Purpose

The purpose of this submission is to request a change to the current fingolimod capsule listing from Section 85 Authority Required to *Section 85 Authority Required (Streamlined)* in order to reduce administrative burden on prescribers. The reasons that form the basis for this request are discussed below. Novartis is confident that a Streamlined Listing for fingolimod will provide prescribers with more time for patient care without compromising the integrity and intent of the authority system.

Background

Fingolimod 500 mcg capsule was registered by the TGA on 1 February 2011 for the 'treatment of relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse'. The recommended dosage for fingolimod is 500 mcg once a day[1].

The drug was considered by the PBAC at the March 2011 meeting and was recommended by the Committee on the basis of an acceptable cost-effectiveness ratio compared to interferon beta-1a. The listing of fingolimod on the PBS took effect from 1 September 2011.

Criteria for streamlined authority required listing

Streamlined authority process was instituted from 1 July 2007 with the aim of reducing the administrative burden for prescribers, providing them with more time to devote patient care without compromising the integrity of the authority system. According to the Streamlined Authority Initiative Review ('the Review') conducted post implementation at 12 months[2], PBS listings under the streamlined process are limited to medicines

1. That treat chronic and stable long term conditions
2. With stable dosage regimens
3. That are less susceptible to risk of misuse or increased prescribing outside of restrictions

Additionally, the Review also sets a list of criteria for excluding items from the streamlined authority process.

The approach taken in this submission is to assess the appropriateness for fingolimod to be considered for streamlined listing by addressing the criteria as set out in the Review. In addition, updated safety data, type of prescribers and patient compliance for fingolimod are also discussed. A summary of these criteria and a brief note on how fingolimod satisfies them are provided in Table 1 below. Further explanations on how fingolimod meets the requirements for streamlined Authority Required listing are provided in the next section.

Table 1: Brief summary on reasons that a streamlined listing for fingolimod is appropriate

	Criteria to assess appropriateness for streamlined listing	**Brief summary on how fingolimod satisfies these criteria**
I	Treat chronic and stable long term condition	MS is a chronic-progressive autoimmune disorder, and the vast majority of patients show a relapsing-remitting form of MS
II	Stable dosage regimen	Fingolimod is administered as a once daily dose regimen of 500mcg
III	Less susceptible to risk of misuse or increased prescribing outside of restrictions	Misuse of fingolimod is unlikely as there is no abuse potential with the drug. No evidence of prescribing outside of current restrictions have been found
IV	Drugs excluded from streamlined listing by the Review	Fingolimod does not belong to any of the medicines/class excluded from streamlined listing reported in the Review
V	Updated safety data	Global safety data (1 Mar to 31 Aug 2013) showed there has been no change to the efficacy information and the safety data remain in accord with the previous cumulative experience. The TGA-mandated RMP remains in force. Effective first-dose monitoring has been implemented since PBS listing
VI	Type of prescribers	Majority of prescribers are specialist neurologists despite the PBS listing permitting prescription by GPs
VII	Patient compliance	Persistence data from the DUSC analysis last year highlighted that fingolimod persistence is high meaning that patients continue to receive clinical benefit

Note: Criteria I-IV are derived from the Streamlined Authority Initiative Review. Other criteria (V-VII) are further assessed by the submission

I. Treat chronic and stable long term condition

Multiple sclerosis is a chronic and stable long term condition. Fingolimod is registered and reimbursed for the treatment of patients with relapsing-remitting form of MS (RRMS) which is a chronic progressive autoimmune disorder of uncertain cause. RRMS is characterised by recurrent and unpredictable acute episodes of neurological dysfunction (relapses) followed by a full or partial recovery and periods of clinical stability.

