

5.15 FINGOLIMOD

Capsule 250 micrograms (as hydrochloride), Gilenya[®], Novartis Pharmaceuticals Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested the PBS listing of a 250 mcg capsule of fingolimod for the treatment of patients with relapsing-remitting multiple sclerosis.

2 Requested listing

- 2.1 The submission requested the same listing as the currently listed fingolimod 500 mcg capsule.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
FINGOLIMOD, 250 microgram Capsule, 28	1	5	Published: \$2,209.33 Effective: [REDACTED]	Gilenya	Novartis

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple sclerosis
Treatment phase:	Initial treatment
Restriction:	Authority Required - Telephone
Clinical criteria:	<p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</p> <p>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,</p> <p>AND</p> <p>The treatment must be a sole PBS-subsidised disease modifying therapy for this condition,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>Patient must be ambulatory (without assistance or support).</p>
Prescriber instruction	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Treatment phase:	Continuing treatment
Restriction:	Authority Required - Telephone
Clinical criteria:	<p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis,</p> <p>AND</p> <p>The treatment must be a sole PBS-subsidised disease modifying therapy for this condition,</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>Patient must not show continuing progression of disability while on treatment with this drug,</p> <p>AND</p> <p>Patient must have demonstrated compliance with, and an ability to tolerate this therapy.</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

2.2 For patients aged less than 18 years that weigh less than 40 kg, treatment with fingolimod 250 mcg capsules would align with the TGA approved Product Information.

2.3 The requested listing is silent on patient age and weight. In addition to paediatrics that weigh under 40kg, patients who are currently not tolerating the 500 mcg dose may be treated with the 250 mcg dose of fingolimod.

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

3 Background

3.1 Fingolimod 250 mcg capsule was TGA registered on 12 April 2019 for 'the treatment of adult and paediatric patients of 10 years of age and above with relapsing forms of multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability'.

3.2 Fingolimod 500 mcg capsule was TGA registered on 1 February 2011 for "the treatment of relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse." This indication was extended to explicitly include both adult and paediatric patients in April 2019.

3.3 Based on the TGA approved Product Information (PI), in paediatric patients (10 years of age and above), the recommended dose of fingolimod is dependent on body weight:

- Paediatric patients with body weight ≤ 40 kg: one 0.25 mg capsule daily taken orally.
- Paediatric patients with body weight > 40 kg: one 0.5 mg capsule daily taken orally.

Paediatric patients who start on 0.25 mg capsules and subsequently reach a stable body weight above 40 kg should be switched to 0.5 mg capsules.

- 3.4 Following a deferred decision at the March 2011 PBAC meeting, the PBAC made a recommendation to list fingolimod 500 mcg capsule as Authority Required listing for the treatment of clinically relapsing-remitting multiple sclerosis (RRMS) in patients who meet certain criteria.

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

4 Comparator

- 4.1 The minor submission nominated fingolimod 500 mcg capsule as the main comparator, but noted that based on the existing use of PBS-subsidised treatments in paediatric patients, peginterferon (IFN) β-1a and natalizumab are also potential comparators. As the current PBS-listing of fingolimod 500 mcg is silent on patient age, it is likely that the existing use of fingolimod 500 mcg will be replaced by fingolimod 250 mcg in paediatric and adolescent patients. The proportion of use of PBS-subsidised RRMS therapies in paediatric patients is shown in Table 1.

Table 1: PBS 10% sample data on medications used to treat patients aged <18 years with RRMS, July 2017 to June 2018

Drug	Script frequency	Proportion of total
Tysabri (natalizumab)	240	34%
Gilenya (fingolimod)	200	29%
Plegridy (peginterferon β -1a)	160	23%
Aubagio (teriflunomide)	40	6%
Zinbryta (daclizumab)	0	6%
Ocrevus (ocrelizumab)	30	4%
Tecfidera (dimethyl Fumarate)	30	4%
Total	700	100%

Source: Table 1.2 of the submission. Proportions <1% removed.

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 and welcomed the input from two organisations via the Consumer Comments facility on the PBS website. The comments described the need for a greater number of treatments for RRMS in paediatrics and low weight patients, and how relapses can result in short and long term disabilities, which significantly affect the lives of families who care for these patients.

Clinical trials

5.3 The minor submission presented a direct randomised trial which compared the efficacy of fingolimod 500 mcg capsules in patients >40 kg and fingolimod 250 mcg capsules in patients ≤40 kg to IM IFN β-1a in children/adolescent patients aged 10 to less than 18 years (Study 2311).

