PUBLIC SUMMARY DOCUMENT
Product: Fingolimod, capsule, 0.5 mg (as hydrochloride), Gilenya®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority Required listing for the initial and continuing treatment of clinically relapsing-remitting multiple sclerosis (RRMS) in an ambulatory patient who has experienced at least two documented attacks of neurological dysfunction, believed to be due to multiple sclerosis in the preceding two years who meets certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Fingolimod 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. Safety and efficacy of fingolimod beyond 2 years are unknown.

4. Listing Requested and PBAC's View

Authority required

Initial treatment of clinically definite relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients who have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years. The diagnosis must be confirmed by magnetic resonance imaging of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient. The authority will be limited to the maximum quantity and number of repeats indicated in the schedule;

Continuing treatment of clinically definite relapsing-remitting multiple sclerosis in patients previously issued with an authority prescription for this drug who do not show continuing progression of disability while on treatment with this drug and who have demonstrated compliance with, and an ability to tolerate, this therapy. Authorities will be limited to the maximum quantity and number of repeats indicated in the schedule.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Multiple sclerosis (MS) is a chronic-progressive autoimmune disorder of uncertain cause. MS causes inflammation and neurodegeneration, characterised by demyelination, axonal loss, gliosis and failure of effective repair. The vast majority of patients (between 65 % and 85%) show a relapsing-remitting form of MS (RRMS), which is characterised by recurrent and unpredictable acute episodes of neurological dysfunction (relapses), followed by a full or partial recovery and periods of clinical stability. The repeated damage to the myelin sheaths and other parts of nerves can lead to the accumulation of serious disability over time.

The submission proposed that the place in therapy of fingolimod 0.5 mg capsules is to provide an additional treatment option for patients with relapsed remitting multiple sclerosis. There are currently five treatment options listed on the PBS.

6. Comparator

The submission nominated intramuscular interferon beta-1a (Avonex) as the main comparator. The submission also nominated interferon beta-1b (Betaferon) and natalizumab as secondary comparators.

The PBAC considered that the main comparator, intramuscular (IM) interferon beta-1a, was appropriate, and that the comparison presented with natalizumab as a secondary comparator, was informative.

7. Clinical Trials

The submission presented one direct randomised comparative trial (plus its extension study) comparing fingolimod and interferon beta-1a (TRANSFORMS) and one direct randomised comparative trial (plus its extension study) comparing fingolimod and placebo (FREEDOMS).

The results of the FREEDOMS trial were used in indirect comparisons of fingolimod versus interferon beta-1b and natalizumab as a supportive analysis.

The trials and associated reports presented in the submission are summarised in the table below:

Trial ID/First author	Protocol title / Publication title	Publication citation
Direct randomised trials of fingolimod		
2302 (TRANSFORMS) Cohen JA, et al.	Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis.	N Engl J Med 2010;362(5):402-415. Published online on 20 January at NEJM.org
2302E1 (TRANSFORMS extension) Khatri B et al.	24-month efficacy and safety outcomes from the TRANSFORMS extension study of oral fingolimod (FTY720) in patients with relapsing-remitting multiple sclerosis.	Neurology 2010; 74(9 Suppl 2): A239. [Conference Paper].
2301 (FREEDOMS) Kappos L et al	A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis.	N Engl J Med. 2010;362(5):387-401. Published online on 20 January 2010 at NEJM.org
Kappos L et al	Oral fingolimod (FTY720) vs placebo in relapsing-remitting multiple sclerosis: 24-month clinical efficacy results from a randomized, double-blind, placebo-controlled, multicenter phase III study (FREEDOMS).	Neurology 2010; 74(9 Suppl 2): A194 [Conference Paper].
Radue EW et al.	Oral fingolimod (FTY720) reduces inflammatory activity vs placebo in relapsing-remitting multiple sclerosis: 24-month MRI results from a randomized, double-blind, placebo-controlled, multicenter phase III study (FREEDOMS).	Neurology 2010; 74(9 Suppl 2): A194. [Conference Paper].
2309 (FREEDOMS II) Calabresi PA et al	Oral fingolimod (FTY720) in relapsing-remitting multiple sclerosis: baseline patient demographics and disease characteristics from a 2-year phase III trial (FREEDOMS II).	Neurology 2010; 74 (9 Suppl 2): A416-A417 [Conference Paper].
Direct randomised trials of interferon beta-1b		

