CONSULTATION

PHARMAC
Pharmaceutical Management Agency

26 June 2013

Proposal to widen access to imiglucerase for type 1 and type 3 Gaucher disease

PHARMAC is seeking feedback on a proposal to widen access to imiglucerase from 1 September 2013. In summary the proposal would result in

- patients with Gaucher disease Type 3 having access to funded imiglucerase;
- the maximum funded dose of imiglucerase being increased from 15 iu/kg per month to 30 iu/kg per month for children meeting certain criteria

Details of the proposal can be found below and on the following page.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by **5pm Wednesday, 10 July 2013** to:

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

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 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 proposal

Imiglucerase (Cerezyme) is currently listed in Section B of the Pharmaceutical Schedule. Eligibility criteria currently apply to all funded prescribing of imiglucerase in Section B of the

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Pharmaceutical Schedule. We propose that these restrictions be amended from 1 September 2013.

From 1 September 2013 the criteria that apply to the listings of imiglucerase in Section B of the Pharmaceutical Schedule would be amended as follows (additions in **bold** and deletions in ~~strikethrough~~):

ELIGIBILITY CRITERIA FOR IMIGLUCERASE

~~*ACCESS CRITERIA FOR TREATMENT WITH IMIGLUCERASE (CEREZYME)*~~
ELIGIBILITY CRITERIA FOR IMIGLUCERASE FUNDING
These guidelines are intended to assist relevant practitioners in gauging which patients are likely to be approved for imiglucerase. In view of the complexity of Gaucher disease severity assessment, each application is thoroughly evaluated by the Gaucher Panel to determine the appropriate imiglucerase treatment.

All requested studies should be carried out in line with the relevant professional guidelines. Patients with Gaucher disease who meet the following criteria may be eligible for initiation of imiglucerase treatment based on current clinical evidence.

~~**Schedule 1: Guidelines for use of imiglucerase**~~
Patients eligible for initial approval of Special Authority

1. The **patient must have a** diagnosis of symptomatic type 1 **or type 3** Gaucher disease ~~must have been established~~ by the demonstration of:

    - Specific deficiency of glucocerebrosidase in leukocytes or cultured skin fibroblasts; and
    - Genotypic analysis

    Histology and genotype tests to be supplied with the initial application once available. Baseline MRI whole body Short Tau Inversion Recovery (STIR) and serum chitotriosidase reports must be provided.

2. **Patients who have Gaucher type 2 disease are not eligible for subsidised treatment.** If a patient has a medical condition which significantly impacts on life expectancy or the treatment would not have a significant chance of causing an improvement in the patient's condition, it is considered inappropriate to initiate therapy with imiglucerase.

~~3. Animal reproductive studies have not been conducted with imiglucerase. It is also not known whether imiglucerase can cause foetal harm when administered to a pregnant woman, or can affect reproductive capacity. Imiglucerase should be given to a pregnant woman only where the perceived benefits outweigh the potential risks.~~

4. Patients who receive government funded imiglucerase treatment must be willing to participate in the long term evaluation of the efficacy of the treatment, as approved, if necessary, by an ethics committee. Collated data collected may be made available to international investigators. Patient anonymity should be preserved.

5. Unless otherwise agreed by PHARMAC, imiglucerase shall not be subsidised at a dose exceeding ~~15~~ **30** iu/kg/month rounded to the nearest whole vial.

6. The **Gaucher** Panel will consider applications and provide advice on the appropriate management of any other patients referred to it by PHARMAC.

~~**Criteria for Commencement of Treatment**~~
Initial Treatment criteria

Imiglucerase 15 iu/kg/month
One of the following clinical parameters would be severe enough to cause symptoms and as such are considered sufficient to warrant therapy **with imiglucerase 15 iu/kg/month.**

Imiglucerase 30 iu/kg/month for children*
Any three of the following clinical parameters, or bone crisis, or severe/significant bone marrow abnormalities on MRI would indicate severe disease and warrant initial therapy with imiglucerase 30 iu/kg/month. Unless there are exceptional circumstances only children are eligible for a starting dose of 30 iu/kg/month.

