

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125561Orig1s000

CHEMISTRY REVIEW(S)

**Drug Product Addendum: Arulvathani Arudchandran, Ph.D.
DBRR II, OBP, OPQ, CDER**

Amendments reviewed:

STN 0092- 10/14/15:	Drug product manufacturing process validation protocol (PPVA VV 35217E/01), analytical comparability design to assess critical product quality attributes at release and stability of lots from the (b) (4) facility
STN 0094- 11/4/ 15:	Certificate of analysis – (b) (4)
STN 0095- 11/12/15:	Release and characterization of the engineering lot 5J901
STN 0099- 11/25/15:	Comparative force degradation studies and data for the engineering lot 5J901
STN 0102- 12/4/15	One-month stability data for the engineering lot 5J901, release and characterization of the DP PPQ1 lot 5K001, data for process validation run 1

Review:

Introduction:

In the original application, Sebelipase alfa (Kanuma) drug product is manufactured at the (b) (4) facility, (b) (4) (FEI # (b) (4)). Due to compliance issues discovered during cGMP inspection ((b) (4)), the (b) (4) site is classified deficient for approvals of new drugs. To facilitate regulatory review of Kanuma, the Sponsor, Alexion moved drug product manufacturing operation to a contract manufacturing facility in (b) (4) (FEI # (b) (4)). Given the product is highly efficacious and the patients are in dire need of the product, a decision to expedite regulatory action for BLA125561 is made. The Agency worked with Alexion and reached a concurrent validation/concurrent release strategy. The strategy includes the following:

1. Comparability of PPQ DP lots manufactured at (b) (4) to Kanuma clinical lots from (b) (4) is assessed based on an analytical comparability protocol. Lots meeting the acceptance criteria specified by the protocol will be released for commercial distribution

- 30 days after the data are submitted to the FDA or after FDA concurrence of the data, whichever comes first.
2. Process validation will be governed by a PV protocol. Interim PV reports together with analytical comparability results should be submitted to support the manufacturing process validation. Successful execution of the PV protocol in the PPQ runs is essential for approval.
 3. Stability of lots manufactured in (b) (4) could be supported by stability results from the engineer run lot at (b) (4). One-month stability data from the ER run would be adequate to support stability prior to BLA action.
 4. Comparability data for accelerated and forced-degradation stability of the ER lot will be submitted to the Agency for review when the data become available. The data will be used as supportive data to facilitate FDA's regulatory action.
 5. The (b) (4) facility will be re-evaluated once Office of Compliance concluded the site is cGMP compliant. It will not be part of the regulatory action for this BLA.

There are no changes identified for the following sections and therefore, corresponding reviews could be found in the drug product quality review (6/8/2015).

3.2.P.1.	Description and Composition of the Drug Product
3.2.P.2.	Pharmaceutical Development
3.2.P.3.2	Batch formula
3.2.P.4	Control of excipients
3.2.P.5.	Control of drug product
3.2.P.5.1 and 3.2.P.5.6	Specification(s) and Justification of Specification(s)
3.2.P.5.2 and 3.2.P.5.3	Analytical Procedures and Validation of Analytical Procedures
3.2.P.5.5	Characterization of Impurities.
3.2.P.6	Reference standard

The following review is to assess whether Sebelipase alfa drug product from (b) (4) Halle facility will be produced with a high degree of assurance of meeting all attributes they are intended to possess, as per 21 CFR 211.100(a) and 211.110(a). The primary focus for the assessment is on:

- analytical comparability designs implemented
- manufacturing process validation (3.2.P.3.5)
- characterization, release, and stability of the engineering lot ; characterization and release of the PPQ 1 lot (3.2.P.5.4 Batch Analysis, 3.2.P.8. Stability)

Analytical Comparability Design:

Data:**Table 1: Comparability Data Available by 08 December 2015**

(b) (4) (b) (4) Lot	Fill Date	Release & Characterization	Historical Data comparison	Forced Degradation ^a	Stability
Engineering	06 Oct	✓	✓	✓	✓ (1M)
PPQ1	11 Nov	✓	✓	–	–
PPQ2	18 Nov	–	–	Not Applicable	–
PPQ3	26 Nov	–	–		–

^a Separate comparative stress stability studies will be performed with (b) (4) DP comparators for the Engineering lot and PPQ 1.

Two engineering lots, lot 5I900 and lot 5J901 have been filled at the current (b) (4) facility. The first lot failed fill weight criterion and is not used to support licensure. The second filled lot 5J901 met the acceptance criteria. Therefore, release, characterization, and stability data of the (b) (4) engineering lot 5J901 is evaluated to demonstrate the analytical comparability. In addition, release and comparability data of the PPQ1 lot will be submitted prior to action. The sponsor committed to submit analytical data for PPQ2 and PPQ3 lots as CBE-0 post-approval supplements in addition to the stability data for all three PPQ lots. The validation protocol for the DP manufacturing process, PPVA VV 35217e/01 is reviewed in 3.2.P.3.5 Process Validation and/or Evaluation section.

Reviewer comment:

The proposed strategy to support the comparability of lots from the (b) (4) to (b) (4) although not conventional, is found appropriate under this special situation. The data from the single engineering lot would be considered to be an acceptable alternative to the usual PV process to support commercialization. The proposal of releasing PPQ lots from the (b) (4) facility as per concurrent release is acceptable due to the urgent need of this drug. However, the sponsor is requested during the teleconference held on November 3 2015 to submit analytical data for the PPQ 2 and PPQ3 lots as CBE-30 not as CBE-0.

Historical lots for comparability assessment:

The sponsor proposed to utilize data from drug product lots manufactured at the (b) (4) facility by using different sources of drug substance lots. For example, the following control chart indicates the origin of different DP lots those would be used to assess the comparability of the enzyme activity, (b) (4)

(b) (4)

Table 4: Control Chart for DP Enzyme Activity



Reviewer comment:

The proposal is found appropriate as adequate numbers of lots from different sources are considered to evaluate the comparability of lots from (b) (4) facility.

Release and characterization tests for analytical comparability exercise:

Table 4: Proposed Biochemical Analyses

Release Assays	Additional Characterization Analyses
Appearance	Enzyme Activity, (b) (4) ^b
pH	Macrophage Cell Uptake ^b
RP-HPLC Content, sebelipase alfa concentration	
SDS-PAGE Western ^a	
RP-HPLC Purity ^a	
Enzyme Activity (b) (4) ^a	
Volume in Container	
Subvisible Particulates (HIAC)	

^a These assays may need to be modified relative to typical release testing to allow for the analysis of multiple samples in a side-by-side manner.

^b These assays will be performed in a side-by-side manner.

Table 8: Proposed Comparability Acceptance Criteria

Test	Release Specification	Proposed Comparability Criteria	Rationale
Appearance	Pass ^a	Pass ^a	Consistent with historical dataset
pH	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
Concentration of sebelipase alfa (RP-HPLC)	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
SDS-PAGE Western blot (reduced and non-reduced) Purity	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
RP-HPLC Purity	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
Enzyme Activity (b) (4)	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
Volume in Container	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
Subvisible Particulates (HIAC)	(b) (4)	(b) (4)	Min-max range of (b) (4) DP historical data
		(b) (4)	
Enzyme Activity, (b) (4)	Not Applicable	(b) (4)	(b) (4)
Macrophage Cell Uptake (EC ₅₀ µg/mL)	Not Applicable	(b) (4)	

^a Pass is defined as “Clear to slightly opalescent colorless to slightly colored liquid with no visible foreign particulate matter. May contain white or translucent, irregularly shaped or fibrous particles.”

Reviewer comment:

The sponsor proposed tests and acceptance criteria based on historical experience, including the knowledge obtained from clinical drug product lots from (b) (4) facility. Therefore, tests and acceptance criteria listed (Table 4, Table 8) to assess the comparability of lots manufactured from (b) (4) facility to those from (b) (4) facility are found appropriate.

Stability: stress condition:

The sponsor, Alexion proposed the stress condition as (b) (4) C that was applied in studies to support the drug substance comparability from (b) (4) and from (b) (4) facilities. In addition, DS lot 14MM5535004 will be used in the comparability analysis as a side-by side manner.

Table 9: (b) (4)

(b) (4)

Reviewer comment:

The sponsor used the knowledge gained from previous experience to set appropriate condition to demonstrate the accelerate stability of lots manufactured from the (b) (4) facility.

Concentration, purity, and potency are assessed under the protocol. In addition, data from the DS lot 14MM5535004 would further validate the comparability assessment. Information provided is sufficient to indicate that the sponsor has a suitable stability protocol to bridge (b) (4) DP lots with previous lots from (b) (4)

Stability: Long-term and accelerated conditions:

Comparability stability program includes storage of DP at long-term ($5 \pm 3 \text{ }^\circ\text{C}$) and accelerated ($25 \pm 2 \text{ }^\circ\text{C}$) storage conditions. Time points, test methods, and acceptance criteria are identical to the stability program submitted in BLA 125561.

