

**5.21 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,  
Glatira<sup>®</sup>,  
Juno Pharmaceuticals Pty Ltd**

**1 Purpose of Application**

- 1.1 The minor submission requested a complex generic brand listing for glatiramer (Glatira<sup>®</sup>) 40 mg/mL for the treatment of multiple sclerosis (MS). Glatiramer is a complex heterogeneous mixture of synthetic polypeptides.
- 1.2 The Department has specifically referred the listing of the 40 mg product to the PBAC in the absence of a statement of bioequivalence from the TGA. Applications to list generic brands of products already listed on the PBS are usually processed by the Department without referral to the PBAC in circumstances where acceptance of bioequivalence has been stated by the TGA.
- 1.3 The minor submission also requested listing of Glatira 20 mg/mL injection on the PBS.
- 1.4 Listing of the both 20 mg/mL and 40 mg/mL injections was requested based on a cost-minimisation analysis to the Copaxone<sup>®</sup> brand of glatiramer.

**2 Background**

***Registration status***

- 2.1 Glatira was TGA registered on 12 November 2020 with the same listed indications as Copaxone: 'Reduction of the frequency of relapses in patients with Relapsing Remitting Multiple Sclerosis' and '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'.
- 2.2 The TGA clinical evaluator (TGA Clinical Evaluator Report p27) was satisfied that the efficacy of Glatira was equivalent to that of Copaxone in patients with MS, and the safety profiles were comparable.

***Previous PBAC consideration***

- 2.3 Glatiramer 40 mg/mL injection with the brand name Copaxone is currently listed on the PBS as an Authority Required (STREAMLINED) listing for the treatment of MS.

- 2.4 Glatiramer 40 mg/mL with the brand name Glatira had not been considered by the PBAC.
- 2.5 Copaxone 20 mg/mL injection was first listed on the PBS in June 1999 with a maximum quantity of 28 units with 5 repeats. It was the sole glatiramer strength at the time on the PBS. The PBAC recommended listing of the 40 mg/mL injection at the March 2015 meeting. The 40 mg strength is administered 3 times a week and was intended to reduce injection burden relative to the 20 mg strength (once daily dosing).
- 2.6 The sponsor of Copaxone (Teva Pharma Australia Pty Limited) requested deletion of glatiramer 20 mg/mL injection from the PBS on the basis of clinician and patient preference for the Copaxone 40 mg/mL presentation for subcutaneous administration 3 times a week. The deletion request was considered by the PBAC in November 2018. The PBAC acknowledged the clinical use of 20 mg/mL daily injection was diminishing and therefore had no objections to this deletion request. Copaxone 20 mg/mL injection was delisted on 1 July 2019. There is currently no PBS listing for glatiramer 20 mg/mL injection.

### 3 Requested listing

- 3.1 The minor submission requested the following new listings. Suggested additions are in italics and deletions are in strikethrough.

*Add new medicinal product pack (20 mg/mL strength) and new a-flagged trade product (Glatira 40 mg/mL) as follows:*

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
GLATIRAMER ACETATE					
<i>glatiramer acetate 40 mg/mL injection, 12 x 1 mL syringes</i>	10416F	1	12	5	<sup>a</sup> <i>Glatira</i> <sup>a</sup> Copaxone
<i>glatiramer acetate 20 mg/mL injection, 28 x 1 mL syringes</i>	<i>NEW</i>	1	28	5	<i>Glatira</i>
<b>Restriction Summary 7698 / Treatment of Concept: 7695</b>					
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [7695]				
	<b>Administrative Advice:</b> <i>No increase in the maximum quantity or number of units may be authorised.</i>				
	<b>Administrative Advice:</b> <i>No increase in the maximum number of repeats may be authorised.</i>				
	<b>Indication:</b> Multiple Sclerosis				
	<b>Treatment Phase:</b> <i>Initial treatment</i>				
	<b>Clinical criteria:</b>				
	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; or				
	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis, with 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				

