

**6.02 GLATIRAMER,  
Injection containing glatiramer acetate 20 mg in 1 mL  
single dose pre-filled syringe,  
Injection containing glatiramer acetate 40 mg in 1 mL  
single dose pre-filled syringe,  
Copaxone<sup>®</sup>, TEVA Pharma Australia Pty. Ltd.**

**1 Purpose of Application**

1.1 The submission requested an Authority Required listing for glatiramer (as glatiramer acetate) for the treatment of a clinically isolated syndrome suggestive of multiple sclerosis in patients thought to be at high risk of subsequent diagnosis with multiple sclerosis.

**Table 1: Key components of the clinical issues addressed in the submission**

Component	Description
Population	Patients with a demyelinating event indicative of multiple sclerosis, including at least one clinical event and positive magnetic resonance imaging (MRI) of the brain. Other diagnoses need to have been excluded.
Intervention	Glatiramer acetate (20 mg injected subcutaneously once daily or 40 mg injected subcutaneously three times a week).
Comparator	Placebo.
Outcomes	Delayed development of multiple sclerosis, reduced subclinical measures (based on MRI) of disease activity.
Clinical claim	In patients with clinically isolated syndrome, glatiramer acetate has superior effectiveness, and inferior (but tolerable) safety to placebo in extending time to diagnosis of clinically definite multiple sclerosis.

Source: Table 1-1, p.1-9 Section 1 of the submission

1.2 There were a number of key clinical issues associated with the submission, including the patient population (definition of high risk group; use of diagnostic criteria) and outcomes (time to next relapse or time to conversion).

**2 Requested listing**

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	DPMQ	Proprietary Manufacturer	Name and
GLATIRAMER ACETATE					
20 mg/mL injection, 28 x 1 mL syringes	1	5	\$ [REDACTED]	Copaxone <sup>®</sup>	Teva Pharma Australia Pty Ltd.
40 mg/mL injection, 12 x 1 mL syringes	1	5	\$ [REDACTED]		
Category / Program:	Section 85 (general schedule)				
PBS Indication:	Clinically isolated syndrome				
Treatment phase:	Initial/continuing				

Restriction:	Authority required (STREAMLINED)
Treatment criteria:	Patient must be diagnosed by a neurologist
Clinical criteria:	<p>Patient must have had a demyelinating event that is indicative of multiple sclerosis. Other diagnoses need to have been excluded.</p> <p><u>Criteria:</u></p> <ul style="list-style-type: none"> <li>• Patient must have experienced at least 1 documented attack due to a demyelinating event (clinically isolated syndrome), <b>AND</b></li> <li>• The diagnosis must be supported by positive MRI imaging of the brain <b>AND</b></li> <li>• Patient must meet the following clinical and brain MRI criteria: <ul style="list-style-type: none"> <li>○ T2 hyperintense MRI brain lesions <math>\geq 9</math> <b>or</b> OCB positive; <b>and</b></li> <li>○ EDSS <math>\geq 2</math>; <b>and</b></li> <li>○ Brain MRI with at least one T1 GdE lesions <b>or</b> at least one T2 hyperintense MRI brain lesion in a juxtacortical <b>or</b> infratentorial <b>or</b> periventricular location.</li> </ul> </li> </ul>
Population criteria:	Patient must have had a demyelinating event that is indicative of multiple sclerosis. Other diagnoses need to have been excluded.

- 2.1 Listing was requested on the basis of a cost-utility analysis compared with placebo.
- 2.2 The proposed restriction would require additional patient characteristics to identify those thought to be at high risk of conversion to clinically definite multiple sclerosis. These criteria were based on a multivariable regression analysis conducted using a cohort of patients with clinically isolated syndrome from the MSBase multiple sclerosis database to identify patients' characteristics associated with increased risk of subsequent diagnosis with multiple sclerosis. It is unclear whether the regression model is robust enough to identify high risk patients in a clinical population. The submission claimed that internal validation was undertaken; however the results of this were not provided. The PSCR (p3) provided additional details on the statistical analysis used to identify a high risk subgroup of the MSBase population. The PSCR assumed that the validation of the published MSBasis analysis also represents validation of the MSBase analysis presented in the submission. While related, these were two separate studies that identified two different risk nomograms for patients with clinically isolated syndrome and therefore validation of MSBasis does not constitute validation of MSBase. Overall, the ESC advised that the MSBasis study appears to be a more robustly conducted analysis with prospective follow-up of patients (including data from 2004) rather than retrospective analysis of patient registry data (including data from 1993) presented for the MSBase analysis.
- 2.3 The identified model was very narrowly defined; it identified 16.8% of patients in the initial treatment naïve MSBase cohort used for the analysis, and only 7% in the PreCISe trial. The proportion of patients in the high risk group subsequently diagnosed with multiple sclerosis within a five year period was 93% compared with 85% in the complement group. The evaluation considered that use of the model will exclude patients who will benefit from treatment. The ESC noted that the submission did not adequately discuss these discrepancies in the proportion of potential eligible patients, which is likely to be an issue regarding the applicability of evidence to the defined population. The pre-PBAC response (p2) stated that the sponsor would be amenable to discussing less severe restriction criteria for the proposed PBS listing.

The PBAC was uncertain as to whether the population defined in the restriction, which was based on analysis of the MSBase dataset, was representative of patients at high risk of developing clinically definite multiple sclerosis. The PBAC agreed with the evaluation that the restriction criteria proposed by the submission may exclude patients who may benefit from treatment. The Committee also noted the submission did not propose discontinuation criteria in the restriction.

- 2.4 The risk of use outside the restriction in this population was considered to be high. The submission did not present any specific clinical evidence for treatment effect in the population eligible for treatment under the requested restriction. The key trial was based on a broader clinically isolated syndrome population and post hoc analyses in high risk subgroups were not sufficiently powered to assess the treatment effect in a population similar to the requested restriction, although the effect in these populations was generally less favourable.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

### **3 Background**

- 3.1 TGA status: glatiramer acetate 20 mg was TGA registered on 17 December 2003 for the reduction of frequency of relapses in relapsing remitting multiple sclerosis (RRMS).
- 3.2 Glatiramer acetate 20 mg was approved for registration by the TGA on 4 December 2008 for the treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent magnetic resonance imaging (MRI) lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.
- 3.3 Glatiramer acetate is currently PBS-listed for the treatment of RRMS.
- 3.4 Glatiramer acetate has not previously been considered by the PBAC for clinically isolated syndrome.
- 3.5 The PBAC has previously considered the effectiveness and safety of interferons in clinically isolated syndrome (for interferon beta-1a) and in early multiple sclerosis as defined by the McDonald criteria (for interferon beta-1b).
- Interferon beta-1a (Avonex) was considered by the PBAC in July 2004 for patients who have had a single demyelinating event at risk of developing clinically definite multiple sclerosis. The PBAC rejected the submission due to uncertain clinical benefit and the resulting uncertain and unfavourable cost-effectiveness. The PBAC expressed doubt over whether the evidence provided an adequate basis to define a high-risk patient group. The PBAC considered there was no clear evidence to support the submission's argument that early intervention can alter long-term outcomes of the disease.
  - Interferon beta-1b (Betaferon) was considered by the PBAC in March 2007 to extend the existing multiple sclerosis listing to include patients matching the McDonald criteria (allowing for a second attack in time to be defined by a new lesion appearing on MRI rather than a second clinical attack). The PBAC rejected

the submission due to the uncertain specificity of the proposed restriction and the uncertain long-term benefits and harms associated with treatment.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **4 Population and disease**

- 4.1 Clinically isolated syndrome refers to an initial clinical episode of central nervous system inflammatory demyelinating symptoms (such as optic neuritis, a brain stem and/or cerebellar syndrome, a spinal cord syndrome, or cerebral hemispheric dysfunction) lasting for at least 24 hours, accompanied by abnormal MRI scans that are suggestive of multiple sclerosis.
- 4.2 Conversion from clinically isolated syndrome to multiple sclerosis is highly variable, ranging from several months to more than 10 years, with some patients never converting to typical multiple sclerosis disease courses.
- 4.3 The proposed algorithm positioned glatiramer acetate as a first line treatment option in a subgroup of patients with clinically isolated syndrome thought to be at high risk of being diagnosed with multiple sclerosis within five years. The use of glatiramer acetate according to the requested restriction would be narrower than both the TGA indication, and that recommended by clinical treatment guidelines. The PSCR (p4) stated that, if the PBAC believes that a broader population of patients with clinically isolated syndrome should be treated, the sponsor would be amenable to discussing this. The ESC noted the use of glatiramer for clinically isolated syndrome would impact on the treatments used for RRMS.
- 4.4 The ESC noted that the submission did not discuss patient preferences in the management of clinically isolated syndrome. The ESC considered that some patients may choose not to seek treatment given the relatively lower impact on disability compared to, for example, treatment of RRMS, and that treatment is associated with adverse events such as injection site reactions.

