4 December 2015

Decisions relating to Multiple Sclerosis Treatments

PHARMAC is pleased to announce the approval of proposals to fund two new treatments for Multiple Sclerosis (MS) – dimethyl fumarate and teriflunomide – and to make amendments to the Special Authority criteria relating to MRI requirements for all MS treatments. This decision was the subject of a consultation letter dated 16 October 2015, available on PHARMAC's website.

In summary, the effect of the decision is that from 1 February 2016:

- two new treatments:
    - dimethyl fumarate (Tecfidera), supplied by Biogen NZ Biopharma Limited ("Biogen"); and
    - teriflunomide (Aubagio), supplied by Sanofi-Aventis New Zealand Limited ("Sanofi");

  will be funded in the community and in DHB hospitals, subject to the same restrictions that apply to natalizumab (Tysabri) and fingolimod (Gilenya); and,
- there will be changes to the Special Authority criteria for all MS treatments relating to MRI requirements.

In addition, following consideration of feedback to consultation, the wastage rule will apply to dispensings of dimethyl fumarate and teriflunomide, so pharmacies will be able to claim for any unused stock from partly dispensed packs.

Details of the decision

Dimethyl fumarate:

- Dimethyl fumarate (Tecfidera) will be listed in Section B and in Part II of Section H (the Hospital Medicines List, or HML) of the Pharmaceutical Schedule, as a result of a provisional agreement with Biogen, at the following price and subsidy from 1 February 2016 (ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Dimethyl fumarate	Cap 120 mg	Tecfidera	14	$520.00
Dimethyl fumarate	Cap 240 mg	Tecfidera	56	$2,000.00

- A confidential rebate will apply to Tecfidera, reducing its net price.

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand
Phone: 64 4 460 4990 - Fax: 64 4 460 4995 - www.pharmac.govt.nz

- The wastage rule will apply to dispensings of dimethyl fumarate, so pharmacies will be able to claim for any unused stock from partly dispensed packs.

- Dimethyl fumarate will be subject to the following Special Authority criteria in Section B of the Pharmaceutical Schedule from 1 February 2016; please note that these criteria are the same as those for natalizumab, fingolimod and teriflunomide.

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).

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 new inflammatory activity on an MR scan within the past 24 months**,** any of the following:
            i. a gadolinium enhancing lesion; or
            ii. a Diffusion Weighted Imaging positive lesion; or
            iii. a T2 lesion with associated local swelling; or
            iv. a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse; or
            v. new T2 lesions compared with a previous MR scan; and
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 dimethyl fumarate; and
7) patients must have not previously had intolerance to dimethyl fumarate; and
8) patients 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; or
    b) 1.0 to 3.0, or
    c) 1.5 to 3.5; or

d) 2.0 to 4.0; or
e) 2.5 to 4.5; or
f) 3.0 to 4.5; or
g) 3.5 to 4.5; or
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); or
3) intolerance to dimethyl fumarate; or
4) non-compliance with treatment, including refusal to undergo annual assessment.

Note:
Switching between natalizumab, fingolimod, dimethyl fumarate and teriflunomide 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.

- Dimethyl fumarate will be subject to the following access criteria in Part II of Section H of the Pharmaceutical Schedule from 1 February 2016:

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).

Teriflunomide:

- Teriflunomide (Aubagio) will be listed in Section B and in Part II of Section H (the Hospital Medicines List, or HML) of the Pharmaceutical Schedule, as a result of a provisional agreement with Sanofi, at the following price and subsidy from 1 February 2016 (ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size	Price and subsidy
Teriflunomide	Tab 14 mg	Aubagio	28	$1,582.62

- A confidential rebate will apply to Aubagio, reducing its net price.
- Aubagio will have subsidy and delisting protection until 31 October 2017.
- The wastage rule will apply to dispensings of teriflunomide, so pharmacies will be able to claim for any unused stock from partly dispensed packs.
- Teriflunomide will be subject to the following Special Authority criteria in Section B of the Pharmaceutical Schedule from 1 February 2016; please note that these criteria are the same as those for natalizumab, fingolimod and dimethyl fumarate:

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).

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 new inflammatory activity on an MR scan within the past 24 months, any of the following:
            i. a gadolinium enhancing lesion; or
            ii. a Diffusion Weighted Imaging positive lesion; or
            iii. a T2 lesion with associated local swelling; or
            iv. a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse; or
            v. new T2 lesions compared with a previous MR scan; and
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 teriflunomide; and
7) patients must have not previously had intolerance to teriflunomide; and
8) patients 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; or
    b) 1.0 to 3.0; or
    c) 1.5 to 3.5; or
    d) 2.0 to 4.0; or
    e) 2.5 to 4.5; or
    f) 3.0 to 4.5; or
    g) 3.5 to 4.5; or
    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 teriflunomide; or
4) non-compliance with treatment, including refusal to undergo annual assessment.

Note:
Switching between natalizumab, fingolimod, dimethyl fumarate and teriflunomide 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.

- Teriflunomide will be subject to the following access criteria in Part II of Section H of the Pharmaceutical Schedule from 1 February 2016:

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).

Changes to Multiple Sclerosis treatments Special Authority Criteria:

- From 1 February 2016 the note in the Special Authority Criteria for the Multiple Sclerosis Treatments natalizumab, and fingolimod in Section B of the Pharmaceutical Schedule will be replaced with the following:

Note:
Switching between natalizumab, fingolimod, **dimethyl fumarate and teriflunomide** 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.

- From 1 February 2016 criterion 3 (a) of the Special Authority criteria for Multiple Sclerosis treatments, natalizumab and fingolimod, in Section B of the Pharmaceutical Schedule will be replaced with the following:

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 new inflammatory activity on an MR scan within the past 24 months**,** either:
            i. a gadolinium enhancing lesion; or
            ii. a Diffusion Weighted Imaging positive lesion; or
            iii. a T2 lesion with associated local swelling; or
            iv. a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse; or
            v. new T2 lesions compared with a previous MR scan; and

Changes to Other Multiple Sclerosis treatments Special Authority Criteria:

- From 1 February 2016 criterion 3 (a) of the Special Authority criteria for Other Multiple Sclerosis treatments, interferon beta-1a, interferon beta-1-b and glatiramer acetate, in Section B of the Pharmaceutical Schedule will be replaced with the following:

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 new inflammatory activity on an MR scan within the past 24 months**,** either:
            i. a gadolinium enhancing lesion; or
            ii. a Diffusion Weighted Imaging positive lesion; or
            iii. a T2 lesion with associated local swelling; or
            iv. a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse; or
            v. new T2 lesions compared with a previous MR scan; and

Funding for the beta-interferons (interferon beta-1a (Avonex), interferon beta-1beta (Betaferon)) and glatiramer acetate (Copaxone):

- The beta-inferferons and glatiramer acetate remain as funded treatment options for those patients who cannot take fingolimod and natalizumab for clinical reasons. Patients are not required to be contraindicated or unable to tolerate dimethyl fumarate and teriflunomide to access funding for the beta-interferons or glatiramer acetate treatments.

Feedback received

We appreciate all of the feedback that we received and acknowledge the time people took to respond. All consultation responses received by 6 November 2015 were considered in their entirety in making a decision on the proposed changes. Most responses were supportive of the proposal, and the following issues were raised in relation to specific aspects of the proposal:

Theme	Comment
Welcome the option of two additional oral treatments for patients to choose from. Provides an alternative treatment to fingolimod for those unable to tolerate the interferons / glatiramer acetate and for whom natalizumab is not an option.	Noted.
The use of these oral preparations, rather than IV natalizumab, will be accompanied by other cost savings.	Noted. Cost-offsets were included in our analysis.
Confusion was expressed with the number of funded treatments available, which treatment would be best and whether they would have to change from their current treatment to one of the new funded treatments.	Patients do not have to change from their current treatment, and can stay on their existing treatment provided the stopping criteria (for which they were approved for) are not met. Patients should discuss with their doctor which treatment option would be best for them. They may change to dimethyl fumarate or teriflunomide if they meet the criteria. The MS treatments Questions and Answers section on the PHARMAC website will be updated to address any questions that people raise about the funding and access criteria for the treatments.