	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised <i>disease</i> modifying therapy for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be ambulatory (without assistance or support)
	<b>Prescribing Instructions:</b> <i>Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.</i>
<b>Restriction Summary 6860 / Treatment of Concept: 6860</b>	
	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [6860]
	<b>Administrative Advice:</b> <i>No increase in the maximum quantity or number of units may be authorised.</i>
	<b>Administrative Advice:</b> <i>No increase in the maximum number of repeats may be authorised.</i>
	<b>Indication:</b> Multiple Sclerosis
	<b>Treatment Phase:</b> Continuing <i>treatment</i>
	<b>Clinical criteria:</b>
	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must not show continuing progression of disability while on treatment with this drug
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have demonstrated compliance with, and an ability to tolerate this therapy

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 4 Comparator

- 4.1 The minor submission nominated glatiramer (Copaxone) 20 mg/mL (not currently PBS-listed) and 40 mg/mL injections as the main comparators.

## 5 Consideration of the evidence

### **Sponsor hearing**

- 5.1 There was no hearing for this item as it was a minor submission.

### **Consumer comments**

- 5.2 The PBAC noted that no consumer comments were received for this item.

## Clinical trials

5.3 The minor submission presented an overview of the clinical evidence provided to the TGA to demonstrate therapeutic equivalence between Glatira and Copaxone. Details of the clinical trials which formed part of the TGA submission to register Glatira are shown below.

**Table 1: Trials and associated reports presented in the minor submission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial(s)</b>		
GTR001	<p>Phase 3, Multi-centre, randomized, double-blind, placebo-controlled, parallel-group, 9 month, equivalence trial comparing the efficacy and safety and tolerability of GTR (Synthon BV) to Copaxone (Teva) in subjects with relapsing-remitting multiple sclerosis followed by an open-label 15 month GTR treatment part evaluating the long-term GTR treatment effects.</p> <p>The primary objective of the double-blind part of this pivotal phase III trial was to demonstrate that the efficacy of Synthon's glatiramer acetate (GTR) is equivalent to Copaxone in subjects with RRMS, as measured by the number of gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging (MRI) during Months 7 to 9.</p>	<p>Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberyé J, van den Tweel E, Mulder R, Koper N, Voortman G, Barkhof F; Glatiramer Acetate Clinical Trial to Assess Equivalence With Copaxone (GATE) Study Group. Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: A Randomized Clinical Trial. <i>JAMA Neurol.</i> 2015 Dec;72(12):1433-41. doi: 10.1001/jamaneurol.2015.2154</p>
GTR002	<p>Phase 1, single-dose, randomized, double-blinded, replicate study, comparing the occurrence of local injection site reactions (LISRs) of glatiramer acetate 20 mg subcutaneous injection (Synthon BV, The Netherlands) and Copaxone® 20 mg subcutaneous injection (Teva Pharmaceuticals, U.S.) in healthy male and female volunteers.</p> <p>The objective of this study was to compare the occurrence of LISRs for subcutaneously administered Glatiramer acetate 20 mg/mL, solution for injection in pre-filled syringe (Test Drug; Synthon BV, the Netherlands) to subcutaneously administered Copaxone (Glatiramer acetate Injection 20 mg/mL, solution for injection in pre-filled syringe) (Reference Drug; Teva) during short-term exposure in healthy non-smoking (for at least 6 months prior to the study start) male and female volunteers.</p>	<p>TGA Clinical Evaluation Report</p>

Source: TGA Clinical Evaluation Report p10 and p25

5.4 The TGA Delegate considered that the primary efficacy analysis indicated GTR was equivalent to Copaxone, as the 95% CI of the ratio of the number of T1-GdE lesions during Months 7 to 9 was within the predefined equivalence margins. Other MRI endpoints supported the primary efficacy outcome (TGA Clinical Evaluation Report, p19).

5.5 The TGA Delegate (TGA Clinical Evaluation Report) noted the following:

Upon subcutaneous injection, glatiramer rapidly degrades into smaller peptide fractions and free amino acids, resulting in low or undetectable serum concentrations of the drug and its metabolites. Results of pharmacokinetic (PK) studies in healthy volunteers indicate that a substantial fraction of the glatiramer acetate dose is

hydrolysed locally. Considering the complexity of the immune system itself and the diversity seen in the immune system in MS patients, the clinical efficacy of glatiramer may be related to its heterogeneous character, and the drug's multi-epitomal nature may be the source of its clinical efficacy. Consequently, there are no clear pharmacokinetic (PK) or pharmacodynamic (PD) markers to assess bioequivalence.

