PUBLIC SUMMARY DOCUMENT
Product: Teriflunomide, tablet, 14 mg, Aubagio®
Sponsor: Genzyme (Sanofi-Aventis Australia Pty Ltd)
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an Authority Required listing for the initial and continuing treatment of clinically definite relapsing-remitting multiple sclerosis in ambulatory patients who meet certain criteria.

This application was considered under the TGA/PBAC parallel process. TGA Clinical Evaluator Comments and Delegate's Overview were provided during the evaluation.

2. Background

This drug had not previously been considered by the PBAC.

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 accumulation of physical disability'.

4. Listing Requested and PBAC's View

Authority required

Initial treatment 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 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.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

The submission proposed that teriflunomide 14 mg tablets will provide an additional treatment option for patients with relapsing-remitting multiple sclerosis. There are currently six disease modifying treatment (DMTs) options listed on the PBS. The proposed clinical management algorithm in the submission placed interferon beta-1a (I.M or S.C), interferon beta-1b (S.C) and glatiramer (S.C) as first line therapy. Fingolimod (capsule) can be used either in first line or second line therapy, with natalizumab (I.V) considered to be the second line therapy reserved for severe RRMS patients after failure of, or intolerance to, first line

therapy. The orally administered DMTs include fingolimod and teriflunomide.

6. Comparator

The submission nominated interferon beta-1a and interferon beta-1b as comparators. The PBAC considered this is appropriate given that interferon betas are currently the most widely used DMTs on the PBS for RRMS.

7. Clinical Trials

The submission presented one head-to-head, open labelled, randomised trial comparing teriflunomide and interferon beta-1a (TENERE) and one randomised comparative trial comparing teriflunomide and placebo (TEMSO).

The published trials presented in the submission are shown below.

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.
O'Connor et al.	A placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis: clinical efficacy and safety outcomes	*Mult Scler* (2010);16: S23 (conference abstract)
Interferon beta-1b		

Trial ID/First author	Protocol title/Publication title	Publication citation
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(4I): 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.
Jacobs et al.	Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis	*Ann Neuro* 1996;39:285-294
ME 94-103 Wroe	Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis.	*J Int Med Res.* 2005; 33(3):309-318.
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
OWIMS The Once Weekly Interferon for MS Study Group.	Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study.	*Neurology* 1999; 53(4):679-686.

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

Direct randomised evidence: Teriflunomide versus Interferon beta-1a (TENERE)

The following table summarises the results of the primary outcome of time to failure and annualised relapse rate (ARR) for teriflunomide 14 mg or 7 mg tablet daily and interferon beta-1a 44 mcg S.C three times weekly from the TENERE trial. Teriflunomide 14 mg daily is the recommended dose for RRMS treatment in the proposed PI and TGA application.

Summary statistics for primary outcome in TENERE: time to failure, annualised relapse rate (ARR) (ITT population)

Primary Outcome	TER 7 mg (N=109)	TER 14 mg (N=111)	Interferon beta-1a 44 mcg (N=104)
Time to failure			
Number of patients with failure	53 (48.6%)	42 (37.8%)	44 (42.3%)
- Relapse	46 (42.2%)	26 (23.4%)	16 (15.4%)
- Permanent treatment discontinuation	7 (6.4%)	15 (13.5%)	25 (24.0%)
- Other reason for failure[a]	0	1 (0.9%)	3 (2.9%)
Number of censored patients	56 (51.4%)	69 (62.2%)	60 (57.7%)
Hazard ratio (95% CI) vs INFβ-1a[b]	1.12 (0.75, 1.67)	0.86 (0.56, 1.31)	-
Annualised relapse rate (ARR)			
Unadjusted ARR[c]	0.43	0.27	0.22
Adjusted ARR[d]	0.41 (0.27, 0.64)	0.26 (0.15, 0.44)	0.22 (0.11, 0.42)
Relative risk	1.90 (1.05, 3.43)	1.20 (0.62, 2.30)	-
Risk difference	0.19 (0.03, 0.36)	0.04 (-0.11, 0.19)	-
P value[e]	0.034	0.590	

Abbreviations: ARR, annualised relapse rate; TER, teriflunomide; CI, confidence interval.