## **5 Comparator**

- 5.1 The submission nominated placebo as the main comparator. The PBAC considered this to be the appropriate comparator.
- 5.2 The submission acknowledged that the BRACE therapies (intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b and glatiramer acetate; also referred to as ABCR therapies) are likely being used outside the current PBS restrictions for the treatment of clinically isolated syndrome. These therapies are currently TGA registered, but not PBS subsidised for clinically isolated syndrome. The submission argued that these were not secondary comparators, but were included to address issues raised in previous unsuccessful submissions for other drugs in 'early multiple sclerosis'. During the evaluation, these therapies were considered as secondary comparators given the utilisation estimates presented in

the submission predicted substantial substitution of interferons by glatiramer acetate for this patient population on the PBS.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, how the drug would be used in practice and clarified the relationship between clinically isolated syndrome and multiple sclerosis diagnosed by the McDonald Criteria or the Poser Criteria. The PBAC considered that the hearing was informative as it provided a clinical perspective on how the diagnosis of multiple sclerosis has evolved since the first treatments for relapsing-remitting multiple sclerosis were listed on the PBS, and clarified how clinically isolated syndrome and clinically definite multiple sclerosis are diagnosed in practice.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. They strongly supported PBS listing of glatiramer acetate in CIS, and all comments consistently argued that the current PBS criteria to access medicines for the treatment of multiple sclerosis were out-dated and not in step with current medical practice. The comments strongly argued that patients should be able to access effective treatments in CIS and early multiple sclerosis (MS) using the McDonald criteria rather than the current PBS restrictions.
- 6.3 The PBAC noted the advice received from MS Australia and MS Research Australia clarifying the likely use of glatiramer acetate in CIS. The PBAC specifically noted the advice that the use of glatiramer acetate was associated with a 45% reduction in risk of developing MS and time to conversion to MS prolonged by 115% in the PreCISE trial. Both organisations also stated that earlier treatment in CIS or MS provides multiple health and wellbeing benefits, such as many patients retaining their employment, reduced medical investigations, treatments and hospitalisations.
- 6.4 Representatives of the PBAC met with MS Australia prior to the PBAC meeting. The following points provide a summary of the perspectives presented by MS Australia to the PBAC representatives:
- CIS is not a well-defined patient group as many patients may not be aware that they have CIS. Commonly, patients are diagnosed as likely having or not having multiple sclerosis, rather than CIS. Therefore, the experience of MS Australia is predominately with patients who have clinically definite multiple sclerosis.
  - The population of patients diagnosed with CIS is small and both incidence and prevalence are difficult to assess, however the population may decrease over time as improvements in magnetic resonance imaging (MRI) technology allow earlier

diagnosis of clinically definite multiple sclerosis. Some patients may never progress from CIS to clinically definite multiple sclerosis.

- Patients with clinically definite multiple sclerosis and their clinicians value early treatment to slow the disease course by minimising relapses, delaying disability progression, reducing the number of new lesions and delaying brain atrophy. However, not all patients choose to adopt pharmacological treatment, with some patients preferring non-pharmacological options to manage symptoms such as through diet or exercise.
- Early treatment is particularly valued by younger patients with clinically definite multiple sclerosis, for example, the cohort of women aged 20 – 40 years, who may be planning a family and are less willing to “watch and wait”.
- The current PBS eligibility criteria for the treatment of multiple sclerosis are not aligned with the current clinical guidelines and diagnostic tools for multiple sclerosis, such as the McDonald criteria. Overall, however, patients do not report experiencing issues with a lack of access to PBS subsidised treatments.
- Anecdotally, the manner of administration of treatments (e.g. oral versus injectable) has not been a major driver of treatment choice for patients.
- Fatigue and neuropathic pain are reported as the top two symptoms impacting on patients’ quality of life; anecdotally, treatment assists patients in managing the impact of fatigue and neuropathic pain to allow improved functioning in daily living.
- Patients and clinicians value the availability of multiple treatment options that are safe, effective, affordable and represent equitable access across the spectrum of multiple sclerosis types and severities.

### ***Clinical trials***

- 6.5 The submission was based on one head-to-head trial (PreCISe) comparing glatiramer acetate to placebo, in patients with clinically isolated syndrome. Additional longer-term data were provided from the PreCISe open-label extension study.
- 6.6 The submission also included two supplementary comparisons:
- Indirect comparison of glatiramer acetate in clinically isolated syndrome (PreCISe) versus a meta-analysis of trials of intramuscular interferon beta-1a (CHAMPS, Pakdaman 2007), subcutaneous interferon beta-1a (ETOMS, REFLEX) and interferon beta-1b (BENEFIT) in clinically isolated syndrome.
  - A comparison of glatiramer acetate in clinically isolated syndrome (PreCISe) versus meta-analysis of trials of glatiramer acetate in RRMS (Bornstein et al., 1987; Johnson et al., 1995; Comi et al., 2001), to calculate the benefit: harms ratio of glatiramer acetate in these two patient populations. This comparison was considered to be largely non-informative, as it failed to take into account the underlying differences between study populations.
- 6.7 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

<b>Trial ID/First Author</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
<b>Direct randomised trials</b>		
PreCISe	A Multinational Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Early Glatiramer Acetate Treatment in Delaying the Conversion to Clinically Definite Multiple Sclerosis (CDMS) of Subjects Presenting with a Clinically Isolated Syndrome (CIS) Protocol GA/9010 (PreCISe)	February 2008
	A Multinational Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Early Glatiramer Acetate Treatment in Delaying the Conversion to Clinically Definite Multiple Sclerosis (CDMS) of Subjects Presenting with a Clinically Isolated Syndrome (CIS). Results of the long term study period (up to 5-years) following the study report of interim analysis data, issued February 2008	May 2012
	Comi, G., Martinelli, V., et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): A randomised, double-blind, placebo-controlled trial	Lancet 2009; 374(9700): 1503-1511
	Comi G and Filippi M. Treatment with glatiramer acetate delays conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS)	Neurology 2008; 71(2): 153
	Comi, G., Martinelli, V., et al. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome	Multiple Sclerosis Journal 2013; 19(8): 1074-1083
	Arnold, D. L., Narayanan, S. and Antel, S. Neuroprotection with glatiramer acetate: Evidence from the PreCISe trial	Journal of Neurology 2013; 260(7): 1901-1906
<b>Supplementary randomised trials</b>		
Pakdaman	Pakdaman, H., Sahraian, M.A., et al. Effect of early interferon beta-1a therapy on conversion to multiple sclerosis in Iranian patients with a first demyelinating event	Acta Neurologica Scandinavica 2007; 115(6): 429-431
BENEFIT	Kappos, L., Polman, C.H., et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes	Neurology 2006; 67(7): 1242-1249
CHAMPS	Jacobs, L.D., Beck, R.W., et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis	New England Journal of Medicine 2000; 343(13): 898-904
ETOMS	Comi, G., Filippi, M., et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: A randomised study	Lancet 2001; 357(9268): 1576-1582
REFLEX	Comi, G., De Stefano, N., et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (reflex): A phase 3 randomised controlled trial	Lancet Neurology 2012; 11(1): 33-41

Source: Table 2-4, pp.2-10 to 2-11 of Section 2 of the submission; Table 1-1, p.3 of 'Copaxone July 2017 Part of Attachment 7- Indirect comparisons summary', Attachment 7 of the submission.

6.8 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Glatiramer acetate versus placebo</b>						
PreCISe	481	Randomised, double-blind, placebo-controlled multi-centre trial up to 3 years + 2 year extension study	Low	Clinically isolated syndrome	Time to second clinical attack (clinically definite multiple sclerosis)	Hazard ratio
<b>Interferon versus placebo</b>						
Pakdaman	202	Randomised, double-blind, placebo-controlled multi-centre trial 3 years	Unclear	Clinically isolated syndrome	Time to second clinical attack (clinically definite multiple sclerosis)	Not used
BENEFIT	468	Randomised, double-blind, placebo-controlled multi-centre trial 2 years	Low	Clinically isolated syndrome	Time to second clinical attack (clinically definite multiple sclerosis); Time to McDonald multiple sclerosis	Not used
CHAMPS	383	Randomised, double-blind, placebo-controlled multi-centre trial Stopped after 18 month interim analysis	Low	Clinically isolated syndrome	Time to second clinical attack (clinically definite multiple sclerosis)	Not used
ETOMS	309	Randomised, double-blind, placebo-controlled multi-centre trial 2 years	Low	Clinically isolated syndrome	Time to second clinical attack (clinically definite multiple sclerosis)	Not used
REFLEX	517	Randomised, double-blind, placebo-controlled multi-centre trial 2 years	Low	Clinically isolated syndrome	Time to McDonald multiple sclerosis	Not used

Source: compiled during the evaluation

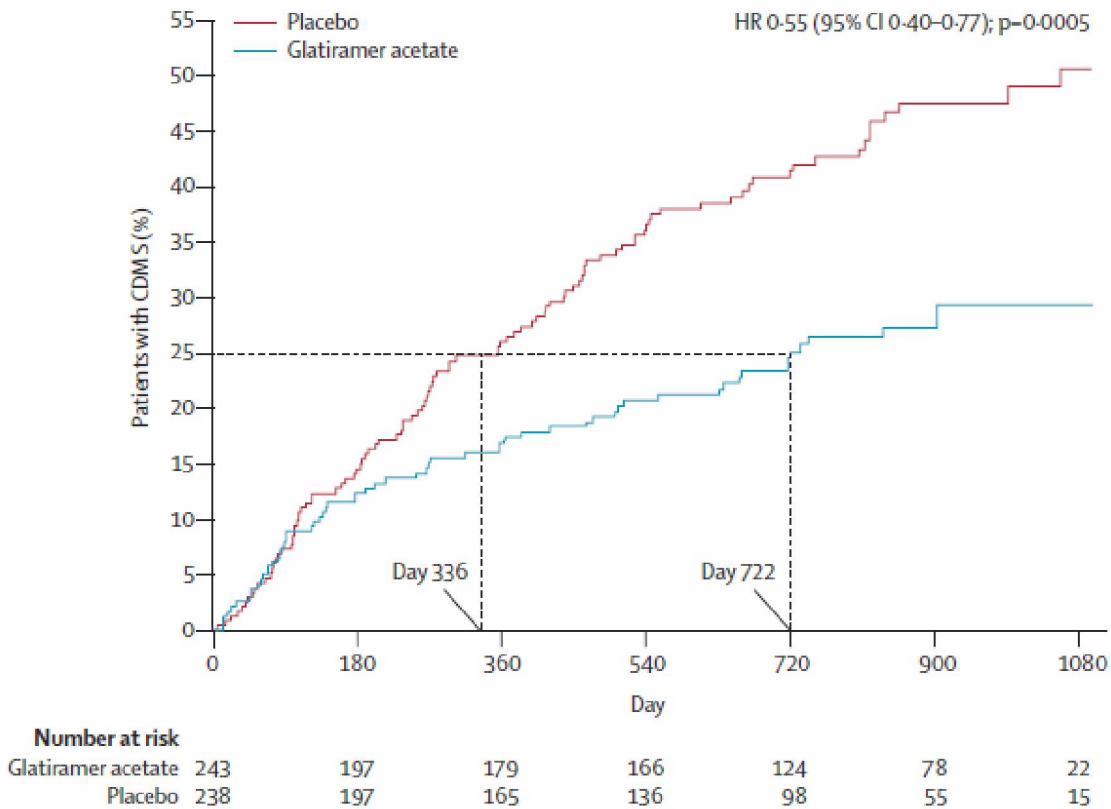
6.9 The primary efficacy outcome in the PreCISe trial was time to diagnosis with clinically definite multiple sclerosis, using the Poser (1983) diagnostic criteria. The Poser criteria require two clinical attacks more than one month apart, together with clinical evidence of lesions in two places within the central nervous system. The McDonald (2010) criteria are more likely to be used in current clinical practice; these allow for a second attack to be defined by a new lesion appearing on MRI rather than a second clinical attack. Due to the differences in these criteria, diagnosis with multiple sclerosis frequently occurs earlier under the McDonald criteria than under the Poser criteria. The PSCR (p3) stated that the Poser and McDonald criteria converge for patients with two clinical attacks, which was the endpoint in these analyses. The PSCR (p3) argued that given the complexity of the diagnosis landscape for multiple sclerosis (with multiple versions of the McDonald criteria), that a solid clinical endpoint, such as a clinical relapse, is a strong endpoint for the analysis, and is consistent with current PBS criteria for initiating therapy.