IFNB MSSG	Pooled results from two identically designed 2-year trial comparing interferon beta-1b 1.6 MIU, beta-1b 8MIU and placebo	
Duquette P et al.	Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial.	Neurology 1993;43:655-661.
Paty DW et al	Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial.	Neurology 1993;43:662-667.
Sibley WA et al.	Interferon beta treatment of multiple sclerosis	Neurology 1994;44:188-190.
Duquette P et al	Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial.	Neurology 1995;45:1277-1285
Direct randomised trials of natalizumab		
AFFIRM	2-year randomised trial comparing natalizumab vs. placebo	
Polman CH et al.	A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis.	N Engl J Med 2006;354:899-910

8. Results of Trials

DIRECT RANDOMISED EVIDENCE: FINGOLIMOD VERSUS INTERFERON BETA-1A (TRANSFORMS)

Aggregate annualised relapse rate (ARR)

The results of the primary outcome of aggregate annualised relapse rate (ARR) of fingolimod 0.5 mg daily and IFN beta-1a 30 μg IM once weekly from the TRANSFORMS trial at 12 months showed are shown in the table below:

	Fingolimod 0.5mg po daily N=429	**IFN beta-1a I.M. 30μg weekly N=431**	**Rate Ratio Fingolimod 0.5mg vs. INFB-1a**
Modified ITT population^ (Primary outcome)			
Number of relapses	75	129	-
Adjusted ARR (95% CI)[c]	0.16 (0.122-0.212)	0.33 (0.262-0.417)	
p-value[a]			**P<0.001**

For the primary study outcome of aggregate annualised relapse rate (ARR), the PBAC noted that the post-hoc sub-group analysis of patients with at least two relapses in the two years prior to randomisation showed that treatment with fingolimod was associated with a statistically significantly lower ARR than interferon beta-1a which was comparable to the results of the modified intention to treat (mITT) population.

The sub-group of patients in the TRANSFORMS study of fingolimod versus interferon beta-1a who had at least 2 relapses in the 2 years prior to randomisation is representative of the population eligible for fingolimod treatment according to the proposed PBS restriction.

3 Months confirmed disability progression

For the study outcome of proportion of patients free of 3-months confirmed disability progression at month 12, the PBAC noted a trend favouring fingolimod in both the mITT population and the sub-group of patients with at least 2 relapses in the 2 years prior to

randomisation, however, the differences did not reach statistical significance. However, the PBAC acknowledged that the TRANSFORMS study was not powered to detect a difference in disability progression at 12 months.

The submission also presented an indirect comparison of fingolimod versus natalizumab using trial outcomes from FREEDOMS and AFFIRM.

For PBAC's view of these results, see Recommendation and Reasons.

The incidence of any adverse event was lower in patients treated with fingolimod 0.5mg versus IFN beta-1a (86% vs 91.6%), however more patients in the fingolimod 0.5 mg treatment group had interrupted drug therapy due to AE (10.5% vs 4.6%).

There were 2 deaths in the fingolimod 1.25 mg treatment arm, but no death was observed with fingolimod 0.5 mg and IFN beta-1a treatments.

The incidence of AEs in the system organ classes of investigations was statistical significantly higher in the fingolimod 0.5 mg than the interferon beta-1a group (20.0% vs 8.6%), neoplasms benign, malignant and unspecified (14.5% vs. 9.7%). Number of patients experiencing ALT raises was higher in the fingolimod treatment group compared to IFN beta-1a (6.5% vs 1.9%).

The incidence of organ class AE of general disorders and administration site conditions was lower in the fingolimod 0.5 mg versus IFN beta-1a group (25.2% vs 62.6%) and influenza-like illness (3.5% vs 36%). Similarly, the incidence of pyrexia was lower in the fingolimod versus interferon beta-1a group (4.2% vs 17.9%), as was myalgia (3.3% vs 10.2%) and arthralgia (2.8% vs 5.6%).

