5.29 GLATIRAMER ACETATE 40 mg/mL injection; Copaxone®, bioCSL

1 Purpose of Application

1.1 The minor submission requests an Authority Required listing for an additional strength of the currently listed drug glatiramer acetate injection for multiple sclerosis.

2 Requested listing

2.1 The submission sought the same restriction as for the existing 20mg/mL listing:

Authority Required
Initial treatment of clinically definite relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients who have experienced at least two documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding two 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.

Authority Required
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.

2.2 The Secretariat remodelled the requested listing into the PharmCIS format to minimise duplication between the criteria and the indication (see below). This remodelled format will also be applied to the 20 mg/mL listing.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
GLATIRAMER ACETATE 40 mg/mL injection, 12	1	5	$1,092.99	Copaxone	bioCSL

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	
Severity:	
Condition:	Multiple sclerosis

PBS Indication:	Multiple sclerosis
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must be ambulatory (without assistance or support), AND Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years, AND The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord, AND Where applicable, the date of the magnetic resonance imaging scan must be provided with the authority application, OR The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by accompanying written certification provided by a radiologist that a magnetic resonance imaging scan is contraindicated because of the risk of physical (not psychological) injury to the patient.
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.

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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	
Severity:	
Condition:	Multiple sclerosis
PBS Indication:	Multiple sclerosis
Treatment phase:	Continuing

Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☒Authority Required – Emergency ☒Authority Required - Electronic ☐Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug, AND Patient must not show continuing progression of disability while on treatment with this drug, AND Patient must have demonstrated compliance with, and an ability to tolerate, this therapy
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised.

3 Background

Glatiramer acetate is TGA registered for the following indication: Reduction of the frequency of relapses in patients with Relapsing Remitting Multiple Sclerosis. Treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent MRI lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded.

3.1 The Delegate recommended approval for Copaxone 40 mg/mL injection in the Delegate's Overview (Request for ACPM Advice) dated 6 November 2014. The Advisory Committee recommended approval for the product at the 301st meeting of the ACPM on 5 December 2014. With respect to the 40mg/mL 3 times per week regime, the TGA Delegate agreed with the Clinical Evaluation Report in stating that this regimen '…is similar in its extent to the treatment benefit (in terms of relapse rate) demonstrated for the 20mg daily dose regimen for glatiramer.'

3.2 Glatiramer acetate 20 mg/mL daily was first listed on the PBS in June 1999.

3.3 Glatiramer acetate in 40 mg/mL syringes have not previously been considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 Glatiramer acetate 40 mg/mL three times weekly is an alternative treatment option for patients either currently taking glatiramer acetate 20 mg/mL daily or for those initiating treatment with glatiramer acetate. The submission does not anticipate that there will be any significant switch from the other established injectable immunomodulators or from any of the more recent oral therapies for relapsing-remitting multiple sclerosis.

5 Comparator

5.1 The minor submission nominates glatiramer acetate 20 mg/mL injection taken daily as the comparator for glatiramer acetate 40 mg/mL three times weekly.

6 Consideration of evidence

Consumer comments

6.1 The PBAC noted and welcomed the input from two organizations via the Consumer Comments facility on the PBS website. The comments indicated the importance of maximising choice for the consumer and the additional benefits of less frequent dosing.

Clinical trials

6.2 The minor submission presented the following clinical trials:

Trials and associated reports presented in the re-submission

Trial ID/ First Author	Protocol title/ Publication title	Publication citation
Indirect randomised trials		
GALA Khan Khan	Glatiramer Acetate Low-frequency Administration Three times weekly glatiramer acetate in relapsing-remitting placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. 24-Month Efficacy and Safety of Glatiramer Acetate 40mg/1mL 3-Times Weekly: Open-label Extension Study of the GALA Trial in Subjects With Relapsing-Remitting Multiple Sclerosis (S31.003).	 Neurology 2013;73(6):705-13 Neurology. April 8, 2014;82(10 Supplement):S31.003.
CONFIRM Fox	Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.	 The New England journal of medicine. 2012;367(12):1087–1097
Supplementary randomised trial		
Comi	European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group.	Annals of neurology. 2001;49(3):290–297.
Johnson	Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group.	Neurology. 1995;45(7):1268–1276.
Bornstein	A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis.	The New England journal of medicine. 1987;317(7):408–414.

