

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

- 1 CEREZYME® (imiglucerase for injection)
- 2 200 Units
- 3 400 Units

4 **DESCRIPTION**

5 **Cerezyme®** (imiglucerase for injection) is an analogue of the human enzyme β -
6 glucocerebrosidase, produced by recombinant DNA technology. β -Glucocerebrosidase (β -D-
7 glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme
8 which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

9 **Cerezyme®** is produced by recombinant DNA technology using mammalian cell culture
10 (Chinese hamster ovary). Purified imiglucerase is a monomeric glycoprotein of 497 amino acids,
11 containing 4 N-linked glycosylation sites ($M_r = 60,430$). Imiglucerase differs from placental
12 glucocerebrosidase by one amino acid at position 495, where histidine is substituted for arginine.
13 The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose
14 sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those
15 on placental glucocerebrosidase. These mannose-terminated oligosaccharide chains of
16 imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages,
17 the cells that accumulate lipid in Gaucher disease.

18 **Cerezyme®** is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product. The
19 quantitative composition of the lyophilized drug is provided in the following table:

Ingredient	200 Unit Vial	400 Unit Vial
Imiglucerase (total amount)*	212 units	424 units
Mannitol	170 mg	340 mg
Sodium Citrates (Trisodium Citrate)	70 mg (52 mg)	140 mg (104 mg)
(Disodium Hydrogen Citrate)	(18 mg)	(36 mg)
Polysorbate 80, NF	0.53 mg	1.06 mg
Citric Acid and/or Sodium Hydroxide may have been added at the time of manufacture to adjust pH.		

20 *This provides a respective withdrawal dose of 200 and 400 units of
21 imiglucerase.

22 An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1
23 micromole of the synthetic substrate para-nitrophenyl- β -D-glucopyranoside (pNP-Glc) per minute
24 at 37°C. The product is stored at 2–8°C (36–46°F). After reconstitution with Sterile Water for
25 Injection, USP, the imiglucerase concentration is 40 U/mL (see **DOSAGE AND**
26 **ADMINISTRATION** for final concentrations and volumes). Reconstituted solutions have a pH
27 of approximately 6.1.

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

28 **CLINICAL PHARMACOLOGY**

29 **Mechanism of Action/Pharmacodynamics**

30 Gaucher disease is characterized by a deficiency of β -glucocerebrosidase activity, resulting in
31 accumulation of glucocerebroside in tissue macrophages which become engorged and are
32 typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and
33 intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in
34 addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including
35 osteonecrosis and osteopenia with secondary pathological fractures. **Cerezyme®** (imiglucerase
36 for injection) catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical
37 trials, **Cerezyme®** improved anemia and thrombocytopenia, reduced spleen and liver size, and
38 decreased cachexia to a degree similar to that observed with Ceredase® (alglucerase injection).

39 **Pharmacokinetics**

40 During one-hour intravenous infusions of four doses (7.5, 15, 30, 60 U/kg) of **Cerezyme®**
41 (imiglucerase for injection) steady-state enzymatic activity was achieved by 30 minutes.
42 Following infusion, plasma enzymatic activity declined rapidly with a half-life ranging from 3.6
43 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean \pm S.D., 14.5 ± 4.0
44 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg
45 (0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of
46 infusion. However, only one or two patients were studied at each dose level and infusion rate.
47 The pharmacokinetics of **Cerezyme®** do not appear to be different from placental-derived
48 alglucerase (Ceredase®).

49 In patients who developed IgG antibody to **Cerezyme®**, an apparent effect on serum enzyme
50 levels resulted in diminished volume of distribution and clearance and increased elimination half-
51 life compared to patients without antibody (see **WARNINGS**).

52 **INDICATIONS AND USAGE**

53 **Cerezyme®** (imiglucerase for injection) is indicated for long-term enzyme replacement therapy
54 for pediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher disease that results
55 in one or more of the following conditions:

- 56 • anemia
- 57 • thrombocytopenia
- 58 • bone disease
- 59 • hepatomegaly or splenomegaly

60 **CONTRAINDICATIONS**

61 There are no known contraindications to the use of **Cerezyme®** (imiglucerase for injection).
62 Treatment with **Cerezyme®** should be carefully re-evaluated if there is significant clinical
63 evidence of hypersensitivity to the product.

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

64 **WARNINGS**

65 Approximately 15% of patients treated and tested to date have developed IgG antibody to
66 **Cerezyme®** (imiglucerase for injection) during the first year of therapy. Patients who developed
67 IgG antibody did so largely within 6 months of treatment and rarely developed antibodies to
68 **Cerezyme®** after 12 months of therapy. Approximately 46% of patients with detectable IgG
69 antibodies experienced symptoms of hypersensitivity.

