ONTARIO GUIDELINES FOR TREATMENT OF GAUCHER DISEASE BY ENZYME REPLACEMENT WITH IMIGLUCERASE OR VELAGLUCERASE, OR SUBSTRATE REDUCTION THERAPY WITH MIGLUSTAT
(Version 9; August 2011)

Preamble

Gaucher disease (GD) is a rare hereditary condition caused by deficiency of the enzyme, glucocerebrosidase (GCase), 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 GD sometimes 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 GD 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 and may lead to 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 GD 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. A few patients may develop pulmonary hypertension from several possible mechanisms; this may become fatal.

Until the 1990s, treatment of GD 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 GD by enzyme replacement therapy (ERT) represents a major advance in the treatment of genetic disease. The enzyme that is deficient, GCase, was initially extracted from human placenta and chemically modified to enhance its effectiveness. Treatment with this modified product (Alglucerase [Ceredase]; Genzyme Corporation. has dramatic effects on the hematologic, visceral and some bone complications of the

disease **-** on this issue the results of all the reported clinical trials are unambiguous. The efficacy of ERT in the management of other complications is still under investigation. (Alglucerase [Ceredase®] has been replaced by a recombinant enzyme, imiglucerase [Cerezyme®] Sanofi Genzyme.)

Experience has shown that some patients with type I GD (nonneuronopathic GD) do not tolerate ERT, or cannot qualify for medical, religious, or personal reasons. The introduction of novel treatment strategies including substrate reduction (SRT) and enzyme enhancement (EET) (chaperone) therapy represents a potential therapeutic option for patients in this category. SRT aims to decrease the *production* of glucocerebroside, rather than accelerating its elimination; and EET functions by stabilizing misfolded enzyme.

SRT with Miglustat (Zavesca®; Actelion Pharmaceuticals Ltd.) 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 GD. It has also been shown to stabilize therapeutic gains achieved by ERT. The drug is administered orally, which for some, represents a major advantage over intravenous enzyme infusion. SRT with Miglustat provides an alternative for adult type1 Gaucher patients with mild to moderate disease.

Owing to heterogeneity of the condition, the very high cost and advantages / disadvantages of treatments, expert guidance was judged to be necessary for the selection of patients for treatment. What follows are some proposed criteria for the selection of patients and treatment protocol.

At the time of preparation of this document, the following products are commercially available for the treatment of GD.

ERT	SRT
Ceredase (alglucerase)	Zavesca (miglustat)
Cerezyme (imiglucerase)	
Vpriv (velaglucerase)	

The purpose of these guidelines is to assist with eligibility for treatment and treatment modality. The decision to treat will be based on the criteria described below. The choice of modality will be based on

- recommendation by a physician experienced in the treatment of GD
- patient preference
- clinical and financial consideration.

The choice among the available products must be flexible based on the patient's best interests.

Treatment Contract
As per institutional requirements, patients/substitute decision makers may be required to sign a treatment contract outlining the responsibilities of all parties.

Guidelines

General comments
The recommendation to provide financial support for treatment of any given patient with GD will be based on sound clinical judgement; the genotype (i.e. specific GCase 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. 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.

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

Criteria for admission to treatment

Resident of Canada

1. The patient must be a 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 GD must have been established by the demonstration of specific deficiency of GCase in tissue or cultured skin fibroblasts, or by demonstration of the presence, in tissue or peripheral blood leukocytes, of mutations in the GCase gene known to result in severe enzyme deficiency.

2. Other potentially confounding diagnoses, such as Hodgkin disease or other storage disorders, must have been ruled out. The symptoms experienced by the patient should be shown to be attributable to GD and not some other condition that might mimic it. A trial of therapy would normally be considered in situations of uncertainty only if the symptoms were accompanied by objective evidence (hematological or imaging changes consistent with complaints).