5.4 A further study was presented in the minor submission to demonstrate the bioequivalence of 2x250 mcg fingolimod capsules to 1x500 mg fingolimod capsule (Study 2117). As this study is of limited relevance to the submission, results have not been presented here.

5.5 Trials presented in the submission are summarised in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
Study 2311	A two-year, double-blind, randomized, multicentre, active controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a IM once weekly in paediatric patients with multiple sclerosis with five-year fingolimod Extension Phase.	Chitnis T, Arnold DL, Banwell B, Brück W, Ghezzi A, Giovannoni G, et al. Trial of Fingolimod versus Interferon Beta-1a in Pediatric Multiple Sclerosis. NEJM 2018; 379(11): 1017-27
Study 2117	An open label, single dose, crossover study to evaluate the relative bioavailability of a new fingolimod formulation (2x0.25 mg) in comparison to the Final Market Image (FMI, 0.5 mg) in healthy volunteers.	Bhad P, David O, Bende G, Pal P, Schmouder R, Golla G. Clinical Study Report Date 22 Nov 2012.

Source: p48 of the submission

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

Comparative effectiveness

5.6 As fingolimod 250 mcg was likely to replace fingolimod 500 mcg, the comparison between fingolimod and IFN β-1a was considered less relevant to the submission and results of this comparison were not presented here. The pre-PBAC response (p1) maintained that the comparison to IFN β-1a was also relevant as there were no randomised-controlled trials of MS medications in patients aged less than 18 years prior to study 2311.

5.7 The submission presented results of the annualised relapse rate (ARR) from Study 2311 for fingolimod by weight-based subgroups (≤ 40 kg and > 40 kg).

Table 3: Summary of Study 2311 ARR results for fingolimod treatment in paediatric patients weighing ≤ 40 kg (250 mcg dose) and > 40 kg (500 mcg dose)

Result parameter	Results by weight group	
	≤ 40 kg (n=9)	> 40 kg (n=98)
ARR time-based		
Number of relapses	3	22
Time in study (days)	4680	60895
Raw ARR (time-based)	0.234	0.132
ARR subject-based		
Mean (SD)	0.197 (0.40)	0.141 (0.43)
Median	0	0
Range	0 to 1.01	0 to 2.34

ARR (time-based) is calculated by taking the total number of relapses observed for all subjects within a treatment group, divided by the total number of days in study of all subjects within the treatment group and multiplied by 365.25 days.

ARR (subject-based) is the individual subject ARR which is calculated by taking the total number of relapses observed for a subject divided by the total number of days in study of that subject and multiplied by 365.25.

Source: Compiled from table 2.24, p67 of the submission.

5.8 While the ARR for patients weighing ≤ 40 kg treated with fingolimod 250 mcg was similar to the ARR for patients weighing > 40 kg treated with fingolimod 500 mcg, the numbers of patients receiving fingolimod 250 mcg in study 2311 were very low (n=9).

Comparative harms

5.9 The submission stated that separate safety data was not reported for the patients weighing ≤ 40 kg and commencing treatment with fingolimod 250 mcg, thus an assessment of the safety of fingolimod 250 mcg compared with fingolimod 500 mcg was difficult. However, the submission noted that the clinical study report did not identify any concerns with the safety of fingolimod in young patients.

Clinical claim

5.10 The submission claimed that fingolimod 250 mcg in paediatric patients weighing 40 kg or less was non-inferior in comparative effectiveness and non-inferior in comparative safety to fingolimod 500 mcg in adults and children weighing over 40 kg.

5.11 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

5.12 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

Economic analysis

5.13 The submission proposed the same published and effective prices for fingolimod 250 mcg capsules as the current fingolimod 500 mcg capsules, based on equivalent efficacy, safety and systemic exposure of fingolimod 250 mcg in patients weighing ≤40kg with fingolimod 500 mcg in heavier patients.

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

Estimated PBS usage & financial implications

5.14 A market share approach was used to estimate the eligible patient population.

5.15 The submission stated that fingolimod 500 mcg would be replaced by fingolimod 250 mcg for all patients weighing ≤40kg, which would not have any financial impact if the two products are priced the same. Further, the submission estimated that a significant proportion of use of IFN β-1a in patients weighing ≤40kg would be replaced by fingolimod 250 mcg. The proportion of the total scripts for patients ≤40kg that were estimated to be IFN β-1a was 28% in Year 1, reducing to 12% in Year 6. Natalizumab use was not expected to change.

5.16 The minor submission estimated a net cost to the PBS of less than \$10 million in Year 6 of listing, with a total net cost to the PBS of less than \$10 million over the first 6 years of listing.

