

**CANADIAN GUIDELINES FOR TREATMENT OF GAUCHER  
DISEASE BY ENZYME REPLACEMENT WITH IMIGLUCERASE  
OR SUBSTRATE REDUCTION THERAPY WITH MIGLUSTAT  
(Version 8; March 26, 2007)**

**Preamble**

Gaucher disease is a rare hereditary condition caused by deficiency of the enzyme, glucocerebrosidase, which is required for the breakdown of a specialized lipid, called glucocerebroside, that occurs throughout the body but particularly in the liver, spleen, and bone marrow. Accumulation of glucocerebroside in people with Gaucher disease often causes no problems at all. The only problem in many is enlargement of the spleen which may cause alterations in the blood leading to easy bruising or a tendency towards prolonged bleeding following injuries, minor surgery, or the birth of a baby. The bleeding tendency is caused by depletion of blood platelets and is correctable in part by surgical removal of the spleen. However, splenectomy accelerates the accumulation of the lipid in the liver and bone marrow.

Individuals with Gaucher disease often are chronically anemic as a result of replacement of normal bone marrow by "storage cells". Although anemia is common, it is rarely severe. However, in some cases the anemia progresses to a stage requiring regular and frequent blood transfusions; rarely, it leads to death.

In some individuals with the disease, accumulation of glucocerebroside in the bone marrow causes weakening of the bone causing fractures. In a few, disturbances of the circulation to the bone cause periodic attacks of excruciating pain in the hips, knees, and shoulders. In these individuals, interruption of the circulation to the bone often causes destruction of joints resulting in a requirement for major surgical treatment. People with Gaucher disease are also more apt than others to develop bone infections. Accumulation of glucocerebroside in the liver may cause cirrhosis, resulting in bleeding into the stomach and gut, jaundice, swelling of the ankles, and, eventually, death.

Treatment of Gaucher disease in the past has focussed on symptomatic treatment of pain; surgical treatment of fractures, infections, and avascular necrosis of bone; surgical removal of the spleen to relieve the thrombocytopenia caused by hypersplenism; and blood transfusions to correct the anemia of the disease. Patients with very severe disease have also been treated by bone marrow transplantation. However, this requires the availability of a suitable bone marrow donor, and the procedure is associated with prolonged hospitalization and morbidity and with a high mortality rate.

Treatment of Gaucher disease by enzyme replacement therapy represents a major advance in the treatment of genetic disease. The enzyme that is deficient, glucocerebrosidase, has been extracted from human placenta and chemically modified to enhance its effectiveness. Treatment with this modified product has dramatic effects on

the hematologic and bone complications of the disease - on this issue the results of all the reported clinical trials are unambiguous. The efficacy of enzyme replacement in the management of other complications is still under investigation.

Experience has shown that some patients with type I Gaucher disease (non-neuronopathic Gaucher disease) do not tolerate enzyme replacement therapy, or cannot qualify for medical, religious, or personal reasons. The introduction of a new treatment, which aims to decrease the *production* of glucocerebroside, rather than accelerating its elimination, represents a potential therapeutic option for patients in this category. Substrate reduction therapy with miglustat decreases the production of glucocerebroside by inhibiting glucosylceramide synthase (UDP-glucose:ceramide glucosyltransferase). The drug has been shown, in clinical trials, to produce improvements in the enlargement of the liver and spleen and the anemia and decreased platelet counts in patients with type I Gaucher disease. It has also been shown to stabilize therapeutic gains achieved by enzyme replacement therapy. The drug is administered orally, which for some, represents a major advantage over intravenous enzyme infusion. However, treatment with miglustat is associated with side effects which may limit its use, and it has not been evaluated in the treatment of neuronopathic Gaucher disease or in children with type I Gaucher disease. Substrate reduction therapy with miglustat provides an alternative to enzyme replacement therapy in adults who are unsuitable candidates for ERT.