70 Patients with antibody to **Cerezyme®** have a higher risk of hypersensitivity reaction.
71 Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. It
72 is suggested that patients be monitored periodically for IgG antibody formation during the first
73 year of treatment.

74 Treatment with **Cerezyme®** should be approached with caution in patients who have exhibited
75 symptoms of hypersensitivity to the product.

76 Anaphylactoid reaction has been reported in less than 1% of the patient population. Further
77 treatment with imiglucerase should be conducted with caution. Most patients have successfully
78 continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or
79 corticosteroids.

80 **PRECAUTIONS**

81 **General**

82 In less than 1% of the patient population, pulmonary hypertension and pneumonia have also been
83 observed during treatment with **Cerezyme®** (imiglucerase for injection). Pulmonary
84 hypertension and pneumonia are known complications of Gaucher disease and have been
85 observed both in patients receiving and not receiving **Cerezyme®**. No causal relationship with
86 **Cerezyme®** has been established. Patients with respiratory symptoms in the absence of fever
87 should be evaluated for the presence of pulmonary hypertension.

88 Therapy with **Cerezyme®** should be directed by physicians knowledgeable in the management of
89 patients with Gaucher disease.

90 Caution may be advisable in administration of **Cerezyme®** to patients previously treated with
91 Ceredase® (alglucerase injection) and who have developed antibody to Ceredase® or who have
92 exhibited symptoms of hypersensitivity to Ceredase®.

93 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

94 Studies have not been conducted in either animals or humans to assess the potential effects of
95 **Cerezyme®** (imiglucerase for injection) on carcinogenesis, mutagenesis, or impairment of
96 fertility.

97 **Teratogenic Effects: Pregnancy Category C**

98 Animal reproduction studies have not been conducted with **Cerezyme®** (imiglucerase for

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

99 injection). It is also not known whether **Cerezyme®** can cause fetal harm when administered to a
100 pregnant woman or can affect reproductive capacity. **Cerezyme®** should not be administered
101 during pregnancy except when the indication and need are clear and the potential benefit is
102 judged by the physician to substantially justify the risk.

103 **Nursing Mothers**

104 It is not known whether this drug is excreted in human milk. Because many drugs are excreted in
105 human milk, caution should be exercised when **Cerezyme®** (imiglucerase for injection) is
106 administered to a nursing woman.

107 **Pediatric Use**

108 The safety and effectiveness of **Cerezyme®** (imiglucerase for injection) have been established in
109 patients between 2 and 16 years of age. Use of **Cerezyme®** in this age group is supported by
110 evidence from adequate and well-controlled studies of **Cerezyme®** and Ceredase® (alglucerase
111 injection) in adults and pediatric patients, with additional data obtained from the medical
112 literature and from long-term post-marketing experience. **Cerezyme®** has been administered to
113 patients younger than 2 years of age, however the safety and effectiveness in patients younger
114 than 2 have not been established.

115 **ADVERSE REACTIONS**

116 Since the approval of **Cerezyme®** (imiglucerase for injection) in May 1994, Genzyme has
117 maintained a worldwide post-marketing database of spontaneously reported adverse events and
118 adverse events discussed in the medical literature. The percentage of events for each reported
119 adverse reaction term has been calculated using the number of patients from these sources as the
120 denominator for total patient exposure to **Cerezyme®** since 1994. Actual patient exposure is
121 difficult to obtain due to the voluntary nature of the database and the continuous accrual and loss
122 of patients over that span of time. The actual number of patients exposed to **Cerezyme®** since
123 1994 is likely to be greater than estimated from these voluntary sources and, therefore, the
124 percentages calculated for the frequencies of adverse reactions are most likely greater than the
125 actual incidences.

126 Experience in patients treated with **Cerezyme®** has revealed that approximately 13.8% of
127 patients experienced adverse events which were judged to be related to **Cerezyme®**
128 administration and which occurred with an increase in frequency. Some of the adverse events
129 were related to the route of administration. These include discomfort, pruritus, burning, swelling
130 or sterile abscess at the site of venipuncture. Each of these events was found to occur in < 1% of
131 the total patient population.

132 Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients.
133 Onset of such symptoms has occurred during or shortly after infusions; these symptoms include
134 pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and
135 hypotension. Anaphylactoid reaction has also been reported (see **WARNINGS**). Each of these
136 events was found to occur in < 1.5% of the total patient population. Pre-treatment with

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

137 antihistamines and/or corticosteroids and reduced rate of infusion have allowed continued use of
138 **Cerezyme®** in most patients.