5.17 Estimated use and financial implications are detailed in Table 4.

Table 4: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed						
Estimated financial implications of fingolimod 250mcg						
Cost to PBS						
Co-payments						
Cost to PBS less co-payments						
Estimated financial implications for displaced listings						
Cost to PBS						
Co-payments						
Cost to PBS less co-payments						
Net financial implications (effective price)						
Net cost to PBS						

Source: Compiled in minor overview from data provided in attachment 7 of the submission.

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

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required (telephone) listing of fingolimod, in the form 250 microgram capsules, on the general schedule for treatment of relapsing-remitting multiple sclerosis (RRMS) in patients weighing 40kg or less. In making this

- recommendation, the PBAC considered that fingolimod 250 mcg used in RRMS patients weighing 40kg or less was equivalent to fingolimod 500 mcg used in RRMS patients weighing more than 40kg.
- 6.2 The PBAC accepted that fingolimod 500 mcg taken once daily by patients weighing 40kg or less was likely to be replaced by fingolimod 250 mcg, but noted that in addition to this population, patients of any weight currently being treated with fingolimod 500 mcg every second day would also be likely to be prescribed fingolimod 250 mcg.
- 6.3 The PBAC noted that the number of patients weighing 40kg or less in Study 2311 was very low, and therefore considered that the data to support the listing of fingolimod 250 mcg was minimal. While the PBAC considered it was likely that in patients weighing more than 40kg, the use of fingolimod 250 mcg would have inferior efficacy compared to fingolimod 500 mcg, it considered that non-inferior efficacy and safety of fingolimod 250 mcg in patients 40kg or less compared to fingolimod 500 mcg in patients more than 40kg was sufficiently demonstrated.
- 6.4 While the submission requested the same restriction as for the current listing of fingolimod 500 mcg capsule, which is silent on patient age and weight, due to the lack of available data of the use of fingolimod 250 mcg in patients weighing over 40kg, the PBAC considered that it would be more appropriate to limit use of fingolimod 250 mcg to patients weighing 40kg or less.
- 6.5 Due to the likely reduced efficacy of fingolimod 250mcg in patients weighing over 40kg, the PBAC considered that it would be appropriate for fingolimod 250 mcg to be priced equivalent to fingolimod 500 mcg only if the use of the lower strength was restricted to patients weighing 40kg or less.
- 6.6 The PBAC considered that it would be appropriate for the existing subsidisation cap to be increased by the estimated cost of PBS patients under 40kg who are currently being treated with IFN β -1a and will switch to fingolimod 250 mcg, as estimated in the submission. The PBAC agreed with the sponsor that it is unlikely that natalizumab use on the PBS will change, and that any change from the 500 mcg strength of fingolimod will not result in any change to PBS net impact, and therefore these should not be considered for the purposes of the RSA Cap.
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because fingolimod 250 mcg is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over fingolimod 500 mcg, or not expected to address a high and urgent unmet clinical need over fingolimod 500 mcg, 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 advised that, consistent with the existing listing of fingolimod 500 mcg, fingolimod 250 mcg is not suitable for prescribing by nurse practitioners.
- 6.9 The PBAC noted that the Early Supply Rule currently applies to fingolimod 500 mcg, and recommended that it should also apply to fingolimod 250 mcg.

6.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
FINGOLIMOD, 250 microgram Capsule, 28	1	5	Gilenya	Novartis

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Multiple sclerosis
Treatment phase:	Initial treatment
Restriction:	Authority Required - Telephone
Clinical criteria:	<p>The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis by magnetic resonance imaging of the brain and/or spinal cord; OR</p> <p>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,</p> <p>AND</p> <p>The treatment must be a sole PBS-subsidised disease modifying therapy for this condition,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>Patient must be ambulatory (without assistance or support).</p>
Population criteria	Patient must weigh 40 kg or less.
Prescriber instruction	Where applicable, the date of the magnetic resonance imaging scan must be recorded in the patient's medical record.

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Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS indication:	Multiple sclerosis
Treatment phase:	Continuing treatment
Restriction:	Authority Required - Telephone
Clinical criteria:	The condition must be diagnosed as clinically definite relapsing-remitting multiple sclerosis AND The treatment must be a sole PBS-subsidised disease modifying therapy for this condition AND Patient must have previously received PBS-subsidised treatment with this drug for this condition 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.
Population criteria	Patient must weigh 40 kg or less.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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

Novartis is pleased that the PBAC has agreed to provide young patients with multiple sclerosis access to this treatment.