



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

PHARMACOVIGILANCE PLAN REVIEW

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To: BLA 125613/0 File

Applicant: Kamada Ltd.

Product: Rabies Immune Globulin (Human)

Proposed Indication: Passive, transient post-exposure prophylaxis of rabies
infection, when given immediately after contact with rabid or
possibly rabid animal and in combination with rabies vaccine

Submission type/number: BLA 125613/0

Submission Receipt Date: August 29, 2016

Action Due Date: August 29, 2017

1. Objectives/Scope

The sponsor, Kamada Ltd., has submitted an original BLA 125613/0 seeking initial licensure for the product, Kamada-HRIG (proposed trade name, KEDRAB), a human rabies immune globulin product indicated for passive, transient postexposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine. The purpose of this review memorandum is to evaluate the sponsor's proposed plan for postmarketing safety monitoring and to identify potential safety concerns associated with the use of Kamada-HRIG that may need to be addressed through additional postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be approved.

2. Materials reviewed include:

- BLA cover letter
- Pharmacovigilance Plan
- Proposed package insert
- Medical Literature
- Summary of clinical safety
- Verbal and written input from other discipline reviewers on the BLA team

3. Introduction

2.1 Product description including sought indication and use

Kamada-HRIG (proposed trade name, KEDRAB) is a human rabies immune globulin product indicated for passive, transient postexposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine. It should be administered as part of the PEP regimen in patients exposed to animals suspected of being rabid, provided the patient was not vaccinated with rabies vaccine at an earlier date. The dosage proposed is one intramuscular administration of 20 international units (IU) per kilogram.

Kamada-HRIG (b) (4) is manufactured from human hyperimmune plasma of healthy adult donors who have been immunized with rabies vaccine and have developed high titers of rabies antibody, and is fully compliant with FDA and EU regulations for human blood products. The manufacturing process includes a (b) (4) and three viral inactivation steps: solvent-detergent (S/D) treatment, heat treatment and nanofiltration.

Kamada-HRIG drug product is a sterile, nonpyrogenic liquid preparation enriched with antirabies immunoglobulins (not less than 95% protein as IgG). It has a labeled potency of 150 IU/mL. The product is stabilized with 0.3 M Glycine at a pH range of

5.0-6.0 and does not contain preservatives. Kamada-HRIG is supplied in 2 mL and 10 mL (b) (4) glass vials as a ready-to-use solution.

2.2 Regulatory background and international experience

This is an original BLA submission. As such, Kamada-HRIG has not been marketed in the US. Other human rabies immune globulin products (HyperRAB S/D and Imogam Rabies-HT) are approved and marketed in the US. Kamada-HRIG has been in use outside of the US for 10 years. It is approved in El Salvador, India, Israel, Mexico, Russia and Thailand. In three additional countries, Australia, Georgia, and South Korea, Kamada-HRIG is administered in named patient programs. Kamada-HRIG is prescribed to children in India, Israel, Russia and South Korea. The formulation of Kamada-HRIG proposed for approval in the US is (b) (4) to the formulation of the product distributed in Israel since 2012. Kamada-HRIG distributed or marketed in other countries has a wider range of pH values (5.0-(b) (4)).

To date, Kamada-HRIG has been administered to more than 250,000 individuals worldwide. Kamada has not received any adverse reaction reports associated with the clinical use of Kamada-HRIG.

2.3 Public health context

Rabies is a zoonotic disease caused by RNA viruses in the Family *Rhabdoviridae*, Genus *Lyssavirus*. Unique among infectious diseases, rabies infection is almost universally fatal once symptoms appear. The disease presents as an acute, progressive encephalomyelitis. Human infection typically occurs when an infected animal transmits the virus to man through saliva via a bite, scratch, contact with mucous membranes such as the eyes, nose or mouth, or licking of a wound.

Human rabies cases in the US are rare, with only 1 to 3 cases reported annually. Thirty-four cases of human rabies have been diagnosed in the US since 2003, and 10 of these individuals contracted rabies outside of the US. The number of human deaths in the US attributed to rabies has declined since the 1970s, thanks to animal control and vaccination programs, the availability of modern biological products for use in PEP against rabies infection, and successful outreach programs.

Rabies vaccination programs have eliminated domestic dogs as reservoirs of rabies in the US, although between 80 and 100 dogs and >300 cats are diagnosed with rabies each year. These animals usually have not been vaccinated against rabies, and are infected by wildlife.

In the context of a very high case fatality rate, PEP with HRIG and rabies vaccine is vital. There are no contraindications against administering HRIG and rabies vaccine in patients exposed to rabies virus.

