

10 October 2014

Decisions relating to Multiple Sclerosis treatments

PHARMAC is pleased to announce that, from 1 November 2014, it will:

- list fingolimod (Gilenya);
- list natalizumab (Tysabri); and
- change the restrictions for funded access for interferon beta-1-alpha (Avonex), interferon beta-1-beta (Betaferon) and glatiramer acetate (Copaxone)

in both the community and hospital sections of the Pharmaceutical Schedule.

This decision was the subject of a consultation letter dated 7 August 2014, which can be found on PHARMAC's website at: <http://www.pharmac.health.nz/news/consultation-2014-08-07-mstreatments/>

The fingolimod listing is the result of a multiproduct agreement with Novartis. For information about the decision regarding the multi-product agreement (including details on the other products involved), see our website at: <http://www.pharmac.health.nz/news/notification-2014-10-10-multiproduct/>

In summary, the effect of the decision relating to multiple sclerosis (MS) treatments is that from 1 November 2014:

- The new MS treatments (natalizumab and fingolimod) will be subsidised from first confirmed diagnosis of definitive relapsing remitting MS, for patients with an EDSS¹ score of 0–4.0, who meet the funding criteria. The new funding criteria for all MS treatments have reduced relapse rate requirements.
- The currently available treatments – beta interferons and glatiramer acetate – will have changes to funding criteria. These treatments continue to be funded and will also be available for people earlier in their disease, for whom both fingolimod and natalizumab are not tolerated or clinically not appropriate.
- The criterion requiring funded treatment to stop if the patient's relapse rate is stable has been removed. Under the new stopping criteria, funded treatment would stop if patients have an increasing relapse rate. In addition, funding would cease if there is progression of disability by any of the following EDSS points (the first point is the EDSS at treatment entry, the second when treatment stops):
 - 0–3.0, 1.0–3.0, 1.5–3.5, 2.0–4.0, 2.5–4.5, 3.0–4.5, 3.5–4.5, 4.0–4.5
- People currently receiving funded treatments can choose to stay on their existing treatment, or change to one of the new treatments (provided they meet the new EDSS entry criteria; 0–4).

¹ The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in MS and is used to measure and assess disability and disease progression in MS.

- People currently receiving funded treatments who do not meet the new EDSS entry criteria, and are therefore not eligible to switch, can continue funded treatment with interferon beta-1-alpha, interferon beta-1-beta or glatiramer acetate until they meet the stopping criteria that existed prior to 1 November 2014.

Following consideration of feedback to consultation some changes have been made to the Special Authority criteria to ensure clarity and/or better reflect the intent of the criteria. In addition to wording changes, there have been some substantive changes to the criteria, as detailed below. Note, a summary of the feedback received is provided in this notification from page 14 onwards.

- The type of applicant for the MS treatments has been amended to include general physicians.
- For the interferons and glatiramer acetate the word 'contraindicated' has been changed to 'clinically inappropriate'. PHARMAC acknowledges that patients' clinical situations are not static and therefore considers it appropriate for patients to be able to access treatment with the interferons or glatiramer acetate first-line, should treatment with both natalizumab and fingolimod be clinically not appropriate.
- The funding criteria for the beta interferons or glatiramer acetate have been expanded to include a transition period for a small group of patients who are not currently accessing funded treatments, but who would actually be eligible under the pre-1 November 2014 funding criteria, as follows:
 - People with an EDSS of 4.5-5.5 and otherwise eligible for current funded MS treatments (e.g. 2 or more significant relapses in the previous year) but who had not previously accessed funded treatments, will have until 31 October 2015 to apply for treatment with one of the interferons or glatiramer acetate. Should they access funding they can continue funded treatment until they meet the stopping criteria, in the same way as patients with this EDSS score who are already receiving funding.

For purposes of comparison, the funding criteria that were consulted on can be found at <http://www.pharmac.health.nz/assets/consultation-2014-08-07-mstreatments.pdf>. If you prefer to view all of the specific changes made since consultation as edits with deletions and new text, please email or write to us, we will be happy to provide it in this format.

Details of the decision and a summary of the feedback received can be found on the following pages.

Details of the decision

Natalizumab

- Natalizumab (Tysabri) will be listed in Section B and in Part II of Section H (the Hospital Medicines List, or HML) of the Pharmaceutical Schedule, from 1 November 2014 at the following price and subsidy (ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Natalizumab	Inj 20 mg per ml, 15 ml vial	Tysabri	1	\$1,750.00

- Natalizumab will be subject to the following access criteria in Section B of the Pharmaceutical Schedule:

Special Authority for subsidy

Special Authority approved by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (below)

Application details may be obtained from PHARMAC's website <http://www.pharmac.govt.nz> or:

The coordinator Phone: 04 460 4990
Multiple Sclerosis Treatment Assessment Committee Facsimile: 04 916 7571
PHARMAC PO Box 10 254 Email: mstaccoordinator@pharmac.govt.nz
Wellington

Completed application forms must be sent to the coordinator for MSTAC and will be considered by MSTAC at the next practicable opportunity.

Notification of MSTAC's decision will be sent to the patient, the applying clinician and the patient's GP (if specified).

