CONSULTATION

PHARMAC
Pharmaceutical Management Agency

16 October 2015

Proposals regarding Multiple Sclerosis treatments

PHARMAC is seeking feedback on proposals to list 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.

In summary, the proposals would, from 1 February 2016 result in:

- dimethyl fumarate (Tecfidera), supplied by Biogen NZ Biopharma Limited ("Biogen");

  and

- teriflunomide (Aubagio), supplied by Sanofi-Aventis New Zealand Limited ("Sanofi")

  being funded in the community and in DHB hospitals subject to the same restrictions that apply to natalizumab (Tysabri) and fingolimod (Gilenya); and

- changes to the Special Authority criteria for MS Treatments relating to MRI requirements, to ensure clarity and better reflect the intent of the criteria.

The proposed changes to the Special Authority criteria relating to MRI requirements are not dependent on the proposals to list dimethyl fumarate or teriflunomide.

Feedback sought

PHARMAC welcomes feedback on the proposals. To provide feedback, please submit it in writing by **Friday, 6 November 2015** to:

Adrienne Martin
Senior Therapeutic Group Manager/Team Leader
PHARMAC
PO Box 10 254
Wellington 6143

Email: adrienne.martin@pharmac.govt.nz

Fax: 04 460 4995

All feedback received before the closing date will be considered by PHARMAC's Board (or its delegate) prior to making a decision on the proposals.

Feedback we receive is subject to the Official Information Act 1982 (OIA) and we will consider any request to have information withheld in accordance with our obligations under the OIA. Anyone providing feedback, whether on their own account or on behalf of an organisation, and whether in a personal or professional capacity, should be aware that the content of their feedback and their identity may need to be disclosed in response to an OIA request.

We are not able to treat any part of your feedback as confidential unless you specifically request that we do, and then only to the extent permissible under the OIA and other relevant

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laws and requirements. If you would like us to withhold any commercially sensitive, confidential proprietary, or personal information included in your submission, please clearly state this in your submission and identify the relevant sections of your submission that you would like it withheld. PHARMAC will give due consideration to any such request

Details of the proposals

Dimethyl fumarate:

- Dimethyl fumarate (Tecfidera) would 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 (ex-manufacturer, excluding GST).

Chemical	Presentation	Brand	Pack size	Proposed 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 would apply to Tecfidera, reducing its net price.

- Dimethyl fumarate would be subject to the following funding criteria in Section B of the Pharmaceutical Schedule; please note that these criteria are the same as the current criteria for natalizumab and fingolimod and are also proposed for teriflunomide, although there would be subsequent changes to entry criterion 3 (a) below (regarding MRI activity) affecting all four agents (described later in this consultation document):

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); 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) 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; 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, and dimethyl fumarate 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 would be subject to the following access criteria in the HML 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) would 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 (ex-manufacturer, excluding GST):

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

- A confidential rebate would apply to Aubagio, reducing its net price.

- Aubagio would have subsidy and delisting protection until 31 October 2017.

- Teriflunomide would be subject to the following funding criteria in Section B of the Pharmaceutical Schedule; please note that these criteria are the same as the current criteria for natalizumab and fingolimod and are also proposed for dimethyl fumarate, although there would be subsequent changes to entry criterion 3 (a) below (regarding MRI activity) affecting all four agents (described later in this consultation document):

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
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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); 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) 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; 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, 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 would be subject to the following access criteria in the HML 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, and, should the proposals be approved for dimethyl fumarate and teriflunomide, would be amended as follows (additions in bold, deletions in strikethrough):

Note:
Switching between natalizumab~~, and~~ 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, and, should the proposals be approved for dimethyl fumarate and teriflunomide, would be amended, as follows (additions in bold, deletions in strikethrough):

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~~ **new inflammatory** activity on a**n MR** scan within the past 24 months**,** ~~(either a contrast enhancing lesion or with new T2 lesion(s) compared with a previous scan);~~ **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

