CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125561Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum - Addendum

Date	December 8, 2015
From	Julie Beitz, MD
Subject	Office Director Decisional Memo – Addendum
BLA #	125561
Applicant Name	Alexion Pharmaceuticals Inc. (formerly Synageva BioPharma Corp.)
Date of Submission	January 8, 2015
PDUFA Goal Date	December 8, 2015 (extended from September 8, 2015)
Proprietary Name / Established (USAN) Name	Kanuma (sebelipase alfa)
Dosage Forms / Strengths	20 mg / 10 mL vials
Proposed Indication	Treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency
Recommended Action:	Approval

This memorandum is an addendum to my September 12, 2015 memorandum in which the benefits and risks of Kanuma (sebelipase alfa) for the treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency were discussed.

Substantial GMP violations were identified during an FDA inspection conducted (b) (4), at the (b) (4) drug product manufacturing (fill/finish) facility (b) (4) that precluded approval by the PDUFA goal date of September 8, 2015. Specifically, FDA found that (b) (4) There was no other Kanuma drug product manufacturing fill/finish site identified in the original BLA.

Alexion's responses to FDA's observations and requests regarding manufacturing operations at (b) (4) and details of its plans to transfer manufacturing to an alternative site ((b) (4) submitted on September 2, 2015, were considered a major amendment triggering a 3 month review clock extension.

On October 14, 2015, Alexion submitted its plans to evaluate the comparability of Kanuma drug product manufactured at the (b) (4) site to Kanuma drug product manufactured at the (b) (4) site, and a schedule of submissions of data to support this comparability assessment. In the weeks that followed, Alexion submitted data regarding process controls and analytical test limits, and evidence of their effectiveness in maintaining product quality consistency for drug product manufactured at the (b) (4) site. On November 25, 2015, Alexion amended the Kanuma BLA to add (b) (4) as the drug product manufacturing and sterility testing site, and to remove the (b) (4) site from any manufacturing and testing activities.

The submitted data supported the comparability of the [redacted] drug product to the [redacted] drug product used in clinical trials, and demonstrated that Kanuma drug product manufactured at the [redacted] site is pure, potent, and stable. In a memorandum dated December 7, 2015, the Office of Biotechnology Products (OBP), recommended approval of the BLA for Kanuma (sebelipase alfa), as amended.

In accordance with OBP's recommendation for approval, the Division of Gastroenterology and Inborn Errors Products also recommends approval of the amended BLA for Kanuma (sebelipase alfa) for the treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency. I concur with this recommendation.

Product labeling adequately addresses the safety concerns identified with use of Kanuma (sebelipase alfa), including the risks of hypersensitivity reactions and anaphylaxis. A Risk Evaluation and Mitigation Strategy (REMS) for Kanuma (sebelipase alfa) will not be required.

A postmarketing long-term prospective clinical outcomes trial will be conducted to assess the rate of progression of liver and cardiovascular disease, and changes in anthropometric assessments, in pediatric and adult patients receiving Kanuma (sebelipase alfa).

The applicant has also agreed to conduct several postmarketing studies addressing quality and microbiology for the drug substance and the drug product, as discussed in my September 12, 2015 memorandum. The following are the revised drug product quality microbiology postmarketing studies to be included in the approval letter:

1. Validate the [redacted]. If the [redacted] is revised based on the validation study, update the BLA file accordingly.

2. Perform a microbial retention study to support the proposed [redacted] time limit for [redacted] Limit the validated time for [redacted] to [redacted] until the [redacted] time limit has been approved by the Agency.

3. Perform a study to confirm that the dye ingress test method used for drug product stability samples is capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes [redacted]). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.

4. Conduct a study to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

The approval of the BLA for Kanuma (sebelipase alfa) will occur immediately following CVM's approval of the new animal drug application for the genetically engineered chicken line that produces recombinant human LAL in its egg whites.