2.4 Clinical safety

The three studies with clinical safety data are summarized below:

Clinical Studies ok Kamada-HRIG*

Study Number (link to CSR) Phase Location CRFs Provided?	Type of Study Study Status	Treatment Groups Duration of Follow-up for Each Subject	Number of Subjects per Treatment Group Total Number of Subjects	Study Subjects
Controlled Studies				
Study 003 Phase 2/3 United States CRFs provided for withdrawals and SAEs as applicable	Randomized, double-blind, single-dose, non- inferiority study	<ul style="list-style-type: none">Kamada-HRIG 20 IU/kg as a single IM injection on Day 0 and rabies vaccine (RabAvert) (≥ 2.5 IU/mL) 1.0 mL IM on Days 0, 3, 7, 14 and 28; orComparator HRIG 20 IU/kg as a single IM injection on Day 0 and rabies vaccine (RabAvert) (≥ 2.5 IU/mL) 1.0 mL IM on Days 0, 3, 7, 14 and 28	59	Healthy volunteer subjects Mean age 44.8 years (range: 18 to 72 years) 63.6% female / 36.4% male 93.2% white, 3.4% black or African-American; 0.8% Asian; 2.5% other race 97.5% not Hispanic or Latino Mean weight 75.93 kg (range: 52.9 to 93.6 kg)
	Completed	Subjects were followed for 185 days (6 months) after Day 0.	59	
		Total: 118		
Study 24061 Phase 1 Israel CRFs provided for withdrawals and SAEs as applicable	Randomized, double-blind, placebo-controlled, single-dose, one- period, parallel- group study	<ul style="list-style-type: none">Kamada-HRIG 20 IU/kg as a single IM injection on Day 0 and rabies vaccine (Rabipur) by IM injection on Days 0, 7 and 28; orNormal saline 0.133 mL/kg as a single IM injection on Day 0 and rabies vaccine (Rabipur) by IM injection on Days 0, 7 and 28	8	Healthy volunteer subjects Mean age 27.3 years (range: 19 to 35 years) 43.7% female / 56.3% male 100% white Mean weight 69.7 kg (range: 53.4 to 110.3 kg)
	Completed	Subjects were followed for 42 days after Day 0.	8	
		Total: 16		
Crossover Study				
Study 23630 Phase 1 Israel CRFs provided for withdrawals and SAEs as applicable	Randomized, double-blind, single-dose, 2-period crossover study	<ul style="list-style-type: none">Kamada-HRIG 20 IU/kg as a single IM injection, andBayRab 20 IU/kg as a single IM injection	24	Healthy volunteer subjects Mean age 27.0 years (range: 18 to 37 years) 84.6% male / 15.4% female 100% white Mean weight 66.9 kg (range: 50.3 to 89.0 kg)
	Completed	There was at least a 21-day washout period between administrations. The total duration of follow-up was 42 days from the first study treatment.	25	
		Total: 26; 23 of these subjects received both treatments		

*BLA "Summary of Clinical Safety;" page 7

The 91 subjects receiving Kamada-HRIG in the above studies all received a single 20 IU/kg IM dose. The age and gender breakdown were as follows:

Clinical Trial Exposure to Kamada-HRIG by Age Group and Gender*

Age Group (years)	Number of Persons Exposed	
	Male	Female
18 to <30	22	15
≥ 30 to <40	10	11
≥ 40 to <50	5	4
≥ 50 to <60	3	6
≥ 60 to <70	6	9
Total	46	45

*BLA Pharmacovigilance Plan in 'Risk Management' document; page 6

The sponsor is planning to conduct an open-label study of Kamada-HRIG product 20 IU/kg of subject weight, administered with active rabies vaccine in children exposed or possibly exposed to rabies is planned. In this planned study, a total of 30 children between 0 months and <17 years of age are to be treated.

2.5 Non-clinical safety

The nonclinical data, which include data from a single nonclinical toxicology study of Kamada-HRIG product and an examination of the potential toxicities of Triton X-100, tri(n butyl)phosphate (TnBP), and their combination, reveal no safety concerns for Kamada-HRIG product. No pharmacology, pharmacokinetic or investigational product metabolism studies in animals were performed.

2.6 Postmarketing Exposure

Kamada-HRIG product has been in use outside of the US for 10 years. In worldwide use, between January 2006 and December 2015, a total of (b) (4) 2 mL vials (each equivalent to 300 IU) and (b) (4) 10 mL vials (each equivalent to 1500 IU) of Kamada-HRIG product have been sold. This is sufficient for treating approximately 270,000 individuals (approximately three quarters of the total dosing occurred in Thailand, Mexico, and India), assuming a 70 kg average body weight and the recommended dose of 20 IU/kg.

The sponsor states that no important identified risks have been revealed in over 10 years of postmarketing use of Kamada-HRIG product in over 250,000 persons. The sponsor also states that during postmarketing use, no adverse event reports for patients exposed to Kamada-HRIG product have been received or identified in the biomedical literature.

