



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

To: File STN 125613/0

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Through: Dorothy Scott, MD; CBER/OTAT/DPPT/PDB, 240-402-8236

CC: Jiahua Qian; CBER/OTAT/DRPM/RPMBI

Applicant: Kamada Ltd.

Product: Rabies Immune Globulin (Human)
Proprietary name: KEDRAB
Kamada's current name: Kamada-HRIG [Human Rabies Immune Globulin],
Solution for Injection

Subject: Original BLA, CMC – pharmaceutical development, manufacture, DS and DP
characterization, specifications

Recommendation: Approval with the following CMC PMCs:

1. Kamada commits to perform full scale validation on (b) (4) full scale lots, (b) (4) of the critical operating parameter ranges and times, including the (b) (4) for the (b) (4) step, with in-process testing for (b) (4) at each manufacturing step.

Kamada will submit a validation protocol outlining the operating parameters for each lot, and (b) (4) tests along with the acceptance criteria, as a Post Marketing Commitment – Product Correspondence prior to manufacture of these lots. The final report will be submitted as a Post Marketing Commitment – Final Study Report by August 31, 2018.

These lots will be placed on stability and a final stability report will be submitted as a Postmarketing Commitment – Final Study Report by February 28, 2022.

Final Protocol Submission: October 31, 2017

Final Report Submission: August 31, 2018

Final Stability Report Submission: February 28, 2022

2. Kamada commits to perform validation of an improved (b) (4) method and determine the (b) (4) specifications accordingly.

A final validation report as well as the method SOP and specifications will be submitted to FDA by October 31, 2017, as a CBE-30 Supplement. In case a method different from that provided by CBER will be chosen for the validation, a full characterization of the (b) (4) will be performed.

The final method specification will include (b) (4).

The submission will include the acceptance criteria for (b) (4).

Final Report Submission: October 31, 2017

Background

Other rabies immunoglobulin (RIG) products licensed by FDA are as follows:

- Rabies Immune Globulin (Human) Grifols Therapeutics 101144, 1974, Active
- Rabies Immune Globulin (Human) Sanofi Pasteur SA 103932, 2000 Active
- Rabies Immune Globulin (Human) Pasteur Merieux Serum et Vaccins, 101997, 1984, Revoked

Human Rabies Immunoglobulin (HRIG) background provided by Kamada:

- The formulation proposed for the US is (b) (4) to formulation of the product distributed in Israel since 2012.
- The product has been in use outside of the US for 10 years.
- Kamada-HRIG is approved in El Salvador, India, Israel, Mexico, Russia and Tailand.
- Kamada-HRIG is administered in named patient programs in Australia, Georgia and South Korea.
- Kamada-HRIG is prescribed to children in India, Israel, Russia and South Korea.
- Kamada-HRIG distributed or marketed in other countries has a wider range of pH values (5.0 – 7.2) compared to the product proposed for the US (5.0 – 6.0).
- Kamada-HRIG has been administered to more than 250,000 people. Kamada has not received any adverse reaction reports associated with the clinical use of the product.

Review

A proprietary name KEDRAB was found acceptable (FDA Letter dated 11/14/16), thus, I am using this product name in my memo.

KEDRAB indication is for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine.

KEDRAB is manufactured from human hyperimmune plasma of healthy donors who have been immunized with rabies and have developed high titers of rabies antibody.

Dose: 20 IU/kg

Labeled potency: 150 IU/mL

Formulation: 0.3M Glycine, pH 5.0-6.0, no preservative

Vials: 2 mL and 10 mL (b) (4) glass

Table 1. Composition of KEDRAB

| | Quantity per 1 mL | Quantity per vial | | Function |
|---------------------------------------|-------------------|-------------------|-------------------|---------------------------|
| | | 2 ml fill | 10 ml fill | |
| HRIG (Human Rabies Immunoglobulin) DS | 150 IU | 300 IU | 1500 IU | Active component |
| Glycine | 22.5 mg | 45 | 225 | Stabilizing agent |
| WFI (Water for Injection) | quantity to 1 ml | quantity to 2 ml | quantity to 10 ml | Solvent |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) | pH adjustments to 5.0-6.0 |

DP and DS Specifications

KEDRAB DP and DS testing was compared to other RIG product testing and was found acceptable with several modifications (details below).