- 6.10 Whilst the primary outcome (time to next multiple sclerosis relapse) in the PreCISe trial is clinically important, it is unclear how many high risk patients may have already converted to a multiple sclerosis disease course. Further, the extent to which delayed time to diagnosis with multiple sclerosis impacts upon patient relevant outcomes such as disability progression was unclear. No significant impact on disability (according to the Expanded Disability Status Scale [EDSS] score) was shown in the PreCISe trial at either 3 or 5 years of follow up.
- 6.11 The PSCR (p2) stated that the population of patients with clinically isolated syndrome is dynamic, and that patients with two or more events would be eligible for currently listed PBS medicines for multiple sclerosis. The PSCR (p2) reiterated that the proposed PBS population is for patients with clinically isolated syndrome who have certain high risk prognostic variables and have had only one event. The ESC considered that the lack of significant impact on disability according to EDSS in the PreCISe trial was an important issue, given that health states in the economic model were based on the EDSS. The PBAC noted that results of the open label extension phase of the PreCISe trial showed no significant impact on disability progression at 5 years of follow up. Therefore the PBAC considered that there was insufficient evidence to determine whether the delay in progression to clinically definite multiple sclerosis was also indicative of reductions in disability.
- 6.12 The population in the PreCISe trial (all patients with clinically isolated syndrome) was not the high risk group requested in the PBS restriction ( $\geq 9$  T2 hyperintense MRI brain lesions or OCB positive; EDSS  $\geq 2$ ; brain MRI with  $\geq 1$  T1 GdE lesions or  $\geq 1$  T2 hyperintense MRI brain lesion in a juxtacortical, infratentorial or periventricular location). The trial population was therefore not representative of the eligible population under the proposed PBS listing. It is unknown whether the treatment effect from the PreCISe trial can be generalised to the proposed PBS population (high risk group identified in a multivariable analysis of MSBase). The PSCR (p1) indicated that, compared to the full trial population, the time to conversion was similar in the exploratory subgroup analyses of baseline characteristics that are part of, or similar to, the high risk group patients with clinically isolated syndrome, where patient numbers were large enough for  $T2 \geq 9$  and  $T \geq 1$ . The PSCR (p1) argued that the subgroup sample sizes were insufficient to determine statistical significance, but that the similar results indicated that the proposed PBS population would likely experience the outcomes seen in the PreCISe trial. The ESC considered there was insufficient data to conclude that the effect observed in the trial population would be observed in the proposed high risk subgroup (see 6.13 below).
- 6.13 The PBAC noted that the submission proposed a minimal clinically important difference (MCID) of a 20% relative reduction in the risk of conversion to clinically definite multiple sclerosis. The PBAC considered that the submission's proposed MCID appeared arbitrary, and that applying a MCID based on a proportional change to an outcome based on rates may not be clinically meaningful.

**Comparative effectiveness**

6.14 Time to diagnosis with clinically definite multiple sclerosis (primary outcome) with glatiramer acetate versus placebo is summarised in Figure 1 below.

Figure 1: Kaplan-Meier cumulative incidence curves for time to diagnosis with clinically definite multiple sclerosis using the Poser (1983) diagnostic criteria as reported by during the placebo controlled phase of PreCISe (ITT)



Source: Figure 2.5, p.84 of Section 2 of the submission

6.15 Treatment with glatiramer acetate was associated with a statistically significant increase in time to diagnosis with clinically definite multiple sclerosis (HR: 0.55; 95% CI 0.44, 0.77). The extent to which time to relapse relates to on-going patient disability and quality of life, is unclear.

6.16 The extent of treatment effect is unknown in the longer term, with the data beyond the initial 3 year follow up period of the randomised trial being contaminated in the open-label follow-up due to all patients on placebo being able to cross over to treatment with glatiramer acetate at the end of the placebo-controlled phase of the trial. The PSCR (p2) referred to published literature to argue that reduction in relapses is associated with delays in disability progression. The ESC considered that this may be plausible, however in the absence of long term data, it is more conservative to assume that patients treated with glatiramer eventually “catch up” in disability. The ESC noted that there was no evidence of any mortality gains with glatiramer treatment.

- 6.17 The PBAC noted the PreCISe trial was designed and conducted based on the Poser criteria (minimum of two clinical attacks required to diagnose multiple sclerosis); however the McDonald criteria (which allow for a second attack in time to be defined by a new lesion appearing on MRI rather than a second clinical attack) are more likely to be used in clinical practice to diagnose multiple sclerosis.
- 6.18 The PBAC noted in the open label extension phase of the PreCISe trial, a higher proportion of subjects in the delayed start treatment group were diagnosed with clinically definite multiple sclerosis, as determined by Poser criteria, than in the early start group, 49.6% versus 32.9%, respectively (HR: 0.59; CI: 0.44, 0.80; p=0.0005). Based on the Kaplan Meier survival time estimates for the 35th percentile, subjects in the early start treatment group had a longer time to diagnosis with clinically definite multiple sclerosis (1497 days) compared to subjects in the delayed start treatment group (525 days).
- 6.19 The PBAC also noted that a higher proportion of subjects in the delayed start treatment group were diagnosed with clinically definite multiple sclerosis, as determined by the McDonald criteria, than in the early start group, 84.9% versus 77.4%, respectively, however the difference between treatment groups was not statistically significant (HR: 0.83; CI: 0.66, 1.03; p=0.0829). The numbers of patients diagnosed with multiple sclerosis using the McDonald criteria were substantially higher than the numbers diagnosed with the Poser criteria. The number of patients with McDonald multiple sclerosis at baseline was not reported, however it is likely that a number of patients would have met these criteria prior to the commencement of the trial.
- 6.20 Subgroup analyses of the PreCISe trial using available patient characteristics of the proposed high risk group are summarised in Table 4 below.

**Table 4: Analysis of time to conversion for subgroups of the PreCISe trial**

Subgroup	Estimated conversion (2 years), % (95% CI)		Difference (95% CI)	Hazard ratio (95% CI)
	Glatiramer acetate (early)	Placebo (delayed)		
All subjects (n=481)	25.1 (19.3, 30.9)	42.0 (35.4, 48.6)	-16.9 (-25.7, -8.1)	0.54 (0.39, 0.74)
T2≥9 only (n=404)	26.8 (20.2, 33.3)	43.5 (36.2, 50.7)	-16.7 (-26.5, -6.9)	0.56 (0.40, 0.78)
T1≥1 only (n=209)	29.5 (19.8, 39.1)	49.0 (39.4, 58.6)	-19.5 (-33.1, -5.9)	0.50 (0.32, 0.79)
T2≥9 and EDSS≥2 (n=80)	42.8 (27.6, 58.1)	60.4 (43.0, 77.8)	-17.6 (-40.7, 5.6)	0.76 (0.41, 1.43)
T2≥9 and EDSS≥2 and T1≥1 (n=32)	47.1 (23.3, 70.8)	73.8 (49.4, 98.2)	-26.7 (-60.8, 7.3)	0.67 (0.26, 1.70)
EDSS≥2 and T1≥1 (n=34)	45.0 (21.8, 68.2)	68.4 (43.8, 93.0)	-23.4 (-57.2, 10.4)	0.70 (0.27, 1.77)
T2≥9 and T1≥1 (n=193)	30.2 (20.2, 40.2)	46.9 (36.7, 57.0)	-16.7 (-30.9, -2.4)	0.54 (0.34, 0.87)

Source: Table 2-61, p.2-104, Table 2-62, p.2-105, Table 2-63, p.2-106, Table 2-64, p.2-107, Table 2-65, p.2-108, Table 2-66, p.2-109 Section 2 of the submission

- 6.21 The ESC noted that the submission stated that the difference in the hazard ratios for the ITT population in Table 4 and Figure 1 (0.54 vs 0.55) was due to an adjustment for covariates in the results in Figure 1.