- Full details of the current Special Authority criteria are available on pages 146-151 of the Pharmaceutical Schedule available at: http://www.pharmac.govt.nz/2015/10/01/Schedule.pdf

Changes to Other Multiple Sclerosis treatments Special Authority Criteria:

- From 1 February 2016 the Special Authority Criteria for Other Multiple Sclerosis treatments, interferon beta-1a, interferon beta-1-b and glatiramer acetate, would be amended as follows (additions in bold, deletions in strikethrough), again to specify MRI diagnostic criteria:

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~~ **new inflammatory** activity on a**n MR** scan within the past 24 months**,** ~~(either a contrast enhancing lesion or with new T2 lesion(s) compared with a previous scan);~~ **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

- Full details of the current Special Authority criteria are available on pages 146-151 of the Pharmaceutical Schedule available at: http://www.pharmac.govt.nz/2015/10/01/Schedule.pdf

Background

There are currently five funded MS treatments: Natalizumab, fingolimod, the beta interferons (interferon beta-1-beta, interferon beta-1-alpha) and glatiramer acetate.

There are funding criteria in place for these treatments; patients' eligibility for funded treatment is determined by a panel of clinicians contracted by PHARMAC, the Multiple Sclerosis Treatment Assessment Committee (MSTAC).

- Natalizumab and fingolimod are funded from first confirmed diagnosis of definitive relapsing remitting MS, for patients with an EDSS score of 0–4.0, who meet the funding criteria. (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)
- The beta interferons and glatiramer acetate are funded for those patients who can't take fingolimod or natalizumab for clinical reasons, and for patients who had SA approvals issued before 1 November 2014.

There are approximately 800 patients currently receiving funding for MS treatments. This proposal, if approved, would mean that there would be an additional two new treatments for MS for patients to choose from. Based on the clinical advice we have received there may be a small additional number of approximately 10 to 20 patients over five years as a result of two new treatments.

For the avoidance of doubt, the beta-interferons and glatiramer acetate would remain as funded treatment options for those patients who can't take fingolimod or natalizumab for clinical reasons.

Dimethyl fumarate and teriflunomide

Dimethyl fumarate is indicated for the treatment of relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability. The exact mechanism of action of dimethyl fumarate is unknown, although it is thought to have anti-inflammatory and immunomodulatory properties. Dimethyl fumarate is a capsule taken orally twice daily.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties. Leflunomide (Arava), which is fully funded on the Pharmaceutical Schedule is the parent compound of teriflunomide. Teriflunomide is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the progression of physical disability. Teriflunomide is a tablet taken orally once daily.

Dimethyl fumarate and teriflunomide do not require first dose monitoring under medical supervision, and treatment could therefore be started by the patient in their home. Dimethyl fumarate and teriflunomide would be dispensed by a community pharmacy.

The Pharmacology and Therapeutics Advisory Committee (PTAC) has provided advice on the funding of dimethyl fumarate and teriflunomide for MS.

In summary PTAC recommended that:

- Dimethyl fumarate be funded with a medium priority subject to the same access criteria as natalizumab and fingolimod, provided it was no more expensive than the beta-interferons or glatiramer acetate.

- Teriflunomide be funded with a low priority subject to the same criteria that applies to natalizumab and fingolimod.

Dimethyl fumarate and teriflunomide minutes can be found here:

http://www.pharmac.health.nz/assets/ptac-minutes-2014-11-updated.pdf

Changes to the SA criteria for all MS treatments

MSTAC and members of the Neurological Subcommittee of PTAC have suggested that some amendments could be made to criterion 3 (a) of the MS treatments Special Authority criteria, relating to MRI evidence of active inflammatory disease, to ensure clarity and better reflect the intent of the criteria.

The clinical advice we have received is that these changes would be unlikely to have any significant impact on the numbers of eligible patients accessing MS treatments. However it may mean that some patients who would have needed to have further MRI studies to demonstrate new inflammatory MRI activity may not need additional MRI studies and would, therefore with the proposed amendments, be treated slightly earlier. This may result in a reduction on the impact for MRI services.