Entry Criteria

- 1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
- 2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
- 3) patients must have:
 - a) EDSS score 0 – 4.0 and:
 - Experienced at least 1 significant relapse of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
 - Evidence of MRI activity on a scan within the past 24 months (either a contrast enhancing lesion or with new T2 lesion(s) compared with a previous scan)
- 4) A significant relapse must:
 - a) be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the relapse but the neurologist/physician must be satisfied that the clinical features were characteristic and met the specified criteria);
 - b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
 - c) last at least one week;
 - d) start at least one month after the onset of a previous relapse;
 - e) be severe enough to change either the EDSS or at least one of the Kurtzke Functional System scores by at least 1 point;
 - f) be distinguishable from the effects of general fatigue; and
 - g) not be associated with a fever ($T > 37.5^{\circ}\text{C}$); and
- 5) applications must be made by the patient's neurologist or general physician; and

- 6) treatment must be initiated and supervised by a neurologist who is registered in the Tysabri Australasian Prescribing Programme operated by the supplier; and
- 7) patients must have no previous history of lack of response to natalizumab; and
- 8) patients must have not previously had intolerance to natalizumab; and
- 9) either
 - a) Patient is JC virus negative, or
 - b) Patient is JC virus positive and has given written informed consent acknowledging an understanding of the risk of progressive multifocal leucoencephalopathy (PML) associated with natalizumab
- 10) patient will not be co-prescribed beta interferon or glatiramer acetate

Stopping Criteria

Any of the following:

- 1) Confirmed progression of disability that is sustained for six months. Progression of disability is defined as progress by any of the following EDSS points:
 - a) from starting at EDSS 0 increasing to (i.e. stopping on reaching) 3.0,
 - b) 1.0 to 3.0,
 - c) 1.5 to 3.5,
 - d) 2.0 to 4.0,
 - e) 2.5 to 4.5,
 - f) 3.0 to 4.5,
 - g) 3.5 to 4.5,
 - h) 4.0 to 4.5
- 2) increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment) (see note);
- 3) intolerance to natalizumab; or
- 4) non-compliance with treatment, including refusal to undergo annual assessment

Note:

Natalizumab can only be dispensed from a pharmacy registered in the Tysabri Australasian Prescribing Programme operated by the supplier.

Switching between natalizumab and fingolimod is permitted provided the EDSS stopping criteria are not met. Switching to interferon or glatiramer acetate is only permitted provided the EDSS stopping criteria are not met and both fingolimod and natalizumab are either not tolerated or treatment with both agents would be clinically inappropriate.

Continued relapses on treatment would be expected to lead to a switch of treatment provided the EDSS stopping criteria are not met.

If a relapse has resulted in an increased EDSS score that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months is allowed from the start of the relapse for recovery to occur.

- Natalizumab will be subject to the following restrictions in the HML:

Restricted

Only for use in patients with approval by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (set out in Section B of the Pharmaceutical Schedule).

Fingolimod

- Fingolimod (Gilenya) will be listed in Section B, and in Part II of Section H (the Hospital Medicines List, or HML) of the Pharmaceutical Schedule from 1 November 2014, at the following price and subsidy (ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Fingolimod	Cap 0.5 mg	Gilenya	28	\$2,650.00

- A confidential rebate will apply to Gilenya, reducing its net price.
- Gilenya will have subsidy and delisting protection until 31 October 2017.
- The wastage rule will apply to fingolimod, so pharmacies will be able to claim for any unused stock from partly dispensed packs.
- Fingolimod will be subject to the following access criteria in Section B of the Pharmaceutical Schedule:

Special Authority for Subsidy

Special Authority approved by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (below).

Application details may be obtained from PHARMAC's website <http://www.pharmac.govt.nz> or:

The coordinator
 Multiple Sclerosis Treatment Assessment Committee
 PHARMAC PO Box 10 254
 Wellington

Phone: 04 460 4990
 Facsimile: 04 916 7571
 Email: mstacordinator@pharmac.govt.nz

Completed application forms must be sent to the coordinator for MSTAC and will be considered by MSTAC at the next practicable opportunity.

Notification of MSTAC's decision will be sent to the patient, the applying clinician and the patient's GP (if specified).

Entry Criteria

- 1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
- 2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
- 3) patients must have:
 - a) EDSS score 0 – 4.0 and:
 - Experienced at least 1 significant relapse of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
 - Evidence of MRI activity on a scan within the past 24 months (either a contrast enhancing lesion or with new T2 lesion(s) compared with a previous scan);
- 4) A significant relapse must:
 - a) be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the relapse but the neurologist/physician must be satisfied that the clinical features were characteristic and met the specified criteria);
 - b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
 - c) last at least one week;
 - d) start at least one month after the onset of a previous relapse;
 - e) be severe enough to change either the EDSS or at least one of the Kurtzke Functional System scores by at least 1 point;
 - f) be distinguishable from the effects of general fatigue; and
 - g) not be associated with a fever (T>37.5°C); and
- 5) applications must be made by the patient's neurologist or general physician; and
- 6) patients must have no previous history of lack of response to fingolimod; and
- 7) patients must have not previously had intolerance to fingolimod; and

- 8) patient must not be co-prescribed beta interferon or glatiramer acetate.

Stopping Criteria

Any of the following:

- 1) Confirmed progression of disability that is sustained for six months. Progression of disability is defined as progress by any of the following EDSS points:
 - a) from starting at EDSS 0 increasing to (i.e. stopping on reaching) EDSS 3.0,
 - b) 1.0 to 3.0,
 - c) 1.5 to 3.5,
 - d) 2.0 to 4.0,
 - e) 2.5 to 4.5,
 - f) 3.0 to 4.5,
 - g) 3.5 to 4.5,
 - h) 4.0 to 4.5
- 2) increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment)(see note);
- 3) intolerance to fingolimod; or
- 4) non-compliance with treatment, including refusal to undergo annual assessment.

Note:

Switching between natalizumab and fingolimod is permitted provided the EDSS stopping criteria are not met. Switching to interferon or glatiramer acetate is only permitted provided the EDSS stopping criteria are not met and both fingolimod and natalizumab are either not tolerated or treatment with both agents would be clinically inappropriate.