- 6.22 The economic model assumed that the treatment effect from the entire population of the PreCISe trial would apply to the high risk group identified in the proposed restriction. The ESC noted that the analyses for the high risk subgroups when EDSS $\geq$ 2 was included suggested a smaller treatment effect (with HR ranging between 0.67 and 0.76) compared with the full trial population (HR = 0.54), although acknowledged the small sample sizes for these subgroups. The ESC noted this may have been due to the higher conversion rate in the placebo arm for these subgroups. The ESC therefore considered that the treatment effect of glatiramer acetate may be less in the high risk group (which includes EDSS in the nomogram) than in the overall population of patients with clinically isolated syndrome. The pre-PBAC response (p1) argued that the difference in treatment effect between the glatiramer acetate and placebo arms was maintained, but the results were not statistically significant due to the small patient numbers in the subgroups. The pre-PBAC response argued that the proposed high risk PBS population would therefore likely experience the same treatment effect as the population in the PreCISe trial.
- 6.23 The PBAC considered it was unclear if the treatment effect was maintained in the nominated high risk subgroup, as the subgroup had only 32 patients (7% of the trial population). The PBAC therefore considered that there was inadequate clinical evidence to conclude that the extent of treatment effect of glatiramer acetate in the overall trial population would be the same in the high risk group.
- 6.24 Table 5 summarises the results of the indirect comparison of glatiramer with the meta-analysis of interferon trials in clinically isolated syndrome.

**Table 5: Indirect comparison of hazard ratios for time to diagnosis with multiple sclerosis with glatiramer acetate vs. meta-analysed interferon trials using a placebo common comparator**

Trial	Glatiramer acetate n/N (%)	Placebo n/N (%)	Interferon	Treatment difference (95% CI)
<b>Diagnosis with multiple sclerosis</b>				
PreCISe	60/243 (24.7)	102/238 (42.9)	-	Hazard ratio: 0.55 (0.44, 0.77)
Pakdaman 2007	-	57/98 (58.2)	38/104 (36.5)	Hazard ratio: 0.54 (0.36, 0.81)
Kappos 2006	-	45/176 (25.6)	28/292 (9.6)	Hazard ratio: 0.50 (0.36, 0.70)
Jacobs 2000	-	73/190 (38.4)	46/193 (23.8)	Hazard ratio: 0.56 (0.38, 0.81)
Comi & Filippi 2001	-	69/154 (44.8)	52/154 (33.8)	Hazard ratio: 0.65 (0.45, 0.94)
Comi 2012	-	98/171 (57.3)	63/171 (36.8)	Hazard ratio: 0.48 (0.31, 0.73)
Meta-analysis of interferon trials ( $I^2 = 0\%$ )				Hazard ratio: 0.54 (0.46, 0.64)
Indirect estimate of effect (results < 1 favour glatiramer acetate)				<b>Hazard ratio: 1.02 (0.70, 1.47)</b>

Source: compiled during the evaluation from Table 49, p.76 of E3518 Copaxone for CIS 2017 03 07 report (Attachment 7 of the submission); trial reports and publications

- 6.25 Overall, there is no difference in treatment effect between glatiramer acetate and interferons in treating clinically isolated syndrome. This result should be interpreted with caution, as the meta-analysis of the interferons may not be appropriate and there were significant differences between trials. There was variability in the rates of diagnosis with multiple sclerosis in the placebo arm across trials, differences in diagnostic criteria applied to the primary outcomes, and wide confidence intervals in

the indirect estimate of effect. A non-inferiority margin was not nominated for this outcome. Overall, the PBAC considered that the indirect comparison of glatiramer with the meta-analysis of interferon trials in clinically isolated syndrome was not informative.

### **Comparative harms**

- 6.26 In the PreCISe trial, the incidence of adverse events leading to discontinuation was higher in the glatiramer acetate treatment group than in the placebo group. The adverse event profile primarily included injection site reactions and immediate post-injection reaction. The ESC noted that the literature has raised the possibility that increased injection site reactions in the active treatment arm may lead to a degree of unblinding in the trial<sup>1</sup>.
- 6.27 Other common adverse events reported in the PreCISe trial included lymphadenopathy, urticaria, influenza-like illness, constipation, pruritus, erythema, vomiting, rash and blurred vision.
- 6.28 Based on an extended assessment of harms, identified and potential risks associated with glatiramer acetate include: immediate post injection reaction, injection site reactions, injection site necrosis and atrophy, hypersensitivity, benign neoplasms of the skin and soft tissues, convulsions and anxiety, and liver injury and glomerulonephropathies.
- 6.29 There were no statistically significant differences between results of the glatiramer acetate trial and the meta-analyses of the interferon trials for either total discontinuations, or discontinuations due to adverse events (used as a proxy outcome for safety). There was a high degree of heterogeneity between trials. Treatment with either glatiramer acetate or interferons is associated with known tolerability issues.
- 6.30 The PBAC noted that glatiramer acetate has been PBS subsidised since 1999 and has a well-established safety profile. The PBAC also noted a recent TGA Periodic Safety Update Report (PSUR) to 30 November 2016, which did not identify any new safety issues or signals with glatiramer acetate.

### **Benefits and harms**

- 6.31 A summary of the comparative benefits and harms for glatiramer acetate versus placebo is presented in Table 6.

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<sup>1</sup> Cottrell DA. *The Case for delaying treatment of clinically isolated syndrome. Int J MS Care 2009; 11(2): 103-106.*

**Table 6: Summary of comparative benefits and harms for glatiramer acetate and placebo**

Benefits	Glatiramer acetate	Placebo	Absolute difference (25 <sup>th</sup> percentile)	HR (95% CI)
<b>PreCISe (ITT analysis)</b>				
Diagnosis with clinically definite multiple sclerosis, n/N(%)	60/243 (24.7%)	102/238 (42.9%)	386 days	0.55 (0.44, 0.77)
Time at which 25% of patients diagnosed, days (95% CI)	722 (505, NE)	336 (260, 456)		
Harms	Glatiramer acetate	Placebo	Incidence rate <sup>1</sup>	
			Glatiramer acetate	Placebo
Immediate post-injection reaction	134/47 (19.3%)	17/12 (5.0%)	10.9	3.1
Injection site reactions	347/135 (55.6%)	96/56 (23.5%)	31.3	14.7

Source: Table 2-48, p.2-81, Table 2-49, p.2-83, Section 2 of the submission; clinical trial report

<sup>1</sup> Incidence rate = (number of subjects who experienced the event/subject years) × 100

- 6.32 Over a period of approximately 36 months, 24.7% of patients with clinically isolated syndrome treated with glatiramer acetate would be diagnosed with multiple sclerosis, versus 42.9% of patients treated with placebo.
- 6.33 On the basis of the direct evidence presented in the submission, for every 100 patients with clinically isolated syndrome treated with glatiramer acetate compared with placebo there would be:
- Approximately 18 additional patients would have delayed diagnosis with clinically definite multiple sclerosis over a period of approximately 36 months
  - Approximately 14 additional patients who would experience immediate post injection reaction over a period of approximately 36 months
  - Approximately 32 additional patients who would experience injection site reactions (including pain, inflammation and hypersensitivity) over a period of approximately 36 months
- 6.34 These results were based on an analysis of the entire PreCISe trial population, and not the high risk group identified in the proposed restriction.
- 6.35 The PSCR (p1) argued that the benefits and harms ratios were misleading, as they showed absolute incidence, rather than incidence rates for adverse event outcomes. The PSCR also contended that using incidence is incorrect because patients on glatiramer acetate received a longer duration of therapy (as placebo patients switched to active therapy after relapse), hence experiencing a greater exposure to treatment and a greater risk of adverse events compared with placebo. The PBAC considered that the placebo-controlled phase of the randomised trial accurately reflected the relevant question of whether to start treatment earlier than is possible according to the current PBS criteria, because Australian patients, who are required to have two relapses (thus consistent with the primary outcome of the trial) in order to be eligible to start PBS-subsidised active therapy, are reflecting the placebo arm of the trial.

**Clinical claim**

- 6.36 The submission described glatiramer acetate 20 mg injected subcutaneously once daily, or 40 mg injected subcutaneously three times weekly, as superior in terms of effectiveness and inferior, but tolerable, in terms of safety compared to placebo. The efficacy and safety claims are reasonable, however the impact of any advantages in terms of on-going patient disability is unclear, given the non-statistically significant results for these outcomes in the trial. The PSCR (p2) acknowledged that the PreCISe trial had limited follow up, however explained that this was for ethical reasons as patients must be allowed to switch to active treatment once clinically definite multiple sclerosis occurs or if they reached the end of the 2-3 year trial period. The PSCR (p2) referenced the CHAMPS extension study (Kinkel et. al., 2015) as evidence that there were quality of life benefits (based on the 36-item Short Form Health Status Survey (SF-36) physical and mental component summary scores) in patients who had delayed development of clinically definite multiple sclerosis.
- 6.37 The PSCR (p2) referred to a systematic review (Fahrbach et al., 2013) that demonstrated a significant association between disease modifying therapy treatment effects on relapse rate and EDSS, with lower treatment effect associated with higher relative rates of disease progression. The ESC considered that the applicability of the systematic review was limited as the majority of studies were conducted in RRMS and secondary progressive multiple sclerosis (SPMS) populations (there were insufficient data to conduct an independent analysis of clinically isolated syndrome studies) and the main relapse outcome was annualised relapse rate rather than time to next relapse. The ESC considered that it was not possible to assess the surrogate to final outcome relationship between relapses and disability progression based on this study.
- 6.38 The PSCR (p2) stated that the goals of treating multiple sclerosis lies in preventing relapses and minimising disease progression and that a key benefit of early treatment focuses on the importance of irreversible brain atrophy, and the delay/avoidance of this outcome and minimising long term disability.
- 6.39 The ESC noted that the underlying premise throughout the submission and PSCR is that patients cannot convert to clinically definite multiple sclerosis prior to a second clinical attack. This approach is not consistent with the current understanding of multiple sclerosis, in which patients may be diagnosed with clinically definite multiple sclerosis prior to the second clinical attack (as per the McDonald criteria).
- 6.40 The PBAC considered that the claim of superior comparative effectiveness of glatiramer acetate versus placebo was reasonable only for the overall trial population of PreCISe, but was not adequately supported by the data for the proposed high risk group. The PBAC also considered that the long term impact on disability and quality of life remained unclear beyond the duration of the placebo-controlled phase of the trial, after which all patients remaining on placebo were permitted to switch to glatiramer acetate.
- 6.41 The PBAC considered that the claim of inferior comparative safety of glatiramer acetate versus placebo was reasonable.

