SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Cerezyme. This scientific discussion has been updated until 01 August 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Gaucher disease, also called glucosylceramide lipidosis or ß-glucocerebrosidase (GCR) deficiency, is the most common of the sphingolipidoses or lipid storage diseases, a group of diseases that are inherited in an autosomal recessive manner. It is characterised by the accumulation of glucocerebroside in tissue macrophages. Gaucher disease presents in three subtypes: type 1, the non-neuronopathic form; type 2, the acute neuronopathic form; and 3, the chronic neuronopathic form. Of these, type 1, non-neuronopathic form, is the most frequent and type 2, acute neuronopathic, is the least frequent. It has been estimated that type 1 Gaucher disease affects more than 20,000 patients world-wide. The clinical features of Gaucher disease include anaemia and thrombocytopenia due to splenic sequestration and bone marrow replacement by accumulating Gaucher cells. Splenomegaly and hepatomegaly are other frequent signs. Skeletal disease eventually leading to pain, stress fractures and osteonecrosis are common symptoms in type 1 and 3 Gaucher disease. The neuronopathic forms also present neurological abnormalities such as seizures, dementia, spasticity, ataxia and loss of intellectual functions.

Enzyme replacement therapy (ERT) of Gaucher disease has been made feasible by the introduction of mannose-terminated ß-glucocerebrosidase. Mannose is a sugar, which is abundant on the surfaces of micro-organisms. It may be bound by the mannose receptor of macrophages. The mannose-termination of ß-glucocerebrosidase leads to a selective uptake of the enzyme by macrophages that are present in liver, spleen and skeleton.

Alglucerase was the first mannose-terminated ß-glucocerebrosidase designed for enzyme replacement therapy in Gaucher disease. Alglucerase is the active ingredient of Ceredase, which was registered in 1994 in the EU following a Concertation Procedure (#39). It is derived from human placental tissue and has exposed mannose residues on the oligosaccharides side chains.

Imiglucerase is the recombinant form of alglucerase. The use of recombinant technology reduces the theoretical risk of contamination with viruses. Cerezyme contains imiglucerase, powder for concentrate for solution for infusion. The indication for imiglucerase is the use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease and who exhibit clinically significant non-neurological manifestations of the disease.

It is recommended that due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage should be individualised for each patient based on a comprehensive evaluation of the clinical manifestations of the disease. A range of dosage regimens has proven effective towards some or all of the non neurological manifestations of the disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 2.5 U/kg of body weight three times a week or 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters.

2. Chemical, pharmaceutical and biological aspects

Cerezyme is a powder for concentrate for solution for infusion that is reconstituted and diluted prior to administration.

The 200 U vial of Cerezyme contains 200 units of imiglucerase as active ingredient and mannitol, sodium citrate, citric acid monohydrate and polysorbate 80 as excipients. After reconstitution the solution contains 40 units of imiglucerase per ml.

The container is a 20 ml borosilicate type I glass vial with a siliconised butyl rubber stopper and a tamper-proof cap.

The 400 U vial, approved in January 2000 via an extension application, contains twice the amount of active substance and excipients as the 200 U vials, and is to be reconstituted in 10.2 ml instead of 5.1 ml resulting in the same strength of product in the reconstituted solution (40 U/ml). The container closure system is the same as for the 200 U presentations.

The formulation of the batches used in clinical studies is considered to be identical to the proposed marketed product formulation. Differences between clinical batches and the product to be licensed exist on production scale. Clinical studies were performed with material manufactured at a 160 litre scale cell culture process, while the proposed manufacturing scale is 2000 litre. This increase in production scale has no impact on product quality as demonstrated by genetic stability data and characterisation data of the active ingredient.

Development studies with the excipients showed a stable formulation with good caking properties. A citrate buffer is included to control the pH. The choice of the excipients, the sterilisation procedure and the container has been sufficiently justified. After reconstitution an overage of 0.3 ml (for the 200 U vial) and 0.6 ml (for the 400 U vial) is included, which is acceptable without further experimental data since this overage is equal to the recommended excess volume for 5.0 ml (for the 200 U vial) and 10.0 ml (for 400 U vial) injections in the USP.