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/s/

JULIE G BEITZ
12/08/2015

Office Director Decisional Memorandum

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From	Julie Beitz, MD
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Proprietary Name / Established (USAN) Name	Kanuma (sebelipase alfa)
Dosage Forms / Strengths	20 mg / 10 mL vials
Proposed Indication	Treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency
Recommended Action:	Approval, pending satisfactory resolution of GMP violations observed at the drug product manufacturing facility

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
Medical Officers	Lauren Weintraub, MD / Juli Tomaino, MD
Cross Discipline Team Leader	Jessica Lee, MD, MMSc
Pharmacology /Toxicology	Tamal Chakraborti, PhD
Deputy Division Director, DGIEP	Andrew Mulberg, MD
Statistics	Benjamin Vali, MS
Office of Biotechnology Products	Christopher Downey, PhD/ Juhong Liu, PhD
Product Quality Microbiology	Colleen Thomas, PhD / Bo Chi, PhD
DPMH	Leyla Sahin, MD / Ethan Hausman, MD
Clinical Pharmacology	Jing Fang, PhD / Sarah Dorff, PhD
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OSE/DMEPA	Matthew Barlow, RN
OSI	Susan Leibenhaut, MD
Office of Compliance/OMQ	Carmelo Rosa, MS, PsyD

DGIEP = Division of Gastroenterology and Inborn Errors Products
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
OMQ = Office of Manufacturing Quality
OND = Office of New Drugs
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific Investigations

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Kanuma (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL) and a new molecular entity. LAL is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and fatty acids. Kanuma (sebelipase alfa) is produced by recombinant DNA technology in the egg whites of eggs laid by genetically engineered (GE) chickens. This will be the first approval of a GE biopharm animal (i.e., a GE animal that produces medical products) containing articles regulated by the Center for Veterinary Medicine (CVM) and the Center for Drug Evaluation and Research (CDER).

I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Kanuma (sebelipase alfa) for the treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency pending satisfactory resolution of the GMP violations observed at the drug product manufacturing (fill/finish) facility.

Lysosomal acid lipase (LAL) deficiency is a rare, autosomal recessive lysosomal storage disorder. Infants with LAL deficiency (also known as Wolman disease) have absent or less that 1% of normal LAL enzyme activity, and a clinical course that is fulminant and rapidly fatal in the first 3 to 12 months of life. Clinical features include massive hepatosplenomegaly, liver cirrhosis/failure, growth failure, malnutrition and cachexia.

In contrast, older children and adults with LAL deficiency (also known as cholesterol ester storage disease or CESD), have low (1 to 12% of normal) LAL enzyme activity and a clinical course that is variable. Laboratory and clinical features include elevated transaminases, dyslipidemia, hepatosplenomegaly, hepatic fibrosis with progression to cirrhosis, and accelerated atherosclerosis. Premature demise is due to liver failure and/or accelerated atherosclerotic disease secondary to chronic hyperlipidemia.

There are no FDA-approved therapies for LAL deficiency. Kanuma (sebelipase alfa) will be the first approved enzyme replacement therapy for this disease. The recommended starting dose for patients with Wolman disease is 1 mg/kg administered intravenously once weekly. For patients who do not achieve an optimal clinical response, the recommended dose is 3 mg/kg once weekly. For CESD patients, the recommended dose is 1 mg/kg administered intravenously once every other week. Doses are infused over two hours using a low-protein binding infusion set with an in-line, low-protein binding 0.2 micron filter.

Kanuma (sebelipase alfa) was efficacious for the treatment of LAL deficiency in infants (Wolman disease) and in older children and adults (CESD) in clinical trials. Six of 9 patients with Wolman disease were alive at 12 months of age as compared to 0 of 21 patients in an untreated historical cohort with a similar age at disease presentation and clinical characteristics. Improvements in weight-for-age z-scores were observed in surviving patients.

In CESD patients treated with sebelipase alfa, statistically significant reductions in LDL-c, non-HDL-c and triglyceride levels, and improvements in HDL-c levels

were noted at 20 weeks as compared to placebo. The effects of sebelipase alfa on cardiovascular morbidity and mortality have not been established.

At 20 weeks, CESD patients treated with sebelipase alfa had larger reductions from baseline in ALT values and liver fat content (as measured by MRI) compared to placebo. The significance of these findings with respect to progression of liver disease in responding patients has not been established. CESD patients treated for up to 36 weeks demonstrated continued improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT values. Patients on placebo during the double-blind period who were switched to sebelipase alfa treatment exhibited similar improvements.

The overall safety profile of sebelipase alfa for the treatment of patients with a diagnosis of lysosomal acid lipase deficiency is acceptable. Hypersensitivity reactions, including rare cases of anaphylaxis, were reported with sebelipase alfa treatment. These remain the most common, potentially serious adverse reactions associated with enzyme replacement therapies. These reactions will be highlighted in the Warnings and Precautions section of product labeling and medical interventions that could be employed should these reactions occur will be described.