Continued relapses on treatment would be expected to lead to a switch of treatment provided the stopping criteria are not met.

If a relapse has resulted in an increased EDSS score that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months is allowed from the start of the relapse for recovery to occur.

- Fingolimod will be subject to the following access criteria in the HML from 1 November 2014:

Restricted

Only for use in patients with approval by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (set out in Section B of the Pharmaceutical Schedule).

Interferon beta 1 alpha, interferon beta 1 beta and glatiramer acetate

- Interferon beta-1-alpha (Avonex) will be listed in Section B and Part II of the Pharmaceutical Schedule from 1 November 2014 at the following prices and subsidies (ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Interferon beta-1-alpha	Inj 6 million iu prefilled syringe	Avonex	4	\$1,170.00
Interferon beta-1-alpha	Injection 6 million iu per 0.5 ml pen injector	Avonex Pen	4	\$1,170.00
Interferon beta-1-alpha	Inj 6 million iu per vial	Avonex	4	\$1,170.00

- There will be no change to the price or subsidy of interferon beta-1-beta (Betaferon) or glatiramer acetate (Copaxone).
- Interferon beta-1-alpha, interferon beta-1-beta and glatiramer acetate will be subject to the following access criteria in Section B of the Pharmaceutical Schedule from 1 November 2014 until 31 October 2015:

Special Authority for Subsidy

Special Authority approved by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (below)

Application details may be obtained from PHARMAC's website <http://www.pharmac.govt.nz> or:

The coordinator Phone: 04 460 4990
 Multiple Sclerosis Treatment Assessment Committee Facsimile: 04 916 7571
 PHARMAC PO Box 10 254 Email: mstacordinator@pharmac.govt.nz
 Wellington

Completed application forms must be sent to the coordinator for MSTAC and will be considered by MSTAC at the next practicable opportunity.

Notification of MSTAC's decision will be sent to the patient, the applying clinician and the patient's GP (if specified).

These agents will NOT be subsidised if dispensed from a community or hospital pharmacy.

Regular supplies will be distributed to all approved patients or their clinicians by courier.

Prescribers must send quarterly prescriptions for approved patients to the MSTAC coordinator.

Only prescriptions for 6 million iu of interferon beta-1-alpha per week, or 8 million iu of interferon beta-1-beta every other day, or 20 mg glatiramer acetate daily will be subsidised.

Switching between treatments is permitted within the 12 month approval period without reapproval by MSTAC. The MSTAC coordinator should be notified of the change and a new prescription provided.

Entry Criteria

- 1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
- 2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
- 3) patients must have:
 - a) EDSS score 0 – 4.0 and:
 - Experienced at least 1 significant relapse of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
 - Evidence of MRI activity on a scan within the past 24 months (either a contrast enhancing lesion or with new T2 lesions(s) compared with a previous scan)
- 4) A significant relapse must:
 - a) be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the relapse but the neurologist/physician must be satisfied that the clinical features were characteristic and met the specified criteria);
 - b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
 - c) last at least one week;
 - d) start at least one month after the onset of a previous relapse;
 - e) be severe enough to change either the EDSS or at least one of the Kurtzke Functional System scores by at least 1 point;
 - f) be distinguishable from the effects of general fatigue; and
 - g) not be associated with a fever ($T > 37.5^{\circ}\text{C}$); and
- 5) applications must be made by the patient's neurologist; and
- 6) patients must have no previous history of lack of response to beta-interferon or glatiramer acetate; and
- 7) patients must have either
 - a) intolerance to **both** natalizumab and fingolimod; **or**
 - b) treatment with **both** natalizumab and fingolimod is considered clinically inappropriate

- 8) patient will not be co-prescribed natalizumab or fingolimod

Stopping Criteria

Any of the following:

- 1) Confirmed progression of disability that is sustained for six months during a minimum of one year of treatment. Progression of disability is defined as progress by any of the following EDSS points:
 - a) from starting at EDSS 0 increasing to (i.e. stopping on reaching) EDSS 3.0,
 - b) 1.0 to 3.0,
 - c) 1.5 to 3.5,
 - d) 2.0 to 4.0,
 - e) 2.5 to 4.5,
 - f) 3.0 to 4.5,
 - g) 3.5 to 4.5,
 - h) 4.0 to 4.5
- 2) increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment)(see note);
- 3) intolerance to interferon beta-1-alpha, and/or interferon beta-1-beta and/or glatiramer acetate; or
- 4) non-compliance with treatment, including refusal to undergo annual assessment

Note:

Treatment with interferon beta -1-beta, interferon beta-1-alpha and glatiramer acetate, is permitted only if treatment with both natalizumab and fingolimod is not tolerated or treatment with both would be clinically inappropriate. Beta-interferon or glatiramer acetate will not be funded as second line treatments if EDSS progression has occurred on treatment with natalizumab or fingolimod.

Patients who have an increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment) and who do not meet the EDSS Stopping Criteria at annual review may switch from either of the beta-interferon's [interferon beta-1-beta or interferon beta-1-alpha] to glatiramer acetate or vice versa. Patients may switch from either of the beta-interferon's [interferon beta-1-beta or interferon beta-1-alpha] to glatiramer acetate or vice versa for increased relapses only once, after which they will be required to stop funded treatment if they meet any of the Stopping Criteria at annual review (including the criterion relating to increasing relapse rate over 12 months of treatment).

If a relapse has resulted in an increased EDSS score that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months is allowed from the start of the relapse for recovery to occur.

In this setting anti-JCV antibody positive status may be accepted as a clinically inappropriate reason for treatment with natalizumab.