**Economic analysis**

6.42 The submission presented a modelled cost-utility analysis comparing glatiramer acetate to placebo in patients with clinically isolated syndrome.

**Table 7: Summary of model structure and rationale**

Component	Summary
Time horizon	Life time (80 years) in economic model base case versus up to 3 years in the key trial (with an open-label extension phase up to 5 years)
Outcomes	Quality-adjusted life years gained, delay in time to clinically definite multiple sclerosis progression
Methods used to generate results	Markov microsimulation model
Health states	<p>The 18 modelled health states are defined by multiple sclerosis status (clinically isolated syndrome, relapsing remitting multiple sclerosis, or secondary progressive multiple sclerosis), Expanded Disability Status Scale (EDSS) score, and death:</p> <ul style="list-style-type: none"> <li>• Clinically isolated syndrome (EDSS=2)</li> <li>• Clinically definite multiple sclerosis/ relapsing remitting multiple sclerosis (EDSS=2, 3, 4, 5, 6, 7, 8, 9)</li> <li>• Secondary progressive multiple sclerosis (EDSS=2, 3, 4, 5, 6, 7, 8, 9)</li> <li>• Death (all cause and multiple sclerosis-related (transition from EDSS 9 to EDSS 10) mortality)</li> </ul> <p>Two treatment arms are modelled: early treatment, delayed treatment; with two additional arms modelled to capture the life expectancy of non-CIS/MS patients (all-cause mortality) and a 'Natural History' of multiple sclerosis cohort, natural history of multiple sclerosis (untreated), and standard Australian life expectancy.</p>
Utilities	Derived from literature
Cycle length	1 year
Transition probabilities	Derived from literature and clinical trials

Source: Table 3-1, p4, Section 3 of the submission

6.43 The model structure was consistent with other economic models for clinically isolated syndrome and multiple sclerosis in that health states were defined by EDSS stage, however there were substantial differences:

- patients in the clinically isolated syndrome state could not move to improved or more severe levels of disability
- patients in multiple sclerosis health states could not transition more than once or more than one step on the EDSS scale within each annual cycle
- patients could not progress to a lower (improved) EDSS state.

6.44 The PSCR (p7) stated that modelled patients with clinically isolated syndrome are assumed to not transition to improved EDSS scores because these are patients with an EDSS $\geq$ 2 (in accordance with the proposed indication) and therefore these patients are more likely to be on the progression pathway. The PSCR stated that limiting RRMS patients to annual EDSS decline was a simplifying assumption in the model and across the cohort, on average, patients decline, even if individual patients experience temporary respites.

6.45 The model may not be an accurate representation of the true relapsing remitting multiple sclerosis disease course, which frequently includes remission back to the baseline level of disability prior to the relapse as well as worsening of disability symptoms.

6.46 Key issues with the economic model are summarised in Table 8.

**Table 8: Key issues with the model**

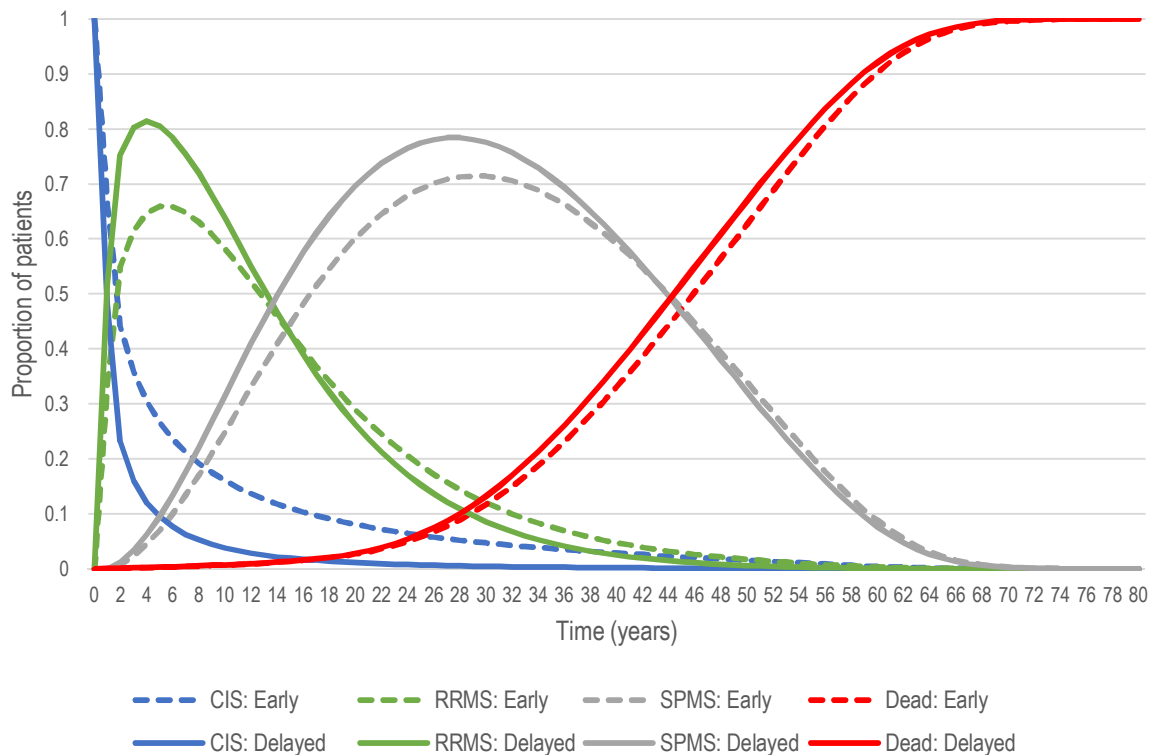
Description	Method/Value	Impact
Model structure	The trial outcome, delay in time to diagnosis with multiple sclerosis, is linked to QALYs via an inflexible model structure which does not allow patients with delayed diagnosis of multiple sclerosis to “catch up” in disability and mortality terms to those with earlier onset. The ESC considered given the lack of EDSS differences in the PreCISe trial, this is important. The assumption of sustained benefit is unjustified. The model’s representation of the impact of early treatment on the natural history of MS may not be valid.	High, favours glatiramer
Treatment effect	The treatment effect, based on the overall clinically isolated syndrome population from the PreCISe trial, was assumed to apply to the high risk population and to remain constant over the duration of the model. The hazard ratio used in the economic model is based on the placebo-controlled phase of the PreCISe trial (up to 3 years of treatment), extrapolated over 80 years. The model is likely to over-estimate treatment effect. The ESC noted this resulted in some patients never converting to clinically definite multiple sclerosis (cure rather than delay).	High, favours glatiramer
Modelled population	The model calculations were based on a hypothetical cohort of patients thought to be at high risk of diagnosis with multiple sclerosis within 5 years, based on an analysis of the MSBase patient database. The predictive nomogram derived from this analysis has not been validated; it is unclear whether it will identify patients at equally high risk of diagnosis with multiple sclerosis in a routine Australian population. The ESC considered there may also be patients who do not meet the nomogram criteria who may benefit from the intervention.	Unclear
Extrapolation	The submission extrapolated estimates of time to diagnosis with multiple sclerosis by fitting a Weibull curve to data from the MSBase cohort analysis. Overall extrapolation was severely limited by the small number of values (conversion probabilities at 2 and 5 years) used to inform estimates. Extrapolated time to diagnosis with multiple sclerosis was substantially higher than estimates from the PreCISe trial. The PSCR (p7) argued that with discounting, the uncertainty over the model timeframe is substantially mitigated. The ESC considered that a shorter time horizon may be more appropriate; in this regard, the ESC noted that treatment with glatiramer in the model was limited to 20 years. The PBAC considered that the time horizon in the model was long and inconsistent with published economic models for clinically isolated syndrome, which typically had time horizons ranging from 15 – 50 years.	High, favours glatiramer acetate
Utilities	Utilities for MS-related health states were based on Prosser (2004). This source was inadequately justified and may not adequately reflect different levels of severity in EDSS states. The disutility for relapse was also based on Prosser (2004). The average disutility did not adequately adjust for severity level or duration of relapse. Treatment related disutilities were derived from a cost-effectiveness analysis of major depressive disorder treatments (Soini and Hallinen, 2009). The estimates were based on numerous poorly supported assumptions and the disutility associated with glatiramer treatment is likely to be substantially underestimated.	Moderate, favours glatiramer
Transition probabilities	The ESC noted the source for the transition probabilities was the London Ontario study with data collected from 1972-1984. The ESC noted it was not possible to transition to a lower EDSS state and that this does not reflect the progression of disease for RRMS.	Unclear
Costs associated with treatment	The submission failed to separate costs of disease modifying therapies for RRMS from other disease-management associated costs. These costs should have been applied separately in the model, to enable the costs of disease modifying therapies to be removed from the health states where treatment is not expected to occur. Annual disease management costs were based on a study which reviewed the economic impact of multiple sclerosis using longitudinal data from the Australian Multiple Sclerosis Longitudinal	Unclear

Description	Method/Value	Impact
	<p>Study (AMSLS; Covance et al., 2010). The PBAC has previously raised concerns regarding the appropriateness of the source data for annual disease management costs (contradictory costs between different levels of disability; November 2012 fampridine PSD). Furthermore, EDSS state was not directly measured during the costing study, but was mapped from the self-reported Disease Steps scale data obtained as part of the Australian MS Longitudinal Study (AMSLS) and therefore may not be reliable.</p> <p>The PSCR identified that the commentary incorrectly stated that comparator cost was one of the main drivers of the economic model. The evaluation mislabelled disease management costs as comparator costs.</p>	

Source: compiled during the evaluation (reference sections/tables/spreadsheets within the submission)

6.47 The proportion of patients in each health state (combining the EDSS states in RRMS and SPMS) over the 80 year duration of the model is shown in Figure 2.

Figure 2: Model traces of the proportions of patients in CIS, RRMS, SPMS and dead health states



Source: constructed during the evaluation from the 'CIS – (Step 4 Base Case)' TreeAge model provided with the submission  
 Abbreviations: CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

6.48 The model delays progression to RRMS in patients treated with glatiramer acetate in the clinically isolated syndrome state (CIS: Early), which leads to a reduction in the time spent in RRMS, SPMS and in the dead state. There was no clinical evidence presented to support the effect of early treatment with glatiramer acetate on the reduction in time spent in multiple sclerosis states.

6.49 The average time in health states from the model is summarised in Table 9.

**Table 9: Average time in health states**

Health state in model	Glatiramer	Placebo	Increment
Clinically isolated syndrome	6.24	2.19	4.05
Relapsing remitting multiple sclerosis	13.06	13.64	-0.58
Secondary progressive multiple sclerosis	25.47	27.69	-2.22
Total time	44.77	43.52	1.25

Source: Table 3-23, p63, Section 3 of the submission

- 6.50 The model estimated an approximately four year delay on average in time to diagnosis with clinically isolated syndrome. This is significantly longer than the delay to diagnosis with clinically definite multiple sclerosis in the PreCISe trial (2.66 years based on the difference at the 35<sup>th</sup> percentile for the open label follow-up of the PreCISe trial). The submission claimed that this is due to the modelled population being restricted to patients with a high risk of rapid conversion. The economic model could not be robustly validated against the PreCISe trial as the model was not structured to include lower risk patients (and therefore it was unclear whether other factors may also be affecting the time to RRMS conversion). The pre-PBAC response (p3) argued that the modelled delay in progression is longer than the trial’s 2.66 years because the open label phase underestimates the clinical benefit as placebo patients were actively treated once they progressed. The pre-PBAC response (p3) argued that the true number of years delayed (if there was no crossover in the trial) would have been greater. The PBAC considered that applying a longer delay in average time to diagnosis with clinically isolated syndrome in the model compared to the trial results (4 years instead of 2.66 years) was not appropriate and favoured glatiramer acetate.
- 6.51 The trial outcome of delay in time to diagnosis with multiple sclerosis is linked to the final outcome of QALYs via an inflexible model structure which does not allow patients with delayed diagnosis of multiple sclerosis to “catch up” in disability and mortality terms to those with earlier onset. The ESC therefore considered that the model may have overestimated mortality due to multiple sclerosis, as the difference in median mortality for the natural history arm versus all-cause mortality is high (approximately 12 years, greater than the 7-8 years quoted in the submission). This contributes to a mortality benefit associated with early treatment with glatiramer acetate. The assumption of sustained mortality benefit is unjustified. The pre-PBAC response (p3) stated that the central clinical proposition of the submission lies in the clinical rationale that treatment prevents brain atrophy. The pre-PBAC response argued that once brain atrophy occurs it cannot be reversed, therefore treating patients later does not allow “catch up” of brain atrophy. The PBAC noted that the clinical evidence presented by the submission did not indicate any significant impact on long term disability.
- 6.52 The ESC noted that the Weibull extrapolation for time to diagnosis with multiple sclerosis relied on only 2 data points from the MSBase cohort analysis and considered that this led to considerable uncertainty in the modelled results, and likely favoured glatiramer acetate. The pre-PBAC response (p3) argued that using

only 2 time points to fit the Weibull extrapolation was reasonable given that only 2 time-points were available. The pre-PBAC response argued that given 92.7% of patients are taken to have progressed without treatment by 5 years, this did not favour glatiramer acetate.

**Table 10: A summary of health state utilities used in the submission using utilities identified in published literature**

EDSS	Prosser (2004)	Orme (2007)	Kobelt (2006)	Ahmad (2016)
2	0.954	0.71	0.73	0.61
3	0.87	0.58	0.58	0.61
4	0.87	0.62	0.63	0.51
5	0.87	0.52	0.52	0.51
6	0.769	0.46	0.47	0.51
7	0.769	0.3	0.32	0.4
8	0.491	-0.04	-0.03	0.4
9	0.491	-0.19	-0.18	0.4

Source: Table 3-5, p.30 Section 3 of the submission

- 6.53 The submission assumed utility estimates for each EDSS score (2-8) based on the Prosser (2004) publication for the base case and used Orme (2007) RRMS utilities, Kobelt (2006) and Ahmad (2016) to derive utility estimates for sensitivity analyses. There was no justification provided for the selected estimates for each EDSS score. All identified studies derived utilities for health states defined by different groups based on EDSS score (e.g. Prosser 2004 reported utilities for EDSS 0-2.5, 3-5.5, 6-7.5 and 8-9.5). The use of utilities derived using health states based on different definitions to the model may not be appropriate as the approach assumes no utility decrement with increasing disability (e.g. no change in utility between EDSS 3 to EDSS 5).
- 6.54 The ESC considered that, given an EDSS 3 score represents moderate disability with no impairment to walking, and an EDSS 5 score represents disability severe enough to impair full daily activities and the patient can only walk without aid or rest for 200m, usage of the same utilities for these two health states lacked face validity.
- 6.55 The results of the modelled economic evaluation are summarised in Table 11.

Table 11: Results of the stepped economic evaluation

	Glatiramer	Placebo	Increment
<b>Step 1: trial based costs (placebo controlled phase) per year delay in diagnosis with clinically definite multiple sclerosis (approx. 3 year time horizon)</b>			
Costs	\$██████	\$0	\$██████
Time to conversion to MS	722 days (2.0 years)	336 days (0.9 years)	386 days (1.1 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Step 2A: trial based costs (open label extension phase) per year delay in diagnosis with clinically definite multiple sclerosis (approx. 5 year time horizon)</b>			
Costs	\$██████	\$0	\$██████
Time to conversion to MS	1,497 days (4.1 years)	525 days (1.4 years)	972 days (2.7 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Step 2B: trial based costs (open label extension phase) per year delay in diagnosis with clinically definite multiple sclerosis (approx. 5 year time horizon) including comparator costs</b>			
Costs	\$██████	\$██████	\$██████
Time to conversion to MS	1,497 days (4.1 years)	525 days (1.4 years)	972 days (2.7 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Step 3A: modelled cost per year delay in diagnosis with clinically definite multiple sclerosis for high risk group (5 year time horizon; drug costs only)</b>			
Costs	\$██████	\$0	\$██████
Time to conversion to MS	894 days (2.4 years)	565 days (1.5 years)	329 days (0.9 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Step 3B: modelled cost per year delay in diagnosis with clinically definite multiple sclerosis for high risk group including comparator costs (5 year time horizon)</b>			
Costs	\$██████	\$██████	\$██████
Time to conversion to MS	887 days (2.4 years)	562 days (1.5 years)	325 days (0.9 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Step 4: modelled cost per year delay in diagnosis with clinically definite multiple sclerosis for high risk group including comparator costs (lifetime [80 year] time horizon; 5% discounting applied)</b>			
Costs	\$██████	\$██████	\$██████
Time to conversion to MS	2,278 days (6.2 years)	799 days (2.2 years)	1,479 days (4.1 years)
Incremental cost per additional year delay to MS diagnosis			\$██████
<b>Base case modelled economic evaluation: modelled cost per QALY for high risk group including comparator costs (lifetime [80 year] time horizon; 5% discounting applied)</b>			
Costs	\$██████	\$██████	\$██████
QALYs	13.93	13.42	0.51
Incremental cost per QALY gained			\$██████

Source: Table 3-20, p.62 of the submission

Abbreviations: MS, multiple sclerosis; QALY, quality adjusted life year

6.56 Based on the economic model, treatment with glatiramer acetate was associated with an incremental cost per quality adjusted life year (QALY) gained of \$15,000 - \$45,000 compared with placebo.

6.57 The ESC noted that, based on the stepped economic analysis, glatiramer acetate is less cost effective in the high risk group than when used in the overall population of patients with clinically isolated syndrome (the cost per additional year delay to MS is \$ [REDACTED] for the overall population [Step 2A] compared with \$ [REDACTED] for the high risk group [Step 3A]). The PBAC remained concerned that the treatment effect of glatiramer acetate in the overall population may not be maintained in the high risk group, and that this will further reduce the cost-effectiveness of glatiramer acetate in the proposed PBS population.

6.58 Table 12 summarises the results of key sensitivity analyses. The submission did not specify a randomisation seed or number of iterations used to generate the base case results. During the evaluation, analyses were performed using 100,000 iterations and a randomisation seed of 3.

**Table 12: Results of key sensitivity analyses**

	Incr cost	Incr QALYs	ICER
<b>Base case</b>	\$ [REDACTED]	0.505	\$ [REDACTED]
Using upper limit of 95% CI from PreCISe 3 year placebo-controlled phase (HR=0.77)	\$ [REDACTED]	0.173	\$ [REDACTED]
RR relapse and progression from alemtuzumab (base case estimates based on glatiramer)	\$ [REDACTED]	0.427	\$ [REDACTED]
Model time horizon (base case 80 years)			
Model time horizon 50 years	\$ [REDACTED]	0.478	\$ [REDACTED]
Model time horizon 20 years	\$ [REDACTED]	0.260	\$ [REDACTED]
Health state utilities (base case: based on Prosser (2004))			
- utilities based on Orme (2007)	\$ [REDACTED]	0.562	\$ [REDACTED]
- utilities based on Kobelt (2006)	\$ [REDACTED]	0.495	\$ [REDACTED]
Relapse disutility			
Adjusting disutility relapse for time in state (as per 'CIS - variables list' spreadsheet; -0.026 versus -0.13953)	\$ [REDACTED]	0.431	\$ [REDACTED]
Alternative estimate for the disutility of relapse from Orme (2007): -0.071	\$ [REDACTED]	0.460	\$ [REDACTED]
Treatment related disutility (base case: glatiramer -0.00034; placebo -0.00009)			
Glatiramer: -0.01; placebo 0	\$ [REDACTED]	0.468	\$ [REDACTED]
Glatiramer: -0.02; placebo 0	\$ [REDACTED]	0.429	\$ [REDACTED]
Glatiramer: -0.05; placebo 0	\$ [REDACTED]	0.312	\$ [REDACTED]
MS costs by EDSS state: reduce by 25%	\$ [REDACTED]	0.505	\$ [REDACTED]

Abbreviations:; CIS, clinically isolated syndrome; ICER, incremental cost-effectiveness ratio; MS, multiple sclerosis; QALY, quality-adjusted life year; RRMS, relapsing remitting multiple sclerosis; RR, relative risk; SPMS, secondary progressive multiple sclerosis; EDSS, Expanded Disability Status Score

Source: Table 3-25, p66, Section 3 of the submission and additional calculations performed during the evaluation using 'CIS - (Step 4) Base Case' TreeAge model provided with the submission

6.59 The model is most sensitive to assumptions regarding the treatment effect of glatiramer in patients with clinically isolated syndrome, the modelled time horizon, and treatment-related disutilities. The ESC noted that when a more conservative hazard ratio was applied (0.77, per the sensitivity analyses in Table 12), the ICER

increased to \$105,000/QALY – \$200,000/QALY. The ESC noted that the hazard ratio of 0.77 was closer to results for the high risk subgroups when EDSS $\geq$ 2 was included (refer to paragraph 6.13) and considered that applying a more conservative hazard ratio in the economic model may be appropriate. The ESC also noted that the model was sensitive to the discount rate (5%) and that this favoured placebo.

- 6.60 The model structure is inflexible and does not allow modelling of alternative populations such as the broader population included in the PreCISE trial.

**Drug cost/patient/year: \$ [REDACTED]**

- 6.61 The drug cost per patient per year for early treatment with glatiramer acetate is \$ [REDACTED], equivalent to 13.04 prescriptions per year at the proposed DPMQ (\$ [REDACTED]). This is equivalent to the DPMQ for glatiramer acetate for RRMS.

**Estimated PBS usage & financial implications**

- 6.62 This submission was considered by DUSC.
- 6.63 The submission used a combined epidemiology/market share approach to estimate the utilisation and financial implications associated with the PBS listing of glatiramer acetate for the treatment of clinically isolated syndrome over the first six years of listing.

**Table 13: Estimated utilisation and cost to the PBS in the first six years of listing**

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Australian population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CIS incidence rate per 100,000	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of incident CIS patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of prevalent CIS patients (incident population × 5 years)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total CIS patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
No. eligible for treatment: high risk (25%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Proportion of patients willing to be treated	80%	80%	85%	85%	90%	95%
Total high risk CIS patients willing to be treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Patients otherwise treated if glatiramer not listed (80%)						
- Patients receiving treatment (CIS patients outside PBS restriction)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
- Proportion willing to switch to glatiramer acetate	50%	75%	100%	100%	100%	100%
- Number glatiramer patients switching from other therapies	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Newly treated patients (20%)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Total patients treated with glatiramer</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
<b>Total scripts glatiramer (13.04/year)<sup>a</sup></b>	█	█	█	█	█	█
Total cost glatiramer (DPMQ \$█)	\$█	\$█	\$█	\$█	\$█	\$█
Total patient co-payments (\$█/script)	\$█	\$█	\$█	\$█	\$█	\$█
<b>Total cost (DPMQ excluding co-payments)</b>	\$█	\$█	\$█	\$█	\$█	\$█

Abbreviations: CIS, clinically isolated syndrome; DPMQ, dispensed price for maximum quantity;

Source: constructed during the evaluation using 'CIS - Section 4 Base Case (6 March 2017)' spreadsheet provided with the submission

<sup>a</sup>Assumed 41.92% 20 mg and 58.08% 40 mg scripts; both have the same DPMQ

6.64 The redacted table shows that at year 6, the estimated number of patients was less than 10,000. The net cost of listing glatiramer acetate for clinically isolated syndrome on the PBS was estimated to be \$20 – \$30 million in Year 6, with an estimated cumulative cost in the first six years of listing of \$60 – \$100 million. The estimates were highly uncertain due to the following issues:

- The proposed listing of glatiramer acetate for clinically isolated syndrome is associated with significant uncertainties regarding the number of patients eligible for treatment.
- The submission assumed that 25% of patients with clinically isolated syndrome would be considered high risk and eligible for glatiramer treatment based on the MSBase dataset (inflated to account for the availability of a subsidised treatment option). Patients in the MSBase dataset were a selected group of patients and may not be representative of the broader population with clinically isolated syndrome.
- There is a substantial risk of use outside the proposed restriction, given that if recommended this would be the first PBS listed treatment for clinically isolated syndrome, and it is likely that a substantial proportion of patients with clinically isolated syndrome are already being treated with disease modifying therapies.
- The submission claimed substantial cost offsets due to displaced therapies, which were poorly described in the submission.

6.65 The corresponding changes in number of scripts displaced and MBS items accessed by clinically isolated syndrome patients associated with the listing of glatiramer acetate are summarised in Table 14.

Table 14: Estimated change in utilisation and cost of displaced treatments and MBS items

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Patients switching from other therapies to glatiramer	█	█	█	█	█	█
Total scripts displaced (13.04/year)	█	█	█	█	█	█
Cost of displaced medicines (DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Displaced medicines patient co-payments (\$ █ per script)	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Total savings from displaced medicines (DPMQ excluding co-payments)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net changes to MBS items</b>						
Reduction in MRIs (MBS #63049)	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Increase in consultations (MBS #116)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net cost to the MBS</b>	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

Abbreviations: DPMQ, dispensed price for maximum quantity; IM, intramuscular; SC, subcutaneous; MRI, magnetic resonance imaging; MBS, Medicare Benefits Schedule

Source: constructed during the evaluation using 'CIS - Section 4 Base Case (6 March 2017)' spreadsheet provided with the submission

<sup>a</sup>Includes fingolimod, teriflunomide, natalizumab and dimethyl fumarate

6.66 The total cost savings due to displaced therapies (primarily interferons and glatiramer acetate) was estimated to be less than \$10 million in Year 1, increasing to \$10 – \$20 million in Year 6. The estimated cumulative cost saving in the first six years of listing was \$60 – \$100 million.

6.67 The listing of glatiramer acetate for the treatment of clinically isolated syndrome is expected to increase the number of specialist consultations in this population but decrease the number of MRI scans, based on expert advice (not provided with the submission). The estimated cumulative net saving to the MBS was \$ █ over 6 years. These estimates were highly uncertain. It was unclear whether the estimates are based solely on treatment for clinically isolated syndrome or also include downstream treatment for multiple sclerosis.

6.68 The net cost to government is summarised in Table 15.

Table 15: Net cost to government

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
Cost of glatiramer (DPMQ excluding co-payments)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost of displaced medicines (DPMQ excluding co-payments)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net cost to PBS/RPBS</b>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net cost to the MBS</b>	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
<b>Net cost to the government</b>	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Abbreviations: DPMQ, dispensed price for maximum quantity

Source: constructed during the evaluation using 'CIS - Section 4 Base Case (6 March 2017)' spreadsheet provided with the submission

6.69 The net cost to the PBS/RPBS of listing glatiramer acetate was estimated to be \$ █ million in Year 1, with smaller costs in subsequent years, due to increasing switching rates from displaced therapies (50% in Year 1; 75% in Year 2; 100% in subsequent

- years). The estimated cumulative cost in the first six years of listing was less than \$10 million.
- 6.70 The DUSC considered the estimates presented in the submission to be overestimated and highly uncertain. The main issues were identified as follows.
- 6.71 There was a lack of detail on the expert advice that was used to inform the assumptions for the financial estimates. As such, DUSC questioned the validity of all assumptions related to the expert advice.
- 6.72 The estimate of incident patients was added to the estimate of prevalent patients which results in an average duration with clinically isolated syndrome of six years rather than five years.
- 6.73 The submission assumes patients defined as being in the high risk group are likely to convert to multiple sclerosis early. The DUSC commented that it is therefore unlikely these patients will be in the prevalent pool of patients with clinically isolated syndrome five years after their initial attack. Calculating the prevalent pool from incident patients prior to applying the proportion of high risk patients is likely to overestimate the number of eligible patients with clinically isolated syndrome.
- 6.74 The submission assumed that 25% of patients with clinically isolated syndrome would be considered high risk and eligible for glatiramer treatment based on the MSBase dataset (inflated to account for the availability of a subsidised treatment option). The MSBase dataset may be biased, as enrolment was not compulsory and patients eligible for treatment may be more likely to be enrolled in the dataset. It is unknown if the MSBase data reflects overall Australian patients.
- 6.75 It is very unlikely patients being treated with oral therapies for early stage multiple sclerosis or clinically isolated syndrome outside PBS restrictions will be willing to switch to glatiramer.
- 6.76 The PBAC agreed with the DUSC and considered the projected PBS usage and financial implications were uncertain, as the number of patients eligible for treatment was difficult to estimate and there was a significant risk of use outside the requested restriction. The PBAC also considered that the substantial cost offsets estimated due to displaced therapies being used outside the PBS restriction were highly uncertain.