Haematological complications:

1. Haemoglobin <95g/l, after other causes of anaemia, such as iron deficiency have been treated or ruled out, or severe symptoms from anaemia at a higher level of haemoglobin.
2. Thrombocytopenia < 50 x 10E9/L on two separate occasions at least one month apart.
3. Bleeding complications associated with thrombocytopaenia, irrespective of the platelet count.
4. At least two episodes of severely symptomatic splenic infarcts confirmed by CT or other imaging of the abdomen.
5. Massive symptomatic splenomegaly.

Skeletal complications:

1. One acute bone crisis severe enough to require hospitalisation and or major pain management strategies.
2. Radiographical MRI evidence of incipient destruction of any major joint, such as the hips or shoulder.
3. Spontaneous fractures or vertebral collapse.
4. Chronic bone pain not controlled by the administration of non-narcotic analgesics or anti-inflammatory drugs, or requiring continuous medication or causing a significant loss of time from work or school.

Hepatic complications:

1. Evidence of significant liver dysfunction, such as incipient portal hypertension, attributable to Gaucher disease (treatment should start before this stage is reached).
2. Significant hepatomegaly e.g., ~~5 cms below the right costal margin~~ **>2.5 times the normal liver volume** or significant abnormality of the liver function tests.

Pulmonary complications:

Reduced vital capacity from clinically significant or progressive pulmonary disease due to Gaucher disease.

Systemic complications

Growth failure in children: significant decrease in percentile linear growth over a 6-12 month period.

Test reports, including MRI whole body STIR, serum chitotriosidase and haematological data, must accompany the initial application.

'Children' can be defined by an upper age of 18 or the attainment of radiological evidence of skeletal maturity (whichever is the latter).

Patients eligible for renewal of Special Authority

Renewal applications must be submitted to the Gaucher Panel for an annual review.

~~**Criteria for Cessation of Treatment**~~
Renewal of imiglucerase treatment - 15/iu/kg/month

~~a) In the event that the Panel determines by some measurable method (for example of a patient refuses on **more than three** > 3 occasions to have injection, or loses product) that the patient has failed to comply adequately with the treatment or measures to evaluate the effectiveness of the therapy, the Panel is to :~~

~~(i) notify PHARMAC of its concerns in respect of that patient; and~~

~~(ii) make a recommendation to PHARMAC regarding whether funding of imiglucerase for that patients should be withdrawn, and if not, the period and specific conditions under which the Panel would recommend continuance of funding for treatment.~~

b) If the patient has demonstrated a symptomatic improvement or no deterioration in the main symptom for which therapy was initiated as set out below:

- bleeding abnormalities;

- chronic fatigue;
- gastro intestinal complaints;
- bone pain; or
- psychosocial function,

combined with clinically objective improvement or no deterioration in haemoglobin levels, platelet counts and liver and spleen size, then treatment should be continued.

~~c) The results of treatment will be re-evaluated every 12 months by the Panel. If there has been no significant response to treatment after 12 months (visceral or haematological), Imiglucerase will be discontinued. Bony changes may require a longer period of treatment and cases will be assessed on an individual basis by the panel.~~

~~d) In the event of a severe drug reaction treatment may have to be discontinued earlier.~~

Renewal of imiglucerase treatment - 30/iu/kg/month:

~~Success Criteria~~
Success of ~~the trial~~ **imiglucerase treatment at 30 iu/kg/month** will be based on improvements, or no deterioration **in the symptoms for which treatment was initiated**.
Primary success measures

a) Radiological (MRI) signs of bone activity performed one year and then two years after treatment begins. At two years there needs to be no deterioration shown by the MRI, compared with MRI taken immediately prior to commencement of therapy increased dose; and

b) serum chitotriosidase levels show a decrease (preferably of 10%) compared with level taken immediately prior to commencement of increased dose. Serum chitotriosidase levels during treatment are to be taken at least at 6 month intervals.

~~Secondary measures (to be assessed for monitoring, but not markers of exit)~~

a) Visceral and haematological indices (haemoglobin levels, platelet counts, bleeding episodes associated with thrombocytopaenia at any level, liver size, liver function tests, spleen size, episodes of splenic infarction, pulmonary vital capacity); and/or

b) frequency and/or severity of acute bone crises, radiographic signs of incipient major joint destruction, spontaneous fractures or vertebral collapse; and/or

c) systemic complications (namely growth failure); and/or

d) the main symptom(s) for which therapy was initiated +/- increased bleeding abnormalities; chronic fatigue; gastro intestinal complaints; bone pain (chronic bone pain not controlled by the administration of non-narcotic analgesics or anti-inflammatory drugs, or requiring continuous medication or causing a significant loss of time from work or school); or psychosocial function.