Entry Criteria for patients with an EDSS of 4.5-5.5 who have not had an application for funding considered prior to 1 November 2014

- 1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis should as a rule include MRI confirmation. For patients diagnosed before MRI was widely utilised in New Zealand, confirmation of diagnosis via clinical assessment and laboratory/ancillary data must be provided; and
- 2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
- 3) patients must have either:
 - a) EDSS score 4.5-5.5 with 2+ relapses:
 - Experienced at least 2 significant relapses of MS in the previous 12 months, and
 - An EDSS score of between 4.5-5.5; and
- 4) Each relapse must:

- a) be confirmed by a neurologist or general physician (the patient may not necessarily have been seen during the relapse but the neurologist/physician must be satisfied that the clinical features were characteristic and met the specified criteria);
 - b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
 - c) last at least one week;
 - d) follow a period of stability of at least one month;
 - e) be severe enough to change either the EDSS or at least one of the Kurtzke functional systems scores by at least 1 point;
 - f) be distinguishable from the effects of general fatigue; and
 - g) not be associated with a fever ($T > 37.5^{\circ}\text{C}$); and
- 5) applications must be made at least four weeks after the date of the onset of the last known relapse; and
 - 6) patients must have no previous history of lack of response to beta-interferon or glatiramer acetate (see criteria for stopping).
 - 7) applications must be submitted to the Multiple Sclerosis Treatment Assessment Committee (MSTAC) by the patient's neurologist or a general physician; and
 - 8) patients must agree (via informed consent) to co-operate if as a result of their meeting the stopping criteria, funding is withdrawn. Patients must agree to the collection of clinical data relating to their MS and use of those data by PHARMAC; and
 - 9) patients must agree to allow clinical data to be collected and reviewed by MSTAC annually for each year in which they receive funding for beta-interferon or glatiramer acetate.

Stopping Criteria for patients with an EDSS of 4.5-5.5 who have not had an application for funding considered prior to 1 November 2014

- 1) Confirmed progression of disability that is sustained for six months during a minimum of one year of treatment. Progression of disability is defined as any of:
 - a) an increase of 1 EDSS point where starting EDSS 3.5 or greater; or
 - b) an increase in EDSS score to 6.0 or more; or
- 2) stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment)(see note); or
- 3) pregnancy and/or lactation; or
- 4) within the 12 month approval year, intolerance to interferon beta-1-alpha, and/or interferon beta-1-beta and/or glatiramer acetate; or
- 5) non-compliance with treatment, including refusal to undergo annual assessment or refusal to allow the results of the assessment to be submitted to MSTAC; or
- 6) patients may, subject to conclusions drawn from published evidence available at the time, be excluded if they develop a high titre of neutralising anti-bodies to beta-interferon or glatiramer acetate.

Note:

Patients who have a stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment) and who do not meet any of the other Stopping Criteria at annual review may switch to a different class of funded treatment (i.e. patients may switch from either of the beta-interferon's [interferon beta-1-beta or interferon beta-1-alpha] to glatiramer acetate or vice versa). Patients may switch classes of treatment for this reason only once, after which they will be required to stop funded treatment if they meet any of the Stopping Criteria at annual review (including the criterion relating to stable or increasing relapse rate over 12 months of treatment)

- Interferon beta-1-alpha, interferon beta-1-beta and glatiramer acetate will be subject to the following access criteria in the HML from 1 November 2014:

Restricted

Only for use in patients with approval by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (set out in Section B of the Pharmaceutical Schedule).

- The Special Authority criteria for interferon beta-1-alpha, interferon beta-1-beta and glatiramer acetate in Section B of the Pharmaceutical Schedule from 1 November 2015 will be amended as follows (deletions in strikethrough); please note that deletions will occur at the end of the 12-month transition period:

Special Authority for Subsidy

Special Authority approved by the Multiple Sclerosis Treatment Assessment Committee (MSTAC). Applications will be considered by MSTAC at its regular meetings and approved subject to eligibility according to the Entry and Stopping criteria (below)

Application details may be obtained from PHARMAC's website <http://www.pharmac.govt.nz> or:

The coordinator Phone: 04 460 4990
 Multiple Sclerosis Treatment Assessment Committee Facsimile: 04 916 7571
 PHARMAC PO Box 10 254 Email: mstacordinator@pharmac.govt.nz
 Wellington

Completed application forms must be sent to the coordinator for MSTAC and will be considered by MSTAC at the next practicable opportunity.

Notification of MSTAC's decision will be sent to the patient, the applying clinician and the patient's GP (if specified).

These agents will NOT be subsidised if dispensed from a community or hospital pharmacy.

Regular supplies will be distributed to all approved patients or their clinicians by courier.

Prescribers must send quarterly prescriptions for approved patients to the MSTAC coordinator.

Only prescriptions for 6 million iu of interferon beta-1-alpha per week, or 8 million iu of interferon beta-1-beta every other day, or 20 mg glatiramer acetate daily will be subsidised.

Switching between treatments is permitted within the 12 month approval period without reapproval by MSTAC. The MSTAC coordinator should be notified of the change and a new prescription provided.