[a.] Includes patients who were never treated or received the wrong treatment.

[b.] Derived using the Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c.] The total number of relapses that occurred during the treatment divided by the total number of patient-years treated in the study.

[d.] Poisson model with the total number of relapses onset between randomisation date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed treatment duration as an offset variable.

[e.] Chi-square test from estimating the rate ratios.

For the primary outcome of time to failure and annualised relapse rate (ARR) of the direct, randomised TENERE trial, the PBAC noted that whilst there were no statistically significant differences in number of patients with time to failure between teriflunomide 14 mg and interferon beta-1a (37.8% vs. 42.3%), the increased number of patients who met the primary outcome due to a first relapse in the teriflunomide group was of concern (23.4% vs.15.4%). The PBAC also noted that higher ARR was observed in teriflunomide group (0.26 vs. 0.22), although the difference in ARR compared with interferon beta-1a was not statistically significant (RR: 1.20, 95%, CI: 0.62, 2.30). The PBAC considered that the overall statistical power of the TENERE trial was low and the statistical analysis relating to the primary outcomes was limited.

Indirect comparison: Teriflunomide versus Interferon beta 1a/1b

The following table summarises the indirect comparisons of annual relapse rate (ARR) between teriflunomide and interferon beta-1a/1b.

Outcome	TER	Placebo	Interferon beta	Rate Ratio (95% CI)Treatment vs placebo
TEMSO: Teriflunomide 14 mg vs Placebo				
ARR (ITT)	N=358 0.37 (0.31, 0.44)	N=363 0.54 (0.47, 0.62)	-	0.68 (0.55, 0.85)
IFNBMSSG: INF beta-1b 250 mcg S.C vs. Placebo (results at 2 years)				
ARR (ITT)	-	N=112 1.27	N=115 0.84	0.66 (0.54 0.81)
ARR (MITT)[a]	-	N=110 1.18	N=107 0.85	0.72 (0.54, 0.97)
Indirect relative rate ratio (TER vs INF beta-1b): ITT				1.04 (0.77, 1.39)
Indirect relative rate ratio (TER vs INF beta-1b): M-ITT				0.95 (0.66, 1.37)

Outcome	TER	Placebo	Interferon beta	Rate Ratio (95% CI)Treatment vs placebo
PRISMS: INF beta-1a 44 mcg S.C vs. Placebo				
Rate over 2 years (ITT)	-	N=187 2.56	N=184 1.73	0.68 (0.51, 0.89)
Indirect relative rate ratio (TER vs INF beta-1a 44 mcg S.C)				1.01 (0.72, 1.43)
MSCRG: INF beta-1a 30 mcg I.M vs. Placebo				
ARR (ITT)	-	N=187 0.82	N=158 0.67	0.82 (0.67, 0.99)
Indirect relative rate ratio (TER vs INF beta-1a 30 mcg I.M)				0.84 (0.63, 1.12)

Abbreviations: ARR, annualised relapse rate; CI, confidence interval; ITT, intention-to-treat population; M-ITT, modified intention-to-treat population; TER, teriflunomide; INF, interferon I.M, intramuscular injection; S.C, subcutaneous injection.

[a.] Result reported in Duquette et al. 1995 with a modified intent-to-treatment analysis in which all data available for any given patient to the point of study completion or dropout were used.

The PBAC noted that the indirect comparisons of ARR between teriflunomide and interferon betas (IFNBMSSG, PRISMS and MSCRG) were not statistically significant. In the subgroup analyses of patients with 4 relapses in the preceding 2 years, the differences in ARR between teriflunomide 14 mg and placebo were not statistically significant, although the results favoured teriflunomide (RR 95%CI: 0.91 (0.53, 1.56)). In patients with RRMS subtype analyses, there were statistically significant reductions in ARR for teriflunomide 14 mg (RR 95%CI: 0.66 (0.53, 0.82)).