The most common adverse reactions reported with sebelipase alfa treatment in patients with Wolman disease were diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis and urticaria. The most common adverse reactions reported with sebelipase alfa treatment in patients with CESD were headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation and nausea.

In clinical trials, breakdown of accumulated lysosomal lipid led to transient increases in LDL-c and triglyceride levels in the majority of patients treated with sebelipase alfa. Improvement in dyslipidemia was observed within 8 weeks of the start of treatment.

Anti-drug antibodies (ADA) to sebelipase alfa can develop, but titers decline with continued treatment in most patients. In patients with Wolman disease, hypersensitivity reactions were noted more commonly in ADA positive patients than in ADA-negative patients. There is no clear association between the development of ADA and decreased efficacy in CESD patients.

Product labeling adequately addresses the safety concerns identified with use of Kanuma (sebelipase alfa), including the risks of hypersensitivity reactions and anaphylaxis. A Risk Evaluation and Mitigation Strategy (REMS) for Kanuma (sebelipase alfa) will not be required.

A post-approval long-term prospective clinical outcomes trial will be conducted to assess the rate of progression of liver and cardiovascular disease in pediatric and adult patients receiving Kanuma (sebelipase). The applicant will also address several issues related to quality and microbiology for the drug substance and the drug product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Lysosomal acid lipase (LAL) deficiency is a rare, autosomal recessive lysosomal storage disorder caused by mutations in the lysosomal acid lipase (*LIPA*) gene, resulting in absent or low levels of LAL enzyme activity. LAL catalyzes the hydrolysis of cholesteryl esters and triglycerides into free cholesterol, glycerol, and fatty acids in lysosomes. Deficient LAL enzyme activity results in lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the intestine, liver, spleen, and walls of blood vessels. Lipid accumulation in the liver may lead to increased liver fat content and progression of liver disease, including fibrosis and cirrhosis. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidemia due to impaired degradation of lysosomal lipid is common, resulting in elevated LDL-c and triglyceride levels and low HDL-c levels. The diagnosis of LAL deficiency is based on *LIPA* gene sequencing and the measurement of LAL enzyme activity in peripheral blood leukocytes. There are two phenotypes of LAL deficiency: 1) Wolman disease, characterized by the absence of or less than 1% of normal LAL enzyme activity, and (2) cholesteryl ester storage disease (CESD), characterized by low (1 to 12% of normal) LAL enzyme activity.[1,2] Wolman disease, a very rare condition with an estimated incidence of 1 in 500,000 live births, is a fulminant disease with massive infiltration of the liver, spleen, and other organs by macrophages filled with cholesteryl esters and triglycerides. Patients typically present in infancy (2 to 4 months of age) with vomiting, diarrhea with steatorrhea, and massive hepatosplenomegaly. About 50% have adrenal calcifications. Feeding difficulties and malabsorption lead to malnutrition, growth retardation and cachexia, which together with liver cirrhosis/failure, contribute to demise in the first 3 to 12 months of life.	Lysosomal acid lipase (LAL) deficiency is a rare, autosomal recessive lysosomal storage disorder. Infants with LAL deficiency (Wolman disease) have absent or less than 1% of normal LAL enzyme activity and a clinical course that is fulminant and rapidly fatal in the first 3 to 12 months of life. Clinical features include massive hepatosplenomegaly, liver cirrhosis/failure, growth failure, malnutrition and cachexia. Older children and adults with LAL deficiency (CESD) have low (1 to 12% of normal) LAL enzyme activity and a clinical course that is variable. Patients present with elevated serum transaminases, dyslipidemia and hepatosplenomegaly. Disease progression is highly variable. Complications include hepatic fibrosis with progression to cirrhosis and liver failure, and accelerated atherosclerosis. Premature demise is due to liver failure and/or accelerated atherosclerotic disease secondary to chronic hyperlipidemia.

[1] Bernstein DL, Hulkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol* 58:1230-43, 2013.