~~Schedule 2: Access Criteria for Treatment with Higher Doses of Imiglucerase (Cerezyme) (30 iu/kg/month)~~

Dose Increase Criteria for children
~~Should the Panel consider that a patient meets the following criteria, the Panel may make a recommendation to PHARMAC for access to treatment with a higher dose of imiglucerase for that patient.~~

~~Any decision regarding funding of an increased dose will be made by the PHARMAC Board.~~

~~Indications for recommending higher dose~~

Eligibility criteria for children who have not responded or show poor improvement on 15 iu/kg/month. Clinicians may apply for an increased dose of up to 30 iu/kg/month, rounded to the nearest whole vial. Test results for the following clinical markers, including a repeat MRI whole body STIR and repeat serum chitotriosidase levels must be provided.

Patients are on standard imiglucerase treatment (15 iu/kg/month) and adhering to treatment, and either:

a) (Earlier stage) objective indications of lack of improvement +/- incipient clinical deterioration:
   (i) MRI signs of persistent ongoing or increased bone activity; and
   (ii) Persistent significantly elevated serum chitotriosidase levels; or
   (iii) Failure to demonstrate a decline in serum chitotriosidase levels
   and/or:

b) (Later stage) deterioration in other laboratory and radiological measures of visceral, haematological or skeletal deterioration (haemoglobin levels, platelet counts, hepatomegaly, liver function tests, splenomegaly, radiological signs of pathological fracture joint destruction), and/or:

c) (Later stage) frank symptomatic deterioration in main initiating symptoms (bleeding abnormalities; chronic fatigue; gastro intestinal complaints; bone pain, osteonecrotic sequelae, etc.)

The during treatment serum chitotriosidase levels are to be taken at least 6 monthly, and an MRI performed at 12 and 24 months after beginning new treatment dose.

Dose stopping criteria for all patients

a) In the event that the Panel determines by some measurable method (for example of a patient refuses on **more than three** ~~> 3~~ occasions to have injection, or loses product) that the patient has failed to comply adequately with the treatment or measures to evaluate the effectiveness of the therapy, the Panel is to :
   (i) notify PHARMAC of its concerns in respect of that patient; and
   (ii) make a recommendation to PHARMAC regarding whether funding of imiglucerase for that patients should be withdrawn, and if not, the period and specific conditions under which the Panel would recommend continuance of funding for treatment.

b) In the event of a severe drug reaction treatment may have to be discontinued ~~earlier~~.

c) If there has been no significant response to treatment at 15iu/kg/month or 30iu/kg/month after 12 months (visceral or haematological), Imiglucerase will be discontinued. (Bony changes may require a longer period of treatment and cases will be assessed on an individual basis by the panel).

Background

Currently, imiglucerase is listed in the Pharmaceutical Schedule in New Zealand for type 1 Gaucher disease at a dose of 15 iu/kg/month under agreed eligibility criteria, given as fortnightly intravenous infusions.

Imiglucerase was reviewed by PTAC in August 2011. PTAC recommended that access be widened with high priority, restricted by the eligibility criteria (as proposed above) to patients with type 1 and type 3 Gaucher disease.

PTAC recommended in August 2011 that the eligibility criteria be amended to:

- Widen access to children with type 1 Gaucher disease to receive up to 30 iu/kg/month if they meet the proposed eligibility criteria
- List imiglucerase for type 3 Gaucher disease under the proposed eligibility criteria so they would be eligible to receive up to 30 iu/kg/month.

More detailed information on PTACs discussion can be found here: http://www.pharmac.health.nz/ckeditor_assets/attachments/55/2011_08_ptac_web_minutes.pdf

Details of PHARMAC's assessment of the application to date, along with minutes from PTAC can be found in PHARMAC's Application Tracker at http://www.pharmac.govt.nz/patients/ApplicationTracker?SearchTerm=imiglucerase