Table 10: Drug Product Stability Protocol at $5 \pm 3 \text{ }^\circ\text{C}$, (b) (4)

Attribute	Specification	Timepoint (months)									
		0 ^a	1	3	6	9	12	18	24	36	
Appearance	Pass ^b	(b) (4)									
pH	(b) (4)										
Concentration of sebelipase alfa											
Concentration of HSA											
Enzyme Activity											
Purity (Western blot)											
Purity (RP-HPLC)											
Sterility/Container-closure integrity ^c	Pass ^d										
Sub-visible Particulates	(b) (4)										

^a Release test results will be reported for the initial time point (T = 0)

^b Pass is defined as “Clear to slightly opalescent colourless to slightly coloured liquid with no visible foreign particulate matter. May contain white or translucent, irregularly shaped or fibrous particles.”

^c Container closure integrity is performed on stability in lieu of sterility for annual timepoints

^d Pass is defined as “sterile” for time zero and “no dye ingress” for container-closure integrity testing

Table 11: Drug Product Stability Protocol at 25 ± 2 °C, (b) (4)

Attribute	Acceptance Criteria ^a	Timepoint (months)			
		0	1	3	6
Appearance	(b) (4)				(b) (4)
pH					
Concentration of sebelipase alfa					
Concentration of HSA					
Enzyme Activity					
Purity (Western blot)					
Purity (RP-HPLC)					
Subvisible Particulates					

^a Specifications are only applied to the long-term storage condition and are shown in this table for information only.

^b Pass is defined as “Clear to slightly opalescent colorless to slightly colored liquid with no visible foreign particulate matter. May contain white or translucent, irregularly shaped or fibrous particles.”

Reviewer comment:

The sponsor proposed to submit one-month stability data from the engineering lot to demonstrate the stability of DP lots from (b) (4) facility in order to expedite approval for BLA 125561. All three PPQ lots will be placed under the stability program and the sponsor commits to inform any out of specification results to FDA. Therefore, the current proposal is found acceptable to demonstrate the stability of DP lots from the (b) (4) facility. Of note, in the t-con with Alexion on November 3, 2015, the agency and Alexion reached agreement that the forced degradation data for PPQ1 need to be submitted as a product correspondence after FDA’s regulatory decision.

Manufacturing Process Comparability:

Comparator lot selection:

Three DP lots, # 1501A08, 1501A10, and 1501A12 manufactured from (b) (4) during May-July 2015 are used as comparator lots to demonstrate the process validation. The proposed comparator lots are produced from the DS manufactured at (b) (4) (b) (4) by using egg whites from two different sources. The sponsor stated that drug product lots are selected by considering the availability of the number of vials and closest manufacturing dates.

Table 2: DS Lots Manufactured at (b)(4) by Commercial Process Available for (b)(4) PPQ in November

DS Lot Numbers	EW Source	DS Comparability	Use	
			(b)(4) DP Lot Number	(b)(4) DP Lot Number
MM2015084553	(b)(4)	Yes: All lots in study of DS from (b)(4) EW sources	1501A10 ^a	Lot 5J901 ^b
MM2015145583	(b)(4)		None	TBD
MM2015115058	(b)(4)		1501A12 ^c	TBD
MM2015125324	(b)(4)		None	TBD

TBD = To Be Determined

^a Filled 17 June 2015

^b Engineering Lot filled 06 October 2015; additional use TBD

^c Filled 20 July 2015

Reviewer comment:

Alexion proposed to fill two PPQ DP lots from the (b)(4) DS, egg white source is from (b)(4). The third PPQ DP will be filled from the (b)(4) DS manufactured from (b)(4) sourced egg white. The comparability data of the DS from (b)(4) to the (b)(4) is not submitted yet, the DS analytical comparability data will be demonstrated post-licensure. Therefore, the suitability of the drug substance lot for the PPQ3 DP will be determined once the sponsor submitted comparability data of the drug substance lots manufactured from (b)(4) and (b)(4) sourced egg whites. However, the proposed drug substance lots for PPQ1, PPQ2, and ER lots are found suitable as the data for these lots demonstrate the purity, potency, and safety.

Manufacturing process comparability design:

Manufacturing process comparability is reviewed under 3.2.P.3.3 Description of Manufacturing Process and Process Controls by considering critical process parameters (CPP), in-process control testing (IPC), manufacturing scale, process steps, and container closer system.

3.2.P.3. Manufacture

3.2.P.3.1 Manufacture(s)

The sponsor, Alexion pharmaceuticals Inc. moved drug product manufacturing operations for Kanuma from (b)(4) (FEI (b)(4)) to a contract manufacturing facility in (b)(4) (FEI # (b)(4)). Drug product lots will be released as per concurrent release.

Facilities for Quality control testing, packaging, and labelling remain same – refer to the drug product review (6/8/15).

Table 1: Drug Product Manufacturers

Activity	Location
Manufacturing	(b) (4)
Quality Control (QC) Testing	(b) (4)
Packaging and Labelling	(b) (4)

^a Sterility Testing^b Pyrogen Testing

(b) (4)
A prior approval inspection of fill and finished areas was conducted in (b) (4) with no 483 observation. (b) (4)

Reviewer comment:

(b) (4)
No additional product quality information is provided in the SN0090 submission. Further, the facility inspection performed during (b) (4) identified no issues, (b) (4)

Alexion has adequate tests in place to identify sebelipase alfa (b) (4)
In addition, suitable tests are employed at the state of release to assess the purity of the drug product. Therefore, no additional action is necessary as per product quality perspective. However, review of the adequacy of cleaning procedures and product separation related operations will be reviewed by facility reviewers.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

There are no major changes in the drug product manufacturing process, the process consists of (b) (4)

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/s/

ARULVATHANI P ARUDCHANDRAN
12/07/2015

JUHONG LIU
12/07/2015



First Approval for Indication

Recommendation: Approval

**BLA 125561
Addendum: Executive Summary
Review Date: December 7, 2015**

Drug Name/Dosage Form	Kanuma for Infusion
Strength/Potency	20mg/10ml
Route of Administration	Intravenous (IV)
Indication	Lysosomal acid lipase deficiency
Rx/OTC Dispensed	Rx
Applicant/Sponsor	Alexion Pharmaceuticals, Inc.
US agent, if applicable	Not Applicable

**Submissions
Reviewed**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	REVIEW COMPLETED
Amendment 93	October 14, 2015	yes
Amendment 95	November 4, 2015	yes
Amendment 96	November 12, 2015	yes
Amendment 100	November 25, 2015	yes
Amendment 102	December 3, 2015	yes
Amendment 103	December 4, 2015	yes

Clearance History

Name	Title
Juhong Liu, Ph.D.	Team Leader, OPQ/OBP/DBRR II
David Frucht, M.D.	Acting Director, OPQ/OBP/DBRR II

Disclaimer

This Addendum only provides evaluation of sections related to the transfer of Kanuma Drug Product manufacturing from (b) (4) to (b) (4). General characterization, testing, and risk management for sebelipase drug substance and drug product manufacturing processes, as detailed in the Executive Summary for the original application, remain unchanged.

I. Recommendation

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 125561 for Kanuma manufactured by Alexion Pharmaceuticals, Inc. from product quality and manufacturing process control perspectives. The data submitted in this application are adequate to support the conclusion that the manufacturing process of Kanuma is well controlled and leads to a product that is pure, potent, and stable under the sponsor's propose storage conditions. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
 - Drug substance: (b) (4)
 - Drug product – (b) (4)
- Fill size and dosage form – 20mg in 10ml (2mg/ml) solution in a single-dose vial
- Dating period:
 - Drug product: 24 months at 2 – 8°C
 - Drug substance: (b) (4) months at (b) (4)°C
- Stability option: We have approved the stability protocol(s) in the license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Rationale if exempted – Kanuma is exempted from lot release because it is a specified product per 601.2 (a).