4. Safety Specification

3.1 Important identified risks: None

3.2 Important potential risks: (Note: To date, the sponsor has not identified any reports of any of these potential risks following Kamada-HRIG; these are potential product class effects)

3.2.1 Thrombosis

3.2.2 Hemolysis

3.2.3 Hypersensitivity (including anaphylactic) reactions in patients with:

- Selective IgA deficiencies
- Hypersensitivity to Kamada-HRIG or any of its components

3.2.4 Interaction with (and potential prevention of immune response to) attenuated live virus vaccines

3.2.5 Transmission of infectious agents

Reviewer Note: All important potential risks noted above appear adequately addressed in the proposed package insert.

3.3 Important missing information:

- 3.3.1 Pediatric use: The sponsor has planned an open-label study of Kamada-HRIG product administered as a single dose with active rabies vaccine in 30 children ages 0 months to <17 years who have been exposed to rabies.
- 3.3.2 Safety information in pregnant or lactating women (no planned studies)

5. Pharmacovigilance Plan

The sponsor is planning the following routine pharmacovigilance practices for Kamada-HRIG:

4.1 Postmarketing safety surveillance data will be captured via the following sources:

- Suspected adverse drug reactions will be spontaneously reported to Kamada (and/or its product distributors) by health care providers, consumers or the FDA;
- Results of literature searches (searches of the literature for safety reports relevant to Kamada-HRIG will be performed at least quarterly);
- Unsolicited reporting from any other source. Results from clinical studies, including serious adverse events, will also be analyzed as part of routine post-marketing surveillance activities.

4.2 All reports on suspected adverse drug reactions (ADRs) will be entered into the Kamada Safety Database.

4.3 Creation and reporting of individual case safety reports (ICSRs), expedited ADR reports, preparation of Periodic Reports and/or other summary safety reports, and monitoring of the safety profile of Kamada-HRIG product (including signal detection, issue evaluation, updating of labeling and generating risk-benefit assessments) will be continuously performed.

4.4 The sponsor states ‘(t)opics of special interest’ such as the development of allergic-type reactions and the possibility of transmission of infectious agents will be closely monitored. Aside from these two examples, the sponsor has not provided any additional details regarding or definition of topics of special interest, though from context it is understood to pertain to identified safety concerns (see following table).

The sponsor has provided the following summary of safety concerns and planned pharmacovigilance actions:

Summary of Safety Concerns and Planned Pharmacovigilance Actions*

Safety concern	Planned action(s)
<u>Important Potential Risk:</u> Hypersensitivity reaction in patients with selective IgA deficiencies who have known antibodies against IgA and patients hypersensitive to the product or to any of its component	Routine pharmacovigilance activities: <ul style="list-style-type: none"> • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form) • Search of the biomedical literature for case reports relevant to Kamada-HRIG
<u>Important Potential Risk:</u> Transmission of infectious agents	Routine pharmacovigilance activities: <ul style="list-style-type: none"> • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form) • Monitoring of literature to identify new potential sources of blood-borne infection
<u>Important Potential Risks:</u> Thrombosis and hemolysis	Routine pharmacovigilance activities: <ul style="list-style-type: none"> • Analysis of reported AEs • Follow-up of reports (including specific questions in the specific ADR follow-up form)
<u>Important Missing Information:</u> Pediatric use	An open-label study of Kamada-HRIG product administered as a single dose with active rabies vaccine in children exposed to rabies will be conducted. A total of 30 children between the ages of 0 months to <17 years will be enrolled.

Abbreviations: ADR: adverse drug reaction; AE: adverse event; HRIG: human rabies immune globulin; IgA: immunoglobulin A

*BLA Pharmacovigilance Plan in 'Risk Management' document; page 19

6. Review of other data sources

Other rabies immune globulin products on the US market (HyperRAB S/D and Imogam Rabies-HT) have been under OBE/DE routine surveillance using multiple data sources including reported postmarketing AEs, data mining, and medical literature. No safety concerns have been identified among these data sources that warrant the addition of further elements to the above pharmacovigilance plan. A more current PubMed literature review using the search terms "rabies" and "immune globulin" conducted on January 3, 2017, did not identify any new safety concerns regarding the use of Kamada-HRIG or other marketed rabies immune globulins.

7. Integrated risk assessment

The above pharmacovigilance plan proposed by the sponsor appears adequate for the sought indication. Class effect adverse events (e.g., thrombotic events) seen in other immune globulin products could potentially present in association with this product. The sponsor's aforementioned plan for conducting routine pharmacovigilance appears reasonable in view of available Kamada-HRIG safety data. The review team has not

identified any clinical safety concern related to the administration of Kamada-HRIG to date that would warrant additional pharmacovigilance measures.

8. Conclusions/Recommendations

- The sponsor's plan for conducting routine pharmacovigilance practices is adequate for the sought indication.
- Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.
- Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.
- The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint.