CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125291

OFFICE DIRECTOR MEMO

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EV ALUA TION AND RESEARCH

DATE: May 24, 2010
TO: BLA STN 125291 Lumizyme (alglucosidase alfa) (4000 L)
Genzyme Corporation

FROM: Julie Beitz, MD Julie Beitz MD 5/24/10
Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Lumizyme (alglucosidase alfa) consists of the human enzyme acid α-glucosidase (GAA) and is produced by recombinant DNA technology in a Chinese hamster ovary cell line at the 4000 L bioreactor scale.[1] In contrast, Myozyme, another member of the class of alglucosidase alfa biological products, is produced at a 160 L bioreactor scale. Both Lumizyme and Myozyme provide an exogenous source of GAA that is taken up into cells and is transported into lysosomes where the enzyme acts to hydrolyze glycogen. These products have been evaluated in Pompe disease, an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of GAA. Glycogen accumulation in various tissues leads to the development of progressive muscle weakness, including impairment of respiratory function in all patients, as well as hypertrophic cardiomyopathy in patients with infantile-onset Pompe disease. When Pompe disease presents in infants, it is rapidly progressive resulting in cardiorespiratory failure and death before the age of 2 years; the course of the disease in late (non-infantile) onset patients is more slowly progressive.

Apart from Myozyme (alglucosidase alfa, 160 L), which has been shown to improve ventilator-free survival in infantile-onset patients, there are no other approved treatments for Pompe disease in the US. Due to manufacturing constraints, Genzyme has limited access to Myozyme to patients less than 18 years of age. Lumizyme (alglucosidase alfa) produced at the 2000 L bioreactor scale[2] was made available to adult US patients 18 years and older via a temporary access program (under IND 10,780), although manufacturing problems resulted in the need for dose conservation strategies in these patients; in fact, the program was closed to new patient enrollment in April 2008. At FDA's request, the program was amended in 2009 to allow US patients to receive Lumizyme 4000 L.

This memorandum documents my concurrence with the Division of Gastroenterology Product's (DGP's) recommendation to approve Lumizyme 4000 L for the treatment of patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy. Negotiation of product labeling, post marketing

[1] Lumizyme (alglucosidase alfa) produced at the 4000 L scale will be referred to as Lumizyme 4000 L.
[2] Lumizyme (alglucosidase alfa) produced at the 2000 L scale will be referred to as Lumizyme 2000 L.

commitments and requirements has been completed. Lumizyme 4000 L will be approved with a REMS (risk evaluation and mitigation strategy).

REGULATORY HISTORY

BLA 125291 was originally submitted on May 30, 2008, to support approval of Lumizyme 2000 L. The application was granted a priority review and was discussed before the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on October 21, 2008. In closed session, the Advisory Committee was briefed on the biochemical differences between Lumizyme 2000 L and Myozyme (alglucosidase alfa, 160L), and their potential impact on the relative efficacy and safety of the two products. In open session, deliberations centered on the demonstration of efficacy based on the effects of Lumizyme 2000 L on the 6-minute walk test (6MWT) in a single placebo-controlled trial. A majority of Committee members voted in favor of accelerated approval of Lumizyme 2000 L based on its effects on a surrogate endpoint, percent of predicted forced vital capacity (FVC), arguing that a positive effect on the 6MWT had not be demonstrated.

On February 27, 2009,[3] a complete response letter was issued requesting the applicant to 1) address CGMP deficiencies identified during FDA's October 2008 inspection of the Allston Landing, MA manufacturing facility, 2) address deficiencies involving chemistry, manufacturing, and controls (CMC) in the BLA, 3) reach agreement with FDA on the design of the post-approval trial to be conducted under accelerated approval regulations to verify the clinical benefit of Lumizyme 2000 L, and 4) submit a revised proposed REMS. A Warning Letter issued on February 27, 2009 provided further details regarding the CGMP deficiencies identified during the Allston Landing inspection.

On May 15, 2009, Genzyme responded to FDA's February 2009 complete response letter. The applicant also implemented some corrective actions to address the issues raised in the Warning Letter. Re-inspections of the Allston Landing, MA, facility in May 2009, and again in October and November 2009, however, led to the identification of several 483 deficiencies. On November 6, 2009, the Office of Compliance recommended that approval of the BLA be withheld. A second complete response letter was issued on November 13, 2009.