Imiglucerase and alglucerase have many common structural characteristics. The differences have been well documented and do not result in a difference in clinical efficacy as proven by the clinical trials.

Some bovine source materials are used during cell bank establishment and drug substance production. All of these are sourced from BSE free countries (New Zealand, USA). Virus validation studies are considered acceptable.

In most areas, Part II of the dossier is of good standard. The application meets the relevant EC guidelines. No major objections are present against a marketing authorisation for Cerezyme on the basis of the high quality documentation submitted for Part II and the consideration that Cerezyme, produced by recombinant DNA technology, has an inherent lower theoretical risk for viral transmission.

The finished product release specifications, which are identical for Cerezyme 200 U and 400 U with the exception of those specifications relating to fill volume and labelling/packaging, are adequate to control the finished product.

A shelf life of 24 months at 2 – 8 °C is considered acceptable for both the 200 U and 400 U presentations.

The company has responded adequately to the majority of the questions and has provided additional information. All the main objections have been resolved.

Taken together all currently available information demonstrates a consistent production of imiglucerase and the finished product with the required quality and properties for intravenous use in humans.

Therefore, a positive opinion with regard to the chemical-pharmaceutical and biological issues is recommended subject to the condition that the company commit to provide any reasonable requested additional information within the agreed timeframe.

3. Toxico-pharmacological aspects

Pharmacodynamics

The efficacy of Cerezyme has not been studied in vivo in preclinical studies, because no satisfactory animal model of Gaucher disease exists. Receptor binding has been characterised in vitro using rat

alveolar macrophages. Safety pharmacology of the cardiovascular and respiratory system was studied in a pilot monkey study. No effects were seen.

Data from preclinical studies show similar pharmacodynamic actions of imiglucerase and alglucerase. Therefore, no separate clinical pharmacodynamic studies have been performed.

Pharmacokinetics

The biodistribution of imiglucerase and alglucerase was similar in mice. The clearance of both molecules from the circulation was very rapid. Up to 50% of the administered imiglucerase and alglucerase activity could be traced to the various body organs. Elevated levels of GCR enzymatic activity were found in the liver (> 94%), brain (about 1.5-3%) and spleen (0.7-2%). In the liver, a higher proportion of administered imiglucerase was located in Kupffer cells than alglucerase (about 15% versus 7.0%). It appears that there is a difference in Kupffer cell targeting in mouse liver for imiglucerase versus alglucerase, which may not be due to differences in formulation.

Single dose pharmacokinetics was studied in cynomolgus monkeys within the safety pharmacology study. The serum half-life of imiglucerase was 7-8 minutes.

Toxicology

Acute toxicity was studied in rats only. No toxicity occurred. The lack of a second species is acceptable.

Repeated i.v. dose toxicity (13 weeks) was studied in rats and in cynomolgus monkeys. The duration of treatment, dose level and dose frequency are acceptable.

In male rats, mild nephropathy was seen at high dose level, but not at the lower dose level. The margin of safety is acceptable, particularly in view of the paucity of the kidney changes seen.

Anti-imiglucerase antibodies were detected in all dose groups.

In the monkey study, spleen weight was increased in females at the high dose level. At the same dose level, local toxicity was seen in some males. In monkeys, the anti-imiglucerase antibody response was more prominent than in rats. The onset of the antibody response and the number of animals responding was dose-dependent.

Exogenous GCR enzymatic activity was not detectable in livers of rats at one-week injection of both dose regimens. This observation strengthens the doubts about the level of effective systemic exposure in the rat study.

Cerezyme was negative in the Ames test. Further testing is not needed. No reproduction and carcinogenicity studies were performed. This is acceptable.

After the initial assessment one objection and a few points for clarification regarding part III were raised. The company has adequately addressed this objection and these points for clarification.

From a preclinical point of view a positive opinion is recommended.

4. Clinical aspects

Part IV B of the initial dossier consists of a pivotal trial evaluating safety and efficacy of imiglucerase (RC91-0110), an extended study (RC92-0501) and a study conducted in Israel (RC92-0301) comparing the safety and efficacy of two dosage regimens of imiglucerase.

In the pivotal trial (RC91-0110) 60 U/kg b.w. imiglucerase were administered i.v. every 2 weeks. In the extended study (RC92-0501) dose reductions in 50% increments were individualised after 9 months of therapy.

In the Israeli trial two dose regimens were compared, i.e. 15 U/kg b.w. every other week and 2.5 U/kg b.w. 3 times per week.

These studies included a limited number of patients (30 in the pivotal/extended trial; 10 in the Israeli trial) however, due to the low incidence of Gaucher disease it is unrealistic to ask for a larger number of patients to be studied. Many of the patients who participated in the clinical evaluation of

imiglucerase were involved in more than one of the clinical studies. None of the patients studied had ever been treated with enzyme replacement therapy before. No placebo-controlled studies were conducted, due to ethical considerations.

Pharmacokinetics

The pharmacokinetic profile of imiglucerase is independent of the dose in the dose range 7.5 to 60 U/kg, independent of the infusion time period within the range of 7.5 to 60 min and not statistically different from the profile of alglucerase.

Efficacy

Primary efficacy parameters used in all three trials include an increase in hemoglobin, an increase in platelet count and decrease in liver and spleen volume as assessed by MRI or CT.

Secondary efficacy parameters include an increase in haemoglobin level, improvement in liver function (evidenced by a decrease in serum transaminases), decreased acid phosphatase or angiotensin converting enzyme, and improved skeletal status.

The pivotal/extended study has demonstrated an equal efficacy with respect to haematological parameters and organomegaly of the placental and recombinant DNA derived products, whereas the Israeli trial demonstrated equal activity concerning these parameters of a low dose regimen administered with different frequencies. These data are corroborated by extensive post-marketing data. It has also been shown that patients may safely switch from alglucerase to imiglucerase treatment. Data regarding skeletal status obtained with the dosage used in the pivotal/extended trial show some improvement of bone parameters.

Safety

Safety measures monitored throughout the studies include the formation of antibodies, routine laboratory values and adverse events. Alglucerase and imiglucerase have a comparable safety profile.

Antibody formation does not appear to occur more often with imiglucerase and is not associated with any new undesirable event. Overall, it can be calculated that 4 out of 25 (16%) patients have developed antibodies while on imiglucerase therapy. This incidence accords with the percentage mentioned in the SPC (± 15%).

Theoretically imiglucerase has a lower risk of viral contamination than alglucerase.

After the initial assessment no objections were raised on part IV. Only one point for clarification was raised regarding the method of gathering data on the frequency and timing of antibody formation and the clinical significance with respect to allergic reactions and occurrence of neutralising activity. This point has been addressed by the MAH. It is stated that to streamline and facilitate the gathering of immunological data within the International Collaborative Gaucher Group (ICGG) a specific procedure has been developed concerning the antibody serum sample collection and transportation, together with an information package for the treating physician regarding the advised time points for antibody testing. The results will be submitted to the CPMP on a regular basis. The answer from the MAH is considered satisfactory, given that the company undertakes to collect and submit data on antibody formation in the same manner as it did for Ceredase. These data should be submitted together with the scheduled Periodic Safety Update Report. Within the framework of Genzyme's World-wide Pharmacovigilance System, the immunological profile of Cerezyme will be carefully reviewed in the course of the preparation of the Periodic Safety Update Reports for Cerezyme, which has been submitted to the CPMP bi-annually in the first 2 years after Marketing Approval was obtained, and annually in the following 3 years. Following the 5-year renewal (December 2002) the PSUR is submitted as requested by the CPMP. Antibody formation, as well as any change in the safety and efficacy profile, are carefully evaluated on a current basis and presented in the Periodic Safety Update Reports.

The MAH applied in December 2002 for an extension of indication for Cerezyme to the chronic neuronopathic (Type 3) Gaucher disease. Data obtained from literature and from the International Collaborative Gaucher Group Registry were submitted.

All studies published between January 01, 1989 and July 01, 2000, in which ERT was used in patients with chronic neuronopathic (Type 3) Gaucher disease were reviewed. In total, fifteen publications

were identified, describing 33 patients (6 adults, 27 children). Duration of ERT (Ceredase or Cerezyme) ranged from 6 to 54 months. Dosages ranged from 27.6 U/kg per month to 480 U/kg per month. The mean dosage per patient was estimated to be 113.1 U/kg of enzyme every 4 weeks. An unpublished study (with chronic neuropathic (type 3) Gaucher disease patients, n=21) and an additional 5 publications (covering the period between 01.07.2000 and 01.05.2002) were also considered. In these literature studies, clinical parameters such as hepatomegaly, splenomegaly, anaemia and thrombocytopenia, neurological symptoms and other outcomes such as pulmonary involvement, quality of life, bone symptoms, growth retardation, fatigue, bone marrow infiltration or kyphosis were reviewed.

From the International Collaborative Gaucher Group Registry, data were collected from 2637 Gaucher patients, with 130 neuronopathic Gaucher patients, of whom 117 have received ERT (mainly of children, ≤ 17 years of age). From these data, the efficacy comparison analyses of chronic neuronopathic versus non-neuronopathic Gaucher patients was performed. Where possible, in the analysis the clinical response of non-neuronopathic patients was compared with the small subgroup of chronic neuronopathic patients who received a comparable dosage regimen. Platelet, haemoglobin, hepatomegaly, splenomegaly were reviewed. Concerning the neurological symptoms, no meaningful analysis of the treatment response could be conducted due to the minimal data collected.

Based on the limited clinical information on this ultra-rare subset of patients (approximately 130 in Europe), no specific recommendation for the dosage can be given for treatment of Type 3 patients except that the dose must be individualised according to the systemic symptoms of the patients.

During the approval of this extension of indication to the chronic neuronopathic (Type 3) Gaucher disease, the MAH commits to improve the Gaucher Registry to allow a better collection of neurological signs for Type 3 patients and to submit data from the Registry on an annual basis with reports on safety, neurological and systemic responses as well as the use of different dose regimens and dose modification. It also commits to present in the next PSURs safety information for Type 1 and Type 3 Gaucher patients separately.

Post-marketing experience

Seven Periodic Safety Update Reports (PSUR) have been submitted by the MAH until 01 August 2003.

The outcome of the PSURs did not change the benefit/risk ratio of imiglucerase. As a result of the first PSUR (covering the period 1.12.97 – 31.05.98), changes have been implemented in the SPC and PL to include rigors in the list of adverse events and to report the occurrence of pulmonary hypertension in a small number of patients. Pulmonary hypertension is a known complication of Gaucher's disease; a causal relationship with ERT has not yet been established. After the second PSUR (covering the period 1.6.98-30.11.98), two unlabelled adverse events (tachycardia and cyanosis) were introduced in the SPC and PL. The company also included under Special warnings and special precautions for use that 'In rare cases anaphylactoid reactions have been noted'. No changes of the SPC/PL were necessary after the assessment of the third PSUR (period 1.12.98-31.05.99) and the fourth PSUR (period 1.06.99-30.11.99). Following the fifth (period 1.12.99-30.11.99), sixth (period 1.12.00-31.05.01) and seventh (period 1.06.01-31.05.02) PSUR, the MAH will provide the results of an on-going study with Cerezyme in treating skeletal disease in patients with type 1 Gaucher disease. As regards the effect of antibodies on the treatment response, no difference in responsiveness was observed between antibody positive and antibody negative Cerezyme naive patients. However, definite answers could not be drawn, as the number of patients with antibodies studied was still too small. The Monitoring is continuing.

5. Overall conclusions and benefit/risk assessment

Submitted studies have demonstrated equal efficacy with respect to haematological parameters and organomegaly of the placental and recombinant derived products in a dose of 60 U/kg b.w. every two weeks followed by dose reductions of 50% increments. Two low dose regimens administered at different frequencies showed comparable activity concerning these parameters. No significant differences were found. These data are corroborated by extensive post-marketing data. It has been

shown that patients may safely switch from alglucerase to imiglucerase treatment. Data regarding skeletal status obtained with the 60 U/kg b.w. Every two weeks dosage showed some improvement in bone parameters.

Alglucerase and imiglucerase have a comparable safety profile.

The pharmacokinetic profile of imiglucerase is not statistically different from the profile of alglucerase.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Cerezyme was favourable in the treatment of Type 1 and Type 3 Gaucher disease.

During its September 2002 meeting, the CPMP granted a positive opinion for the 5-year renewal of Cerezyme.