Owing to the very high cost of treatment, and the risk and inconvenience associated with the need for frequent intravenous injections of a foreign protein derived from the extraction of human tissues, some guidance was judged to be necessary for the selection of patients for treatment with the newly available compound, imiglucerase (Cerezyme<sup>®</sup>), which has replaced alglucerase (Ceredase<sup>®</sup>) for the treatment of the disease and, in what settings, the use of miglustat (Zavesca<sup>®</sup>) is appropriate. What follows are some proposed criteria for the selection of patients and treatment protocol.

## **Guidelines**

### ***General comments***

The recommendation to provide financial support for treatment of any given patient with Gaucher disease will be based on sound clinical judgement; the genotype (i.e. specific glucocerebrosidase mutations) will not be a factor. The variables providing the best indication of the severity of disease are the platelet count, hemoglobin concentration, the size of the spleen and/or liver relative to total body mass, and the amount of bone marrow replacement by storage cells. The assessment of hematologic involvement and organ size is relatively easy; the assessment of bone involvement is more difficult. In adults, changes on MR scanning of the epiphyses about the knees correlate well with other evidence of bone involvement, such as pain; there is insufficient experience to be able to apply this technique as confidently in children with the disease.

The results of any deliberations by the Review Committee will be communicated to appropriate officials of the Ministry of Health. The Committee will not communicate directly with patients under review. When a member of the Committee is also one of the

physicians involved with the medical care of a patient under review, he or she will be asked to present the case for treatment, but would be asked to absent themselves while a decision regarding support for treatment is reached by the remaining Committee members.

The Committee reserves the right to review and revise these guidelines from time to time to ensure that they remain consistent with their original purpose.

### ***Criteria for admission to treatment***

#### **Resident of Canada**

1. The patient must be Canadian resident who is eligible for drug coverage under one of the Canadian provincial or territorial health plans or a federally funded plan such as for drug funded through the Department of Aboriginal Affairs.

#### **Diagnosis of Gaucher disease**

1. The diagnosis of Gaucher disease must have been established by the demonstration of specific deficiency of glucocerebrosidase in tissue or cultured skin fibroblasts, or by demonstration of the presence, in tissue or peripheral blood leukocytes, of mutations in the glucocerebrosidase gene known to result in severe enzyme deficiency.
2. Other potentially confounding diagnoses, such as Hodgkins disease, must have been ruled out. The symptoms experienced by the patient should be shown to be attributable to Gaucher disease and not some other condition that might mimic it. A trial of therapy would normally only be considered in situations of uncertainty if the symptoms were accompanied by objective evidence (hematological or imaging changes consistent with complaints).
3. The patient should not have any Gaucher disease-related or other medical condition that might reasonably be expected to compromise their response to treatment. In some patients with Gaucher disease, secondary pathologic changes, such as avascular necrosis of bone, may already have occurred that would not be expected to respond to enzyme replacement. In such patients, reversal of the pathology is unlikely. Treatment of patients with significant secondary pathology would be directed at preventing further progression of the disease. In these cases, the extent to which symptoms, such as bone pain, are due to active progression of the disease, rather than the secondary pathology, can only be established by a trial of therapy.
4. Pregnancy is not considered a contraindication to imiglucerase treatment.
5. Patients to be considered for reimbursement of drug costs for imiglucerase or miglustat treatment must be willing to participate in the longterm evaluation of the efficacy of treatment by periodic medical assessment . Failure to comply with recommended medical assessment and investigations may result in withdrawal of financial support of drug therapy.

**Severity of disease** (or, in children, evidence from the rate of progression of symptoms that the disease is likely to become severe within a few years)

1. At the current time, financial support for the treatment of asymptomatic patients is not provided due to the absence of data which shows that the therapy of asymptomatic patients alters long term outcomes.
2. Patients exhibiting primary neurological disease due to Gaucher disease would not normally be considered eligible for treatment (see Neuronopathic Gaucher Disease below).
3. The designation of the severity of disease in any particular patient will rest with Clinical Review Committee. The Committee will take a number of issues into consideration in its assessment of severity, including any one of the following:

*Hematological complications*

(a) Hemoglobin <85% of lower limit of age- and sex-appropriate normal after other causes of anemia, such as iron deficiency, have been treated or ruled out, and/or

(b) Platelet count <30 x 10<sup>9</sup>/L on two separate occasions at least one month apart.