- 5.6 Glatiramer is extensively degraded at the site of subcutaneous injection therefore its concentration in plasma or other body fluids cannot be determined. However, Glatira has the same quantitative and qualitative composition as Copaxone with regard to active substance and excipients, and it is presented in the same dosage form (TGA Clinical Evaluation Report, p9).

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### **Clinical claim**

- 5.7 The minor submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of Glatira compared with Copaxone.
- 5.8 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety of Glatira compared with Copaxone was adequately supported by the data.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### **Economic analysis**

- 5.9 As a minor submission, the economic analysis has not been independently evaluated.
- 5.10 The minor submission presented a cost-minimisation analysis of Glatira compared with Copaxone. The minor submission estimated the equi-effective doses to be:
- 20 mg Glatira = 20 mg Copaxone
  - 40 mg Glatira = 40 mg Copaxone
- 5.11 Although Copaxone 20 mg is no longer PBS-listed, the pricing of Glatira 20 mg in 1 mL PFS, 28, was based on the previous PBS price of Copaxone 20 mg in 1 mL PFS (pack of 28). Before the delisting of the 20 mg form, the AEMP for the 20 mg in 1 mL PFS (pack of 28) and 40 mg in 1 mL PFS (pack of 12) were the same (\$791.54).
- 5.12 The minor submission assumed no differences in the utilisation of other healthcare costs between Glatira and Copaxone and therefore presented the cost-minimisation analysis as a comparison of drug costs only (see Table 2).
- 5.13 The minor submission expected the listing of Glatira to trigger a 25% statutory price reduction to the AEMP of glatiramer under s99ACB of the *National Health Act 1953*.

**Table 2: Proposed pricing of Glatira**

Product	AEMP	Maximum Qty units	Maximum Qty packs	DPMQ
<b>Copaxone pricing at 1 March 2021</b>				
Copaxone 40 mg in 1 mL PFS	\$791.54	12	1	\$894.98*
<b>Minor submission proposed pricing (including application of a 25% statutory price reduction)</b>				
Glatira 40 mg in 1 mL PFS	\$593.66	12	1	\$677.24*
Glatira 20 mg in 1 mL PFS	\$593.66	28	1	\$677.24*

\*The DPMQs have been updated from that presented in the submission to represent the correct DPMQ for Copaxone as of 1 Jan 2021  
Source: Table 3.2 pg 29 of submission

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### **Estimated PBS usage & financial implications**

- 5.14 The minor submission used a market share approach to estimate the financial impact of Glatira.
- 5.15 The minor submission used historical PBS data from 2016-2019 for Copaxone to forecast the future PBS utilisation of glatiramer.
- 5.16 The minor submission estimated that the listing of Glatira would result in a net save to the PBS in Year 6 of listing, with a total net save to the PBS over the first 6 years of listing due to the trigger of a 25% statutory price reduction to the AEMP of glatiramer upon listing.
- 5.17 This is summarised in Table 3.

**Table 3: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Estimated financial implications of Glatira</b>						
Cost to PBS/RPBS	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
Copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
Cost to PBS/RPBS less copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
<b>Estimated financial implications for Copaxone</b>						
Forecasted reduction in scripts	-█ <sup>2</sup>	-█ <sup>2</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>	-█ <sup>1</sup>
Savings to PBS/RPBS <sup>b</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>
Copayments	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>	\$█ <sup>3</sup>
Cost to PBS/RPBS less copayments	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>
<b>Net financial implications</b>						
Net cost/savings to PBS/RPBS (Glatira only)	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>
Net cost/savings to PBS/RPBS (Glatira and Copaxone) <sup>c</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>	-\$█ <sup>3</sup>

<sup>a</sup> Based on assumed uptake rate of 20% in Year 1 increasing to 50% in Year 6

<sup>b</sup> Based on current the AEMP of Copaxone (\$791.54)

<sup>c</sup> Includes cost savings from a 25% statutory price reduction on the AEMP for Copaxone

Source: Table 4.4, 4.5, 4.6 pg 33-34 of submission

The redacted values correspond to the following ranges:

<sup>1</sup> 5,000 to < 10,000

<sup>2</sup> 500 to < 5,000

<sup>3</sup> \$0 to < \$10 million

5.18 The minor submission assumed that glatiramer would move to the F2 formulary and be subject to price disclosure following the listing of Glatira.