A study conducted in Australia reported the median survival time from onset of symptoms (at ages between 20 – 39 years old) to death was 42 years[3]. A patient who is non-ambulatory (classified with DSS 6 or higher) is no longer eligible for treatment with fingolimod on the PBS. Based on the estimated progression of disability curve, the study reported that the expected time to reach Disability Status Scale 6 (require intermittent or unilateral constant assistance to walk) was 27 years. Therefore, fingolimod is used in a chronic condition that may affect patients for more than 20 years. A Streamlined Listing for fingolimod to facilitate prescribing whereby majority of prescriptions are written by specialist neurologists (to be discussed later) would be appropriate to reflect the chronic nature of the condition.

II. Stable dose regimen

Fingolimod has a stable dosage regimen. The recommended dosage for fingolimod is a once daily 500mcg capsule that can be taken with or without food. This represents a stable dose regimen for use in a chronic condition.

III. Risk of misuse or increased prescribing outside of restrictions

A review of all complete and incomplete case reports of overdose, abuse and misuse (with or without associated adverse reactions) from the Novartis global safety data did not reveal any use patterns or other safety information relevant to the benefit-risk assessment for fingolimod. The global safety data also noted that current information do not indicate specific risk in off-label use, and that there is no evidence of significant use of fingolimod outside of the approved indication of adult patients with RRMS.

Current clinical practice in MS management has evolved over time to more closely align with the McDonald criteria rather than the Poser criteria. The listing of fingolimod under a Streamlined listing *per se* is unlikely to have a significant impact on the adoption of the more clinically relevant McDonald criteria which has already occurred.

IV. Drugs excluded from streamlined listing by the Review

A set of criteria were also developed by the Review (p11) for excluding items from the streamlined authority process. These criteria are reproduced in Table 2 and are assessed against fingolimod. Overall, fingolimod does not belong to any of the medicines/class excluded from streamlined listing reported in the Review. Other exclusion requirements (e.g. Section 100, price premiums and listing on the RPBS) are not applicable to fingolimod. In the instance whereby increased quantities and/or repeats are requested by prescribers, prior approval from the Department of Human Services would be needed (i.e. Authority Required listing continues to apply).

Overall, fingolimod does not fit into any of the exclusion criteria as set out in the Review.

Table 2: Drugs excluded from Authority Required (Streamlined) listing as at 1 July 2007

Medicine/Class	Rationale for Exclusion	*Comments specific to fingolimod*
Antiinfectives	Short term use and risk of antimicrobial resistance	*Fingolimod is not an anti-infective*
Drugs to treat nausea in chemotherapy	Short term use, variable and complex dosage regimes	*Fingolimod is not used to treat nausea in chemotherapy*
Anabolic steroids, androgens, antiandrogens	Potential for illicit diversion	*Fingolimod is not an anabolic hormone with potential for illicit diversion*
Antigonadotropics	Some restrictions for short term use	*Fingolimod is not an antigonadotropic*
Antineoplastic (cytotoxic) agents	Short term use and variable and complex dosage regimes	*Fingolimod is not an anti-neoplastic agent and has a simple once a day dosage regimen*
Narcotics	Potential for dependence and illicit diversion	*Fingolimod is not a narcotic*
Benzodiazepines	Potential for dependence and possible illicit diversion	*Fingolimod is not a benzodiazepine*
Psychostimulants	Potential for dependence and illicit diversion	*Fingolimod is not a psychostimulant*
Bupropion	Short term use for cessation of smoking	*Fingolimod is not used in this indication*
Special dietary foods	Short term use and need for continual review/management	*Fingolimod is not a special dietary food*
Palliative care medications	Usually short term use, variable and complex dosage regimes	*Fingolimod is not a used in the palliative care setting*
Section 100 items	High cost items often short term use/ requiring demonstration of clinical response	*Fingolimod is not listed under Section 100*
Special Pharmaceutical Benefit and Therapeutic Group Premium Exemptions	Waiver of SPC or TGP premium on clinical grounds requires contact with Medicare Australia	*Fingolimod does not have an SPC or TGP*
Repatriation Pharmaceutical Benefits	Repatriation pharmaceutical benefits may be authorised for uses outside of approved PBS use	*Fingolimod is not listed as a Repatriation Pharmaceutical Benefit*
Requests for increased quantities and / or repeats above those set out in the PBS schedule.	All requests for increased quantities and/or repeats above those set out in the PBS schedule require approval from Medicare Australia.	*For increased quantities and/or repeats, fingolimod will continue to require prior approval (i.e. Authority Required)*