Source: Submission p.10

Comparative effectiveness

6.3 An indirect comparison of the effect of glatiramer acetate 20 mg/mL versus glatiramer acetate 40 mg/mL using placebo as the common comparator is summarised in the table below. The submission claimed that CONFIRM is the most relevant trial to compare with GALA, as it was conducted over the same time period and, used the same diagnostic criteria for multiple sclerosis, had similar baseline characteristics, and similar relapse rates in the placebo arm.

Relapse rate reduction: Glatiramer acetate 20 mg/mL versus 40 mg/mL

Glatiramer acetate 20 mg/mL versus placebo			
	Glatiramer acetate 20 mg/mL	Placebo	Relapse Rate reduction
Johnson et al 1995; ARR measured over 2 years	(N=125) 0.59	(N= 126) 0.84	29% (p=0.007)
Comi et al 2001; ARR measured over 9 months	(N=119) 0.81	(N=120) 1.21	33% (p=0.012)
Fox et al 2012 (CONFIRM); ARR measured over 2 years	(N=350) 0.29	(N=363) 0.40	29% (p<0.05)
Glatiramer acetate 40 mg versus placebo			
	Glatiramer acetate 40 mg/mL (N=943)	Placebo (N=461)	Relapse Rate reduction
GALA; ARR over 1 year	0.33	0.51	34% (p<0.0001)
Indirect treatment comparison analysis using GALA and CONFIRM*			
Risk ratio glatiramer acetate 40 mg/mL versus glatiramer acetate 20 mg/mL (95% CI)			0.92 (0.66 – 1.28)

Source: Submission p.7
ARR = Annual relapse rate
* Performed using the adjusted indirect method described by Bucher et al .

6.4 The submission stated that the relapse rate reduction for glatiramer acetate 40 mg/mL compared to placebo (34%) is similar to that for glatiramer acetate 20 mg/mL compared to placebo (29-33%).

6.5 The PBAC noted that a formal evaluation of the indirect comparison was not carried out as this submission was presented as a minor submission.

Comparative harms

6.6 The submission stated that the adverse drug reactions (ADRs) seen in patients treated with glatiramer acetate 40 mg/mL three times weekly were those already known and reported for glatiramer acetate 20 mg/mL daily and were mostly reported at a similar or lower frequency.

6.7 The submission stated that injection site reactions and immediate post-injection reactions, commonly reported in patients treated with glatiramer acetate 20 mg/mL, were reported in the glatiramer acetate 40 mg/mL three times weekly group, but at lower frequency – most likely due to the lower frequency of injection. Chest pain, described in 13% of patients exposed to glatiramer acetate 20 mg/mL in the five placebo controlled trials, was seen at a rate of approximately 2% of patients exposed to glatiramer acetate 40 mg/mL in the GALA trial.

Clinical claim

6.8 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of glatiramer acetate 40 mg/mL three times per week compared with glatiramer acetate 20 mg/mL daily.

Economic analysis

6.9 As a minor submission, there was no economic comparison presented.

6.10 The minor submission requested that the monthly treatment price of 40 mg/mL three times a week (total of 480 mg per month) should be same as that of a monthly regiment of 20 mg/mL taken daily (total of 560 mg per month).

Estimated PBS usage & financial implications

6.11 The minor submission estimated there to be no financial implications from changes in PBS usage as the submission expected glatiramer acetate 40 mg/mL three times per week to substitute for glatiramer acetate 20 mg/mL daily, for the same monthly price.

7 PBAC Outcome

7.1 The PBAC recommended the listing of glatiramer acetate 40 mg/mL injection for the treatment of multiple sclerosis.

7.2 The PBAC noted that the submission requested the same price for glatiramer acetate 40 mg/mL three times weekly (providing 480 mg per month) as for glatiramer acetate 20 mg/mL daily (providing 560 mg per month). The PBAC noted that the TGA was satisfied that the three-times-weekly regimen would deliver a similar treatment benefit in terms of relapse rate compared with the daily regimen, and therefore concluded that the sponsor's claim of non-inferiority in terms of efficacy and safety was reasonable.

7.3 The PBAC indicated that while not all patients would select three-times-weekly dosing, it may present an option where ADRs are a problem with a daily dosing regimen.

7.4 The PBAC advised that the Safety Net 20 Day Rule should not apply as it does not currently apply for glatiramer acetate 20 mg/mL.

7.5 The PBAC advised that glatiramer acetate is not suitable for prescribing by nurse practitioners.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

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Severity:	
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9 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.

10 Sponsor's Comment

Teva Pharma Australia Pty Limited welcome the PBAC recommendation and look forward to making a significant new treatment option available to neurologists caring for relapsing and remitting multiple sclerosis patients.