 months SDP.

The individual trials did not show significant differences in disability progression, however the PBAC noted pooled TOWER and TEMSO analysis suggested improvement in 3 months

progression (HR 0.69, 95% CI 0.54, 0.89 and in subgroup with more than 2 relapses HR 0.61, 95% CI 0.46, 0.82).

Overall, the PBAC considered that although the indirect comparison was not robust, it was reasonable to conclude that teriflunomide has sufficiently similar comparative effectiveness to INFβ to conclude non-inferiority.

With regard to comparative harms, the re-submission provided updated safety data from the TOWER trial and presents additional discussion to some of the concerns raised by the PBAC previously (November 2012). The re-submission did not present safety results specific to the PBS eligible subgroup.

The re-submission claimed that the safety outcomes observed in the TOWER trial were similar to those seen in TEMSO and there were no significant new or unexpected events. However, the PBAC noted that in TOWER there were a higher percentage of patients who discontinued treatment due to treatment emergent adverse events in the teriflunomide arm (15.6%) than in TENERE (10.9%) or TEMSO (10.9%).

The PBAC noted that a higher proportion of teriflunomide patients, compared to placebo in the TOWER trial having hepatic disorders (21.8% vs. 15.1%), and that the US Federal Drug Administration (FDA) has applied a black box warning for hepatotoxicity. The PBAC noted also higher rates of bone marrow disorders (13.7% vs. 4.9%), cardiac arrhythmias (2.4% vs. 1.0%), and embolic and thrombotic disorders (1.1% vs. 0.3%) with teriflunomide compared to placebo treatment.

The PBAC noted that teriflunomide, compared to placebo was associated with higher levels of neutropenia in the TEMSO (4.5% vs. 0.6%) and the TOWER trial (9.4% vs. 2.9%), however the percentage of patients with neutropenia was not statistically significantly different between teriflunomide and interferon beta-1a in the TENERE trial (3.6% vs. 5.9%).

The most frequent treatment-related adverse events leading to permanent treatment discontinuation with teriflunomide treatment in the TEMSO trial were gastrointestinal disorders (1.8%), hair thinning (2.7%) and ALT increase (3.6%), and in the TOWER trial neutropenia (2.2%), gastrointestinal disorders (2.7%), hair thinning (1.6%), ALT increase (2.4%). Neutropenia was not identified as a reason for discontinuation in the TEMSO trial.

Overall, the PBAC concluded that teriflunomide has a different but non-inferior safety and tolerability profile to INFβ.

9. Clinical Claim

The submission claimed that teriflunomide is non-inferior to interferon β-1a and interferon β-1b. The PBAC accepted the claim.

10. Economic Analysis

The re-submission presented a cost-minimisation analysis, based on a claim of non-inferiority compared to IFNβ for annualised relapse rate outcome. Additional costs and offsets were included for adverse events, premedications, administration, and monitoring.

The PBAC noted that the equi-effective doses from the trials were teriflunomide 14 mg once daily to Rebif 42.09 mcg three times weekly to Avonex 30 mcg once weekly to Betaferon 8 million IU every second day.

The PBAC noted that none of the sensitivity analyses resulted in a cost-saving for teriflunomide. This was attributed to the higher compliance rate assumed for teriflunomide compared to interferon-beta. The submission based compliance rates on the Treatment Compliance Report, whereby the teriflunomide compliance is based on fingolimod compliance.

11. Estimated PBS Usage and Financial Implications

The submission took a market share approach, with teriflunomide expected to substitute for current RRMS drugs (interferons, glatiramer acetate (the ABCR drugs), fingolimod, natalizumab), as well as in patients who would otherwise receive no treatment.

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5. The PBAC considered this a likely underestimate.

The submission estimated a net cost to the PBS for teriflunomide of between $30 million - $60 million in year 5 of listing.

The PBAC noted the re-submission's claim of between $10 million - $30 million cost saving in Year 5 of listing. The PBAC noted the re-submission attributed the cost-saving to substitution of patients currently treated with fingolimod and natalizumab, which are both substantially more expensive than the proposed price for teriflunomide. The financial implications are to be further verified.

Overall, the PBAC did not accept the submission's estimates of utilisation and costs but noted the sponsor's willingness to engage in a risk share arrangement.

12. Recommendation and Reasons

The PBAC recommended teriflunomide 14 mg tablet as an Authority required listing for the initial and continuing treatment of relapsing-remitting multiple sclerosis (RRMS) in ambulatory patients who meet certain criteria on a cost minimisation basis to interferon β-1a and interferon β-1b.

The PBAC considered that teriflunomide is non-inferior to interferon β-1a and interferon β-1b for comparative effectiveness, with a different but non-inferior safety profile.

The PBAC noted that the equi-effective doses from the trials were teriflunomide 14 mg once daily to Rebif 42.09 mcg three times weekly to Avonex 30 mcg once weekly to Betaferon 8 million IU every second day.

The PBAC agreed that the number of teriflunomide patients was likely to be underestimated. The submission had assumed a low uptake rate and a stable market. The PBAC noted that the initial uptake for fingolimod, another oral RRMS medication, was rapid and saw a large

increase in patient numbers. The PBAC considered that as an oral formulation there was also potential for rapid uptake of teriflunomide.

The PBAC considered claims of cost-savings from reduced RRMS medication were not clearly substantiated as demonstrated by the sensitivity analysis.

The PBAC noted approximately fifty consumer comments, both from patients and prescribers, noting the clinical need for an alternative drug available in an oral formulation.

The PBAC recommended a risk share arrangement given that utilisation, based on the re-submission's estimates of patient numbers, was difficult to estimate.

The PBAC recommended under Section 101(3BA) of the *National Health Act* that teriflunomide should not be considered substitutable on an individual patient basis with any other therapies currently listed on the PBS.

Outcome
Recommended

Recommended Listing:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
TERIFLUNOMIDE				
Tablet 14 mg	28	5	Aubagio	Genzyme

Condition/Indication:	Multiple sclerosis
Restriction:	Authority required TO BE FINALISED
Treatment phase:	Initial treatment

Condition/Indication:	Multiple sclerosis
Restriction:	Authority required TO BE FINALISED
Treatment phase:	Continuing treatment

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Genzyme (Sanofi) is very pleased with the recommendation of the PBAC and is looking forward to ensuring clinicians and Australians with RRMS have access to a new oral treatment.