Entry Criteria

- 1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
- 2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and
- 3) patients must have:
 - a) EDSS score 0 – 4.0 and:
 - Experienced at least 1 significant relapse of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
 - Evidence of MRI activity on a scan within the past 24 months (either a contrast enhancing lesion or with new T2 lesions(s) compared with a previous scan)
- 4) A significant relapse must:
 - a) be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the relapse but the neurologist/physician must be satisfied that the clinical features were characteristic and met the specified criteria);
 - b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
 - c) last at least one week;
 - d) start at least one month after the onset of a previous relapse;
 - e) be severe enough to change either the EDSS or at least one of the Kurtzke Functional System scores by at least 1 point;
 - f) be distinguishable from the effects of general fatigue; and
 - g) not be associated with a fever ($T > 37.5^{\circ}\text{C}$); and
- 5) applications must be made by the patient's neurologist; and
- 6) patients must have no previous history of lack of response to beta-interferon or glatiramer acetate; and
- 7) patients must have either
 - i. intolerance to **both** natalizumab and fingolimod; **or**
 - ii. treatment with **both** natalizumab and fingolimod is considered clinically inappropriate
- 8) patient will not be co-prescribed natalizumab or fingolimod

Stopping Criteria

Any of the following:

- 1) Confirmed progression of disability that is sustained for six months during a minimum of one year of treatment. Progression of disability is defined as progress by any of the following EDSS points:
 - a) from starting at EDSS 0 increasing to (i.e. stopping on reaching) EDSS 3.0,
 - b) 1.0 to 3.0,
 - c) 1.5 to 3.5,
 - d) 2.0 to 4.0,
 - e) 2.5 to 4.5,
 - f) 3.0 to 4.5,
 - g) 3.5 to 4.5,
 - h) 4.0 to 4.5
- 2) increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment)(see note);
- 3) intolerance to interferon beta-1-alpha, and/or interferon beta-1-beta and/or glatiramer acetate; or
- 4) non-compliance with treatment, including refusal to undergo annual assessment

Note:

Treatment with interferon beta -1-beta, interferon beta-1-alpha and glatiramer acetate, is permitted only if treatment with both natalizumab and fingolimod is not tolerated or treatment with both would be clinically inappropriate. Beta-interferon or glatiramer acetate will not be funded as second line treatments if EDSS progression has occurred on treatment with natalizumab or fingolimod.

Patients who have an increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment) and who do not meet the EDSS Stopping Criteria at annual review may switch from either of the beta-interferon's [interferon beta-1-beta or interferon beta-1-alpha] to glatiramer acetate or vice versa. Patients may switch from either of the beta-interferon's [interferon beta-1-beta or interferon beta-1-alpha] to glatiramer acetate or vice versa for increased relapses only once, after which they will be required to stop funded treatment if they meet any of the Stopping Criteria at annual review (including the criterion relating to increasing relapse rate over 12 months of treatment).

If a relapse has resulted in an increased EDSS score that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months is allowed from the start of the relapse for recovery to occur.

In this setting anti-JCV antibody positive status may be accepted as a clinically inappropriate reason for treatment with natalizumab.

~~Entry Criteria for patients with an EDSS of 4.5-5.5 who have not had an application for funding considered prior to 1 November 2014~~

- ~~1) Diagnosis of multiple sclerosis (MS) must be confirmed by a neurologist. Diagnosis should as a rule include MRI confirmation. For patients diagnosed before MRI was widely utilised in New Zealand, confirmation of diagnosis via clinical assessment and laboratory/ancillary data must be provided; and~~
- ~~2) patients must have Clinically Definite Relapsing Remitting MS with or without underlying progression; and~~
- ~~3) patients must have either:
 - a) EDSS score 4.5-5.5 with 2+ relapses:
 - Experienced at least 2 significant relapses of MS in the previous 12 months, and
 - An EDSS score of between 4.5-5.5; and~~
- ~~4) Each relapse must:
 - a) be confirmed by a neurologist or general physician (the patient may not necessarily have been seen during the relapse but the neurologist/physician~~

- must be satisfied that the clinical features were characteristic and met the specified criteria);
- b) be associated with characteristic new symptom(s)/sign(s) or substantial worsening of previously experienced symptom(s)/sign(s);
- c) last at least one week;
- d) follow a period of stability of at least one month;
- e) be severe enough to change either the EDSS or at least one of the Kurtzke functional systems scores by at least 1 point;
- f) be distinguishable from the effects of general fatigue; and
- g) not be associated with a fever ($T > 37.5^{\circ}\text{C}$); and
- 5) applications must be made at least four weeks after the date of the onset of the last known relapse; and
- 6) patients must have no previous history of lack of response to beta interferon or glatiramer acetate (see criteria for stopping);
- 7) applications must be submitted to the Multiple Sclerosis Treatment Assessment Committee (MSTAC) by the patient's neurologist or a general physician; and
- 8) patients must agree (via informed consent) to co-operate if as a result of their meeting the stopping criteria, funding is withdrawn. Patients must agree to the collection of clinical data relating to their MS and use of those data by PHARMAC; and
- 9) patients must agree to allow clinical data to be collected and reviewed by MSTAC annually for each year in which they receive funding for beta interferon or glatiramer acetate.

Stopping Criteria for patients with an EDSS of 4.5-5.5 who have not had an application for funding considered prior to 1 November 2014

- 1) Confirmed progression of disability that is sustained for six months during a minimum of one year of treatment. Progression of disability is defined as any of:
 - a) an increase of 1 EDSS point where starting EDSS 3.5 or greater; or
 - b) an increase in EDSS score to 6.0 or more; or
- 2) stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment)(see note); or
- 3) pregnancy and/or lactation; or
- 4) within the 12 month approval year, intolerance to interferon beta 1 alpha, and/or interferon beta 1 beta and/or glatiramer acetate; or
- 5) non-compliance with treatment, including refusal to undergo annual assessment or refusal to allow the results of the assessment to be submitted to MSTAC; or
- 6) patients may, subject to conclusions drawn from published evidence available at the time, be excluded if they develop a high titre of neutralising anti bodies to beta interferon or glatiramer acetate.