### ***Quality Use of Medicines***

- 6.77 The sponsor described a telephone-based support system and in-home injection training by nurse advisors to assist patients in administering glatiramer acetate.
- 6.78 The current PBS multiple sclerosis listings do not specify the use of the Poser or McDonald criteria for the diagnosis of multiple sclerosis. Rather, the current PBS listings for relapsing-remitting multiple sclerosis are restricted to populations with active disease, defined as 'patients who have had 2 or more relapses in the preceding 2 years'. PBS treatment of clinically isolated syndrome (1 clinical attack) and patients with active disease (patients with 2 or more relapses in 2 years) leaves a potential gap for patients who have been diagnosed with multiple sclerosis (e.g.

using the McDonald criteria), but have not yet reached a sufficient relapse frequency to justify treatment under current multiple sclerosis listings.

- 6.79 The proposed listing for glatiramer acetate (which does not include a discontinuation criterion) would allow treatment in former clinically isolated syndrome patients with less active multiple sclerosis. Cost-effectiveness has not been demonstrated in this population. Additionally, the introduction of glatiramer acetate for clinically isolated syndrome, which reduces relapse frequency (but not necessarily disability progression) may delay access to more effective multiple sclerosis treatments (which have demonstrated improvements in disability progression). The PSCR argued that discontinuation criteria would not be in the best interest of patients, and cited an analysis of MSBase (Kirste et al 2016) that indicated the time to confirmed disability progression was significantly shorter amongst patients who stopped disease modifying therapies compared to those who continued treatment.
- 6.80 The DUSC considered that the risk of injection site reactions is very high. In the pivotal trial, 55% of patients experienced injection site reactions. The DUSC considered that patients would benefit from ongoing support to manage these events and in home injection training.

### ***Financial Management – Risk Sharing Arrangements***

- 6.81 The sponsor did not propose a risk share arrangement, stating that it would be difficult in practice to effectively separate clinically isolated syndrome from multiple sclerosis prescribing, which would possibly result in pre-defined annual risk share caps being inadvertently exceeded. No special pricing arrangement was sought by the sponsor.
- 6.82 The sponsor stated that, in order to reduce uncertainty, the proposed restriction requires that a neurologist has made the diagnosis before treatment can be initiated.

*For more detail on PBAC's view, see section 7 "PBAC outcome".*

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of glatiramer acetate for the treatment of patients with clinically isolated syndrome, on the basis of uncertain extent of clinical benefit and resulting cost-effectiveness, concerns about the plausibility of assumptions used in the economic model, and uncertainty with the utilisation estimates due to issues with defining the target PBS population.
- 7.2 The PBAC noted the consumer comments and acknowledged that there was a need to address the current PBS criteria for treatments for multiple sclerosis. However, the PBAC considered that the need to review the PBS criteria for RRMS treatments was an issue applicable for all PBS listed medicines for multiple sclerosis, and not isolated to glatiramer acetate. The PBAC also noted the value placed by patients to access treatment as early as possible in the multiple sclerosis disease pathway.

- 7.3 The PBAC considered that the requested restriction, which included only patients with clinically isolated syndrome at high risk of developing clinically definite multiple sclerosis, was narrowly defined and may exclude patients likely to benefit from treatment. The PBAC was concerned that the regression model derived from the analysis of MSBase may not be a robust method to identify high risk patients in the PBS setting and was not the appropriate basis to develop the PBS restriction.
- 7.4 The PBAC accepted placebo as the appropriate main comparator. The PBAC also considered that ABCR/BRACE therapies could be secondary comparators, and noted the submission's utilisation estimates assumed substantial substitution of interferons by glatiramer acetate.
- 7.5 The PBAC noted that the primary analysis in the PreCISe trial was based on the Poser criteria. The PBAC noted that during the open label extension phase of the PreCISe trial, a higher proportion of subjects in the delayed start to treatment group were diagnosed with clinically definite multiple sclerosis by the Poser criteria than those in the early treatment group (49.6% in the delayed group vs. 32.9% in the early group). The Committee noted that under the McDonald criteria it was likely that a number of patients diagnosed with clinically isolated syndrome at baseline in the PreCISe trial would be diagnosed with clinically definite multiple sclerosis. The PBAC further noted that, under the McDonald criteria, the time from randomisation to diagnosis with clinically definite multiple sclerosis was not statistically significant for glatiramer acetate over placebo.
- 7.6 The PBAC considered that the extent of treatment effect was unclear in the longer term, given that the data beyond the initial 3 year follow up period of PreCISe included patients in the placebo arm of the trial who crossed over to treatment with glatiramer acetate. The PBAC noted that the open label extension phase of the PreCISe trial showed no significant impact on disability according to EDSS at 5 years follow up and considered that there was insufficient evidence to conclude whether a delay in progression to clinically definite multiple sclerosis is also reflective of long term disability reductions.
- 7.7 The PBAC noted the subgroup analyses presented in the submission were post-hoc, based on very small patient numbers, and were associated with higher point estimates (with HR ranging between 0.67 and 0.76) and statistically insignificant results compared with the overall trial population (HR = 0.54). The PBAC was concerned that there was insufficient clinical evidence to determine whether the treatment effect of glatiramer acetate in the overall trial population would be the same in the proposed high risk group.
- 7.8 The PBAC considered that the claim of superior comparative effectiveness of glatiramer acetate compared to placebo was reasonable only for the primary outcome of extension of time to diagnosis with clinically definite multiple sclerosis as defined by the Poser criteria (not the McDonald criteria). The PBAC considered the claims of superior comparative effectiveness for the outcomes of disability progression and quality of life outcomes were not adequately supported.

- 7.9 The PBAC noted that adverse events leading to treatment discontinuation in the PreCISe trial were higher in the glatiramer acetate group than the placebo group and noted that injection site reactions and immediate post-injection reactions were also higher in the glatiramer acetate group. The PBAC considered the claim of inferior, but tolerable, comparative safety of glatiramer acetate versus was adequately supported.
- 7.10 The PBAC considered that the incremental cost per QALY gained of \$15,000 - \$45,000 for glatiramer acetate over placebo, presented in the submission's base case analysis, was highly uncertain and was likely to be significantly underestimated due to several issues with the economic model, including:
- the treatment effect used in the base case analysis from the overall trial population (HR = 0.54) may have overestimated the treatment effect for the proposed high risk group (HR: 0.67 – 0.76). The PBAC noted the economic model was most sensitive to the treatment effect of glatiramer acetate, and that when a more conservative hazard ratio of the upper limit of the 95% confidence interval (0.77) for the overall population was applied, the ICER increased to \$105,000 – \$200,000/QALY;
  - most of the health benefit in the model is derived via quality of life improvements based on EDSS score progressions in diagnosed multiple sclerosis. This lacks face validity given a statistical difference in EDSS was not observed in the PreCISe trial;
  - the hazard ratio used in the economic model was based on the placebo-controlled phase of the PreCISe trial (up to 3 years of treatment), extrapolated to 80 years. This time horizon was not appropriate and likely to have overestimated the net effect of early treatment in the model;
  - the Weibull extrapolation for time to diagnosis with multiple sclerosis relied on only 2 data points from the MSBase cohort analysis, and is therefore uncertain;
  - the model did not allow treatment discontinuation in clinically isolated syndrome. The cost of glatiramer is applied in the clinically isolated syndrome health state for the first 20 years of the model only. However, the treatment effect from the PreCISe trial is applied for the 80 year duration of the model.
  - the model structure was inflexible and did not allow patients with clinically isolated syndrome to move to improved or more severe levels of disability. Patients in multiple sclerosis health states cannot transition more than once or more than one step on the EDSS scale within each annual cycle. The PBAC considered that this was implausible and did not adequately reflect the disease pathway of patients with clinically isolated syndrome/multiple sclerosis.
- 7.11 The PBAC considered that earlier commencement of treatment for the multiple sclerosis disease pathway (i.e. starting with clinically isolated syndrome) requires a larger absolute reduction in the rate of subsequent exacerbations and/or a reduced price compared to the currently listed PBS price for RRMS. This is because when treatment is commenced earlier, its cost effectiveness is less favourable as the main

disutilities and cost offsets generated are delayed (compared to later treatment) and thus discounted to a greater extent.

7.12 The PBAC noted the submission used a combined epidemiology and market share approach to estimate the use and financial implications of the listing of glatiramer acetate. The PBAC considered there was substantial uncertainty with the utilisation and financial estimates, due to:

- the risk of use outside the proposed restriction, given that if recommended, glatiramer acetate would be the first PBS subsidised treatment for clinically isolated syndrome;
- a lack of detail provided on the expert advice used to underpin the estimates. The PBAC considered that the assumptions for the incidence of clinically isolated syndrome based on the expert advice were likely to be unreliable;
- the estimate of incident patients was added to the estimate of prevalent patients, resulting in an average duration of clinically isolated syndrome of six years rather than the five years estimated in the economic model;
- the use of the MSBase dataset to inform the assumed proportion (25%) of patients defined as high risk of converting to clinically definite multiple sclerosis. The PBAC noted that enrolment in the MSBase dataset was not compulsory and considered using that dataset as a basis for estimating eligible patients may not be reliable or representative of the potential PBS population.

7.13 The Committee agreed that some therapies which are currently subsidised for relapsing-remitting multiple sclerosis are likely being used outside their restriction, including in clinically isolated syndrome, however considered that it was difficult to predict the extent to which this was occurring. The PBAC considered that the claimed cost offsets for substituted therapies being used outside PBS restrictions were highly uncertain.

7.14 The PBAC considered that any resubmission for glatiramer acetate for clinically isolated syndrome would require a major submission including a new economic model and financial estimates that addresses the Committee's concerns. The PBAC considered that demonstration of a greater absolute benefit in treating clinically isolated syndrome, and/or a price reduction would be required to achieve a cost-effective listing for glatiramer acetate for clinically isolated syndrome.

7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 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.

## **9 Sponsor's Comment**

The sponsor will work with the department towards resolution of the identified issues.