Since Lumizyme 2000 L was produced exclusively at the Allston Landing, MA facility, and a rapid resolution of the manufacturing deficiencies at that site appeared unlikely, FDA considered the possibility that the complete response could be addressed by product quality and manufacturing information on Lumizyme 4000 L produced at other sites. On November 20, 2009, Genzyme was informed that such information (already submitted under IND 10,780) could be submitted to address the deficiencies cited in the November 2009 complete response letter. Additionally, FDA informed the applicant that a safety update that included all post-marketing safety information on Lumizyme 4000 L (marketed in the EU since February 2009), and safety information from patients receiving

[3] A major amendment extended the review clock by three months.

4000 L product in the temporary access program within the US (since October 2009) should be submitted in the complete response.

EFFICACY

The efficacy of Lumizyme 2000 L was evaluated in the first two review cycles.

I. First Review Cycle

Lumizyme 2000 L was studied in a multicenter, double-blind, placebo-controlled trial of 90 late-onset Pompe disease patients (Late-Onset Treatment Study or LOTS). Enrollment was restricted to patients 8 years and older who were naïve to enzyme replacement therapy, ambulatory, did not require invasive ventilatory support, and had an FVC between 30 and 79% of the predicted normal value in a healthy population. Patients were allocated 2:1 to either 20 mg/kg or placebo administered intravenously every two weeks for a total of 78 weeks.

Several statistical issues were raised by the FDA regarding the interpretation of the efficacy results for LOTS. Using FDA's preferred analysis (ANCOVA), the mean change from baseline to last observation in % predicted upright FVC was 1.2% for Lumizyme-treated patients as compared to -2.2% for placebo-treated patients. This resulted in a treatment difference of 3.4% (95% CI: 1.3,5.5). The mean change from baseline to last observation in distance walked in the 6MWT was 25 meters for Lumizyme-treated patients and -3 meters for placebo-treated patients. This resulted in a treatment difference of 28 meters (95% CI: -1,52; p=0.06).

Based on these results, the Advisory Committee voted 16-1 that the effectiveness of Lumizyme 2000 L had been demonstrated in patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy. Eleven members recommended that accelerated approval be granted based on the results for % predicted FVC. Following this advice, FDA's February 2009 complete response letter indicated that marketing approval may be granted under the accelerated approval regulations (21 CFR 601.41-46) based on the effect of Lumizyme 2000 L on a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval would be subject to the requirement that the applicant further study the product post-approval to verify and describe its clinical benefit.

II. Second Review Cycle

In the weeks that followed the complete response action, a series of discussions were held with the applicant to determine an optimal design for a post-approval clinical trial that would verify the clinical benefit of Lumizyme 2000 L. At DGP's request, the applicant submitted data collected in the Pompe Registry from infantile-onset patients who received Lumizyme 2000 L commercially outside the US. The Pompe Registry is a multi-center, multi-national, voluntary, observational disease registry. Fifteen infantile-onset patients enrolled in the registry that had received Lumizyme 2000 L prior to 6

months of age were matched to an untreated historical control group (the same historical control group that was used to base the original approval of Myozyme).

The median duration of Lumizyme 2000 L treatment in these infantile-onset patients was 15 months (range 3-48 months). Estimated survival in Lumizyme-treated patients was 57% at 18 months and 37% at 36 months, compared to 2% in the historical control group at both time points. The median age of death or last follow-up was 19 months (range 5-51 months). DGP concluded, and I concurred, that the survival data in Lumizyme-treated infantile-onset patients could be used to support the findings from LOTS and provide sufficient evidence of efficacy for Lumizyme 2000 L for the treatment of patients 8 years and older with late-onset Pompe disease, without the need for an additional clinical trial.

It should be noted that we do not believe that the efficacy findings from LOTS and the survival data in Lumizyme-treated infantile-onset patients from the Pompe Registry support approval of Lumizyme 2000 L for all ages. The reasons for this determination include: 1) Pompe disease patients less than 8 years of age are at risk for rapid disease progression, 2) there are residual concerns that the biochemical differences between Lumizyme and Myozyme may lead to differences in potency, 3) the clinical information on patients enrolled in the Pompe Registry is limited, and 4) the potential exists for selection bias, that is, patients with improved survival may more likely be included in the registry. In accordance with this determination, Lumizyme 2000 L, if approved, will be required to have a REMS designed to ensure that Lumizyme is used as indicated, i.e., for the treatment of late (non-infantile) onset Pompe disease patients 8 years and older who do not have evidence of cardiac hypertrophy.

CLINICAL PHARMACOLOGY

The pharmacokinetics of Lumizyme 2000 L dosed at 20 mg/kg every other week was studied in 32 patients ranging in age from 21 to 70 years who were enrolled in LOTS. The pharmacokinetics were not time-dependent for patients who did not develop high titers of inhibitory antibody. Parameter values did not change across visits at Weeks 0, 12, and 52.