[2] Reiner Z, Guardamagma O, Nair D, Soran H, Hovingh K, Bertolini S, Jones S, Coric M, Calandra S, Hamilton J, Eagleton T, Ros E. Lysosomal acid lipase deficiency - An under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis 235:21-30, 2014.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In contrast, CESD, with an estimated prevalence between 1/40,000 and 1/300,000, is a milder, later-onset disorder. Mean age at symptom onset is 5 years of age, although clinical presentation has been documented in adults in their 50s and 60s. Patients present with elevated serum transaminases, dyslipidemia and hepatosplenomegaly. Disease progression is highly variable. Complications include hepatic fibrosis with progression to cirrhosis and liver failure, and accelerated atherosclerosis. Premature demise is due to liver failure and/or accelerated atherosclerotic disease secondary to chronic hyperlipidemia.	
Current Treatment Options	There are no FDA-approved therapies for LAL deficiency. Existing approaches focus on supportive care to reduce the burden of disease complications. Statins (HMG-CoA-reductase inhibitors) as monotherapy or in combination with other drugs, such as cholestyramine, have been shown to reduce LDL-c levels, lower cardiovascular risk and reduce liver size in some patients. Despite these improvements, liver fibrosis continues to progress in responding patients. Hematopoietic stem cell transplantation has been performed in a few infants with LAL deficiency, however this approach has had limited success and attendant serious toxicity. There is limited information on long-term outcomes in patients who underwent liver transplantation for liver failure. One patient developed end stage renal disease seven years post-transplant due to glomerular sclerosis and atherosclerosis, whereas a second patient reported no renal involvement six years post-transplant.[3]	There are no FDA-approved therapies for LAL deficiency. Existing therapeutic approaches include supportive care, use of lipid-lowering drugs, hematopoietic stem cell transplantation, and liver transplantation. Kanuma (sebelipase alfa) will be the first approved enzyme replacement therapy for this disease.
Benefit	The efficacy of Kanuma (sebelipase alfa) was established in two clinical trials of patients with LAL deficiency: an open-label, historically controlled trial in infants (Wolman disease), and a double-blind, placebo-controlled trial in older children and adults (CESD).	Kanuma (sebelipase alfa) was efficacious for the treatment of LAL deficiency in infants (Wolman disease) and in older children and adults (CESD) in clinical trials.