Source: Streamlined Authority Initiative Review, Table 1.1, p11

V. Updated safety data

The ongoing post-market monitoring of fingolimod use by Novartis has shown that the benefit/risk assessment for the drug remains favourable and unchanged. The safety data established below from two main Novartis activities, namely the global safety data and the Fingolimod Risk Management Plan (RMP), support the ongoing optimal use of fingolimod in

clinical practice. Another related activity is the provision of first dose observation services to prescribers who initiate fingolimod treatment for eligible PBS patients with relapsing-remitting MS. Each of these activities is discussed below.

Global safety data

Overall, an analysis of the data showed there has been no change to the efficacy information and the safety data remain in accord with the previous cumulative experience.

Patient exposure

Thus far, the estimated cumulative patient exposure to fingolimod world-wide is 135,800 patient-years comprising of experience both within the clinical trial programme as well as in-market. As summarised in Table 3, the vast majority of the post-marketing experience for efficacy and safety information are being derived from in-market experience (~85%) compared to clinical trial settings (~16%). As in-market patient experience is a better reflection of clinical practice (i.e. clinical trial settings under controlled environments may not be representative of real world fingolimod use), the efficacy and safety data presented are reflective of real world evidence.

Table 3: Estimated patient-year exposure to fingolimod from Novartis safety data in patient-years (%)

	Cumulative exposure
Investigational clinical trials	~21,000 (16%)
Market experience	~114,800 (85%)
Total	**~135,800 (100%)**

In the MS indication, the total exposure to fingolimod in clinical trials is estimated at approximately 21,000 patient-years in close to 12,000 patients with MS. A breakdown on the duration of fingolimod exposure by patient numbers involved in clinical studies is summarised in Table 4. Overall, long term exposure includes more than 7,000 patients who have received therapy for at least 1 year and more than 1,300 patients who have been exposed for more than five years. For the first time in this reporting period, some patients have reached up to 10 years of exposure to fingolimod.

Table 4: Exposure to fingolimod (any dose) by duration from MS trials

Duration of exposure	Patient numbers (completed RCT and other completed/ongoing studies)
≥ 1 day	24634
≥ 180 days	15760
≥ 1 year	10927
≥ 2 years	6673
≥ 3 years	4446
≥ 5 years	2111
≥ 10 years	65

Source: Novartis global safety data

Safety

Overall, there has been no change to the efficacy information during this reporting interval and the safety data remain in accord with previous cumulative experience. Safety information from the last reporting period did not change the cumulative assessment of the identified risks and potential risks in terms of event frequency, specificity or severity. In addition, review of potential drug interactions did not identify any safety concerns (see Table 5).

The updated data from the reporting period on fatal cases does not change the cumulative experience thus far. There is no evidence of excess risk from the comparison of mortality rate in the clinical trial setting and what is expected in the MS population.

The benefit-risk profile of fingolimod in the indication of relapsing MS remains positive, as the benefits of stronger and sustained efficacy as compared to placebo and standard of care continue to outweigh the well-characterized and manageable identified key risks. The expanding clinical experience with over 135,000 patient-years of treatment with fingolimod provides a robust body of evidence supporting both the known benefits and risks of fingolimod in the real world setting.