Note:

Patients who have a stable or increasing relapse rate over 12 months of treatment (compared with the relapse rate on starting treatment) and who do not meet any of the other Stopping Criteria at annual review may switch to a different class of funded treatment (i.e. patients may switch from either of the beta interferon's [interferon beta 1 beta or interferon beta 1 alpha] to glatiramer acetate or vice versa). Patients may switch classes of treatment for this reason only once, after which they will be required to stop funded treatment if they meet any of the Stopping Criteria at annual review (including the criterion relating to stable or increasing relapse rate over 12 months of treatment).

Feedback received

PHARMAC received a large number of detailed responses to this proposal. We appreciate all of the feedback that we received and acknowledge the time people took to respond. All consultation responses received by 31 August 2014 were considered in their entirety in making a decision on the proposed changes. Responses ranged from very supportive to unsupportive of aspects of the proposal. The following table summarises the themes raised in consultation and PHARMAC's comment or response to those themes.

Theme: Wider access	Comment
<p>The entry and exit criteria are too restrictive.</p> <p>Requests for wider access included:</p> <ul style="list-style-type: none"> • Removing the graduated stopping criteria so that patients with an EDSS of 0-4 could continue treatment to 4.5, irrespective of their EDSS score at entry • Extending the entry criteria to allow patients with EDSS of 6.0 or greater to access treatment • If an increase in EDSS to 4.5 or above is due to a clear relapse, then permitting a switch of treatment if EDSS is <5.5 (but if subsequent progressive worsening of EDSS by one point or more due to secondary progression, then not for continued treatment) 	<p>Funding applications for both natalizumab and fingolimod have undergone extensive review by PHARMAC's Pharmacology and Therapeutics Committee (PTAC). The proposed changes are in line with PTAC's clinical advice, which highlights that the newer treatments appear to have greater efficacy than currently funded treatments and are most likely more effective at preventing progression of disease if used at earlier stages of disease.</p> <p>PTAC considered that these treatments should be targeted to the patients likely to benefit most from such treatments. The proposed entry and exit criteria are based on PTAC's advice.</p> <p>Treating these additional EDSS and relapse states would require specific consideration of relative benefits, risks, cost-effectiveness and budget impacts. We would welcome a funding application at any time for wider access.</p>
<p>The cost to NZ (e.g. from lost wages) of not allowing wider access is higher than the cost of the treatments.</p>	<p>Cost-utility analysis is used to provide us with information which helps to determine pharmaceuticals offer the most health gains from the available budget. When calculating the cost and cost effectiveness of a treatment PHARMAC takes into account benefits and any costs to the total health sector. Quality of life benefits to the patient including those relating improvements in physical capabilities are taken into account, but patient costs, such as loss of wages, are not. To do so could bias against those who are not in the paid workforce (retired people, unemployed, children, those unable to work because of chronic co-morbidities – including living with chronic debilitating diseases such as MS).</p> <p>More information about how PHARMAC calculates the cost effectiveness of treatments, including our approach to lost wages, can be found in the Prescription for Pharmacoeconomic Analysis at : http://www.pharmac.health.nz/assets/pfpa-final.pdf page 47</p>
<p>Concern that if a patient has a relapse on treatment there is the chance that their EDSS</p>	<p>The following is permitted under the SA criteria: 'If a relapse has resulted in an increased EDSS</p>

score may increase such that the patient meets the stopping criteria and thus must stop treatment.	score that potentially may lead to discontinuation of treatment according to the stopping criteria, a period of six months is allowed from the start of the relapse in order for recovery to occur. ¹ This means that, if a patient does relapse, six months can elapse before having to reassess whether the symptoms truly persist (and therefore disability has progressed despite MS treatments).
Patients who are currently accessing treatment who choose to switch to a newer treatment should maintain the same stopping criteria under the criteria that applied when the patient was granted their current approval.	Should patients choose to switch treatment, the proposed new stopping criteria would apply. We consider that this is appropriate and would ensure consistency across different patients accessing the new treatments, regardless of the prior treatments that may have been tried.
Treatment duration should be maximised, withdrawal of treatment should be seen as a human rights infringement.	PHARMAC is responsible for achieving the best health outcomes from within the funding provided. We must compare the cost and benefits from all investments we consider. The proposed entry and stopping criteria are based on clinical grounds, consistent with the clinical advice we have received from PTAC. We would welcome a funding application for wider access at any time, including longer treatment duration.
No evidence base for the proposal was included in the consultation to support the entry and exit criteria.	MS treatments have undergone extensive review by our specialist advisory groups, including PTAC and the Neurological Subcommittee of PTAC. Details of the evidence reviewed, and the resulting clinical advice, were included in the PTAC and Neurological Subcommittee meeting minutes. Links to these minutes were included in the consultation document. ²
Has there been any national or international peer review of the proposal?	As described above, MS treatments have undergone extensive review by our specialist advisory groups, including MSTAC, PTAC and the Neurological Subcommittee of PTAC. The proposed changes are in line with PTAC's clinical advice. We have not sought international review of the proposal; however, given our extensive local review we consider that international review, in very different funding and public policy contexts, including cost structures, would not improve analysis or add appreciable new information.
Theme: Patients who are outside of the criteria	Comment
There needs to be a mechanism for consideration of patients who would see benefit from treatment who do not quite fit the proposed criteria.	Clinicians can continue to apply under the Named Patient Pharmaceutical Assessment (NPPA) process for any patients who have unusual circumstances. More information about the NPPA process can be found at http://www.pharmac.health.nz/tools-resources/forms/named-patient-pharmaceutical-assessment-nppa-forms .