Higher mean clearance was observed at Week 52 in 4 of 5 patients that tested positive for antibodies that inhibit the cellular uptake of enzyme. Pharmacokinetics in 4 of these 5 patients over time indicated an increase in clearance with increase in IgG titer. Positive inhibitory antibody status correlated with higher IgG titers in patients who received Lumizyme 2000 L. The relationship between exposure and efficacy has not been defined.

Genzyme has agreed to perform a post-approval pharmacokinetic study in Pompe disease patients aged 8-18 years who are enrolled in the ongoing Pompe Registry.

PRODUCT ISSUES

Lumizyme 2000 L differs from Myozyme (alglucosidase alfa, 160 L) in several biochemical attributes, (b) (4)

[redacted] (b) (4) These differences were the basis of FDA's recommendation that a separate BLA be filed for Lumizyme 2000 L.[4]

In the current review cycle, FDA reviewed CMC information on Lumizyme 4000 L. The Lumizyme 4000 L drug substance is manufactured at the Genzyme facility in Geel, Belgium, and the Lumizyme 4000 L drug product is manufactured at the Genzyme facility in Waterford, Ireland. These facilities were inspected by FDA in September and October 2009, respectively, and were found satisfactory. A demonstration of comparability of Lumizyme 4000 L to Lumizyme 2000 L would allow a path forward for approval (i.e., the CGMP deficiencies involving the Allston Landing facility would not preclude approval of Lumizyme 4000 L).

Overall, the proposed drug substance specifications for Lumizyme 4000 L are unchanged from Lumizyme 2000 L. There were differences in specifications for some critical product quality attributes including [redacted] (b) (4)

[redacted] (b) (4)

There were no substantive differences in the Lumizyme 4000 L drug product lots manufactured at the Waterford, Ireland facility and the Lumizyme 2000 L drug product lots manufactured at the Allston Landing, MA facility.

The Division of Therapeutic Proteins has concluded that Lumizyme 4000 L and 2000 L are highly similar and that the minor differences noted are unlikely to have clinical consequences. Several postmarketing study commitments to further characterize and validate Lumizyme 4000 L production processes have been satisfactorily negotiated; these do not preclude approval of Lumizyme 4000 L.

SAFETY

The most common adverse reactions observed with Lumizyme 2000 L administration were infusion reactions. Both acute reactions, occurring during or within 2 hours of Lumizyme infusion, and delayed onset reactions occurring within 48 hours of completion of the infusion have been reported. The incidence of infusion reactions in LOTS was 50%.

Anaphylaxis and severe allergic reactions were reported in Lumizyme-treated patients during and up to 3 hours after Lumizyme infusion. Some of these reactions were life-threatening and included anaphylactic shock, respiratory arrest, apnea, dyspnea,

[4] See my previous review dated November 13, 2009 for a discussion of CMC deficiencies involving Lumizyme 2000 L, and CGMP deficiencies involving the manufacture of the product at the Allston Landing, MA facility.

bradycardia, tachycardia and hypotension. The incidence of anaphylaxis in LOTS was approximately 7%. These events will be highlighted in a Boxed Warning and in the WARNINGS AND PRECAUTIONS section of the product label which advise that appropriate medical support measures be readily available when Lumizyme is administered. If anaphylaxis or severe allergic reactions occur, immediate treatment discontinuation should be considered. Interrupting the infusion, administering antihistamines, corticosteroids, intravenous fluids and/or oxygen may ameliorate the symptoms. Patients who have experienced such reactions should be treated with extreme care if Lumizyme is re-administered.

In addition, serious immune-mediated reactions involving skin and kidney have been reported with Lumizyme several weeks to 3 years after initiation of therapy and will be highlighted in the Boxed Warning and the WARNINGS AND PRECAUTIONS sections of the product label.

In the current submission, information on 128 adult patients who received at least one infusion with Lumizyme 4000 L in the temporary access program from October 19, 2009 to November 24, 2009 was provided. The maximum exposure in this analysis was three doses. The majority of patients had previously received Lumizyme 2000 L. In this limited uncontrolled clinical experience, there was one report of an infusion reaction, and no reports of anaphylaxis, serious allergic reactions or death.

The applicant also reported on its postmarketing experience with Lumizyme 2000 L and 4000 L (ex-US) in over 750 patients. There were 30 deaths reported, seven occurred during treatment with Lumizyme 4000 L, with the majority assessed as due to the patient's underlying Pompe disease. There were 70 serious adverse events reported including anaphylaxis, infusion reactions, and respiratory distress; there were no reports of immune mediated reactions.

