

Schedule 1: Access Criteria for Treatment with imiglucerase (Cerezyme)

Guidelines for use of imiglucerase

- a) The diagnosis of symptomatic type 1 Gaucher disease must have been established by the demonstration of specific deficiency of glucocerebrosidase in leukocytes or cultured skin fibroblasts, and by genotypic analysis.
- b) If a patient has a medical condition which significantly impacts on life expectancy or if 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.
- c) 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.
- d) 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.
- e) Consent for data collection must be obtained from the patient and his/her legal guardian(s), where appropriate in line with any ethics committee process and/or procedural requirements.
- f) Unless otherwise agreed by PHARMAC, imiglucerase shall not be subsidised at a dose exceeding 15iu/kg/month rounded to the nearest whole vial.
- g) The 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

One of the following clinical parameters would be severe enough to cause symptoms and as such are considered sufficient to warrant therapy.

Haematological complications:

- (i) 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.
- (ii) Thrombocytopenia < 50 x 10⁹/l on two separate occasions at least one month apart.
- (iii) Bleeding complications associated with thrombocytopenia, irrespective of the platelet count.
- (iv) At least two episodes of severely symptomatic splenic infarcts confirmed by CT or other imaging of the abdomen.
- (v) Massive symptomatic splenomegaly.

Skeletal complications:

- (i) One acute bone crisis severe enough to require hospitalisation and or major pain management strategies.
- (ii) Radiographical MRI evidence of incipient destruction of any major joint, such as the hips or shoulder.
- (iii) Spontaneous fractures or vertebral collapse.
- (iv) 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:

- (i) Evidence of significant liver dysfunction, such as incipient portal hypertension, attributable to Gaucher disease (treatment should start before this stage is reached).
- (ii) Significant hepatomegaly e.g., 5 cms below the right costal margin 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.

Criteria for Cessation of Treatment

- (a) In the event that the Panel determines by some measurable method (for example of a patient refuses on > 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) The Panel is to recommend to PHARMAC that funding for imiglucerase treatment be withdrawn if there is a lack of symptomatic improvement 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 a lack of clinically objective improvement in haemoglobin levels, platelet counts and liver and spleen size, then treatment should be discontinued.

- (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.

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

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

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

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.)

Success criteria

Success of the trial will be based on improvements, or no deterioration.

Primary success measures

- a) Radiological (MRI) signs of bone activity performed one year and then two years after the trial begins. At two years there needs to be no deterioration shown by the MRI, compared with MRI taken immediately prior to commencement of increased dose; and
- b) serum chitotriosidase levels show a decrease (preferably of 10%) compared with level taken immediately prior to commencement of increased dose. The during treatment levels 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.

The success of the trial will be assessed two years after the increased dose is commenced. One year into the trial the Gaucher's treatment panel will undertake an interim evaluation of the patients.

Exit Criteria

Patients show deterioration in radiological signs of bone activity (MRI) and no decrease in serum chitotriosidase levels following two years on treatment with increased dose of imiglucerase. 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.