139 Additional adverse reactions that have been reported in approximately 6.5% of patients treated
140 with **Cerezyme®** include: nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache,
141 fever, dizziness, chills, backache, and tachycardia. Each of these events was found to occur in <
142 1.5% of the total patient population.

143 Incidence rates cannot be calculated from the spontaneously reported adverse events in the post-
144 marketing database. From this database, the most commonly reported adverse events in children
145 (defined as ages 2 – 12 years) included dyspnea, fever, nausea, flushing, vomiting, and coughing,
146 whereas in adolescents (>12 – 16 years) and in adults (>16 years) the most commonly reported
147 events included headache, pruritis, and rash.

148 In addition to the adverse reactions that have been observed in patients treated with **Cerezyme®**,
149 transient peripheral edema has been reported for this therapeutic class of drug.

150 **OVERDOSE**

151 Experience with doses up to 240 U/kg every 2 weeks have been reported. At that dose there have
152 been no reports of obvious toxicity.

153 **DOSAGE AND ADMINISTRATION**

154 **Cerezyme®** (imiglucerase for injection) is administered by intravenous infusion over 1–2 hours.
155 Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body
156 weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for
157 which the most data are available. Disease severity may dictate that treatment be initiated at a
158 relatively high dose or relatively frequent administration. Dosage adjustments should be made on
159 an individual basis and may increase or decrease, based on achievement of therapeutic goals as
160 assessed by routine comprehensive evaluations of the patient's clinical manifestations.

161 **Cerezyme®** should be stored at 2–8°C (36–46°F). After reconstitution, **Cerezyme®** should be
162 inspected visually before use. Because this is a protein solution, slight flocculation (described as
163 thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered
164 through an in-line low protein-binding 0.2 µm filter during administration. Any vials exhibiting
165 opaque particles or discoloration should not be used. DO NOT USE **Cerezyme®** after the
166 expiration date on the vial.

167 On the day of use, after the correct amount of **Cerezyme®** to be administered to the patient has
168 been determined, the appropriate number of vials are each reconstituted with Sterile Water for
169 Injection, USP. The final concentrations and administration volumes are provided in the
170 following table:

171

genzyme

Cerezyme® (imiglucerase for injection)

PROPOSED TEXT OF THE LABELING OF THE DRUG

	200 Unit Vial	400 Unit Vial
Sterile water for reconstitution	5.1 mL	10.2 mL
Final volume of reconstituted product	5.3 mL	10.6 mL
Concentration after reconstitution	40 U/mL	40 U/mL
Withdrawal volume	5.0 mL	10.0 mL
Units of enzyme within final volume	200 units	400 units

172 A nominal 5.0 mL for the 200 unit vial (10.0 mL for the 400 unit vial) is withdrawn from each
173 vial. The appropriate amount of **Cerezyme®** for each patient is diluted with 0.9% Sodium
174 Chloride Injection, USP, to a final volume of 100 – 200 mL. **Cerezyme®** is administered by
175 intravenous infusion over 1–2 hours. Aseptic techniques should be used when diluting the dose.
176 Since **Cerezyme®** does not contain any preservative, after reconstitution, vials should be
177 promptly diluted and not stored for subsequent use. **Cerezyme®**, after reconstitution, has been
178 shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2–8°C.
179 **Cerezyme®**, when diluted, has been shown to be stable for up to 24 hours when stored at 2–8°C.

180 Relatively low toxicity, combined with the extended time course of response, allows small dosage
181 adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage
182 administered in individual infusions may be slightly increased or decreased to utilize fully each
183 vial as long as the monthly administered dosage remains substantially unaltered.

184 **HOW SUPPLIED**

185 **Cerezyme®** (imiglucerase for injection) is supplied as a sterile, non-pyrogenic, lyophilized
186 product. It is available as follows:

- 187 200 Units per Vial NDC 58468-1983-1
- 188 400 Units per Vial NDC 58468-4663-1
- 189 Store at 2–8°C (36–46°F).

190 **Rx only**

191 U.S. Patent Numbers: 5,236,838
192 5,549,892

193 **Cerezyme®** (imiglucerase for injection) is manufactured by:

194 **Genzyme Corporation**
195 **500 Kendall Street**
196 **Cambridge, MA 02142 USA**

197 Certain manufacturing operations may have been performed by other firms.

198 6743-01 (X/05)