[3] Bernstein 2013; Reiner 2014

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Infants with LAL Deficiency (Wolman disease): A multi-center, open-label, single-arm clinical trial of sebelipase alfa was conducted in 9 infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months of age. • **Dosing.** Patients received sebelipase alfa at 0.35 mg/kg once weekly intravenously for the first 2 weeks and then 1 mg/kg once weekly. Due to suboptimal clinical responses, doses in all 6 surviving patients were escalated to 3 mg/kg once weekly, between 4 and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg. In one patient, the dose was escalated to 5 mg/kg once weekly at Week 88 due to decreased growth velocity in a setting of positive neutralizing anti-drug antibodies to sebelipase alfa. • **Results.** The efficacy of sebelipase alfa was assessed by comparing the survival of the 9 treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Six of the 9 treated infants survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by 8 months of age. The median age of the 6 surviving treated patients was 18.1 months (range 12 to 42.2 months). Following initiation of treatment with sebelipase alfa at 1 mg/kg once weekly, weight-for-age z-scores improved in 3 of 5 surviving patients with growth failure; all 6 surviving patients demonstrated improvements in weight-for-age z-scores following dose escalation to 3 mg/kg once weekly. **Older Children and Adults with LAL Deficiency (CESD):** A multi-center, double-blind, placebo-controlled trial was conducted in 66 pediatric and adult patients with CESD, aged 4 to 58 years (71% were less than 18 years old).	Six of 9 patients with Wolman disease were alive at 12 months of age as compared to 0 of 21 patients in an untreated historical cohort with a similar age at disease presentation and clinical characteristics. Improvements in weight-for-age z-scores were observed in surviving patients. In CESD patients treated with sebelipase alfa, statistically significant reductions in LDL-c, non-HDL-c and triglyceride levels, and improvements in HDL-c levels were noted at 20 weeks as compared to placebo. The effects of sebelipase alfa on cardiovascular morbidity and mortality have not been established. At 20 weeks, CESD patients treated with sebelipase alfa had larger reductions from baseline in ALT values and liver fat content (as measured by MRI), compared to placebo. The significance of these findings with respect to progression of liver disease in responding patients has not been established. CESD patients treated for up to 36 weeks demonstrated continued improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT values. Patients on placebo during the double-blind period who were switched to sebelipase alfa treatment exhibited similar improvements.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Patients were randomized 1:1 to receive sebelipase alfa at 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 patients had LDL-c levels of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c levels above 190 mg/dL at study entry, and 24% of patients with LDL-c levels above 190 mg/dL remained on lipid-lowering medications. • **Results (double blind period).** At 20 weeks, a statistically significant improvement in percent change from baseline in LDL-c levels was observed in the treated group as compared to placebo (with a mean difference of -22% [95% C.I.: -33%, -15%]). LDL-c levels of less than 130 mg/dL were achieved in 13 of 32 (41%) treated patients vs. 2 of 30 (7%) placebo-treated patients with baseline LDL-c levels of 130 mg/dL or greater. Statistically significant improvements in percent change from baseline at 20 weeks was also observed in the treated group compared to placebo with respect to decreases in non-HDL-c levels (with a mean difference of -21% [95% C.I.: -30%, -15%]) and triglycerides (with a mean difference of -14% [95% C.I.: -28%, -1%]), and increases in HDL-c levels (with a mean difference of 20% [95% C.I.:12%, 26%]). The effects of sebelipase alfa on cardiovascular morbidity and mortality have not been established. CESD patients treated with sebelipase alfa had larger reductions from baseline in ALT values and liver fat content (as measured by MRI), compared to placebo. The significance of these findings with respect to progression of liver disease in responding patients has not been established. • **Results (open label extension).** Sixty-five of the 66 patients who participated in the double-blind period entered the open-label extension and received sebelipase alfa at a dose of 1 mg/kg intravenously once every other week. Patients treated for up to 36 weeks demonstrated continued improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT values. Patients on placebo during the double-blind period who switched to sebelipase alfa	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment exhibited similar improvements. **Animal Disease Model:** In a rat disease model of LAL deficiency[4], sebelipase alfa treatment with doses up to 3m/kg intravenously once weekly was associated with improvement in survival and body weight gain, organ weight reduction, reduction in ALT and AST values, reduction in serum and hepatic lipids, and improvement in liver histopathology.	
Risk	A total of 106 patients with LAL deficiency have received Kanuma (sebelipase alfa) in clinical trials. Of these, 75 patients have received treatment in the pivotal efficacy trials described above: 9 infants treated for up to 165 weeks (median 60 weeks) at escalating doses ranging between 0.35 mg/kg and 5 mg/kg once weekly, and 66 patients, aged 4 to 58 years, treated with 1 mg/kg every other week up for up to 36 weeks. The Warnings and Precautions section of product labeling will describe the following findings: • **Hypersensitivity Reactions Including Anaphylaxis:** In clinical trials, 3 of 106 (3%) patients experienced signs and symptoms consistent with anaphylaxis during infusions of sebelipase alfa. Anaphylaxis has occurred as early as the sixth infusion and as late as 1 year after the start of treatment. Twenty-one of 106 (20%) treated patients (9 of 14 infants with Wolman disease; 12 of 92 patients with CESD) experienced signs and symptoms consistent with a hypersensitivity reaction. Patients were not routinely pre-medicated prior to	The overall safety profile of sebelipase alfa for the treatment of patients with a diagnosis of lysosomal acid lipase deficiency is acceptable. Hypersensitivity reactions, including rare cases of anaphylaxis, were reported with sebelipase alfa treatment. These remain the most common, potentially serious adverse reactions associated with enzyme replacement therapies. These reactions will be highlighted in the Warnings and Precautions section of product labeling and medical interventions that could be employed should these reactions occur will be described. The most common adverse reactions reported with sebelipase alfa treatment in patients with Wolman disease were diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis and urticaria.

[4] "Yoshida" rats are Donryu rats that are LAL deficient due to a spontaneous mutation in the LAL gene. They have approximately 19% of wild type hepatic LAL activity and exhibit hepatomegaly, splenomegaly, lymphadenopathy, thickening and dilatation of the intestine, weight loss and death from cachexia at 120 days of age. *See* Kuriyama M, Yoshida H, Suzuki M, Fujiyama J, Igata A. Lysosomal acid lipase deficiency in rats: lipid analyses and lipase activities in liver and spleen. *J Lipid Res* 31:1605-1612, 1990.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infusion of sebelipase alfa in these trials. The risks and benefits of re-administering sebelipase alfa following a severe reaction should be considered, and patients monitored with appropriate resuscitation measures available, if the decision is made to re-administer the product. • **Hypersensitivity to Eggs or Egg Products:** Sebelipase alfa is produced in the egg whites of genetically engineered chickens. Patients with a known history of egg allergies were excluded from clinical trials. The risks and benefits of treatment with sebelipase alfa in patients with known systemic hypersensitivity reactions to eggs or egg products should be considered. The most common adverse reactions reported in > 30% of infants with Wolman disease treated with sebelipase alfa were diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis and urticaria. The most common adverse reactions reported in ≥ 8% of CESD patients and at a higher incidence than in patients receiving placebo were headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation and nausea. **Hyperlipidemia.** In clinical trials, breakdown of accumulated lysosomal lipid led to increases in LDL-c and triglyceride levels above pre-treatment values in 29 of 36 (81%) and 21 of 36 (58%) patients, respectively, at 2 and 4 weeks following initiation of sebelipase alfa. The maximum mean percentage increase was 18% for LDL-c levels at Week 2 and 5% for triglyceride levels at Week 4. Improvement in dyslipidemia was observed within 8 weeks of the start of treatment. **Immunogenicity Findings in Patients with Wolman disease.** Four of 7 patients with available data developed anti-drug antibodies (ADA) during treatment with sebelipase alfa. Two of these patients were determined to be positive for neutralizing antibodies that inhibit *in vitro* enzyme activity and cellular uptake of the	The most common adverse reactions reported with sebelipase alfa treatment in patients with CESD were headache, fever, oropharyngeal pain, nasopharyngitis, asthenia, constipation and nausea. In clinical trials, breakdown of accumulated lysosomal lipid led to transient increases in LDL-c and triglyceride levels in the majority of patients treated with sebelipase alfa. Improvement in dyslipidemia was observed within 8 weeks of the start of treatment. Anti-drug antibodies (ADA) to sebelipase alfa can develop, but titers decline with continued treatment in most patients. In patients with Wolman disease, hypersensitivity reactions were noted more commonly in ADA positive patients than in ADA-negative patients. There is no clear association between the development of ADA and decreased efficacy in CESD patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	enzyme. At the time of initial ADA positivity, 3 patients were receiving 1 mg/kg once weekly and 1 patient was receiving 3 mg/kg once weekly. One of the 4 ADA-positive patients had persistent ADA titers, whereas ADA titers decreased to undetectable levels in the remaining 3 patients while receiving continued treatment at 3 mg/kg once weekly. Hypersensitivity reactions occurred in all 4 of the ADA-positive patients, and in only 1 of the 3 ADA-negative patients. None of the patients discontinued treatment. In 1 patient, decreased growth velocity in the setting of neutralizing antibodies to sebelipase alfa was observed. **Immunogenicity Findings in Patients with CESD.** Five of 35 CESD patients who were treated with sebelipase alfa and completed the 20-week double-blind period developed ADA. All patients were receiving 1 mg/kg once every other week. In 3 patients with measurable ADA titers at multiple time points, titers decreased to undetectable levels with continued treatment. Two patients developed *in vitro* neutralizing antibodies during the open label extension after 20 weeks and 52 weeks of treatment, respectively. There is no clear association between the development of ADA and decreased efficacy in these patients. The safety of sebelipase alfa in specific populations can be summarized as follows: • **Pregnancy and Lactation:** There are no data in pregnant women to inform any risks associated with sebelipase alfa treatment. Animal reproductive studies showed no evidence of embyolethality, fetotoxicity, teratogenicity, or abnormal early embryonic development with treatment of sebelipase alfa doses up to 164 and 526 times the human dose of 1 mg/kg every other week (based on AUC) in rats and rabbits, respectively. There are no data available regarding the presence of sebelipase alfa in human breast milk, effects on the breastfed infant, or effects on milk production. • **Pediatrics:** The safety and effectiveness of sebelipase alfa have been established	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in pediatric patients aged 1 month and older. In clinical trials, 56 pediatric patients with Wolman disease or CESD were enrolled. Because sebelipase alfa has an orphan designation for these indications, the pediatric study requirement under PREA is waived. • **Elderly:** There were no patients over the age of 65 enrolled in clinical trials of sebelipase alfa. It is not known whether they respond differently from younger patients.	
Risk Management	**Labeling:** Product labeling will address the safety concerns identified, including that: • Hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with sebelipase alfa; and • The risks and benefits of treatment with sebelipase alfa in patients with known systemic hypersensitivity reactions to eggs or egg products should be considered. **Risk Mitigation:** A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Kanuma (sebelipase alfa). **Post-approval Studies and Trials:** Post-approval, the applicant will conduct a long-term prospective clinical outcomes trial to assess the rate of progression of liver and cardiovascular disease in pediatric and adult patients receiving Kanuma (sebelipase alfa). Dosing regimens and reasons for dose modifications will be captured. Data on hypersensitivity reactions, including, anaphylaxis, will be collected. Eligible patients will be enrolled over an initial period of 3 years, and followed for a minimum of 10 years from the time of enrollment or until death, whichever comes first. The applicant will also address several issues related to quality and microbiology for the drug substance and the drug product. See Section 2 of this review for further details.	Product labeling adequately addresses the safety concerns identified with use of Kanuma (sebelipase alfa), including the risks of hypersensitivity reactions and anaphylaxis. A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Kanuma (sebelipase alfa). A post-approval long-term prospective clinical outcomes trial will be conducted to assess the rate of progression of liver and cardiovascular disease in pediatric and adult patients receiving Kanuma (sebelipase). The applicant will also address several issues related to quality and microbiology for the drug substance and the drug product.