B. Recommendation on Phase 4 (Post-Marketing) Commitments

No new PMCs are identified during the review of the transition of drug product manufacturing facility from (b) (4) to (b) (4). However, due to the extension of the review cycle, the final milestones for some of the PMCs are revised. The PMCs and corresponding final report due dates are listed below:

1. 2920-10: Characterize the potential levels of (b) (4) in the drug substance. Final Report Submission: March 31, 2016
2. 2920-11: Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants. Final Report Submission: January 31, 2017
3. 2920-12: 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. Final Report: April 30, 2017

4. 2920-13 Conduct a study 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 Report Submission: February 29, 2016
5. 2920-14: Develop and implement an improved SDS-PAGE test or another purity test to quantitate high molecular weight product-related species with greater sensitivity and precision than the current SDS-PAGE test. Final Report Submission: January 31, 2017
6. 2920-15: Implement the (b) (4) test method for drug product release specifications. Final Report Submission: April 30, 2016
7. 2920-16 : Implement an assay for uptake of sebelipase alfa into (b) (4) for drug product release specifications. Final Report Submission: June 30, 2016
8. 2920-17 : Develop and implement a (b) (4) receptor binding assay for drug product release specifications. Final Report Submission: January 31, 2017
9. 2920-18 : Conduct studies to determine whether the (b) (4) receptor binding assays are stability-indicating. Implement the stability-indicating assays into the drug product stability specifications with acceptance criteria supported by stability data. Final Report Submission: January 31, 2018
10. 2920-19 : Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity. Final Report Submission: January 31, 2016
11. 2920-20: Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses. Final Report Submission: December 31, 2016
12. 2920-21: 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. Final Report Submission: October 31, 2016
13. 2920-22 : 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. Final Report Submission: July 31, 2016

C. Drug Product Kanuma Quality Summary

In the Executive Summary for the original BLA 125561 application, an “Approval” recommendation was made from Kanuma drug substance and drug product quality and process control perspectives. During the inspection of the Kanuma drug product manufacturing facility,

(b) (4) FDA ORA inspectors identified significant deficiencies of the quality systems of the facility. ORA, FDA Office of Compliance, and OPQ/OPF issued non-concurrence for approval due to lack of assurance of sterility of the final drug product. An extension of the PDUFA review cycle to December 8, 2015 was issued by the Agency to the sponsor of Kanuma, Alexion, on September 3, 2015 to allow review of significant new information submitted in response to the inspectional issues and to give Alexion additional time to resolve the inspectional issues.

To facilitate timely delivery of this life-saving medication to patients, and based on the sponsor's experience obtained from manufacturing of (b) (4) clinical and commercial scale lots at (b) (4) Alexion and the Agency agreed on a solution in which Alexion would move the manufacture of Kanuma final product to (b) (4) and seek approval of Kanuma final product lots manufactured at (b) (4) through a protocol-based, concurrent validation and concurrent release strategy. To expedite FDA's review of the (b) (4) process and product, the Agency instructed Alexion to submit relevant sections pertinent to process control and product testing on a rolling submission basis. The strategy and sequence of submission include the following regulatory filing elements and sequence:

1. (b) (4) process validation (PV) protocol based on previous manufacturing experience
2. Analytical comparability protocol for comparing (b) (4) product to (b) (4) product with appropriate acceptance criteria
3. Process control and monitoring results and release and comparability results for the engineering (ER) lot produced at (b) (4) prior to commercial process validation
4. Stability data of the ER lot stored at long-term storage, accelerated, and stressed conditions
5. Release testing, analytical comparability results, and the interim PV report for the first PV lot (PPQ1)
6. Stability data of the first PV lot to be submitted as a product correspondence post-BLA approval
7. Release, analytical comparability, stability and interim PV report for the second PV lot to be submitted as CBE-30 supplement post-BLA approval
8. Release, analytical comparability, stability for the third PV lot and the final PV report to be submitted as CBE-30 supplement post-BLA approval

Alexion submitted all data as planned. This addendum evaluates the process controls and analytical test limits and their effectiveness in maintaining consistency of critical product quality for drug product manufactured at (b) (4). Our overall evaluation of the submission in its final form concludes:

1. The process validation protocol (including sampling plan throughout the process validation campaign) is sufficient to evaluate the minor manufacturing changes at (b) (4) compared to (b) (4)

2. The analytical comparability protocol identified critical quality attributes and established acceptance criteria based on testing results from (b) (4) historical lots that were sufficient to evaluate the quality of (b) (4) lots.
3. The release, analytical comparability, and stability data demonstrate the critical product quality attributes of the ER and the PPQ1 lots are comparable with the clinical and commercial scale lots manufactured at (b) (4)
4. The process report for the ER lot and the interim process validation report for the PV1 lot demonstrate the manufacturing process at (b) (4) is sufficiently controlled to operate within the limits previously reviewed and deemed acceptable for the (b) (4) process. The minor process changes from the (b) (4) to accommodate equipment configurations did not impact product quality.

In summary, the currently available data and control strategies demonstrate that the (b) (4) is capable of manufacturing Kanuma drug product that is pure, potent, and stable and is comparable to the (b) (4) manufactured product used in pivotal clinical trials. The (b) (4) -manufactured product is therefore suitable for human use. The process control data indicate the process controls in place at (b) (4) are sufficient to address the drug product process risks identified in Table 3 in the original Executive Summary. The predefined control limits from the process validation protocol and the analytical comparability protocol are capable of providing adequate assurance of the consistency of the manufacturing process and product quality for future commercial lots. From product manufacturing and product quality perspectives, I recommend approval of Kanuma license application.

F. Establishment Information

OVERALL RECOMMENDATION: Approval				
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
DP Manufacturer and sterility testing	(b) (4)	(b) (4)	NAI (b) (4)	PAI Waived

G. Lifecycle Knowledge Management – phase 4 plans can be described here

b. Drug Product

- i. Protocols approved:
 - 1) Analytical comparability protocol to support concurrent validation, concurrent release of Kanuma product manufactured at (b) (4)
 - 2) Drug Product Manufacturing process validation protocol to support concurrent validation, concurrent release of Kanuma product manufactured at (b) (4)
- ii. Future inspection: OPF recommends an inspection of the (b) (4) facility within 4 months after approval.

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/s/

JUHONG LIU
12/07/2015

DAVID M FRUCHT
12/07/2015

Pre-License Inspection Waiver Memorandum

Date: 12/2/2015

From: Christina Capacci-Daniel, Ph.D., OPQ/OPF/DIA
Colleen Thomas, Ph.D., OPQ/OPF/DMA
Arulvathani Arudchandran, Ph.D., OBP/DBRRII

To: BLA 125561/0

Through: Zhihao (Peter) Qiu, Ph.D., Branch Chief, OPQ/OPF/DIA/Branch 1

Subject: Inspection waiver memo for manufacture of Kanuma drug product at the (b) (4)

Applicant: Alexion Pharmaceuticals, Inc.

Facility: (b) (4)
FEI # (b) (4)

Product: Kanuma (sebelipase alfa) for Injection

Dosage: Concentrated solution (2mg/mL) for injection, 20 mg/vial Kanuma

Indication: (b) (4) for patients with lysosomal acid lipase deficiency (LAL Deficiency)

Waiver Recommendation

The Kanuma drug product will be manufactured on (b) (4) at the (b) (4). The proposed commercial drug product manufacturing operations for Kanuma include (b) (4) which are similar to the approved processes for other sterile small molecule products manufactured at (b) (4). The facility was inspected by ORA IOG from (b) (4), and classified NAI. CGMP coverage was provided for (b) (4) and (b) (4) profiles during the inspection, and there were no concerns related to manufacture of sterile product by (b) (4) at the facility. Based on the firm's compliance history, current acceptable GMP status, and experience with similar operations, we recommend that the pre-license inspection of the (b) (4) facility be waived for BLA 125561.

Kanuma drug product manufacturing was transferred to (b) (4) late in the review cycle for BLA 125561. Process Performance Qualification batches were manufactured in November 2015. To perform an on-site evaluation of the completed

studies and confirm the cGMP compliance of the facility, a post-approval inspection is recommended between 1 – 4 months following approval of the BLA.

Summary

BLA STN 125561 was initially submitted by Synageva Biopharma and later transferred to Alexion Pharmaceuticals. The manufacture of formulated Kanuma drug substance is performed at (b) (4) (FEI (b) (4)). The BLA provided information and data to support the manufacture of Kanuma for Injection, 20 mg/vial at (b) (4) (FEI (b) (4)). Following a (b) (4) OAI inspection, Alexion subsequently withdrew this facility and proposed (b) (4) (FEI (b) (4)) for commercial drug product manufacturing. The current waiver recommendation applies to drug product manufacture at (b) (4) (FEI (b) (4)).

Facility Information

The Kanuma drug product manufacturing process consists of (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Evaluation of criteria that may warrant inspection

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*

(b) (4) has not been approved for the manufacturing of a licensed product. However this facility is approved for manufacture of 22 NDA products,

(b) (4)

2. *FDA has not inspected the establishment in the last 2 years.*

(b) (4) was inspected (b) (4) and found to be NAI. (b) (4) operations were covered and found to be acceptable.

3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The facility was inspected by IOG from (b) (4), found to be NAI, and included coverage of profiles (b) (4). CGMP coverage for (b) (4) was performed. Inspectional guidance was afforded through CPGM 7356.002, Drug Manufacturing Inspections; 7356.002A, Sterile Drug Process Inspections; and 7346.832, Pre-Approval Inspections.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities / buildings / areas.*

The manufacturing areas, including the (b) (4), are currently approved for two NDA products. This area has been qualified for (b) (4) products and (b) (4) products. Filling operations for drug product manufacture of Kanuma are similar to these approved operations.