² minutes: natalizumab <http://www.pharmac.govt.nz/patients/ApplicationTracker?ProposalId=613>, fingolimod <http://www.pharmac.govt.nz/patients/ApplicationTracker?ProposalId=555>

Theme: Access to first line treatment with the interferons or glatiramer acetate	Comment
<p>People should still be able to access interferon-betas and glatiramer acetate as first line treatments if their neurologist believes that one of these drugs is the most appropriate.</p> <p>The word 'contraindicated' should be changed to 'clinically inappropriate'. This terminology is important as it acknowledges safety issues and that the clinical appropriateness of a particular treatment in an individual patient may change over time. For example, if a patient was planning a pregnancy, the clinician and the patient may want to opt for the treatments that have the longest safety record (the beta-interferons or glatiramer acetate) and may therefore deem treatment with natalizumab and fingolimod to be clinically inappropriate. Following birth, the patient's clinical situation may change and therefore treatment with natalizumab and fingolimod may then be deemed clinically appropriate.</p>	<p>PHARMAC acknowledges that most countries who fund MS treatments include beta-interferons or glatiramer acetate as first-line treatments and that patients' clinical situations are not static. It is appropriate for patients to be able to access treatment with the beta-interferons or glatiramer acetate first-line should treatment with both natalizumab and fingolimod be clinically inappropriate.</p> <p>The proposed Special Authority criteria have been amended as a result of this feedback.</p>
<p>First-line treatment should be to start with an interferon or glatiramer acetate unless the person has more active disease, in which case natalizumab or fingolimod should be used. If there are ongoing relapses with the interferons or glatiramer acetate then treatment should be escalated to fingolimod or natalizumab</p>	<p>PTAC has provided advice to PHARMAC that the newer MS treatments appear to have better evidence of effectiveness and that natalizumab and fingolimod should be funded as first-line agents, with funding for the interferons and glatiramer only if treatment with both of the recommended first-line agents is not tolerated or is contraindicated (amended to 'clinically inappropriate' in the decision as noted above).</p>
<p>The interferons and glatiramer acetate may be more accessible to people with MS who may not be able to access hospital based treatments due to specific circumstances.</p>	<p>Fingolimod will be available as an oral treatment option for patients who cannot access natalizumab in hospitals due to their specific circumstances.</p> <p>Patients will be able to access treatment with the beta-interferons or glatiramer acetate first-line should treatment with both natalizumab and fingolimod be clinically inappropriate.</p>
<p>Clinicians will need to be trained to use the new treatments.</p>	<p>Both suppliers have training programmes planned to assist clinicians with using the new products.</p>
Theme: Special Authority clarity	Comment
<p>The Special Authority is very clinically focused and is difficult for people who are not clinically trained to understand.</p>	<p>A questions and answers section will be included on the PHARMAC website to assist people with interpretation of the changes. The intent of the Special Authority is to define the clinical parameters for funding and therefore requires a clinical focus.</p> <p>PHARMAC however acknowledges that the criteria are complex and difficult to follow; this reflects in part the complexities of MS itself in terms of its natural history and relapsing-remitting and progressive course. Treating clinicians will</p>

	<p>be experienced in these clinical aspects, as part of their everyday practice in neurology and internal medicine specialties, and will be best placed to help patients interpret the criteria.</p>
<p>It is not clear if a patient with clinically isolated syndrome fulfilling the McDonald 2010 diagnostic criteria for MS, could access treatment under the proposed Special Authority criteria.</p>	<p>Under the proposed SA criteria patients must have clinically definite relapsing remitting MS, this means a first event and at least 1 significant relapse in the past 12 months or 2 relapses in the past 24 months, and evidence of MRI activity on a scan within the past 24 months.</p> <p>PTAC recommended that funding for treatment with natalizumab, fingolimod, interferon or glatiramer acetate for clinically isolated syndrome fulfilling the McDonald 2010 diagnostic criteria for MS be declined, but noted that the Committee would review this recommendation should new evidence become available.</p>
<p>Confusion was expressed around the necessity for four weeks to have elapsed after a relapse to make an application.</p>	<p>PHARMAC has removed this sentence from the SA criteria. It was previously included (under the old access criteria) as during these four weeks patients' EDSS score may have improved such that they did not meet eligibility criteria. Due to the proposed entry criteria being EDSS 0-4.0, this requirement is no longer necessary.</p>
<p>Will eligibility criteria be based purely on clinical grounds (relapses in a patient with definite MS) or also require evidence of recent MRI activity?</p>	<p>The entry criteria require that the diagnosis of MS be confirmed by MRI. Eligibility for MS treatments therefore includes evidence of MRI activity. PHARMAC has changed the wording of the SA criteria to read more clearly and/or better reflect the intent of the criteria.</p>
<p>Patients with current funding who apply to switch to natalizumab or fingolimod may not have had one relapse in the past year or two relapses in the past two years due to them receiving treatment, would they still be eligible to switch?</p>	<p>It would be presumed that the patient will have met the relapse requirement prior to starting their current treatment. This criterion would be presumed to have been met if the patient is already on a funded treatment, and the patient would not have to 're-meet' it. Patients must, however, have an EDSS of 0-4.0 as per the entry criteria to be eligible to switch.</p>
<p>Changing treatment when disease is stable can cause unwanted disease activity and new side effects. Patients should only switch when a treatment has failed them or they have experienced intolerable side effects.</p>	<p>There is no requirement for a stable patient to switch treatment. A decision to switch treatments should be made by the treating clinician in consultation with the patient.</p>
<p>Would children with MS be able to access funding for treatment?</p>	<p>Yes, there are no age limits for access to funding with any of the agents.</p>
<p>If a patient currently receiving treatment with interferon or glatiramer acetate switches to one of the newer treatments, would they be able to switch back if the new medication proved ineffective?</p>	<p>If the stopping criteria were met while the patient was on the new treatment, the patient would not be able to switch back.</p> <p>Switching to interferon or glatiramer will only be permitted provided the EDSS stopping criteria are not met and both fingolimod and natalizumab are either not tolerated or treatment with both agents would be clinically inappropriate.</p>

