



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

Date: October 27, 2009

To: To File (BLA STN 125325/0)

From: Douglas J. Frazier, Biologist, CBER/DH/LPD/HFM-345

Through: Dorothy Scott MD, Chief, CBER/DH/LPD/HFM-345

CC: Cherie Ward-Peralta, RPM, HFM-380

Applicant: Kamada, Ltd.

Product: Alpha-1 Proteinase Inhibitor, Intravenous (Human)
Trade name: Kamada-API

Subject: Midcycle Review, original BLA

Recommendation

Based on the specific CMC topics assigned, this original BLA is recommended for approval. The dating and storage proposals are supported by the provided stability study results, and the final-product QC assay validations reviewed are acceptable.

It should be noted, however, that Kamada has volunteered a post-marketing commitment (PMC) in Section 3.2.S.7.2 of the original BLA submission (p. 5 below), which states that -----(b)(4)-----, with any deviations submitted as required under 21 CFR 600.14. This PMC should be incorporated into the Approval Letter for Kamada-API.

Background Summary

Kamada Ltd., located in Beit Kama, MP Negev 85325, Israel, has submitted an original BLA for their plasma-derived biological drug product Alpha-1 Proteinase Inhibitor, Intravenous (Human), hereafter referred to as API or by the proposed trade name Kamada-API, for the indication of chronic augmentation and maintenance therapy in individuals with congenital deficiency of API and clinical evidence of emphysema. The active raw material, the human plasma fractionation intermediate -----(b)(4)----, is manufactured by -----(b)(4)----- . This BLA submission is supported by clinical data developed under IND-BB -(b)(4)- vial the Phase I and Phase II/III studies API-001 and API-002 respectively.

Clinical summary

Kamada-API is intended for chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1-proteinase inhibitor (also known as API Deficiency or AAT Deficiency) and clinical evidence of emphysema. API deficiency is a chronic, autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of API. API belongs to the family of serine protease inhibitors (PIs) and is primarily produced in the liver, secreted into the circulation and diffuses passively into the lungs. The most important physiological function of API is the protection of pulmonary tissue from aggressive proteolytic enzymes, primarily neutrophil elastase (NE). API deficiency is found in almost all populations but is most prevalent in Caucasians of northern and western European descent and is rare in Mediterranean, Asian and African populations.

Emphysema associated with API deficiency is most frequently diagnosed in the third to fourth decades of life and is manifested by chronic lung inflammation, poor lung function, and frequent exacerbations of chronic bronchitis and is associated with a significantly reduced life expectancy. API acts in the lungs by inhibiting serine proteases such as NE, which is capable of degrading protein components of the alveolar walls and which is chronically present in the lung. Individuals with API deficiency have reduced protection against NE released by neutrophils in their lower respiratory tract. Severe forms of API deficiency are thus frequently associated with slowly progressive, moderate to severe emphysema.

Product characterization summary

Kamada-API is prepared from human plasma obtained from US-licensed plasma collection centers. Plasma is fractionated using a modified version of the cold ethanol fractionation process and the API is then isolated and purified by a series of ----(b)(4)---- chromatographic procedures. The manufacturing process for Kamada-API includes two steps specifically designed to remove or inactivate viruses. i.e., nanofiltration (NF) through a 15 nm filter and solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TnBP) and Polysorbate 80 (Tween 80).

Kamada-API DS is a clear and colorless to yellow-green, non-sterile buffered solution of pH -(b)(4)- containing ----(b)(4)--- active API. The drug substance (DS) has a specific activity of -----(b)(4)----- --- active API/mg protein. The specific activity of the Kamada-API DS is determined by -----(b)(4)-----

method. Kamada-API is formulated as a 2% solution of API in phosphate-buffered saline and is presented in single-use vials containing 50 ml of ready-to-use solution. The recommended dosage of Kamada-API is 60 mg/kg body weight administered once weekly by intravenous infusion.

------(b)(4)-----

Supplement Review Summary

The review tasks undertaken herein include assessments of product stability and of validation studies for drug-product characterization assays for excipients and impurities, not including assays for potency, pyrogen, and sterility.