2. Additional Comments

2.1 Regulatory Milestones

Sebelipase alfa received Orphan Drug designation on July 1, 2010 and Fast Track designation on June 14, 2011. Breakthrough Therapy designation was granted on May 13, 2013 for the rapidly progressive phenotype in infants (i.e., Wolman disease), (b) (4)

On January 8, 2015, the applicant, Synageva BioPharma Corp., completed its rolling submission of BLA 125561 for sebelipase alfa, including all requested data and information from CVM to initiate their review of the genetically engineered chicken in accordance with Guidance for Industry #187.[5] On June 23, 2015, Synageva transferred BLA 125561 to Alexion Pharmaceuticals Inc. Receipt of a major amendment on September 2, 2015 triggered a 3 month review clock extension.

2.2 Quality Review of Genetically Engineered Chickens, Egg Whites, Drug Substance and Drug Product

Alexion's genetically engineered (GE) chicken line produces recombinant human LAL (rhLAL) in its egg whites. For regulatory purposes, the GE egg whites are considered to be the starting material for the bulk drug substance that is subsequently purified to produce the human drug product, sebelipase alfa. CVM regulations provide oversight of the production of the gene expression product in the egg, egg collection and initial processing up to the egg crack, while CDER regulations oversee production steps from the egg crack through all subsequent egg white-related purification activities. CDER regulations also encompass review of the safety and effectiveness of the sebelipase alfa drug product.

Regarding the GE chicken line and the rDNA product it produces, the applicant has met all relevant requirements regarding safety and effectiveness. Briefly, CVM's review found that:

- the rDNA construct encodes the human LAL sequence and, as integrated in the GE chicken genome, is capable of expressing recombinant hLAL;
- the rDNA construct is safe to the target animal;
- other than for the GE trait intentionally introduced, the GE chickens are phenotypically similar to non-GE chickens;
- the rDNA construct is stably integrated and inherited in a Mendelian fashion across multiple generations;
- CVM is prepared to issue a finding of no significant impact (FONSI) on the environment because the animals and their potentially edible products will be sufficiently physically contained and disposed of by incineration so that there is no risk to the human environment of the U.S.;
- biomonitoring inspections of the applicant's animal facilities have found them to be acceptable; the animal husbandry, containment, personnel, and record keeping were

[5] *See* Guidance for Industry: Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Products, dated June 2015.

sufficient to ensure the safety and security of the GE animal and animal products (eggs, waste, etc.);
- the applicant has provided assurances that the GE chickens will not enter the food supply; in the event of an inadvertent release, CVM has determined that it would have a low level[6] of concern regarding food consumption risk, and has established an analytical method to determine if any chicken-derived product is from GE chickens;
- the applicant has validated the claim that GE chicken egg whites contain rhLAL; and
- a rigorous postmarketing record-keeping and reporting program has been developed.

CDER's quality review of the drug substance and drug product found that:

- the manufacturing process of sebelipase alfa is well-controlled and leads to a product that is pure, potent, and stable under the proposed storage conditions;
- there is sufficient testing to ensure batch-to-batch consistency of purity, potency, and stability;
- the drug substance and drug product are free of known endogenous and adventitious infectious agents and meet the parameters recommended by the Agency;
- there is sufficient virus testing to prevent egg whites with high viral load from entering the manufacturing process, and the manufacturing process provides adequate levels of inactivation or removal of viruses not detected by the initial viral testing.

