

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125561Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: September 8, 2015

Reviewer(s): Felicia Duffy, RN, BSN, MEd  
Division of Risk Management

Acting Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Risk Management

Acting Deputy  
Division Director: Reema Mehta, Pharm.D., MPH  
Division of Risk Management

Drug Name(s): Kanuma (sebelipase alfa)

Therapeutic Class: Recombinant human lysosomal acid lipase enzyme

Indication: Indicated for patients with Lysosomal Acid Lipase deficiency

Dosage and Route: 20 mg/10mL (2 mg/mL) solution for intravenous infusion

Application Type/Number: BLA 125561

Applicant/sponsor: Synageva BioPharma Corp.

OSE RCM #: 2014-2480

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation to assess the need for a risk evaluation and mitigation strategy (REMS) for Kanuma® (sebelipase alfa) solution for intravenous injection, BLA 125561.

On October 21, 2014, Synageva BioPharma Corp. (Synageva) began submitting sebelipase alfa as a rolling submission. On January 8, 2015, the Agency received a complete submission for BLA 125561 from Synageva BioPharma Corp. (Synageva), for sebelipase alfa as a solution for intravenous infusion [REDACTED] (b) (4) [REDACTED] for patients with Lysosomal Acid Lipase (LAL) deficiency. The Applicant did not submit a proposed REMS for sebelipase alfa.

### 1.1 PRODUCT BACKGROUND

Sebelipase alfa (SA), an enzyme replacement therapy (ERT), is a recombinant human LAL (rhLAL) enzyme purified from egg white of transgenic hens (*Gallus gallus*) with the same amino acid sequence as the native human enzyme. SA enzyme has a terminal n-acetylglucosamine and mannose structures (e.g. mannose-6-phosphate) that allow binding to cell surface receptors and targeting of the enzyme to cell lysosomes. SA binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. SA catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids.

The proposed indication for Kanuma is the treatment for patients with a diagnosis of LAL deficiency. The recommended dose is:

- Patients with rapidly progressive LAL deficiency presenting within the first 6 months of life:

1 mg/kg administered once weekly as an intravenous infusion as an initial dose followed by escalation to 3 mg/kg once weekly

- Pediatric and adult patients with LAL deficiency:

1 mg/kg administered once every other week as an intravenous infusion

Kanuma will be available as a 20 mg/10 mL (2 mg/mL) solution in single-use vials. There are no proposed contraindications for Kanuma.

### 1.2 DISEASE BACKGROUND<sup>1</sup>

LAL deficiency is a very rare, serious, and life-threatening lysosomal storage disorder caused by mutations affecting a single gene. The gene mutations associated with LAL deficiency lead to a significant decrease or loss in LAL enzyme activity. This enzyme plays a key role in the metabolism and degradation of cholesteryl esters and triglycerides, and its marked (significant) reduction or absence leads to accumulation of these lipid

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<sup>1</sup> Synageva BioPharma Corp. Clinical Overview for Kanuma (sebelipase alfa), received October 21, 2014 (Supplement 000/Sequence 0000).

substrates in the lysosomes of various tissues and cell types throughout the body, particularly affecting the liver, leading to fibrosis, organ dysfunction and failure, as well as the intestine, leading to malabsorption and adverse effects on growth. The disruption of normal lipid metabolism results in significant dyslipidemia due to impaired lysosomal degradation of cholesteryl esters and triglycerides and predisposes patients to accelerated atherosclerosis and increased cardiovascular risk.

Infantile-onset of LAL deficiency is historically referred to as Wolman's disease. LAL deficiency in infants is associated with a variety of private mutations that are thought to result in a complete loss of enzyme function. The incidence of rapidly progressive disease in infancy is estimated to be approximately 1.89 individuals per million. The disease spectrum ranges from the rapidly progressive presentation in infants, who typically die within the first 6 months of life.

LAL deficiency presenting in children and adults, historically referred to as cholesteryl ester storage disease (CESD), is frequently associated with an exon 8 splice mutation. The estimated prevalence of LAL deficiency presenting in children and adults, based on the frequency of the exon 8 splice mutation, has been reported as 25 individuals per million among German subjects and as 7.7 individuals per million in Caucasian and Hispanic subjects. Although disease presentation can be variable, hepatic manifestations typically dominate the clinical picture with hepatomegaly, elevation of transaminases signaling chronic liver injury, increased hepatic tissue levels of cholesteryl esters, and liver fibrosis and cirrhosis manifesting early in life. Dyslipidemia is common, and includes elevations in cholesterol, low-density lipoprotein cholesterol (LDL) and triglycerides, and decreased levels of high-density lipoprotein cholesterol (HDL). These lipid abnormalities coupled with the impairment of degradation of cholesteryl esters are known to be associated with increased cardiovascular risk.