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed fingolimod as superior in terms of comparative effectiveness and with a similar safety profile to interferon beta-1a (Avonex) its main comparator, as well as interferon beta 1b, (Betaferon), interferon beta-1a SC (Rebif) and glatiramer acetate (Copaxone) based on the cost minimisation recommendations of these currently listed treatments with interferon beta-1a (Avonex).

The PBAC accepted that fingolimod was superior in terms of comparative effectiveness and with a similar safety profile to interferon beta-1a.

10. Economic Analysis

A stepped economic evaluation was presented.

The time horizon in the modelled economic evaluation was life time. The model followed patients until death.

The stepped economic evaluation produced a base case incremental cost per extra quality adjusted life year (QALY) gained in the range of $45,000 – $75,000. Sensitivity analyses showed the results are most sensitive to changes in model time horizon. When the model

duration was reduced from an average of 62 years to 5 years, the incremental cost per QALY increased and was estimated to be in the range of $105,000 – $200,000. The results are also very sensitive to changes in discontinuation rates and utility values applied in the modelled economic evaluation.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5.

The financial cost per year to the PBS was estimated to be in the range of $30 – $60 million in Year 5.

12. Recommendation and Reasons

The PBAC agreed that the restriction should stipulate that fingolimod be used as monotherapy as it was not intended for use as add-on therapy and should not be limited to neurologists because of issues with access. The PBAC did not consider switching criteria to be necessary as the requested restriction for initial treatment allows switching provided the initiation criteria are met.

The PBAC considered the submission's main comparator, intramuscular (IM) interferon beta-1a, was appropriate, and that the comparison presented with natalizumab as a secondary comparator, was informative.

The PBAC noted that the sub-group of patients in the TRANSFORMS study of fingolimod versus interferon beta-1a who had at least 2 relapses in the 2 years prior to randomisation is representative of the population eligible for fingolimod treatment according to the proposed PBS restriction. For the primary study outcome of aggregate annualised relapse rate (ARR), the PBAC noted that the post-hoc sub-group analysis showed that treatment with fingolimod was associated with a statistically significantly lower ARR than interferon beta-1a. This was comparable to the results of the modified intention to treat (mITT) population.

For the study outcome of proportion of patients free of 3-months confirmed disability progression at month 12, the PBAC noted a trend favouring fingolimod in both the mITT population and the sub-group of patients with at least 2 relapses in the 2 years prior to randomisation, however, the differences did not reach statistical significance. However, the PBAC acknowledged that the TRANSFORMS study was not powered to detect a difference in disability progression at 12 months.

Overall, the PBAC accepted that fingolimod was superior in terms of comparative effectiveness and with a similar safety profile to interferon beta-1a.

The PBAC noted that the submission did not explicitly claim that fingolimod is non-inferior to natalizumab, however, natalizumab is assumed to have the same treatment benefit as fingolimod when included in a sensitivity analysis of the economic model. The PBAC noted the results of the simple/unadjusted indirect comparison of fingolimod versus natalizumab using placebo as the common comparator from the FREEDOMS and AFFIRM studies (which did not account for differences in patient characteristics of the two trials) suggested a lower ARR for natalizumab. The PBAC did not accept the argument in the submission's Pre-Sub-Committee Response that between-trial differences in trial population characteristics influenced the results of the indirect comparison. However, in the absence of direct head-to-

head evidence comparing natalizumab and fingolimod, the result of this indirect comparison is uncertain/inconclusive.

The PBAC noted the stepped economic evaluation produced a base case incremental cost per extra quality adjusted life year (QALY) gained in the range of $45,000 – $75,000. Sensitivity analyses showed the results are most sensitive to changes in model time horizon. When the model duration was reduced from an average of 62 years to 5 years, the incremental cost per QALY increased and was estimated to be in the range of $105,000 – $200,000. The results are also very sensitive to changes in discontinuation rates and utility values applied in the modelled economic evaluation. The high treatment discontinuation rates used in the model may not be appropriate. When all patients are assumed to be on first line treatment until SPMS (or beyond EDSS 5), the ICER increased and was estimated to be in the range of $75,000 – $105,000. When utility values from Fisk et al (2005) are used the ICER increased and was estimated to be in the range of $45,000 – $75,000. The model is also sensitive to disutility associated with injectable DMTs, which if removed altogether increase the ICER to be in the range of $75,000 – $105,000.