Although limited, the available safety information regarding Lumizyme 4000 L suggests a similar safety profile to that of Lumizyme 2000 L.

IMMUNOGENICITY

In LOTS, all Lumizyme-treated patients with available samples (n=59) tested positive for IgG antibodies to alglucosidase alfa within the first three months of treatment. There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions. Although none of the 59 patients tested positive for inhibition of enzyme activity, antibody titers for cellular uptake inhibition were present in 18 of 59 patients by week 78.

Ten patients in LOTS underwent testing for alglucosidase alfa-specific IgE antibodies; two tested positive, both of whom experienced anaphylactic reactions. A small number of Lumizyme-treated patients in the postmarketing setting have tested positive for the presence of alglucosidase alfa-specific IgE antibodies, and some of these experienced anaphylaxis. Some patients who tested positive for the presence of alglucosidase alfa-specific IgE antibodies were successfully rechallenged with Lumizyme using a slower

infusion rate at lower initial doses and have continued to receive treatment. Patients who develop alglucosidase alfa-specific IgE antibodies appear to be at a higher risk of developing infusion reactions and should be monitored more closely.

PEDIATRIC CONSIDERATIONS

Lumizyme 4000 L is not indicated for use in patients with infantile-onset Pompe disease or late (non-infantile) onset Pompe disease who are less than 8 years of age. The safety and effectiveness of Lumizyme 4000 L in these patients have not been evaluated in controlled clinical trials.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this biological product for this indication has received orphan drug designation, Genzyme is exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

As described in the complete response letter dated February 27, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for Lumizyme 4000 L to ensure that the benefits of the drug outweigh the potential risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age for whom the safety and effectiveness of Lumizyme have not been evaluated. In addition, we have determined that a REMS is necessary to ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme 4000 L, and the potential risks of severe cutaneous and systemic immune mediated reactions to Lumizyme 4000 L are communicated to patients and healthcare professionals.

Genzyme's proposed REMS submitted on May 24, 2010 has been found acceptable. The elements of the REMS will be a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

A communication plan to support implementation of the Lumizyme ACE (Alglucosidase alfa Control and Education) Program will be directed to healthcare professionals (HCPs) who treat patients with Pompe disease, primarily neurologists, metabolic specialists, pulmonologists and geneticists, as well as infusion nurses and pharmacists in hospitals and infusion facilities, and within the preferred distributors (i.e., pharmacists).

The elements to ensure safe use will include: 1) the requirement for patients, healthcare facilities and prescribers to enroll in the Lumizyme ACE Program, 2) special certification for healthcare facilities and prescribers, and 3) a restricted distribution system to ensure that i) all patients being treated with Lumizyme 4000 L are enrolled in the ACE program, and ii) prescribers and healthcare facility staff enrolled in the ACE program understand

that Lumizyme 4000 L is indicated for patients 8 years and older with late (non-infantile) onset Pompe disease who do not have evidence of cardiac hypertrophy, and that the safety and effectiveness of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients or in late-onset disease patients less than 8 years of age.

As part of the implementation system, Genzyme will be required to 1) maintain a validated and secure database of certified healthcare facilities and prescribers, and enrolled patients, 2) monitor re-enrollment of certified participants and take appropriate corrective actions if they do not re-enroll, and 3) monitor certified healthcare facilities and prescribers to ensure that only patients enrolled in the ACE program are receiving Lumizyme 4000 L. Genzyme will monitor use of Lumizyme 4000 L in 1) patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy, (b) (4)

REMS assessments will be required at 6 months, at 1 year, and then annually, from the date of approval of the REMS.

POSTMARKTING REQUIREMENTS UNDER 505(o)(3)

As described in the complete response letter dated February 27, 2009, FDA has determined that Genzyme will be required to conduct postmarketing studies of Lumizyme 4000 L to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions. Specifically, the studies that will be required are:

1. A retrospective immunogenicity study based on the pattern of antibody responses that may predict the development of anaphylaxis, allergic reactions, and immune-complex mediated reactions in patients enrolled in the Late Onset Treatment Study (LOTS) and LOTS Extension Studies.

2. A prospective safety study conducted within the ongoing Pompe Registry to assess the known serious risks of anaphylaxis and severe allergic reactions, and signals of severe cutaneous and systemic immune complex-mediated reactions with Lumizyme 4000 L treatment.

TRADENAME REVIEW

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "Lumizyme" is acceptable.