Although there are differences in the age at the onset of symptoms, many manifestations of LAL deficiency are prominent across the disease spectrum, including hepatomegaly; liver injury, fibrosis, and cirrhosis; growth impairment; and dyslipidemia. Currently, there is no treatment for this life-threatening disease.

### **1.3 REGULATORY HISTORY**

The following is a summary of the regulatory history relevant to the evaluation to assess the need for a REMS for BLA 125561/S-000:

- July 2010: The Agency grants orphan drug designation for SA.
- October 21, 2014: Synageva began rolling submissions for BLA 125561.
- January 8, 2015: The Agency received a complete submission for the BLA from Synageva for Kanuma for the treatment of patients with LAL deficiency. The Applicant did not submit a proposed REMS.
- February 20, 2015: The Agency held a listening session via teleconference with 5 patients diagnosed with LAL deficiency/CESD so the Agency could gain a better understanding of the impact of this disease on patients.

- April 23, 2015: The Agency held a Mid-cycle Communication Meeting with the Applicant. DRISK communicated to the Applicant that, “There are no major safety concerns identified at this time, and there is currently no need for a REMS”.

## **2 MATERIALS REVIEWED**

The following is a list of materials used to inform this review:

- Synageva BioPharma Corp. BLA 125561 submission for Kanuma (sebelipase alfa). received January 8, 2015
  - Section 2.5: Clinical Overview
  - Section 2.7.3: Summary of Clinical Efficacy
  - Section 2.7.4: Summary of Clinical Safety
- Synageva BioPharma Corp. Draft Package Insert Labeling for Kanuma (sebelipase alfa), received September 3, 2015.
- Tomaino, J. MD; Weintraub, L. MD, DGEIP Mid-cycle Meeting Slides for BLA 125561, dated April 14, 2015
- Tomaino, J. MD; Lee, J. MD. DGIEP Clinical Review for BLA 125561, dated June 8, 2015

## **3 RESULTS OF REVIEW**

### **3.1 OVERVIEW OF CLINICAL PROGRAM**

The BLA consisted of a two pivotal trials, an open-label, single-arm trial (LAL-CL03) in infants with rapidly progressive disease (Wolman disease) and a randomized, double-blind, placebo-controlled trial (LAL-CL02) in pediatric and adult patients with LAL deficiency (CESD), to support the efficacy of sebelipase alfa in patients with LAL deficiency.

### **3.2 INFANTILE-ONSET LAL DEFICIENCY (LAL-CL03)**

LAL-CL03 is a multicenter (12 clinical sites), multinational (9 countries), single-arm, open-label dose escalation study designed to evaluate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of SA in infants growth failure due to LAL deficiency. A historical control from a retrospective natural history study conducted in Wolman disease (LAL-1-NH01) was used as a comparator group. The primary efficacy endpoint was survival at 12 months of age.

Nine patients who were  $\leq 8$  months of age, and met the criteria for growth failure within the first 6 months of life, on the date of the first study infusion were enrolled. Eight patients received a starting dose of SA 0.35 mg/kg, escalated to a dose of 1 mg/kg, and then to 3 mg/kg weekly based on clinical status. One patient was found to have neutralizing antibodies and suboptimal clinical response and therefore, the dose was escalated to 5 mg/kg. Six of the nine (67%) patients survived to 12 months of age as compared to zero untreated patients in a natural history study conducted by the Sponsor.

### 3.2.1 Children and Adults presenting with LAL deficiency (LAL-CL02)

LAL-CL02 (n=6) is a double-blind, randomized, placebo-controlled Phase 3 study designed to evaluate the safety, efficacy, and pharmacokinetics of SA in subjects  $\geq 4$  years of age with LAL deficiency (CESD phenotype). The trial consisted of a screening period of up to 6 weeks, a 20-week double-blind period, an open-label period of up to 130 weeks, and a follow-up phone call at least 4 weeks after the last dose of study drug. The study compared SA 1 mg/kg IV infusion every other week to placebo. Sixty-six patients were enrolled and randomized.