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.*

The proposed manufacturing operations for Kanuma are simpler than the approved NDA products which consist of (b) (4)

Signed:

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/s/

CHRISTINA A CAPACCI-DANIEL
12/07/2015

REVIEW ADDENDUM

BLA STN 125561

KANUMA (sebelipase alfa)

Sponsor: Alexion Pharmaceuticals (formerly Synageva Biopharma)

**Office of Biotechnology Products
Division of Biotechnology Review and Research – II**

Reviewer: Christopher Downey, PhD

ATL Reviewer: Juhong Liu, PhD

OBP CMC Review Data Sheet

1. **BLA#:** 125561
2. **REVIEW ADDENDUM DATE:**
3. **PRIMARY REVIEW TEAM:**
 - Medical Officers:** Lauren Weintraub (early-onset indication)
Juli Tomaino (late-onset indication)
 - Pharm/Tox:** Tamal Chakroborti
 - Product Quality:** Christopher Downey (Drug Substance)
Arulvathani Arudchandran (Drug Product)
Simon Williams (Analytical Procedures)
 - Immunogenicity:** Joao Pedras-Vasconcelos
 - Quality Micro:** Bo Chi (Drug Substance)
Coleen Thomas (Drug Product)
 - Clinical Pharmacology:** Jing Fang
 - Statistics:** Yeh-Fong Chen
 - OBP Labeling:** Jibril Abdus-Samad
 - RPM:** Kevin Bugin

4. **MAJOR GRMP DEADLINES**
 - Filing Meeting:** December 17, 2014
 - Mid-Cycle Meeting:** April 14, 2015
 - Late-Cycle Meeting:** July 8, 2015
 - Wrap-Up Meeting:** July 28, 2015
 - Primary Review Due:** June 8, 2015
 - Secondary Review Due:** June 22, 2015
 - CDTL Memo Due:** August 7, 2015
 - PDUFA Action Date:** September 8, 2015

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

The communications below represent those related to submissions reviewed in this Addendum. All previous communications during the BLA review cycle are documented in the CMC primary review dated June 8, 2015.

Communication/Document	Date
PMC Discussion Comments	June 8, 2015
Information Request #7	June 18, 2015
Information Request #8	July 7, 2015

6. **SUBMISSION(S) REVIEWED:**

The submissions below represent those related to submissions reviewed in this Addendum. All previous communications during the BLA review cycle are documented in Christopher Downey's primary review dated June 8, 2015.

Submission	Date Received	Review Completed (Yes/No)
STN 125561/0058 (response to PMC comments)	November 21, 2014	yes
STN 125561/0062 (response to IR #7)	June 29, 2015	yes
STN 125561/0063 (response to IR #8)	July 14, 2015	yes
STN 125561/0065 (response to IR #7, Question 11)	July 17, 2015	yes

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The material reviewed in this Review Addendum support the approval recommendations in the original CMC-Product Quality reviews filed on June 8, 2015. Therefore I recommend approval with the Post-Marketing Commitments listed below.

II. CMC Post-Marketing Commitments

The PMCs below reflect the revisions communicated to the sponsor July 31, 2015. Modifications were made to some the original PMCs communicated to the sponsor on June 8, 2015 to facilitate their timely implementation. The CMC-Product Quality PMCs are listed below in the order in which they were listed in our final communication to the sponsor. The PMC numbers in the approval letter will carry the prefix: 2920 -. The individual PMC suffix numbers will reflect the PMCs from all the review disciplines and will not necessarily the numbering here.

Product Quality PMC 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.

Product Quality PMC 2

Implement the [REDACTED] ^{(b) (4)} test method for drug product release specifications.

Product Quality PMC 3

Implement an assay for uptake of sebelipase alfa into [REDACTED] ^{(b) (4)} for drug product release specifications.

Product Quality PMC 4

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

Product Quality PMC 5

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

Product Quality PMC 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.

Product Quality PMC 7

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

Product Quality PMC 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.

Product Quality PMC 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.

Product Quality PMC 10

Characterize the potential levels of [REDACTED] (b) (4) in the drug substance.

Product Quality PMC 11

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

Product Quality PMC 12

To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of [REDACTED] (b) (4) [REDACTED] 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 [REDACTED] (b) (4) characterization tests.

Product Quality PMC 13

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.

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Reviewer Introduction

At the time the primary CMC-Product Quality reviews of the Drug Substance and Drug product sections of the application were filed on June 8, 2015, there were outstanding information request items and ongoing negotiations with the sponsor for the final release and stability specifications and for PMCs. This Review Addendum contains our reviews of additional material submitted by the sponsor after the primary reviews were filed. The material is organized by the relevant CTD sections below. CTD sections with no new information since the original reviews are omitted.

S. DRUG SUBSTANCE

3.2.S.2 Manufacture

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Process Description and Controls for egg white harvest

In response to our June 18, 2015 information request, the sponsor updated section 3.2.S.2.2 include the detailed description of the egg white harvest process originally submitted in Amendment 125561/0014. In addition, the sponsor updated Figure 1 in 3.2.S.2.2 to include egg white harvest in the drug substance manufacturing process.

Reviewer comments:

(b) (4)

The sponsor provided additional details on the egg white harvest process and clarified that they considered this procedure part of drug substance manufacture in its January 12, 2015 IR response (eCTD sequence 0014). At the time, this information was submitted in CTD section 1.11.1. We requested on June 18, 2015 that the sponsor place the information into the manufacturing information in module 3.2.S.2.2. This information was reviewed in section 3.2.S.2.2 of the product quality review filed June 8, 2015. The update places the information in the correct section of the BLA and is acceptable.

(b) (4)

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P DRUG PRODUCT

3.2.P.8 Stability

3.2.P.8.3 Stability Data

In response to the June 18, 2015 information request, the sponsor provided updated stability data for ongoing drug substance and drug product stability studies. The sponsor updated 3.2.P.8.3 with current stability data results for drug substance and drug product, and 3.2.P.8.1 was also revised to reflect these updates.

Reviewer comments:

The stability updates add an additional time point to the long-term storage data for the process validation batches. There are no trends for any of the tested attributes suggested by the new

data. These data, in addition to the 24 months of data for clinical batches previously submitted, support the 24 month storage period for drug substance.

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/s/

CHRISTOPHER D DOWNEY
07/31/2015

JUHONG LIU
07/31/2015



First Approval for Indication

Recommendation: Approval

**BLA 125561
Review 1
Review Date: June 19, 2015**

Drug Name/Dosage Form	Kanuma for Infusion
Strength/Potency	20mg/10ml
Route of Administration	Intravenous (IV)
Indication	Lysosomal acid lipase deficiency
Rx/OTC Dispensed	Rx
Applicant/Sponsor	Synageva BioPharma
US agent, if applicable	Not Applicable

Submissions Reviewed

SUBMISSION(S) REVIEWED	DOCUMENT DATE	REVIEW COMPLETED
STN 125561/0003 (original CMC)	November 21, 2014	yes
Amendment 8	January 5, 2015	yes
Amendment 10	January 8, 2015	yes
Amendment 13 (to IR #1; Q1 – 3)	January 9, 2015	yes
Amendment 14 (to IR #2)	January 12, 2015	yes
Amendment 20 (to IR #3; Review Issue 3g and IR items 2, 5, 7, 8, and 9)	March 13, 2015	yes
Amendment 25 (IR #3; Review Issues 3b and 3c)	March 20, 2015	yes
Amendment 30 (to IR #3; Review Issues 3a, 3d, 3e, 3f, and IR items 4, 6)	March 30, 2015	yes
Amendment 32 (response to IR #4)	April 6, 2015	yes
Amendment 47 (response to IR #5)	May 15, 2015	yes
Amendment 53 (response to IR #6)	May 29, 2015	yes

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Christopher Downey (Lead) Simon Williams (Assay Validation)	DBRR II DBRR II
Drug Product	Arulvathani Arudchandran	DBRR II
Immunogenicity	Joao Pedras-Vasconcelos	DBRR III
Labeling	Jibril Abdus-Samad	OBP
Facility and Microbiology	Bo Chi, Coleen Thomas	DMA
Secondary Reviewer	Juhong Liu	DBRR II
Tertiary Reviewer	David Frucht	DBRR II

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Medical Officers	Lauren Weintraub Juli Tomaino	DGIEP
Pharm/Tox	Tamal Chakroborti	ODEI/DCRP
Clinical Pharmacology	Jing Fang	OTS/OCP/DCPI
Statistics	Yeh-Fong Chen	OTS/OB/DBI
RPM	Kevin Bugin	DGIEP
RPM	Anita Brown	OBP

Quality Review Data Sheet

- 1. LEGAL BASIS FOR SUBMISSION: 351(a)
- 2. RELATED/SUPPORTING DOCUMENTS:
 - A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
 (b) (4)			yes	No review required, as all the relevant information related to the manufacture of this product was in the BLA and the facility was evaluated during a pre-approval inspection
			yes	No review required, as all the relevant information related to compatibility with the product was in the BLA
			yes	No review required, as all the relevant information related to compatibility with the product was in the BLA