3. The patient should not have any GD-related or other medical condition that might reasonably be expected to compromise their response to treatment. In some patients with GD, 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, may only be established by a trial of therapy.

4. Pregnancy is not considered a contraindication to ERT.

5. Patients to be considered for reimbursement of drug costs for ERT or SRT must be willing to participate in the long term 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

1. Evidence from the rate of progression of symptoms, in both adults and children, that the disease is likely to become severe within a few years.

2. At the current time, financial support for the treatment of asymptomatic patients is not provided due to the absence of data which show that the therapy of asymptomatic patients alters long term outcomes.

3. Patients exhibiting primary neurological disease due to GD would not normally be considered eligible for treatment (however, see Neuronopathic GD below).

4. 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 <50 x 10^9/L on two separate occasions at least one month apart. Higher cut offs may be considered in the event that the patient is symptomatic with bleeding or bruising.

(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 marked 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 GD, should be treated with enzyme therapy 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 GD. 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 GD.

Systemic complications

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

Performance status

(a) Impaired performance status and reduction in Quality of Life Score.

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**[1]
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 <50 x 10^9/L on two separate occasions; or bleeding complications associated with thrombocytopenia irrespective of the platelet count.	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 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[2], or BMD)
Spontaneous fractures	Prevention of further fractures
Chronic bone pain	Reduce bone pain
Major joint replacement surgery	Optimize surgical outcome
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 GD	Improvement in pulmonary hypertension[3]
	Improvement in oxygenation
	Reversal of hepatopulmonary syndrome
Growth failure in children	Return to normal range of growth parameters
Evidence from the rate of progression of symptoms, in both adults and children, that the disease is likely to become severe within a few years.	Improvement of those parameters as defined above

[1]Responses are based on those shown for ERT as presented by Pastores et al. Therapeutic Goals in the treatment of Gaucher Disease, Seminars in Hematology, 2004.
[2]QCSI quantitative chemical shift imaging
[3]May require adjuvant treatment for pulmonary hypertension

Neuronopathic Gaucher Disease

ERT and SRT are effective in reversing the visceral manifestations of GD. However, data do not suggest that either ERT or SRT is effective in improving central nervous system involvement in patients with Type 2 and 3 disease. Treatment with ERT or SRT in patients at risk of neuronopathic disease should therefore be guided by the non neurological manifestations of their disease as outlined above but not initiated 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 ERT.

2. Substrate reduction therapy (SRT) with miglustat should be considered in patients with moderate type I GD, who are unable or unwilling to receive ERT, including:

a. Rare cases of severe allergic reactions or hypersensitivity to ERT
b. Failure to maintain intravenous access (including needle phobia)
c. Patients who are sub optimally responsive despite maximum doses of ERT
d. Patients unwilling or unable to receive ERT for medical or personal reasons

3. Cost of therapy may be taken into consideration.

Dosage

1. The dosage of ERT 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

Enzyme Replacement Therapy
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 ERT 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 ERT may be discontinued. In the event of severe drug reaction, treatment may have to be discontinued. ERT has been shown to be well tolerated with minimal toxicity reported.

Miglustat

Patients on treatment with Miglustat should be assessed including nutritional counselling 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, red cell folate and serum vitamin B_{12} levels and whatever other studies the treating physician deems to be indicated in individual cases.

3. Gastrointestinal events, which may require nutritional assessment, counselling and treatment. Nutritional counselling is strongly advised before starting a patient on miglustat.

Adjunctive therapy

1. ERT or SRT may be supplemented by treatment with analgesics, anti-inflammatory drugs, bisphosphonates, 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.

Withdrawal of therapy

The recommendation to provide financial support for ERT or SRT 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 eligible for treatment.

Administration and supervision of therapy

1. All patients with GD in whom ERT or SRT is initiated should be assessed on a 6 -12 monthly basis by a physician who has expertise in the administration and monitoring of such therapy.

2. Semi annual review of all patients on therapy for GD 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.

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