Based on the data collected during Study LAL-CL02, the Division believes LDL-cholesterol (LDL-c) appears to be the most suitable endpoint to assess efficacy in patients with CESD (see Clinical Review for rationale). The mean change from baseline in LDL-c was a decrease of  $28 \pm 22\%$  in the SA group and a decrease of  $6 \pm 13\%$  in the placebo group ( $p < 0.0001$ ). For patients with baseline LDL-c  $\geq 130$  mg/dL, 13/32 (41%) patients in the SA group achieved an LDL-c of  $< 130$  mg/dL as compared to only 2/30 (7%) patients in the placebo group. Therefore, the clinical reviewer concluded that there was a substantially larger proportion of patients treated with SA experienced decreases in LDL-c over the 20-week double-blind treatment period, and 41% of patients were able to achieve LDL-c levels  $< 130$  mg/dL.<sup>2</sup>

### 3.3 SAFETY CONCERNS

There were no treatment-related deaths reported in Study LAL-CL02 or LAL-CL03. In Study LAL-CL02, three of the 66 (5%) patients experienced at least one serious adverse event (SAE); 2/36 (6%) patients in the SA group and 1/30 (3%) patient in the placebo group. Only one of the SAEs was considered as drug-related; a subject that experienced a Grade 3 hypersensitivity reaction after 2 study drug infusions and withdrew from the double-blind treatment period.

Anaphylaxis and hypersensitivity reactions are known adverse reactions associated with enzyme replacement therapies.

In the clinical trials, 3 of 106 (3%) patients treated with SA experienced signs and symptoms consistent with anaphylaxis. These patients experienced reactions during infusion with signs and symptoms including chest discomfort, conjunctival injection, dyspnea, generalized and itchy rash, hyperemia, swelling of eyelids, rhinorrhea, severe respiratory distress, tachycardia, tachypnea, and urticaria. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after treatment initiation.

In the clinical trials, 21 of 106 (20%) SA-treated patients, including 9 of 14 (64%) infants and 12 of 92 (13%) pediatric patients, 4 years and older, and adults experienced signs and symptoms either consistent with or that may be related to a hypersensitivity reaction. Signs and symptoms of hypersensitivity reactions, occurring in two or more patients, included abdominal pain, agitation, fever, chills, diarrhea, eczema, edema, hypertension, irritability, laryngeal edema, nausea, pallor, pruritus, rash, and vomiting. The majority of reactions occurred during or within 4 hours of the completion of the infusion. Patients were not routinely pre-medicated prior to infusion of SA in these clinical trials.

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<sup>2</sup> Tomaino, J. MD; Lee, J. MD. DGIEP Clinical Review for Kanuma (sebelipase alfa), dated June 8, 2015

#### **4 DISCUSSION AND CONCLUSION**

The clinical reviewer concluded that, based on the review of data obtained from Study LAL-CL02 and Study LAL-CL03, the effectiveness of SA has been established in the patient population with CESD, for which there are no other available therapies.<sup>3</sup>

Since the sebelipase study was small size as a result of the rarity of the disease, there will be a clinical PMC registry. The registry will be a prospective, long-term observational study of patients with LAL deficiency being treated with sebelipase alfa that will evaluate clinical outcomes, including the progression of liver and cardiovascular disease.

Overall, the safety profile of sebelipase alfa reported thus far is acceptable. The most serious risk of concern associated with SA are hypersensitivity reactions, which may be due to the derivation of the drug from egg or a component of the enzyme. The incidence of hypersensitivity reactions was low in the clinical trials. Nevertheless, the label will include recommendations regarding the risk of hypersensitivity reactions, including anaphylaxis in the Warnings and Precautions section of the prescriber information.

Based on the currently available data, DRISK does not recommend a REMS for this product at this time.

#### **5 CONCLUSION**

In conclusion, risk mitigation measures beyond professional labeling are not warranted for SA at this time. SA has proven efficacy and safety for the treatment of patients with a diagnosis of LAL deficiency, which at this time has no other treatment options. Thus, the benefit-risk profile for sebelipase alfa is acceptable and the risks can be adequately communicated through professional labeling.

Should DGIEP have any concerns of questions, or feel that a REMS may be warranted for this product after further review, please contact DRISK.

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<sup>3</sup> Tomaino, J. MD; Lee, J. MD. DGIEP Clinical Review for Kanuma (sebelipase alfa), dated June 8, 2015

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/s/  
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JAMIE C WILKINS PARKER  
09/08/2015

REEMA J MEHTA  
09/08/2015  
I concur.