(c) At least two episodes of severely symptomatic splenic infarcts confirmed by CT or other imaging of the abdomen

*Skeletal complications*

(a) A single acute bone crisis severe enough to require hospitalization or severe incapacitation.

(b) Radiographic or MRI evidence of incipient destruction of any major joint, such as hips, shoulders.

(c) Spontaneous fractures with evidence from imaging studies that recurrence is likely.

(d) Chronic bone pain, not controllable by administration of non-narcotic analgesics or anti-inflammatory drugs, causing significant loss of time from work or school.

(e) A recommendation is made that patients who are scheduled for major joint replacement surgery, made necessary by skeletal complications of Gaucher disease, should be treated with imiglucerase at a dosage of at least 30 units/kg every 2 weeks for at least 6 months before the joint replacement surgery and the dose continued until rehabilitation from the surgery is complete.

*Gastrointestinal complications*

(a) Evidence of significant liver dysfunction, such as portal hypertension or impaired hepatic synthetic function, attributable to Gaucher disease. Elevation of transaminase levels with no evidence of portal hypertension or impairment in synthetic function is not an indication for ERT.

(b) Significant discomfort due to enlargement of the spleen or liver.

*Pulmonary complications*

(a) Evidence of clinically significant and/or progressive pulmonary disease due to Gaucher disease.

*Systemic complications*

(a) Growth failure in children: significant decrease in percentile linear growth over a 3 - 6 month period

4. Severity of the disease will be re-assessed at least annually.

A summary table of the indications for therapy and the expected response for each indication is shown below.

Indication for therapy	Expected Response <sup>1</sup>
Hemoglobin <85% of lower limit of age- and sex-appropriate normal	Increase hemoglobin levels to >110 for women and children and >120 for men
Platelet count <30 x 10 <sup>9</sup> /L on two separate occasions	Increase platelet count to level sufficient to prevent spontaneous bleeding
	Normalization of platelet count in splenectomized patients
	In patients with intact spleen, an increase of at least 1.5X in baseline value
Two episodes of severely symptomatic splenic infarcts	Reduction of spleen volume by 50%
	Prevention of further splenic infarcts
Acute bone crises	Prevent bone crises
Radiographic or MRI evidence of incipient destruction of any major joint,	Improvement in imaging parameters (either MRI, QCSI <sup>2</sup> , or BMD)
Spontaneous fractures	Prevention of further fractures
Chronic bone pain	Reduce bone pain
major joint replacement surgery	?
significant liver dysfunction	Improvement in hepatic function
Symptomatic hepatosplenomegaly	Reduction of spleen volume by 50%

	Reduction in liver volume by 30%
progressive pulmonary disease due to Gaucher disease	Improvement in pulmonary hypertension <sup>3</sup>
	Improvement in oxygenation
	Reversal of hepatopulmonary syndrome
Growth failure in children	Return to normal range on height percentiles

<sup>1</sup>Responses are based on those shown for enzyme replacement therapy as presented by Pastores et al. Therapeutic Goals in the treatment of Gaucher Disease, Seminars in Hematology, 2004.

<sup>2</sup>QCSI quantitative chemical shift imaging

<sup>3</sup>May require adjuvant treatment for pulmonary hypertension

### ***Neuronopathic Gaucher Disease***

ERT and SRT are effective in reversing the visceral manifestations of Gaucher disease. However, data do not suggest that ERT is effective in improving central nervous system involvement in patients with Type 3 disease. Treatment with ERT in patients at risk of neuronopathic disease should therefore be guided by the visceral manifestations of their disease as outlined above but not initiated for in asymptomatic patients who have a genotype which increases their risk of neuronopathic involvement (4,5).