Table 5: Safety risks and drug interactions

Identified risks	Potential risks	Potential drug interactions
• Bradyarrhythmia (including conduction defects and hypotension complication) occurring post-first dose • Hypertension • Liver transaminase elevation • Posterior reversible encephalopathy syndrome (PRES) • Macular oedema • Infections • Leucopenia and lymphopenia • Reproductive toxicity • Varicella zoster virus infections	• Skin cancer • Other malignant neoplasms • Lymphoma • Hemophagocytic syndrome • Acute disseminated encephalomyelitis-like (ADEM-like) events • Thrombo-embolic events • QT interval prolongation • Convulsions • Progressive multifocal leukoencephalopathy (PML) • Herpes viral infections other than VZV • Off-label use • Pulmonary oedema • Atypical or severe MS relapse • Hypersensitivity	• Ketoconazole • Carbamazepine • Beta blocking agents • Class Ia and III anti-arrhythmic agents

Risk Management Plan (RMP)

In Australia, a robust Risk Management Plan (RMP) for fingolimod agreed with the TGA has been in place since its registration was approved. This RMP includes a targeted education programme for prescribers and patients. Educational material is distributed to prescribers from whom it is made available to patients. The goal of this programme is to educate physicians and patients on safety areas of interest (bradyarrhythmias upon treatment initiation, infections, reproductive toxicity, macular oedema and liver transaminase elevation). The RMP also includes a set of pharmacovigilance activities designed to monitor and further characterize the safety profile of fingolimod. Taken together, the RMP can be seen as a framework to ensure appropriate prescribing of fingolimod in clinical practice, and that the change from the Authority Required listing to an Authority Required (Streamlined) listing will not jeopardise patient safety.

VI. Type of prescribers

With the exception of natalizumab, all current PBS listings for drugs used in the treatment of RRMS permits prescribing by either general practitioners or neurologists. In the case of fingolimod, the vast majority of fingolimod prescriptions are written by neurologists rather than prescribed in general practice. Supporting evidence is discussed below, using data from

the Bettering The Evaluation And Care Of Health (BEACH) Program[4]. The BEACH Program continuously collects information about the clinical activities in general practice in Australia.

An estimation of the proportion of fingolimod prescriptions arising from general practice is described as follows. Between September 2011 and December 2013, there were 214,500 patient encounters with general practitioners (GPs) recorded in the BEACH data set (see Table 6). Over this time there were only 4 prescriptions for fingolimod, a rate of 1.86 per 100,000 encounters (95% CI: 0.04-3.69). During the 2012-13 financial year, there were 128,700,000 GP items of service claimed through the Medicare Benefits Schedule. Extrapolating the rate of fingolimod prescription to this total figure means that we estimate the total number of fingolimod prescriptions in general practice to be between 0 and 4,800 prescriptions, with the best estimate at 2,400 prescriptions. During the same period (July 2012 – June 2013), Medicare Australia statistics show that there were 34,721 services for fingolimod (item 5262Y). Therefore, approximately 7% (2,400/34,721) of fingolimod prescriptions are written by GP, with the majority (93%) originating from neurologists.

Table 6: Estimation of fingolimod prescriptions by GPs

		Source
Patient encounters with GP	214,500	BEACH (Sep 2011-Dec 2013)
Fingolimod prescription	4	BEACH (Sep 2011-Dec 2013)
Rate fingolimod	4/214,500 = 1.86	
GP items of service	128,700,000	BEACH (2012/13)
Fingolimod prescriptions by GPs	128,700,000 × 1.86 = 2,400	
Fingolimod services	34,721	Medicare Australia (2012/13)
Fingolimod prescriptions by GPs (%)	(2,400/34,721) × 100% = **7%**	

Neurologists as specialist medical practitioners are highly trained in the clinical practice of treating patients with RRMS. As fingolimod is minimally prescribed by GPs, there is negligible risk on patient safety should fingolimod be listed under a Streamlined listing. In fact, for patients initiating treatment with fingolimod, the PI states all patients should be observed with hourly pulse and blood pressure measurement, for a period of 6 hours for signs and symptoms of bradycardia. The provision of services by Novartis on this important requirement is described below.

In Australia, Novartis is playing an active role to ensure that all patients being initiated on fingolimod are properly observed with the necessary initial and ongoing tests via the provision of two programmes[5], *viz.* (i) the provision of health care facilities as part of the first dose observation and (ii) the assignment of a case manager to each patient prior to treatment initiation.