The PBAC noted the submission claimed that the ICER was likely to be overestimated based on a number of conservative assumptions, such as:

- Indirect costs (e.g., lost productivity, short-term absenteeism, and forced early retirement) or value of informal community care (e.g., care by family members etc) are not considered. (However, it is noted that these are generally not taken into account in the base case ICER by PBAC but may be taken into account in terms of other relevant factors).
- Emotional/physical/health related quality of life burden experienced by families or carers of the patients are not considered (although, including costs and utilities for carers would have been double counting.)
- The model largely disregards the disutility directly attributable to the necessity for frequent injections associated with the existing DMTs itself.
- Administration/monitoring costs are largely ignored. In particular, the model does not include potential economic benefits associated with orally administered fingolimod over self-injected drugs, for example, avoided home nursing services.
- Cost of corticosteroid use for the treatment of relapse is not included.
- Relapse rates are as observed in the clinical trial environment. The MSBase Registry data indicate the presence of considerably higher relapse rates in practice.
- Relapses do not contribute to a permanent change in health state
- MS management costs (i.e., health state costs) for RRMS are applied to SPMS.

However, as was discussed in the evaluation, there were also a number of assumptions used in the model that may not be appropriate and would potentially lead to underestimation of the ICER.The PBAC agreed with the main issues of economic uncertainty as identified by the ESC:

- whether the MSBase registry ABCR drug cohort is representative of the patients likely to be accessing fingolimod on the PBS, given the differences in Expanded Disability Status Scale (EDSS) scores at baseline;
- whether the derivation and application of trial based transition probabilities to the modelled economic evaluation is appropriate, considering whether the use of whole point EDSS transitions, disease modifying treatment (DMT) stopping rule of EDSS >

5 and no more than one transition per year appropriately reflects MS progressions in real life and DMT treatment on the PBS;
- the application of discontinuation rates, given that it is likely that patients who discontinue from treatment will try other DMTs;
- the use of similar relapse rates for RMSS and secondary progressive multiple sclerosis (SPMS);
- whether the submission's assumption of identical relapse rates for natalizumab and fingolimod is appropriate.

The PBAC considered that in the context of these uncertainties, the base case ICER was unacceptably high to recommend listing. The PBAC considered that the uncertainties in the model could be managed with a lower price offer and that an acceptable ICER for fingolimod based on the current model would need to be in the range of $15,000- $45,000 per QALY.

The PBAC therefore deferred its decision on the submission for fingolimod pending further negotiation with the sponsor. The PBAC acknowledged and noted the consumer comments on this item.

Subsequent to the meeting, the sponsor offered a further price reduction. The PBAC therefore recommended out-of-session listing fingolimod on the PBS as an Authority Required benefit for the initial and continuing treatment of clinically relapsing-remitting multiple sclerosis (RRMS) in a patient who meets certain criteria on the basis of an acceptable cost-effectiveness ratio compared with interferon beta-1a.

Recommendation:
FINGOLIMOD, capsule, 0.5 mg (as hydrochloride)

Restriction: Authority required

Initial treatment, as monotherapy, of clinically definite relapsing-remitting multiple sclerosis in an ambulatory (without assistance or support) patient who has experienced at least 2 documented attacks of neurological dysfunction, believed to be due to the multiple sclerosis, in the preceding 2 years. The diagnosis must be confirmed by magnetic resonance imaging of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient. The authority will be limited to the maximum quantity and number of repeats indicated in the schedule;

Continuing treatment, as monotherapy, of clinically definite relapsing-remitting multiple sclerosis in a patient previously issued with an authority prescription for this drug who does not show continuing progression of disability while on treatment with this drug and who has 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.

Max qty: 28

Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis welcomes the PBAC's positive recommendation for fingolimod (Gilenya). Gilenya is the first oral treatment and was recommended by the PBAC on the basis of superiority to interferon beta-1a with acceptable cost-effectiveness for treatment in patients with relapsing-remitting forms of MS who meet certain criteria. Novartis is working closely with the Department of Health to ensure timely listing of Gilenya on the PBS.