### ***Choice of Drug***

1. If a patient meets the criteria for therapy outlined above, the drug of first choice is imiglucerase.
2. Substrate reduction therapy with miglustat should be considered in patients with moderate type I Gaucher disease who are unable or unwilling to receive enzyme replacement therapy, including:
  - a. Rare cases of severe allergic reactions or hypersensitivity to imiglucerase
  - b. Failure to maintain intravenous access
  - c. Patients who are incompletely responsive to maximum doses of ERT
  - d. Patients unwilling or unable to receive ERT for medical or personal reasons
3. The cost of the drug should not be considered when choosing an agent.

### ***Dosage***

1. The dosage of imiglucerase prescribed would depend on the severity of the disease and would be at the discretion of the supervising consultant. However, it would not normally exceed 60 units per kg body weight every 2 weeks.
2. The dosage of miglustat is 100 mg po tid.

### ***Monitoring of therapy***

#### **Imiglucerase**

1. The efficacy of treatment would be re-evaluated every 6 months and adjustments of enzyme dosage made as appropriate. A table of expected responses to imiglucerase is shown above. If there has been no response to treatment after 6 months on a lower dose, the enzyme dosage may be increased to a maximum of 60 units/kg/infusion given every 2 weeks. If there has been no significant response to treatment after 12 months on a dosage of 60 units/kg/infusion given every 2 weeks, treatment with imiglucerase will be discontinued. In the event of severe drug reaction, treatment may have to be discontinued. Imiglucerase has been shown to be well tolerated with few long term toxicities reported.

#### **Miglustat**

Patients on treatment with miglustat should be assessed before the initiation of treatment and at least every 6 months thereafter for:

1. Effectiveness of treatment, using the guidelines developed and periodically modified by the International Collaborative Gaucher Group (see *Seminars in Hematology*, vol 41(Suppl 5), pp 15-22, 2004)
2. Adverse reactions, by neurological examination (including mental state assessment), nerve conduction studies, plasma folate and vitamin B<sub>12</sub> levels, and whatever other studies the treating physician deems to be indicated in individual cases.
3. In the event of adverse events, it is recommended to reduce the dose or even interrupt therapy until the reaction resolves.

#### **Adjunctive therapy**

1. ERT or SRT may be supplemented by treatment with analgesics, anti-inflammatory drugs, or other medications considered to have a beneficial effect on specific complications of the disease. A complete record of such supplementary therapy will be kept.
2. ERT and SRT would not normally be considered a contraindication for any surgical treatment required for the treatment of secondary pathology due to Gaucher disease. However, except under unusual circumstances, such as rupture of the organ, splenectomy (surgical removal of the spleen) would not be done as long as a patient is on imiglucerase treatment.

3. Adverse gastrointestinal reaction to treatment with miglustat are decreased by treatment with a lactose-free diet, supplemented by oral administration of lactase and, in some patients, by treatment with loperamide.

### ***Withdrawal of therapy***

The recommendation to provide financial support for imiglucerase or miglustat therapy would be withdrawn:

1. in the event that the patient fails to comply adequately with treatment or measures taken to evaluate the effectiveness of the therapy.
2. if therapy fails to relieve the symptoms of disease that originally resulted in the patient being classified as severely affected.

### ***Administration and supervision of therapy***

1. All patients with Gaucher disease in whom ERT or SRT is initiated should be assessed on an annual basis by a physician who has expertise in the administration and monitoring of such therapy. The day to day supervision of the enzyme infusions will be done by a physician in the local community in consultation with the Gaucher Disease specialty team.
2. Annual review of all patients on therapy for Gaucher disease should be conducted by a clinical review committee. The composition of such a committee will be dictated by the local expertise in the field. The purpose of the review is to ensure that the patient is compliant with recommended assessments and investigations and that appropriate responses to therapy are being realized.

### ***Further studies***

The group recognized the pressing need for further formal studies to examine the role of SRT in the treatment of patients:

- with type I Gaucher disease who have had a good response and are stable on ERT.
- with mild type I Gaucher disease.
- with type III Gaucher disease.

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