5.19 As a minor submission, the financial estimates have not been independently evaluated.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

### **Quality use of medicine**

5.20 The minor submission did not provide a rationale for the requested listing of the 20 mg strength of Glatira on the PBS. At its November 2018 consideration of the request to delist Copaxone 20 mg/mL injection, the PBAC acknowledged the clinical use of the 20 mg/mL was diminishing. This may be due to more frequent once daily dosing required for the 20 mg/ mL injection compared to three times a week for the 40 mg/mL injection.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 6 PBAC Outcome

- 6.1 The PBAC recommended the listing of a new brand of glatiramer, Glatira<sup>®</sup>, 40 mg/mL injection and 20 mg/mL injection, on the PBS for the treatment of multiple sclerosis, on a cost-minimisation basis to the reference brand, Copaxone<sup>®</sup>.
- 6.2 The PBAC considered that the listings are likely to substitute within the existing glatiramer market and therefore not result in increased utilisation of glatiramer.
- 6.3 The PBAC advised the equi-effective doses were:
- Glatira 40 mg 3 times a week
  - Copaxone 40 mg 3 times a week
  - Copaxone 20 mg once daily (QD)
- 6.4 The PBAC recalled its decision at the November 2018 meeting to delist Copaxone 20 mg/mL from the PBS at the request of the sponsor. The PBAC recalled that its decision was based on diminishing use of the 20 mg/mL injection. The PBAC noted that Copaxone 20 mg/mL was de-listed in July 2019. Although the PBAC considered there was a low clinical need for the 20 mg/mL injection, it had no objection to its listing on the PBS.
- 6.5 The PBAC noted that the TGA was unable to assess bioequivalence based on pharmacokinetic or pharmacodynamic markers, because the concentration of glatiramer in plasma or other body fluids cannot be determined; and glatiramer is extensively degraded at the site of subcutaneous injection. The PBAC considered that based on the available trial evidence using MRI-endpoints, it would be reasonable to consider Glatira and Copaxone as bioequivalent for the purposes of the *National Health Act 1953* (the Act).
- 6.6 The PBAC advised, under Section 101 (4AACD) of the Act, that Glatira 40 mg/mL injection and Copaxone 40 mg/mL injection should be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule).
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Glatira is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Copaxone, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 6.8 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

### Outcome:

Recommended

## 7 Recommended listing

- 7.1 Add new medicinal product pack that has the strength of '20 mg/mL injection' with the trade product 'Glatira' as follows:
- 7.2 Add new trade product 'Glatira' to the existing 40 mg/mL strength listing (PBS item code 10416F) as follows:
- 7.3 Add a-flags between the Glatira and Copaxone trade products for the 40 mg/mL strength as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
GLATIRAMER ACETATE					
glatiramer acetate 40 mg/mL injection, 12 x 1 mL syringes	10416F	1	12	5	<sup>a</sup> Glatira <sup>a</sup> Copaxone
glatiramer acetate 20 mg/mL injection, 28 x 1 mL syringes	NEW	1	28	5	Glatira
					Max Qty multiplier = 1, Repeat increases: Nil
<b>Restriction Summary 7698 / Treatment of Concept: 7695 (as of 1 March 2021)</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [7695]					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Indication:</b> Multiple Sclerosis					
<b>Treatment Phase:</b> Initial treatment					
<b>Clinical criteria:</b>					
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; or					
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis, with 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					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years of commencing a PBS-subsidised disease modifying therapy for this condition					
<b>AND</b>					
<b>Clinical criteria:</b>					
Patient must be ambulatory (without assistance or support)					
<b>Prescribing Instructions:</b>					
Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical records.					
<b>Restriction Summary 6860 / Treatment of Concept: 6860 (as of 1 March 2021)</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					

<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [6860]
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Indication:</b> Multiple Sclerosis
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must not show continuing progression of disability while on treatment with this drug
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have demonstrated compliance with, and an ability to tolerate this therapy

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Juno welcomes the PBAC's recommendation to list Glatira (glatiramer acetate) on the PBS for the treatment of multiple sclerosis