The PBAC noted the incidence of patients with treatment emergent adverse events (TEAEs) was similar in the teriflunomide and interferon beta-1a treatment groups (7 mg teriflunomide: 93.6%; 14 mg teriflunomide: 92.7%; interferon beta-1a: 96.0%). The TEAEs associated more frequent with teriflunomide 14 mg than interferon beta-1a microgram were diarrhoea (20.9% vs. 7.9%), nausea (9.1% vs. 4.0%), hair thinning (20.0% vs. 1.0%), paraesthesia (10.0% vs. 7.9%) and back pain (10.0% vs. 6.9%). Interferon beta-1a was associated with more hepatic disorders (39.6% vs. 12.7%), bone marrow disorders (10.9% vs. 5.5%) and influenza-like illness (53.5% vs. 2.7%). More patients treated with interferon beta-1a discontinued treatment due to TEAEs (21.8% in interferon beta-1a vs. 10.9% in teriflunomide 14 mg group). Overall, the PBAC considered that the clinical importance of different safety profiles between teriflunomide and interferon betas was unclear given the small number of patients included in the teriflunomide trials and the lack of longer term data.

9. Clinical Claim

The submission described teriflunomide as non-inferior in terms of comparative effectiveness and having better tolerability and safety over interferon beta-1a and interferon beta-1b. Based on the evidence presented, the PBAC considered that there was insufficient evidence to accept the submission's clinical claim that teriflunomide is non-inferior in terms of comparative effectiveness and has better tolerability and safety over interferon beta-1a and 1b.

10. Economic Analysis

There was no economic evaluation presented for the cost-minimisation analysis. Instead calculation of a weighted ex-manufacturer price for teriflunomide price, based on the average cost/patient/day (market share) of interferon products derived from Medicare Australia pharmacy claim data, was presented. The weighted price calculation was based on the clinical claim of non-inferior efficacy of teriflunomide over interferon betas, which was

considered not adequately supported by the presented data. Analysis of the TENERE study did not include a dose response curve to establish the appropriate dose relativity between teriflunomide and interferon beta-1a. The PBAC noted that in the Pre-PBAC Response, the sponsor implicitly assumed that the equi-effective doses between teriflunomide and each of the interferons are equal to the daily treatment dosages as prescribed in the relevant Product Information, which are also identical to the dosage regimens used in all the randomised controlled trials presented in the submission.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost per year to the PBS of $50,000-100,000 in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The major submission sought an Authority Required listing for the initial and continuing treatment of clinically definite relapsing-remitting multiple sclerosis in ambulatory patients who meet certain criteria.

The submission nominated interferon beta-1a and interferon-1b as the main comparators. The PBAC agreed that these choices were appropriate.

The PBAC agreed that the requested restriction should specify that teriflunomide be used as monotherapy, according to the pivotal trial (TENERE) presented in the submission teriflunomide was not intended for use as add-on therapy for the treatment of relapsing-remitting multiple sclerosis (RRMS). The PBAC noted that although the proposed restriction required cessation of teriflunomide on disease progression, there was no definition of "disease progression" upon which to base a decision to cease treatment. The PBAC noted in the Pre-Sub-Committee Response the sponsor indicated its willingness to work with the Restrictions Working Group on appropriate wording for the restriction.

The submission presented one head-to-head, open labeled, randomised trial comparing teriflunomide 7 mg and 14 mg and interferon beta-1a 44 mcg (TENERE) and one randomised comparative trial comparing teriflunomide and placebo (TEMSO). The results of the TEMSO trial were used in the indirect comparisons of teriflunomide versus interferon beta-1b (IFNBMSSG) and interferon beta-1a (PRISMS and MSCRG) as supportive analyses, using placebo as the common reference.

The PBAC noted blinding was not possible in the TENERE trial due to the different manners of administration between teriflunomide (oral) and interferon beta-1a (subcutaneous). Further, almost half of the studied population in TENERE trial had less than or equal to 1 relapse in the preceding 2 years; the PBAC therefore considered that the trial population did not fully represent the population for whom PBS listing was sought. There were also exchangeability issues between TEMSO and interferon beta trials regarding inclusion/exclusion criteria, baseline clinical characteristics of patients and the placebo response rates for the outcomes reported varied between the trials.