Table 2. Comparison of assays used in RIG DS/DP testing

| (b) (4) | Kamada RIG DP Specs. | RIG Sanofi Pasteur STN 103932 | RIG Grifols* STN 101144 |
|---------|--|--|----------------------------|
| | Appearance: Clarity and Degree of Opalescence, Degree of Coloration, Visible Particles | Appearance | Appearance |
| | | (b) (4) | |
| | | | (b) (4) |
| | pH | pH | pH |
| | Extractable vol. | Extractable vol. | Vol. fill check |
| | Anti-Rabies potency | Potency (anti-rabies antibodies) | Rabies potency |
| | Glycine | Glycine | Glycine |
| | Protein conc. (b) (4) | Protein content (b) (4) | Protein conc. |
| | Protein composition (b) (4) | Protein composition (b) (4) | Protein composition |
| | (b) (4) | (b) (4) | (b) (4) |
| | Subvisible particles | | |
| | Residual TnBP** | | TNBP |
| | Residual Triton X-100** | | |
| | Sterility | Sterility | Sterility |
| | Pyrogen | Pyrogens | Pyrogen |
| | Bacterial endotoxins | Endotoxins | |
| | | | |
| | | Sodium | |
| | | | (b) (4) |
| | | | Sodium cholate |
| | | | (b) (4) |
| | | Abnormal toxicity 21 CFR 610.11 | Safety, 21 CFR 610.11 |
| | | Antibody content against hepatitis B virus antigen | |
| | | | |
| | Protein identity (b) (4) | Rabies immunoglobulin identification (b) (4) | Identity (b) (4) |
| | Identification by (b) (4) | (b) (4) | |

* Shelf-life specification

(b) (4)

Table 3. KEDRAB DP release specifications

| Test | Acceptance Criteria | Analytical Procedure |
|------------------------------------|--|---|
| General Characteristics Tests | | |
| Clarity and Degree of Opalescence | The solution is clear to slightly opalescent | Visual inspection (b) (4) |
| Degree of Coloration | The solution is colorless to pale yellow | Visual inspection (b) (4) |
| Visible Particles | May contain some protein particles | Visual inspection |
| pH | 5.0 – 6.0 | (b) (4) |
| Extractable volume | NLT 2 ml for the 2 ml vials NLT 10 ml for the 10 ml vials | (b) (4) |
| Subvisible Particles | For monitoring | (b) (4) |
| Identity | | |
| Protein Identity | The main component corresponds to IgG standard | Immunoelectrophoresis (Based on EP 0338) |
| Identification by (b) (4) | (b) (4) | (b) (4) |
| Content | | |
| Anti – Rabies Potency | 150 (b) (4) IU/ml | (b) (4) |
| Glycine Concentration | (b) (4) | (b) (4) |
| Protein Concentration | (b) (4) | (b) (4) |
| Purity & impurities | | |
| Protein Composition | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| Residual Triton X-100 ² | (b) (4) | (b) (4) |

| | | |
|----------------------------|---------|---------|
| Residual TnBP ² | (b) (4) | (b) (4) |
| Biological safety tests | | |
| Sterility | Sterile | (b) (4) |
| Pyrogenicity | Pass | (b) (4) |
| Bacterial Endotoxins | (b) (4) | (b) (4) |

¹ The assay is performed after packaging, in compliance with the 21 CFR 610.14 as recommended by us (see Amendment 32 dated 8/15/17).

The following tests and/or limits have been (are being) improved as a result of FDA discussions with Kamada: Clarity and Degree of Opalescence, Degree of Coloration (Dr. Olga Simakova, PDB, DPPT, OTAT), Visible Particles, Subvisible Particles (the assay added to the specifications for trending upon our request), (b) (4) (discussed by PDB together with Dr. Lokesh Bhattacharya's group, DBSQC), and Identification by (b) (4) (test performed after packaging added upon our request).

The final specifications were found acceptable. However, a development of a more sensitive assay for the (b) (4) is in progress and new specifications which will include (b) (4) an important stability parameter, will be established after the improved assay is validated (see PMCs, Amendment 33).

Particulate matter

A proposed specification for KEDRAB appearance included the following: "May contain some particles." Thus, during inspection, I discussed with Kamada the acceptance criteria for such a specification. Kamada provided a presentation "*Characterization and Identification of Proteinaceous Particles in Kamada-HRIG DS and DP Samples.*"

Kamada performed analysis of visible particles ((b) (4)) by visual inspection, isolation and identification by (b) (4) and characterization by (b) (4) methods. Analysis of subvisible particles ((b) (4)) was performed by light obscuration and analysis of aggregates ((b) (4)) by (b) (4). At the time of inspection, Kamada was in the process of determining how to follow product consistency with respect to visible particles. They performed 100% analysis of (b) (4) product lots. They found that (b) (4) of vials did not contain particles, (b) (4) contained (b) (4) particles and (b) (4) vials contained (b) (4) particles. No vials with MT (b) (4) particles were seen. No correlation between the filling process (the sequential vial number) and the number of proteinaceous particles per vial was found. The (b) (4) analysis showed that the major protein component of the particles is immunoglobulin. (b) (4) batches of DP and (b) (4) of (b) (4) were analyzed by (b) (4)

(b) (4) and the results pointed to the presence of polyamide material, indicative of protein. Analysis using (b) (4) suggested that the majority of particles were proteinaceous. Subvisible particle analysis by (b) (4) which is routinely performed for the product showed low particle counts. For (b) (4) lots of (b) (4) for which the results were provided the range of observed particles was (b) (4). For DP the ranges were (b) (4). The content of aggregates by (b) (4) appeared also low. The current specification for aggregates is (b) (4). After the inspection, Kamada continued the study, provided updated data and implemented visible particles testing performed at the (b) (4) stage (SOP TR-N-3A-034 *Visual Inspection of Product Vials*, Amendment 32) which will include testing of (b) (4) vials of 10 mL and (b) (4) vials of 2 mL with a limit of (b) (4). The current limit will be evaluated after examining (b) (4) additional product lots. Kamada also implemented a specific SOP for particulate count for product release which is a part of the appearance test (TR-N-1P-0001-05 *Testing of Visible Particles in Solution*, Amendment 27). They also included subvisible particle testing in the DP and stability testing (Amendment 27) and improved the method ((b) (4)) in response to our request (SOP TR-N-1P-5348-06, Amendment 32).