B. Other Documents: None

- 3. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Biotech Products, OPS, CDER, recommends approval of STN 125561 for Kanuma manufactured by Synageva BioPharma pending a favorable recommendation from Office of Compliance's assessment of the sponsor's response to facility inspection issues. The data submitted in this application are adequate to support the conclusion that the manufacture process of Kanuma is well controlled and leads to a product that is pure, potent and stable under the sponsor's propose storage conditions. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Action letter language

- Manufacturing location:
 - Drug substance – [REDACTED] (b) (4)
 - Drug product – [REDACTED] (b) (4)
- Fill size and dosage form – 20mg in 10ml (2mg/ml) solution in a single-dose vial
- Dating period:
 - Drug product – 24 months at 2 - 8°C
 - Drug substance – (b) (4) months at (b) (4)°C
 - Stability option:
We have approved the stability protocol(s) in the license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
 - Yes
 - Rationale if exempted – Kanuma is exempted from lot release because it is a specified product per 601.2 (a).

c. Benefit/Risk Considerations

Kanuma is indicated [REDACTED] (b) (4) for patients with lysosomal acid lipase (LAL) Deficiency. LAL Deficiency is a very rare autosomal recessive monogenic disorder in which patients are deficient in a key lysosomal enzyme, lysosomal acid lipase. The deficiency results in lysosomal accumulation of cholesteryl esters and triglycerides in various tissues and cell types throughout the body, which leads to progressive deterioration of multiple systems and generally results in early onset patient death in . Currently there are no safe or effective therapies for this life-

threatening disease. The efficacy of Kanuma for both adult-onset and the more severe, rapidly progressive infant-onset phenotype patients are reported in this application.

One risk associated with use of Kanuma in patients is the high rate of anti-Kanuma antibody development observed in patients under long term Kanuma therapy. (b) (4)

Formation of Kanuma aggregates and particles, as for all other protein biotherapeutics, may augment immune response to Kanuma, potentially leading to occurrence adverse reactions and reduction of efficacy.

(b) (4)

The sponsor has implemented a semi-quantitative SDS-PAGE-western blot analysis for aggregates and has committed to further improve the sensitivity of the assays post-licensure.

The commercial Kanuma manufacturing process has implemented measures to control factors that could adversely impact the manufacture of rhLAL. At the Agency's request, the sponsor has revised manufacturing control limits to be within those validated during its process validation. Critical product quality attributes are tested and controlled to ensure the efficacy, purity and stability of the product. However, due to the rapid product development as a breakthrough therapy product, many of these assays have not been fully optimized. Considering the obvious clinical benefit and the dose ranges used the clinical trials, these current deficiencies are unlikely to expose the patients to unreasonable risk and can therefore be addressed as post-approval commitments.

Kanuma product quality and manufacturing risks are reasonably managed, and we therefore recommend approval of this product with the post-marketing commitments described below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

1. Improve the SDS-PAGE purity test to increase the sensitivity and to quantify the levels of product-related impurities more precisely.

2. Implement the [REDACTED] ^{(b) (4)} test method for drug product release and stability specifications.
3. Implement an assay for the uptake of sebelipase alfa into [REDACTED] ^{(b) (4)} for drug product release and stability specifications.
4. Develop and implement a [REDACTED] ^{(b) (4)} receptor binding assay for drug product release and stability specifications.
5. Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent results for specific activity.
6. Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.
7. Conduct worst-case simulated or worst-case real world shipping studies for both the drug substance and the drug product to determine the potential impact of extreme shipping conditions on product quality.
8. Characterize the potential of rhLAL to form oxidized variants and deamidated variants and determine whether these variants identified are stability-indicating. Implement changes to the drug substance and drug product control strategies as warranted by the data.
9. Characterize the potential levels of [REDACTED] ^{(b) (4)} in the drug substance.
10. Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.
11. To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of [REDACTED] ^{(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 necessarily limited to) the [REDACTED] ^{(b) (4)} characterization tests.
12. 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.

II. Summary of Quality Assessments

A. CQA Identification, Risk, and Lifecycle Knowledge Management

The table below provides a summary of critical quality attributes identification and risk management. For the purposes of this table, critical quality attributes are limited those intrinsic to the sebelipase alfa active pharmaceutical ingredient. Identification and risk management of process-related impurities and general drug substance or drug product critical quality attributes are described in separate risk tables in sections B, Drug Substance Quality Summary, and C,

Drug Product Quality Summary. Product variants listed are those that are fully active, or close to fully active. Product impurities listed are those variants that are inactive or have greatly reduced activity.

Table 1: CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Type	Risk	Introduction	Control Strategy	Other
Enzymatic Activity	Potency	Loss of Potency and Product Efficacy	(b) (4)	Enzyme activity testing at release and on stability	PMC to include (b) (4)
(b) (4)	Potency	Loss of Potency and Product Efficacy		Cell based Bioassay DP Release and Stability Testing	PMC to add to DP release and stability testing
(b) (4)	Potency	Loss of Potency and Product Efficacy		<i>in vitro</i> binding assay	PMC to add to DP release & stability
Peptide Map	Identity	Identification of Product	Not Applicable	RP-HPLC of rhLAL Peptides (b) (4) at DS Release	N/A
(b) (4)	Surrogate for potency	Loss of cellular uptake and potency	(b) (4)	(b) (4)	N/A
(b) (4)	Potency	May affect PK		(b) (4)	PMC to quantify (b) (4) glycans
Charge Variants	Product Variants	May affect PK		Capillary isoelectric focusing (cIEF)	N/A
(b) (4)	Product Variants or impurity	Increased Immunogenicity, Effect on PK unknown	(b) (4)	Not tested	PMC to study relevant peptides, add control if stability-indicating
Aggregates	Product impurity	Loss of Potency and product Efficacy, Increased Immunogenicity, affect on PK unknown		SEC-HPLC (b) (4) & SDS-PAGE western blot for DS and DP Release and Stability Testing	PMC to improve western blot sensitivity

It should be noted that the sponsor has not manufactured sufficient Kanuma DS and DP lots to set optimal acceptance criteria for the above analytic specifications. The sponsor has committed to reevaluate the acceptance criteria of all specifications after a sufficient number of lots have been tested.

B. Drug Substance Sebelipase Alfa Quality Summary

The table below provides a summary of the identification and risk management for process related impurities and general drug substance attributes.

Table 2: Drug Substance Process Risk Identification and Lifecycle Knowledge Management

Category	Source	Risk	Introduction	Control Strategy	Other
	(b) (4)	Can act as adjuvants or allergens and increase immunogenicity		(b) (4) DS release testing	PMC to evaluate clearance of a (b) (4) test at release if necessary
	(b) (4)	None		(b) (4)	Very low level of (b) (4) in starting material
	(b) (4)	Toxic at high levels		(b) (4)	Tested at release
	(b) (4)	Product quality		(b) (4)	Tested in-process with lot rejection criteria
		safety			Tested in-process with lot rejection criteria
Bioburden	Contaminant	Introduction of microbial toxins that can cause adverse reactions in patients, and proteases that can degrade product	Accidental throughout process.		(b) (4) NA
Endotoxin	Contaminant	Adverse reactions in patients, DP failure	Accidental throughout process		(b) (4) NA
Appearance	General	Indicator of manufacturing failure	Intrinsic to drug substance	Release testing	NA
pH	General	DS failure	Formulation	Release testing	NA

a. Names

- Proprietary Name: Kanuma
- Trade Name: Kanuma
- Non-Proprietary/USAN: sebelipase alfa
- CAS name: not established
- Common name: sebelipase alfa
- INN Name: sebelipase alfa
- Compendial Name: not established
- OBP systematic name: none

b. Pharmacologic category – recombinant form of human lysosomal acid lipase.

c. Description

Sebelipase alfa is a ^{(b) (4)} monomeric glycoprotein with a molecular weight of ^{(b) (4)} 55kDa measured by electrospray mass spectrometry (EMS). ^{(b) (4)}

There are 6 N-linked glycosylation sites in the rhLAL amino acid sequence. ^{(b) (4)}

Figure 2: ^{(b) (4)}

^{(b) (4)}

d. Mechanism of action (MOA)

The native lysosomal acid lipase protein functions in the lysosome cell organelle to hydrolyze cholesteryl esters and triglycerides and prevent their accumulation. The products of these hydrolysis reactions are free cholesterol, glycerol, and free fatty acids. Patients with LAL deficiency (Wolman disease and cholesteryl ester storage disease) have absent or significantly reduced LAL function and accumulate cholesteryl esters and triglycerides in their cells, particularly in organs such as the liver and spleen. As a replacement for LAL deficiency, sebelipase is taken up by cells through receptor-mediated endocytosis and subsequent transportation to lysosomes where it compensates the function of the native enzyme. (b) (4)

Once transported to lysosomes, sebelipase cleaves cholesterol esters and triglycerides from endocytosed lipoproteins.

e. Potency Assay

Based on the mechanism of action, potency assays for sebelipase alfa consist of two types of assays: enzymatic activity and affinity to (b) (4). The assays are listed below:

1) (b) (4)

2) (b) (4)

f. Reference material(s)

The sponsor has developed a two tiered reference standard system consisting of a primary reference standard and a working reference standard as recommended by ICH guidance Q6B. Because sebelipase DS and DP both contain HSA, the reference standards are derived from (b) (4) drug substance (b) (4) lots. The current primary reference standard for commercial production was derived from one of the phase III lot (13-1276). The manufacturing process for this lot is very similar to the commercial process. Extensive physicochemical comparability studies demonstrated that this phase III lot was comparable to the commercial lots. The primary reference is stored (b) (4) and is re-qualified every (b) (4) months.