Theme: Comments regarding the Panel	Comment
Concerned that having to apply for funding through a panel makes the process unnecessarily lengthy and complicated. The panel should be reserved for applications where the neurologist is uncertain about the eligibility or where the patient does not meet the criteria but there are valid clinical circumstances.	The MSTAC panel's role is to assess whether a patient meets the Special Authority criteria and is eligible for funding. Due to the complexities of the criteria, in particular those requiring an assessment of EDSS which can be both a subjective and objective measure, the panel ensures consistency of assessment and therefore national equity of access for all patients with MS. Clinicians should continue to apply under the NPPA Policy for funding any patients who have unusual clinical circumstances.
Theme: Self-funded and DHB funded patients	Comment
Patients who are self-funding one of the new treatments should be able to access public funding.	Clinicians can apply for special authority approval for funding for patients who are currently self-funding their treatment. These will be assessed on a case by case basis to determine eligibility for funded treatment, including consideration of whether the entry criteria were met (or not) when the patient was initiated on treatment, and whether or not the stopping criteria are met at the time of application.
Are patients who are not eligible for funding of the new treatments able to purchase the drugs at the PHARMAC listed prices?	The list price is an ex-manufacturer price, and pharmacies add mark-ups and GST to the price listed in the Pharmaceutical Schedule. Additionally, PHARMAC will not be paying the listed price for fingolimod due to a confidential rebate on subsidised sales. Patients who wish to self-fund are encouraged to enquire at multiple pharmacies in order to get the best price possible, as different pharmacies may add different mark-ups to medicines.
Would patients funded on one of the new treatments by a DHB be able to access funding under this proposal, and if so would they be subject to the new stopping criteria.	Patients funded by DHBs who meet the proposed entry criteria will be eligible for funding via Special Authority and applications would be assessed on a case by case basis. The new stopping criteria would be applicable to all patients who receive funding under Special Authority criteria.
Theme: Overseas patients	Comment
Would patients who have been overseas and accessing one of the new treatments be eligible for funding when they return to NZ?	Patients who are eligible for public funding of pharmaceuticals in New Zealand will be assessed on a case by case basis as per the currently self-funding patients.
Theme: Applicant type	Comment
People receive their diagnosis of MS from a neurologist, once this is established it is appropriate for a general physician to apply and monitor treatment. Some areas of NZ are not well serviced by a neurologist and therefore a general physician should be able to make an application for any of the treatments.	PHARMAC notes that the SA criteria require a neurologist to make the diagnosis of MS, and considers the request for general physicians to be included in the applicant type to be reasonable, as a neurologist would still be involved in the patient's care. We consider that it is reasonable to allow general physicians to make applications and that this change would help both patients and clinicians. The proposed Special Authority criteria for all of the MS treatments have been amended accordingly.
Theme: Diagnostic criteria	Comment

<p>The Special Authority criteria should use the McDonald 2010 diagnostic criteria, which allow a diagnosis of MS to be made in patients who have had a first demyelinating event who have MRI evidence of dissemination in time and space.</p>	<p>PTAC recommended that funding for treatment with natalizumab, fingolimod, interferon or glatiramer acetate for clinically isolated syndrome (CIS) fulfilling the McDonald 2010 diagnostic criteria for MS be declined, but noted that the Committee would review this recommendation should new evidence become available.</p> <p>We would welcome a funding application at any time for a change in the diagnostic criteria should new evidence, for fingolimod, natalizumab, interferons or glatiramer in the treatment of CIS fulfilling the McDonald 2010 criteria become available.</p>
<p>Too much emphasis is placed on EDSS as a measure of disease progression.</p>	<p>We would welcome a funding application at any time for a change to the criteria that uses a different measure of progression.</p>
<p>Concern was expressed around the availability and timeliness of MRI scans in NZ in order to support a diagnosis of MS.</p>	<p>Diagnosis of MS requires confirmation by MRI scan. Access to MRI scans is outside of PHARMAC's scope.</p>
<p>Theme: People who live rurally</p>	<p>Comment</p>
<p>Patients who live rurally may be disadvantaged in their access to natalizumab due to their local hospitals not having the required facilities.</p>	<p>At this time it would not be possible for natalizumab to be delivered anywhere other than a hospital because the product license for natalizumab requires that therapy is to be initiated and supervised by neurologists, in centres with timely access to MRI.</p> <p>In addition due to the risk of PML associated with natalizumab, and related to the registration of natalizumab, the supplier (Biogen Idec) requires that any practitioner prescribing natalizumab, or pharmacy dispensing natalizumab, to have taken part in a training programme (the Tysabri Australasian Prescribing Programme, which is operated by the supplier).</p> <p>Patients who do not have access to a hospital with the required facilities to deliver natalizumab have the option of trying fingolimod.</p>
<p>Theme: Other</p>	<p>Comment</p>
<p>Request for funding varicella (chicken pox) vaccination for non-immune patients before commencing fingolimod treatment.</p>	<p>Current Special Authority criteria already permit varicella vaccination for patients with immunosuppression due to immunosuppressive therapies (this includes MS treatments).</p>

More information

If you have any questions about this decision, you can email us at enquiry@pharmac.govt.nz

or call our toll free number (9 am to 5 pm, Monday to Friday) on 0800 66 00 50.