For the primary outcome of time to failure and annualised relapse rate (ARR) of the direct, randomised TENERE trial, the PBAC noted that whilst there were no statistically significant differences in number of patients with time to failure between teriflunomide 14 mg and

interferon beta-1a (37.8% vs. 42.3%), the increased number of patients who met the primary outcome due to a first relapse in the teriflunomide group was of concern (23.4% vs.15.4%). The PBAC also noted that higher ARR was observed in teriflunomide group (0.26 vs. 0.22), although the difference in ARR compared with interferon beta-1a was not statistically significant (RR: 1.20, 95%, CI: 0.62, 2.30). The PBAC considered that the overall statistical power of the TENERE trial was low and the statistical analysis relating to the primary outcomes was limited.

The PBAC further noted that the indirect comparisons of ARR between teriflunomide and interferon betas (IFNBMSSG, PRISMS and MSCRG) were not statistically significant. In the subgroup analyses of patients with 4 relapses in the preceding 2 years, the differences in ARR between teriflunomide 14mg and placebo were not statistically significant, although the results favoured teriflunomide (RR 95%CI: 0.91 (0.53, 1.56)). In patients with RRMS subtype analyses, there were statistically significant reductions in ARR for teriflunomide 14 mg (RR 95% CI: 0.66 (0.53, 0.82)).

The PBAC noted the incidence of patients with treatment emergent adverse events (TEAEs) was similar in the teriflunomide and interferon beta-1a treatment groups (7 mg teriflunomide: 93.6%; 14 mg teriflunomide: 92.7%; interferon beta-1a: 96.0%). The TEAEs associated more frequently with teriflunomide 14 mg than interferon beta-1a microgram were diarrhoea (20.9% vs. 7.9%), nausea (9.1% vs. 4.0%), hair thinning (20.0% vs. 1.0%), paraesthesia (10.0% vs. 7.9%) and back pain (10.0% vs. 6.9%). Interferon beta-1a was associated with more hepatic disorders (39.6% vs. 12.7%), bone marrow disorders (10.9% vs. 5.5%) and influenza-like illness (53.5% vs. 2.7%). More patients treated with interferon beta-1a discontinued treatment due to TEAEs (21.8% in interferon beta-1a vs. 10.9% in teriflunomide 14 mg group). Overall, the PBAC considered that the clinical importance of different safety profiles between teriflunomide and interferon betas was unclear given the small number of patients included in the teriflunomide trials and the lack of longer term data.

Based on the evidence presented, the PBAC considered that there was insufficient evidence to accept the submission's clinical claim that teriflunomide is non-inferior in terms of comparative effectiveness and has better tolerability and safety over interferon beta-1a and 1b.

There was no economic evaluation presented for the cost-minimisation analysis. Instead calculation of a weighted ex-manufacturer price for teriflunomide price, based on the average cost/patient/day (market share) of interferon products derived from Medicare Australia pharmacy claim data, was presented. The weighted price calculation was based on the clinical claim of non-inferior efficacy of teriflunomide over interferon betas, which was considered not adequately supported by the presented data. Analysis of the TENERE study did not include a dose response curve to establish the appropriate dose relativity between teriflunomide and interferon beta-1a. The PBAC noted that in the Pre-PBAC Response, the sponsor implicitly assumed that the equi-effective doses between teriflunomide and each of the interferons are equal to the daily treatment dosages as prescribed in the relevant Product Information, which are also identical to the dosage regimens used in all the randomised controlled trials presented in the submission.

The PBAC noted that the estimated number of patients was based on the inappropriate assumption of 100% compliance to treatment, given the large number of discontinuations

associated with interferon therapy. The likely number of prescriptions and/or costs to the PBS were considered to be underestimated, given the uncertain market uptake rates, omission of potential uptake from fingolimod and glatiramer, the risk of use in combination with other disease modifying treatments for RRMS, and the assumption of full compliance and continuing treatment for all patients.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit, no formal economic analysis provided and uncertain uptake and hence uncertain cost to the PBS.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Reject

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 is disappointed by the recommendation but it is committed to continuing to work with the PBAC to ensure that teriflunomide is available on the PBS for people with relapsing-remitting multiple sclerosis.