The working reference standard lot 14MM5533004 (commercial process) was qualified against an earlier primary reference standard 12-0981. 12-0981 was manufactured using the same phase III process and is comparable to 13-1276. Extensive physico-chemical comparability studies results demonstrated that this commercial lot was comparable to phase III lots. The working reference standard is stored and re-qualified using the same protocol as for the primary reference standard.

The sponsor did not submit a reference standard qualification protocol. Qualification of future reference standards will be submitted as supplements.

g. Critical starting materials or intermediates

Kanuma is produced by transgenic hens and isolated from egg whites. The eggs and egg whites, as critical raw materials of animal origin, are tested thoroughly for adventitious agents. (b) (4)

(b) (4)

(b) (4)

The raw material program is well defined, controlled, and does not use any raw materials that would be considered high risk to patient safety. Critical Raw materials are extensively characterized using appropriate analytical techniques.

h. Manufacturing process summary

Kanuma is the first CDER-regulated biotechnology product derived from a recombinant protein expressed in egg whites by genetically engineered chickens. FDA’s Center of Veterinary Medicine (CVM) is responsible for regulating the genetically engineered animals used to produce the unpurified bulk material to be used in sebelipase alfa manufacture. The “first regulated article” for this product is the recombinant DNA construct in the genetically engineered chickens, and this article is reviewed and must be approved as a New Animal Drug Application (NADA) prior to approval of the BLA for commercial therapeutic use of the sebelipase alfa derived from the chickens.

The CDER-regulated drug substance manufacturing process begins with cracking of eggs and separation of egg yolk from egg white. The egg whites serve as the starting material for downstream purification. (b) (4)

[Redacted]

he sebelipase manufacturing process is validated and well controlled.

[Redacted] (b) (4)

i. Container closure

[Redacted] (b) (4)



(b) (4)

j. Dating period and storage condition

The sponsor requests a Drug Substance shelf life of (b) (4) months at (b) (4) °C. The proposed shelf life was based on stability results for 12 months under long-term (b) (4) °C and 6 months of accelerated (b) (4) °C storage conditions for the three phase III clinical lots. In addition, the sponsor also provided 6 - 9 months long-term and 6 months accelerated stability data from the three process validation lots. The storage container for the drug substance was the same configuration as the validation and clinical lots. A stability protocol was provided in the BLA.

C. Drug Product Kanuma Quality Summary

The table below provides a summary of the identification and risk management for process related impurities and general drug product attributes including overages.

Table 3: Drug Product Process Risk Identification and Lifecycle Knowledge Management

Category	Type	Risk	Introduction	Control Strategy	Other
Sterility	Contaminant	Infections in patients, product stability	(b) (4)	(b) (4)	NA
Endotoxin	Contaminant	Adverse reactions in patients, DP failure	(b) (4)	(b) (4)	NA
Appearance	General	Product stability	(b) (4)	Release testing, instructions in package insert and med guide	NA
pH	General	DP failure	(b) (4)	Release testing	NA
Particulate matter	General	Immunogenicity, patient safety	(b) (4)	Release testing, requires use of an in-line filter for administration, instructions in package insert and med guide	NA
Dose Uniformity	General	Inaccurate dosing	(b) (4)	Process Validation	NA

Volume	General	Process Failure	(b) (4)	Release	NA
Container closure			(b) (4)	Validation studies, release and stability testing (appearance, purity testing, visible particles, container closure integrity).	NA

a. Description

Kanuma drug product is a clear sterile solution for infusion. It is filled in 20ml single-use Type I (b) (4) glass 10R vials, capped with (b) (4) stoppers and sealed with aluminum crimp seals with a (b) (4) flip-off caps. Each vial contains 10 (b) (4) ml solution with 2mg/ml sebelipase drug substance (b) (4).

b. Summary of Product Design

Kanuma is a concentrated solution for intravenous infusion (b) (4) at 1 mg/kg body weight. The dose can be raised to 3mg/kg based on clinical response. Clinical study data support this dosing scheme. Based on patient's body weight, Kanuma is diluted (b) (4) and the diluted Kanuma can be stored for (b) (4) 24 hours at 2 – 8°C. Diluted Kanuma solution is administered via an infusion bags (b) (4). A low protein binding 0.2µm in-line filter must be used for infusion. A table in the package insert instructs health care providers regarding the amount of Kanuma that is to be added to the infusion bags (b) (4). In-use stability study results indicate that Kanuma is stable for up to (b) (4) hours after dilution.

c. List of Excipients

Kanuma (20mg/10ml) is formulated with 15.2mg/ml Trisodium Citrate Dihydrate/Citric Acid, pH 5.9 and (b) (4) HSA.

d. Reference material(s) – The same reference material is used for DS and DP.

(b) (4)

e. Manufacturing Process

(b) (4)

- f. Container Closure
 DP is stored in 20ml glass type I vials that are sealed with 13mm (b) (4) stoppers with (b) (4) coating. The product is sensitive to light, and there are instructions in the package insert advising to protect the product from light. Synageva has requested a 24 month expiration dating when stored at 2 – 8°C. The request is supported by 24 months of long-term stability data from 4 phase III lots and limited stability data from process validation lots under long-term and accelerated conditions. Because physicochemical comparability between the phase III and commercial lots has been demonstrated, the long-term stability data from phase III lots justify the requested expiry dating.

- g. List of co-packaged components, if applicable – not applicable

D. Novel Approaches/Precedents - None

E. Any Special Product Quality Labeling Recommendations – None

F. Establishment Information

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
Egg white harvest & testing	Synageva BioPharma 150 Ben Burton Road Bogart, GA 100 Industrial Drive Holden, MA	3009804853	No 483	Acceptable
		3011161897	8 item 483, District recommends OAI	Pending
DS manufacture, raw material and in-process testing, bioburden and endotoxin release testing,	(b) (4)	(b) (4)	12 item 483, see primary review for issues	Acceptable
Release and stability Testing of UDS, DS and DP			Not inspected during the review cycle.	NAI (last inspection (b) (4))
Analytical Test of Drug Substance			Not inspected during the review cycle.	NAI (last inspection (b) (4))
Adventitious Agent testing			Not inspected during the review cycle.	NAI (last inspection (b) (4))
				VAI (last inspection (b) (4))

		(b) (4)		
Adventitious Agent testing			Not inspected during the review cycle.	NAI (last inspection (b) (4))
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INSPECTIONAL OBSERVATIONS	FINAL RECOMMENDATION
DP Manufacturer and sterility testing		(b) (4)	OAI and Withhold approval recommended by District Inspectors	Pending
Release and stability Testing of UDS, DS and DP			Not inspected during the review cycle.	NAI (last inspection (b) (4))
DP Packaging and Labeling			Not inspected during the review cycle.	NAI (last inspection (b) (4))
DP Packaging and Labeling			Not inspected during the review cycle.	NAI (last inspection (b) (4))

G. Lifecycle Knowledge Management – phase 4 plans can be described here

a. Drug Substance

- i. Protocols approved – None
- ii. Outstanding review issues/residual risk: As a breakthrough product, sebelipase DS manufacturing process development and physicochemical characterization are conducted under an abbreviated program. The product is therefore not fully characterized. The current release and stability testing, while sufficient to ensure safety and efficacy, can be further enhanced to provide comprehensive controls for product consistency. The following items are listed as PMC of which the sponsor can address as they learn more about the molecule and the process: 1) enzyme kinetics assays with a natural substrate, 2) quantitative assessment of its affinity to receptors, 3) amino acid modifications and accumulation of product related impurities during long term storage. In addition, the sponsor will revise release and stability specifications after manufacturing a sufficient number of lots.
- iii. Future inspection points to consider: At requests from FDA reviewers, Synageva has revised the control limits for DS and DP processes that align to the range followed during its process validation campaigns in the BLA. Inspectors should check if the batch records are revised accordingly and if all parameters are within the approved range.