In addition, due to identification of (b) (4), which was visible by (b) (4) in some product lots, Kamada developed an (b) (4) assay that will be used to analyze the (b) (4) content in (b) (4) for trending. The method will be fully validated if a specification will be set. Kamada will evaluate if the test has a stability indicating impact and if it has, the test will be included in stability testing (Amendment 32).

Also, (b) (4) assay was implemented in (b) (4) testing. Assay discussed with Kamada by Dr. Olga Simakova, PDB, DPPT, OTAT and Dr. Mikhail Ovanesov, HB, DPPT, OTAT.

Table 3. KEDRAB DS release specifications

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

(b) (4)

DS manufacturers:

| Facility, Address | Responsibility |
|--|--|
| Kamada Ltd. Beit Kama MP Negev 8532500 Israel | Manufacturing Warehouse Quality Control Testing, including Microbial testing DS Batch Release DS batch data review and release for further processing Stability Testing |

(b) (4)

Contract laboratory for pyrogen testing (Form 356h):

(b) (4)

Contract laboratory for pyrogen and sterility testing (Form 356h):

(b) (4)

Contract laboratory for testing raw materials (Form 356h):

(b) (4)

Table 4. DS batch numbering system



Table 5. DP lot numbering system

| Code | A | A | X | XX | XX | XX | A |
|------------|--------------|--|-------------------------|---|--|---|--|
| Definition | Product Code | Production process and raw material | Product fill volume | Sequential fill number per product per year | Two digits for the month of production | Last two digits of the year of production | Letter to designate sequential packaging |
| Example | R for HRIG | A for US plasma and production process which includes Nanofiltration | 5 for 2 ml, 3 for 10 ml | 01 for first lot | 01 for January | 16 for 2016 | A,B,C etc. |

DS manufacturing

(b) (4)

[REDACTED] Kamada

stated that all blood collection centers adhere to the FDA and PPTA requirements.

(b) (4) manufacturer at (b) (4) and transported at (b) (4).

Deviations are reported to Kamada and resolved per 21 CFR 640.

A summary of controls of (b) (4)

[REDACTED]

DS process description:

(b) (4)

[REDACTED]

12 pages have been determined to be not releasable: (b)(4)

(b) (4)

Drug product

The major steps in the DP manufacturing process include:

(b) (4)

Since 2011, up to (b) (4) full/partial DS batches for the formulation of one KEDRAB lot can be pooled. Aside from the time needed for pooling several Kamada-HRIG DS batches and the validated (b) (4) size of the bulk formulated solution, no additional changes were made as an outcome of this manufacturing change.

The one conformance DP lot was formulated from (b) (4) DS batches in order to validate the use of more than (b) (4) for manufacturing, as part of the lot-to-lot consistency study. This lot was used in phase II/III clinical study (release data and stability data were provided).

A list of PPQ DS batches and DP lots formulated and filled in Suite #1 (validation of formulation and fill in Suite #1) is below:

(b) (4)

In-process and DP testing was performed and the lots were placed on accelerated and long-term stability. The operational parameters and quality attributes met the established limits. The DP lots met the release specifications. Deviations included a rejection of lot (b) (4), which was intended to be part of the PPQ study; however, it was rejected due to (b) (4). The (b) (4) result was observed for a (b) (4) sample. The root cause was identified ((b) (4)) and led to rejection of the lot.

KEDRAB is filled in (b) (4) glass vials (b) (4) and sealed with (b) (4) rubber stopper or (b) (4)

(b) (4) rubber stopper, which is bottom-side (b) (4) coated, top surface (b) (4) coated.

For the following lots 36 months of stability data is available at long term storage conditions and 6 months of accelerated data:

(b) (4)

A combination of (b) (4) vials and (b) (4) stopper has not been studied; thus, Kamada will place the (b) (4) lot manufactured with this container closure combination on stability (Amendment 32).

Conclusion: KEDRAB composition and manufacturing control was found acceptable for licensure. The additional work that Kamada will do, i.e., the manufacture of additional product lots covering the operating ranges with additional (b) (4) characterization, development of a more sensitive (b) (4) method for more sensitive determination of (b) (4), developing a specification for (b) (4) and trending (b) (4) such as (b) (4) and visible particles will enhance the control of the product quality and facilitate evaluating manufacturing consistency in the future.

Recommendation: Approval with PMCs