Stability

Kamada notes: "The stability-indicating product attributes are API activity and -----(b)(4)-----
-----. The activity of API is determined by an --(b)(4)--- assay using -----(b)(4)-----
------. This reviewer agrees that these are the two
significant stability-indicating parameters, given that no significant change is seen in the other tested
parameters, i.e.: appearance, pH, -----(b)(4)-----, pyrogens, sterility, extractibles volume.

Drug Substance

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

Drug Product

Based on the submitted stability data, Kamada makes the following conclusion statements:

- A storage period of 24 months is recommended for Kamada-API DP at $5\pm3^{\circ}\text{C}$.
- Kamada-API should contain -----(b)(4)----- forms at release to market to ensure meeting of the -(b)(4)- shelf life limit after 24 months.
- Kamada-API is stable after -----(b)(4)-----.
- Kamada-API is stable when stored at (b)(4)-----

- Kamada-API is -----(b)(4)---.

Proposed dating period: 24 months at $5\pm3^{\circ}\text{C}$

Based on the combined stability from clinical and conformance drug-product lots at 5°C and -(b)(4)-
(Section 3.2.P.8.3 STABILITY DATA) analyzed by SAS JMP via linear regressions with 95% two-sided
confidence limits (Appendix 2), Kamada-API shows no significant change in protein concentration by
--(b)(4)-- assay or pH. However, -----(b)(4)-----
------. These trends are more marked at -(b)(4)- (see plots, Appendix 4).

Conclusions: the proposed dating period of 24 months at $2-8^{\circ}\text{C}$ is acceptable based on the submitted data.

------(b)(4)-----

Two (2) Pages Determined to be Non-Releasable: (b)(4)

Excipient and Impurity assays

Kamada states that “The analytical methods used to test the API Drug Product (DP) have been validated in accordance with the ICH Topics Q2A, “Text on Validation of Analytical Procedures,” and Q2B, “Validation of Analytical Procedures: Methodology”. All of the validations were performed according to approved validation protocols.”

These assays comprise the following (from Section 3.2.P.5.1 Specifications, Table P.5.1-1, Kamada-API Drug Product Specifications and Release Tests):

Excipients

Sodium	----- (b)(4) -----	----- (b)(4) -----	System precision, method precision, intermediate precision, accuracy, linearity, range, specificity and robustness.
Chloride (as NaCl)	-- (b)(4) --	----- (b)(4) -----	Method precision, intermediate precision and specificity.
Phosphate	---- (b)(4) ---	----- (b)(4) -----	System precision, method precision, intermediate precision, accuracy, linearity, range, specificity and robustness.

Purity and Impurities

----- (b)(4) -----	----- (b)(4) -----		Accuracy, specificity, repeatability, intermediate precision, reproducibility, linearity, limit of detection, limit of quantitation, range and robustness.
		-- (b)(4) --	
Residual TnBP ¹	---- (b)(4) ----	--- (b)(4) -----	Specificity and limit of detection
Residual Tween 80 ¹	---- (b)(4) ----	--- (b)(4) -----	Method precision, specificity and limit of detection
----- (b)(4) -----	---- (b)(4) ----	--- (b)(4) -----	Specificity and limit of detection
		----- (b)(4) -----	

Sodium

----- (b)(4) -----

Chloride

----- (b)(4) -----

Kamada notes:

“The chloride content of Kamada-API DP is calculated as sodium chloride according to current - (b)(4) -
----- for sodium chloride and sodium chloride injection... The solution

containing sodium chloride -----(b)(4)-----...Specificity was determined by -----(b)(4)-----
----- . The acceptance criterion was a recovery of -----(b)(4)----- was obtained, thus meeting the acceptance criterion.”

Reviewer’s comments – chloride content is a quantitative parameter with a specific and narrow acceptance range (-(b)(4)-), not a limit parameter with a one-sided specification. So in principle the assay should be validated for linearity, robustness, etc. However the range is very narrow, while in IG products at least, instability induced by excess sodium chloride occurs progressively but gradually as levels increase above approximately 10 mEq/L. So it does not appear necessary that Kamada provides additional assay validation data, since Kamada-API stability is not exquisitely sensitive to sodium chloride concentration in the proposed acceptance range.

Phosphate

(b)(4)-----

[
--(b)(4)--
]

----- (b)(4) -----

Reviewer’s comments – the assay performance is satisfactory.

Tween 80

(b)(4)-----

[
--(b)(4)--
]

Five (5) Pages Determined to be Non-Releasable: (b)(4)