b. Drug Product

- i. Protocols approved – None
- ii. Outstanding review issues/residual risk – The current testing method for accumulation of product related degradation products is not sensitive to detect degradants a ^{(b) (4)} of total product. The sponsor should enhance the assay as a PMC. Additionally, DP specifications acceptance criteria were established with a small data set. These need to be reevaluated and revised if necessary once a suitable number of lots are manufactured.
- iii. Future inspection points to consider – same as for DS.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
Product Type				
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material		X	
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced	X		
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other		X	
Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (# _____)		X	
16.	Comparability Protocol(s)		X	
17.	End of Phase II/Pre-NDA Agreements tem)		X	
18.	SPOTS (Special Products On-line Tracking System)		X	
19.	USAN Name Assigned	X		
20.	Other		X	
Quality Considerations				
21.	Drug Substance Overage		X	
22.	Design Space	Formulation		X
23.		Process		X
24.		Analytical Methods		X
25.		Other		X
26.	Other QbD Elements		X	
27.	Real Time Release Testing (RTRT)		X	
28.	Parametric Release in lieu of Sterility Testing		X	
29.	Alternative Microbiological Test Methods		X	
30.	Process Analytical Technology in Commercial Production		X	
31.	Non-compendial Analytical Procedures	Drug Product	X	
32.		Excipients		X
33.		Drug Substance	X	
34.	Excipients	Human or Animal Origin	X	
35.		Novel		X
36.	Nanomaterials		X	
37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other		X	

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/s/

JUHONG LIU
06/19/2015

DAVID M FRUCHT
06/22/2015

BLA STN 125561

KANUMA (sebelipase alfa)

Synageva BioPharma

**Office of Biotechnology Products
Division of Biotechnology Review and Research – II**

**Reviewers: Christopher Downey, PhD (Drug Substance)
Arulvathani Arudchandran, PhD (Drug Product)
Simon Williams, PhD (Analytical Procedures and
Validation of Analytical Procedures)**

ATL Reviewer: Juhong Liu, PhD

OBP CMC Review Data Sheet

1. **BLA#:** STN 125561 ([\\cdsesub1\evsprod\BLA125561](#))
2. **REVIEW DATE:**
3. **PRIMARY REVIEW TEAM:**
 - Medical Officers:** Lauren Weintraub (early-onset indication)
Juli Tomaino (late-onset indication)
 - Pharm/Tox:** Tamal Chakroborti
 - Product Quality:** Christopher Downey (Drug Substance)
Arulvathani Arudchandran (Drug Product)
Simon Williams (Analytical Procedures)
 - Immunogenicity:** Joao Pedras-Vasconcelos
 - Quality Micro:** Bo Chi (Drug Substance)
Coleen Thomas (Drug Product)
 - Clinical Pharmacology:** Jing Fang
 - Statistics:** Yeh-Fong Chen
 - OBP Labeling:** Jibril Abdus-Samad
 - RPM:** Kevin Bugin

4. **MAJOR GRMP DEADLINES**
 - Filing Meeting:** December 17, 2014
 - Mid-Cycle Meeting:** April 14, 2015
 - Late-Cycle Meeting:** July 8, 2015
 - Wrap-Up Meeting:** July 28, 2015
 - Primary Review Due:** June 8, 2015
 - Secondary Review Due:** June 22, 2015
 - CDTL Memo Due:** August 7, 2015
 - PDUFA Action Date:** September 8, 2015

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	February 12, 2014
Teleconference 1	January 9, 2015
Information Request #1	December 19, 2014
Information Request #2	January 10, 2015
Information Request #3 (Filing letter with Review issues and additional IR items)	February 20, 2015
Information Request #4	March 23, 2015
Information Request #5	April 24, 2015
Information Request #6	May 15, 2015

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 125561/0003 (original CMC section)	November 21, 2014	yes
STN 125561/0008 (response to IR #1; Q5)	January 5, 2015	yes
STN 125561/0010 (response to IR #1; Q4)	January 8, 2015	yes
STN 125561/0013 (response to IR #1; Q1 – 3)	January 9, 2015	yes
STN 125561/0014 (response to IR #2)	January 12, 2015	yes
STN 125561/0020 (response to IR #3; Review Issue 3g and IR items 2, 5, 7, 8, and 9)	March 13, 2015	yes
STN 125561/0025 (response to IR #3; Review Issues 3b and 3c)	March 20, 2015	yes
STN 125561/0030 (response to IR #3; Review Issues 3a, 3d, 3e, 3f, and IR items 4, 6)	March 30, 2015	yes
STN 125561/0032 (response to IR #4)	April 6, 2015	yes
STN 125561/0047 (response to IR #5)	May 15, 2015	yes
STN 125561/0053 (response to IR #6)	May 29, 2015	yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: KANUMA
- b. Trade Name: KANUMA
- c. Non-Proprietary/USAN: sebelipase alfa
- d. CAS name: not established
- e. Common name: sebelipase alfa
- f. INN Name: sebelipase alfa
- g. Compendial Name: not established
- h. OBP systematic name:
- i. Other Names: SB-102

8. PHARMACOLOGICAL CATEGORY: hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme

9. DOSAGE FORM: single-dose sterile liquid solution for infusion

10. STRENGTH/POTENCY:

- (i) The concentration/strength of the Drug Product: 2 mg/mL (20 mg per 10 mL vial)
- (ii) Type of potency assays: enzymatic activity

11. ROUTE OF ADMINISTRATION: intravenous (IV) infusion

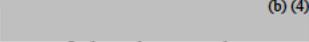
12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)

 (b) (4)	yes	No review required as all the relevant information related to the manufacture of this product was in the BLA, and the facility was evaluated during a pre-approval inspection.
	yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
	yes	No review required as all the relevant information related to compatibility with the product was in the BLA.

13. INSPECTIONAL ACTIVITIES

OBP personnel participated in the following inspections:

- 1) An inspection of Synageva BioPharma in Holden, MA was conducted January 20 – 21, 2015.  (b) (4) Three FDA personnel performed the inspection: Darin Wieggers (Office of Regulatory Affairs), Brinda Dass (Center of Veterinary Medicine), Malini Wileman (Center of Veterinary Medicine), Harlan Howard (Center of Veterinary Medicine), and Joao Pedras-Vasconcelos (CDER, Office of Biotechnology Products). No Form FDA 483 was issued to the firm at the end of the inspection.
- 2) A pre-approval inspection of  (b) (4) was conducted  (b) (4). This facility conducts commercial downstream manufacture of the drug substance; at this facility,  (b) (4). Three CDER personnel performed the inspection: Bo Chi (Office of Process and Facilities, Division of Microbiology Assessment), Christopher Downey (Office of Biotechnology Products), and Simon Williams (Office of Biotechnology Products). Eleven observations were noted in the 483 form issued at the conclusion of the inspection. The observations are stated below. The sponsor's response to these observations is pending. From an OBP perspective, none of these issues preclude approval.

 (b) (4)

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(b) (4)

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

None.

16. PRECEDENTS

This is the first CDER-regulated biotechnology product derived from a recombinant protein expressed in egg whites by genetically engineered chickens. FDA's Center of Veterinary Medicine (CVM) is responsible for regulating the genetically engineered animals used to produce the unpurified bulk material to be used in sebelipase alfa manufacture. The "first regulated article" for this product is the recombinant DNA construct in the genetically engineered chickens, and this article submitted to the FDA as a New Animal Drug Application (NADA) reviewed by CVM. The NADA must be approved prior to approval of the BLA for commercial therapeutic use of the sebelipase alfa derived from the chickens. In February 12, 2014 CMC pre-BLA meeting, CDER, CVM, and the sponsor agreed that the point of separation between the NADA and the BLA is "the point of collection of the contents of the eggs from the transgenic hens." Consequently, the contents of the eggs are the starting material for drug substance manufacture regulated under the BLA.

(b) (4)

(b) (4)

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, PhD Lead Primary Reviewer Division of Biotechnology Review and Research – II	See appended electronic signature
Arulvathani Arudchandran, PhD Primary Reviewer (Drug Product) Division of Biotechnology Review and Research – II	See Drug Product review, filed separately
Simon Williams, PhD Primary Reviewer (Assay Validation) Division of Biotechnology Review and Research – II	See appended electronic signature
Juhong Liu, PhD Team Leader Division of Biotechnology Review and Research – II	See appended electronic signature

B. CC Block

Recipient	Date
Kevin Bugin	Provided Electronically

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We (Christopher Downey, Arulvathani Arudchandran, and Simon Williams) recommend approval of this application, pending final negotiation of PMCs, resolution of outstanding information requests, and the sponsor's response to the 483 items from the facility inspections. Once submitted to the FDA, the review of these items will be filed as an addendum to this review.

The data submitted in this Biologics License Application support the conclusion that the manufacture of sebelipase alfa is adequately controlled and yields a product that is pure and potent. The product is free of known endogenous and adventitious infectious agents and meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. Therefore, we recommend that KANUMA (sebelipase alfa) be approved for human use under conditions specified in the package insert.

We recommend an expiration-dating period of ^{(b)(4)} months for sebelipase alfa drug substance when stored at a ^{(b)(4)} °C.

We recommend an expiration-dating period of 24 months for sebelipase alfa drug product when stored at 2 – 8°C.