Substantial GMP violations were identified during an FDA inspection conducted (b) (4), at the (b) (4) drug product manufacturing (fill/finish) facility (b) (4) that precluded an approval recommendation from the Office of Compliance and the Office of Pharmaceutical Quality by the PDUFA goal date of September 8, 2015. Specifically, FDA found that (b) (4) There is no other drug product manufacturing fill/finish site identified in the BLA.

Alexion and (b) (4) are working to address the GMP issues identified at (b) (4) with the help of third parties. Alexion is concurrently establishing additional filling sites to ensure long-term continuity of drug supply. These additional sites include 1) a contract manufacturer (b) (4) where initial engineering runs will begin in (b) (4), and 2) Alexion's recently acquired fill/finish site in (b) (4) which will come online in (b) (4)

Alexion's responses to FDA's observations and requests regarding manufacturing operations at (b) (4) and details of its manufacturing contingency plans, submitted on September 2, 2015, were considered a major amendment triggering a 3 month review clock extension.

[6] For biopharm animals (i.e., GE animals that produce medical products) of species traditionally consumed as food, CVM determines food safety risk based on whether the concern level in the event that edible products derived from the animals enter the food supply is low, moderate, or high.

2.3 Rare Pediatric Disease Priority Review Voucher

Alexion has been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the FDCA. This PRV has been assigned a tracking number, PRV BLA 125561. This voucher entitles the applicant to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review.

2.4 Advisory Committee Meeting

The BLA for Kanuma (sebelipase alfa) was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with a diagnosis of lysosomal acid lipase deficiency and the application did not raise significant safety or efficacy issues that were unexpected for a biologic drug of this class.

2.5 Postmarketing Commitments to Address Quality and Microbiology Issues

Alexion has agreed to conduct the following postmarketing studies:

Drug Substance Quality Microbiology

1. Increase the bioburden test volume for (b) (4) samples to improve the sensitivity of the bioburden tests. In addition, provide bioburden qualification data for all in-process and drug substance samples from a total of three lots.

2. Provide endotoxin qualification data for the in-process drug substance samples from a total of three lots.

3. Improve the endotoxin method for the (b) (4) samples by optimizing the endotoxin test procedures.

4. Develop and validate a reliable endotoxin test for the unformulated drug substance sample. In addition, validate the (b) (4) and drug substance endotoxin test using the modified endotoxin method involving the use of (b) (4) sample preparation system. Provide the validation information and data.

Drug Product Quality Microbiology

1. (b) (4)

2. Validate the (b) (4) If the

(b) (4) is revised based on the validation study, update the BLA file accordingly.

3. The microbial retention study (b) (4) .

4. Perform a study to confirm that the dye ingress test method used for drug product stability samples are capable of detecting small defects that could allow microbial ingress. The study should be performed with a range of small defect sizes (b) (4)). Revise the positive control defect size used for stability testing based on the results of the study and update the BLA file accordingly.

5. (b) (4)

6. Conduct studies to understand the mechanism of endotoxin masking and/or interference in the drug product. Explore alternative test methods and develop a more suitable *in vitro* test method for the drug product.

Drug Substance Quality

1. Characterize the potential levels of (b) (4) in the drug substance.

2. Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.

3. To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of (b) (4) and establish drug substance release specifications for the critical peaks or groups of peaks. Alternatively, develop an alternative method with better resolution to control the glycan profile, such as (but not limited to) the (b) (4) characterization tests.

4. Conduct studies to improve the formulation to reduce or eliminate the potential for formation of visible proteinaceous particles and other insoluble protein aggregates. If a significantly improved formulation is identified, develop the improved formulation for the commercial product.

Final Drug Product Quality

1. Develop and implement an improved SDS-PAGE or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE method.

2. Implement the (b) (4) test method for drug product release specifications.

3. Implement an assay for uptake of sebelipase alfa into (b) (4) for drug product release specifications.

4. Develop and implement a (b) (4) receptor binding assay for drug product release specifications.

5. Conduct studies to determine whether the (b) (4) eceptor binding assays are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data.

6. Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.

7. Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.

8. Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to assess the potential impact of shipping conditions on product quality.

9. Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.

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/s/

JULIE G BEITZ
09/12/2015