Theme	Comment
Off-label leflunomide may be substantially cheaper than teriflunomide and may offer comparable benefit.	Leflunomide (Arava) is fully funded, without restrictions, on the Pharmaceutical Schedule. Leflunomide's registration does not include the indication of relapsing remitting MS.
Both dimethyl fumarate and teriflunomide are modestly effective and have similar efficacy to the interferons/glatiramer.	Noted.
Expressed concern that PTAC's recommendation to only fund dimethyl fumarate provided it was no more expensive than the interferons/glatiramer, may prevent the listing of dimethyl fumarate. Enclosed a review article (Broadley et al J Clin Neurosci 2014) that was not considered by PTAC, showing comparisons of efficacy for all MS treatments. At present it is not possible to assess in an evidence-based manner whether one drug is superior, due to no head to head trials.	Noted. In providing its advice, PTAC considered PHARMAC's nine decision criteria, in particular *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*
There are accumulating reports of opportunistic infections with dimethyl fumarate and that there have been three cases of progressive multifocal leukoencephalopathy (PML) with dimethyl fumarate. Teriflunomide is generally well tolerated; however, there are risks of hepatic toxicity, opportunistic infections and the potential for teratogenesis. Although the risks of infection and PML associated with dimethyl fumarate are low, and are much lower than natalizumab, that due to the modest efficacy of dimethyl fumarate the safety bar should be a lot higher. Considers that, based on safety concerns they would not recommend that patients use these treatments first line and that all patients prescribed dimethyl fumarate should have JC virus testing performed and if positive should have more frequent MRI scans, making the cost of treatment much higher. In addition close monitoring of lymphocyte should be mandated for patients prescribed dimethyl fumarate.	Noted. Dimethyl fumarate and teriflunomide have been approved by Medsafe for registration in New Zealand. PHARMAC staff note that there is no requirement for either dimethyl fumarate or teriflunomide to be used as first line treatments and that, with regards to monitoring, DHBs are able to put in place guidelines, including any Medsafe recommendations for monitoring, if deemed clinically appropriate.
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 Multiple Sclerosis Treatment Assessment Committee (MSTAC)'s role is to assess whether a patient meets the Special Authority criteria determined by PHARMAC and is therefore eligible for funding. Due to the complexities of the disease and the disease metrics, MSTAC ensures quality and nationally consistent equity of access so this arrangement will remain in place at this time. Clinicians should continue to apply under the NPPA process for any patients who do not meet the Special Authority criteria and who have unusual clinical circumstances.

Theme	Comment
MSTAC should be given discretion around cases that don't quite fit the criteria but meet the intent of the criteria.	MSTAC is able to make a recommendation for consideration by PHARMAC for a Special Authority Waiver when it considers that an application should be approved due to meeting the intent of the criteria.
There needs to be a mechanism for consideration of patients who would see benefit from treatment who do not quite fit the criteria, due to rarity of presenting symptoms.	Clinicians can continue to apply under the NPPA process for any patients who have exceptional circumstances. More information about the NPPA process can be found at http://www.pharmac.health.nz/tools-resources/forms/exceptional-circumstances/#section2
There is a group of patients who often present with a significant and debilitating first demyelinating episode and who would fulfil the McDonald 2010 diagnostic criteria for MS. These patients are a group in whom early treatment would seem highly appropriate, however are not eligible under the current criteria until they have a further 'clinical attack'.	We note that PTAC has previously recommended funding be declined for patients with clinically isolated syndrome (CIS) fulfilling the McDonald 2010 criteria. Funding for subgroups of patients would require specific consideration of relative benefits, risks, cost-effectiveness and budget impacts. We would welcome a funding application at any time for MS treatments for this specific sub-group of patients, should the respondent consider it to be a different group to that previously considered by PTAC, or if new evidence has become available.
The following is permitted under the SA criteria: 'If a relapse has resulted in an increased EDSS 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.' Considers that patients be required to switch treatments and then be reviewed again at the next annual review, then if at the next annual review their EDSS is unchanged or improved and there have been no relapses and no progression on MRI they should remain on treatment.	Extensions of funding for EDSS 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.
The entry and exit criteria are too restrictive.	Treating 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.
Supports the MRI amendments and notes the criteria are substantially improved, however considers the requirements for MRI appear to be based on inclusion criteria in studies rather than based on good evidence.	The clinical advice we have received is that the purpose of requiring MRI activity on a scan is to ensure that patients who present with symptoms that may not be due to active MS are not treated inappropriately, and that treatment is targeted to patients with clinically definite relapsing/remitting MS with active inflammatory disease. There are no other objective measures of disease activity, at this time, that could be used instead of MRI and MR scans are a necessary part of the diagnosis and ongoing management of MS.

Theme	Comment
Supportive of changes to MRI criteria; significantly improve the clarity. The new criteria may slightly reduce the number of scans that are required to confirm eligibility and the amount of patients required gadolinium enhanced MRI scans.	Noted.

More information

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