Pending submission and review of the final negotiated specification limits, we recommend approval of the proposed release and shelf life specifications for sebelipase alfa substance and drug product.

II. List Of Deficiencies To Be Communicated

There are no CMC deficiencies precluding approval of this BLA. Potential deficiencies identified during the review cycle were communicated to the sponsor, and the sponsor's responses are incorporated into the review.

III. List Of Post-Marketing Commitments/Requirement

Post-Marketing Commitments (PMCs) are under negotiation with the sponsor. The final wording of the CMC Post-Marketing Commitments will be listed in an addendum to this review. The preliminary PMCs communicated to the sponsor are listed below:

- 1) Improve the SDS-PAGE purity test to increase the sensitivity and to more precisely quantify the levels of product-related impurities.

- 2) Implement the [REDACTED] ^{(b) (4)} test method for drug product release and stability specifications.
- 3) Implement an assay for uptake of sebelipase alfa into [REDACTED] ^{(b) (4)} for drug product release and stability specifications.
- 4) Develop and implement a [REDACTED] ^{(b) (4)} receptor binding assay for drug product release and stability specifications.
- 5) Improve the enzyme activity assay to increase the range of sebelipase alfa dilutions over which the assay will yield consistent values for specific activity.
- 6) Evaluate and revise as warranted all release and stability specifications after manufacture of sufficient commercial batches for meaningful statistical analyses.
- 7) 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.
- 8) 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.
- 9) Characterize the potential levels of [REDACTED] ^{(b) (4)} in the drug substance.
- 10) Develop and implement a drug substance release test to quantify the percent compositions of the N-terminal variants.
- 11) To improve control of the N-linked glycan profile, identify for the current HPAEC-PAD method peaks representative of [REDACTED] ^{(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 CE-LIF or HILIC characterization tests.
- 12) 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.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Synageva submitted a statement of exemption from preparing an environmental assessment under 21CFR section 25.31(c). This section provides for a categorical exclusion regarding an action on a BLA “when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.” sebelipase alfa is a recombinant version of the naturally occurring human protein lysosomal acid lipase and has metabolizes and degradation products the natural protein. Based on its expected production for all patients of (b) (4) per year for direct human use and a dilution of (b) (4) liters per day of material entering the sewage treatment system, Synageva calculates an expected introduction concentration (EIC) of (b) (4) ppb into the aquatic environment per year. Thus, the EIC at the point of entry into the aquatic environment will be far below 1 part per billion (ppb).

Reviewer comment:

This drug is analogue of a naturally occurring protein, human lysosomal acid lipase. The EIC calculation supports that approval of this product for commercial use will not significantly affect the concentration or distribution in the environment of lysosomal acid lipase, its metabolites, or its degradation products. The environmental assessment information provided is therefore acceptable to demonstrate that this product meets the criteria for categorical exclusion under 21 CFR Section 25.31(c).

V. Primary Container Labeling Review

The labeling is reviewed separately by Jibril Abdus-Samad, PharmD, Office of Biotechnology Products.

VI. Review Of Common Technical Document – Quality Module 3.2

The review of module 3.2.S, 3.2.A, and 3.2.R is below. Refer to the Table of Contents for the individual sections for these CTD modules.

Module 3.2.P is reviewed separately by Arulvathani Arudchandran, PhD, Office of Biotechnology Products.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The immunogenicity assays (Module 5.3.1.4) are reviewed separately by Joao Pedras-Vasconcelos, PhD, Office of Biotechnology Products.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Sebelipase alfa is indicated as an enzyme replacement therapy to treat patients with lysosomal acid lipase (LAL) deficiency. Patients are dosed at either 1 or 3 mg sebelipase alfa per kg. The drug product is single dose vials containing 10 mL liquid product with the composition 2 mg/mL sebelipase alfa formulated in a pH 5.9 (b) (4) solution with (b) (4) human serum albumin. (b) (4)

(b) (4) Sebelipase alfa is purified from the whites of eggs laid by genetically engineered chickens.

S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

KANUMA (sebelipase alfa) is a recombinant human lysosomal acid lipase (rhLAL). The company code for the protein during development was SBC-102, and some documents in the application refer to the enzyme by this name.

The following is the provided nomenclature for sebelipase alfa (adapted directly from the submission):

INN Name: sebelipase alfa

Chemical Abstract Service (CAS): 1276027-63-4

Chemical Name(s): recombinant human lysosomal acid lipase (rhLAL)

Company or Laboratory Code: SBC-102

USAN Name: sebelipase alfa

Other Non-Proprietary Names: esterase, cholesterol (human gene LIPA); lysosomal acid lipase (human gene LIPA)

Anatomical Therapeutic Classification (ATC) Code: A16AB14 sebelipase alfa

3.2.S.1.2 Structure

Sebelipase alfa is a (b) (4) monomeric glycoprotein with a molecular weight of (b) (4) 55 kDa measured by electrospray mass spectrometry (EMS). (b) (4)



There are 6 N-linked glycosylation sites in the rhLAL amino acid sequence.



Figure 2:



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/s/

CHRISTOPHER D DOWNEY
06/09/2015

SIMON WILLIAMS
06/09/2015

JUHONG LIU
06/09/2015

BLA STN 125561

KANUMA (sebelipase alfa)

Synageva BioPharma

**Office of Biotechnology Products
Division of Biotechnology Review and Research – II**

**Reviewers: Christopher Downey, PhD (Drug Substance)
Arulvathani Arudchandran, PhD (Drug Product)
Simon Williams, PhD (Analytical Procedures and
Validation of Analytical Procedures)**

ATL Reviewer: Juhong Liu, PhD

DRUG PRODUCT: Arulvathani Arudchandran, Ph.D., DBRR II, OBP, OPQ, CDER.

3.2.P.1 Description and Composition of the Drug Product

Sebelipase alfa drug product is recombinant human lysosomal acid lipase (rhLAL) purified from egg white of transgenic *Gallus* species. The drug product has been developed as an enzyme replacement therapy (ERT) for lysosomal acid lipase (LAL) deficiency, resulted from the lysosomal accumulation of cholesteryl esters and triglycerides in various tissues of the body. Sebelipase alfa catalyzes the hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids in targeted cells of lysosomes.

The drug product is supplied as sterile liquid in a single use Type I (b)(4) glass 10 R vials with (b)(4) stoppers and aluminum crimp seals with a (b)(4) flip-off caps.

The administration of the drug is through intravenous infusion with the proposed starting dose of 1 mg/kg once weekly. The sponsor also administered 3 mg/kg once weekly during clinical studies and proposed a dose escalation up to 3 mg/kg once weekly during the treatment.

Composition:

Table 1: Dosage Form Composition

Component	Quality Standard	Function	Quantity per vial	Amount per mL
Sebelipase alfa	In-house standard	Active Ingredient	(b)(4)	2 mg
Trisodium Citrate Dihydrate	USP, PhEur, JP		(b)(4)	13.7 mg
Citric Acid Monohydrate	USP, PhEur, JP			1.57 mg
Human Serum Albumin	USP, PhEur, JP			10 mg
				(b)(4)

(b)(4). The sponsor indicated that “prior to administration, the concentrated solution should be further diluted with 0.9% Sodium Chloride”. The dosing of the drug product is based on the weight of patients. The administration is via infusion bags (b)(4)

Reviewer comment:

(b)(4) All excipients are compendial and no new excipients or preservatives were added in the DP formulation. (b)(4)

(b)(4) the over-fill is within the recommended USP<1151> acceptance limits. According to USP<1151>, limited excess volumes are permitted for the withdrawal of the labeled volume from vials and ampules. The studies performed to indicate the stability of the drug product in infusion bags, (b)(4) and in the container closer system are reviewed under pharmaceutical development, stability, and under container closer system sections.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

[Redacted] (b) (4)

3.2.P.2.1.2 Excipients

Table 1: Excipients in sebelipase alfa Drug Product

Excipient	Concentration	Grade
Trisodium Citrate Dihydrate	13.7 mg/mL	USP, PhEur , JP
Citric Acid Monohydrate	1.57 mg/mL	USP, PhEur, JP
Human Serum Albumin	10 mg/mL	USP, PhEur, JP

Reviewer comment:

All excipients, trisodium citrate dihydrate, citric acid monohydrate, and human serum albumin used in the formulation are compendial and the sponsor specified the concentration of each excipient present in the final formulated drug product. Information provided is adequate to indicate that the sponsor has control over the quality and quantity of each component of the DP. No safety issues are identified with the excipients of the sebelipase DP formulation.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Sebelipase alfa DP is formulated as 2 mg/mL in Trisodium Citrate Dihydrate (13.7 mg/mL), Citric Acid Monohydrate (1.57 mg/mL), and in Human Serum Albumin (HSA) (10 mg/mL) at pH 5.9.

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/s/

ARULVATHANI P ARUDCHANDRAN
06/08/2015

JUHONG LIU
06/08/2015