(i) Health care facilities have been set up across all States and Territories to enable patients to be observed for a period of 6 hours for signs and symptoms of bradycardia. These facilities are equipped to measure pulse and blood pressure together with an electrocardiogram being performed prior to dosing and at the end of the 6-hour monitoring period. Should post-dose bradyarrhythmia-related symptoms occur, these facilities can carry out the appropriate management with overnight monitoring as needed. There are over 50 first dose observation sites supported by Novartis in Australia. Neurologists and patients may also have access to other medical facilities that are not part of the Novartis-supported network

(ii) A case manager who is an experienced nurse is assigned to a patient before the start of fingolimod treatment. The case manager supports the patient by booking the necessary medical tests, the first dose observation at a local medical facility together with the follow-up tests. This is a complimentary service for all patients initiated on fingolimod regardless of them being public or private patients. Table 7 summarises the support provided by the case manager to a patient initiated on treatment with fingolimod

Table 7: Case manager support provided to a patient initiated on treatment with fingolimod

1	Pre-dose testing	Book pre-screening test appointments • Blood test (full blood count, Varicella Zoster A/B) • Ophthalmological examination • ECG • Other tests recommended by neurologists
2	Book appointment for FDO	All patients need to be observed for 6 hours after taking the first dose, either at the 50-odd facilities supported by Novartis or other medical facilities Case manager inform the neurologist's office on FDO completion
3	Organise follow-up tests after FDO	Book follow up tests • Ophthalmological examination • Other tests recommended by neurologists

FDO = first dose observation

Given the extensive safety support and ongoing monitoring of patients, together with the clinical management by neurologists of the majority of patients, it is appropriate for fingolimod to be considered for a Streamlined Authority Required listing on the PBS. The resulting reduction in the administration time required by neurologists to seek prior approval (under the current Authority Required listing) would further enhance the clinical management of these patients at the population level.

VII. Patient compliance

Patient compliance to fingolimod is high, resulting in continued clinical benefits being accrued to patients in clinical practice. For example, the predicted versus actual utilisation analysis conducted by the DUSC in June 2013 found that at Year 1, 81% of patients initiated on fingolimod remained on treatment compared to between 56% to 75% for other MS treatments (average 62% across the ABCR). At the time of the analysis, the data from DUSC did not permit an estimation of the median length of treatment. High patient compliance is likely to be maintained should a Streamlined listing be approved, without compromising patient safety due to the RMP activities described earlier.

Conclusion

Fingolimod, with a stable dosage regimen used in the treatment of a chronic condition such as RRMS, is suitable for an Authority Required (Streamlined) listing on the PBS. The global safety data supports the benefit-risk profile which remains positive in the real world setting. Patients are being managed by neurologists in the large majority of cases, and Novartis has been active in providing a case manager as well as a network of medical facilities to ensure first dose monitoring with initiation of fingolimod treatment, followed by subsequent tests as a result of ongoing treatment maintenance. The observed high rate of patient compliance to fingolimod is also an important consideration in the context of a life-long condition such as multiple sclerosis. Moreover, it is unlikely that a Streamlined listing would significantly alter the already changing clinical practice of RRMS treatment whereby the use of the McDonald criteria is becoming prevalent. The prescribing of fingolimod under a Streamlined listing is justifiable on clinical grounds whilst at the same time would ease the administrative burden of requiring neurologists to seek prior approval from Department of Human Services.

References (available on request)

[1] Fingolimod Product Information, 11 October 2012

[2] Streamlined Authority Monitoring Group (SAMG). Streamlined Authority Initiative Review (12-Month Review). May 2009

[3] McLeod JG, Barnett MH, Macaskill P et al. Long-term prognosis of multiple sclerosis in Australia. Journal of Neurological Sciences 2007; 256: 35-38.

[4] Bettering The Evaluation And Care Of Health (BEACH). Family Medicine Research Centre, The University of Sydney. See http://sydney.edu.au/medicine/fmrc/beach/.

[5] Gilenya Go programme. Novartis Pharmaceuticals Australia Pty Ltd.