



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

Date:

To: BLA 125613

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Through: Dorothy E. Scott, M.D., Chief, PDB, DPPT, OTAT

Applicant: Kamada Ltd.

Product: KEDRAB- Human Rabies Virus Immune Globulin Injection

Subject: Preclinical Pharm-Tox Review

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Introduction

KEDRAB is a polyclonal immune globulin (IG) preparation manufactured from hyperimmune human plasma of healthy adult donors with high titers of rabies-specific antibodies collected in US approved plasma centers. The final preparation has a potency of 150 IU/mL and is stabilized with glycine (nominal concentration 300 mM) at pH~5.5 (Table 1).

KEDRAB is intended for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid animal at a single dose of 20 IU/kg body weight administered around the injury and/or intramuscularly (IM).

To assess the safety of the preparation, the manufacturer performed one toxicology study in rats administering up to six times the intended human dose via the intended route of administration. There were no toxicities observed in the animal study. Additionally, the formulation and impurity profile is judged safe for human administration when used according to the intended indication and dose.

Recommendation

There are no pharmacology and toxicology issues that would prevent this BLA from being approved.

Complete Review

Animal Studies

Study number: Kam/130/AIMT

Sponsor: Kamada Ltd.

Testing Facility: (b) (4)

Study Objective: To assess the acute Intramuscular toxicity of KEDRAB following a single administration by intramuscular injection to the rat.

Study Design: A GLP study where (b) (4) female rats (n=6/group) aged 10 weeks and weighing 190-209 g, were randomized to receive 60 (low dose) and 120 IU/kg (high dose) KEDRAB (Batch No. 3816002B) by intramuscular injection. Based on body weight, approximately 0.08 and 0.16 mL dose volume was administered in total for the low and high dose, respectively, in one (low dose) or two (high dose) sites. The total volume injected did not exceed 0.1 mL/site.

Outcome measures: Clinical observations the first 4 hours following dosing, once daily observations until termination on day 14 including: changes in the skin, fur, eyes, mucous membranes, respiratory system, circulatory, autonomic and central nervous systems, activity and behavior pattern; body weight before administration, day 2 and day 7; necropsy and complete gross pathological examination.

Results: There were no aberrant findings in any of the outcome measures evaluated in this study.

Conclusion: Given the lack of toxicities, a dose of 120 IU/kg KEDRAB administered IM in rats can be considered the no-observed-adverse-effect-level, NOAEL. This dose is 6 times higher than the 20 IU/kg, the dose that is being sought for approval in this BLA. This safety factor is acceptable.

Formulation and Impurities

For a subject weighing 75 kg, a dose of 20 IU/kg corresponds to an administered volume of 10 mL (20 IU/kg x 75 IU/mL ÷ 150 IU/mL). Based on the administered volume and the upper bound of the specification of the drug product shown in Table 1, the exposure to product ingredients total protein, glycine, Triton X-100 and TnBP was calculated and is shown in Table 2. To compare the systemic exposure to these constituents the same calculation was performed for an approved IG product with similar formulation, Gammagard® SD (Baxalta, initial approval 1994).

Table 1: Select Release Specifications for KEDRAB

Test	Acceptance Criteria
pH	5.0 – 6.0
Anti – Rabies Potency	NLT 150 IU/ml
Glycine Concentration	(b) (4)
Protein Concentration	(b) (4)
Residual Triton X-100	(b) (4)
Residual TnBP	(b) (4)

Table 2: Comparative analysis of the exposure to inactive components of KEDRAB and Gammagard® SD

	KEDRAB®	Gammagard® SD	Exposure Ratio
Total Protein ²	(b) (4)	100 mg/mL	
	(b) (4)	30,000 mg	(b) (4)
Glycine ²	(b) (4)	NMT 600 mmol/L	
	(b) (4)	180 mmol	0.02 ³
Residual Triton X-100 ² and Residual TnBP ²	(b) (4)	NMT 2 ppm	
	(b) (4)	600 ug	0.17 ³

¹Dose volume for Gammagard SD was calculated using the typical dose and the average adult weight: 400 mg/kg x 75 kg ÷ 100 mg/mL

²Exposure was calculated by multiplying the upper bound of the specification with the administered volume

³Exposure ratio was calculated by dividing the dose received after KEDRAB administration with the dose received after Gammagard® SD.

As shown in Table 2, for all components analyzed the highest exposure following a single administration of KEDRAB is 6-50 times smaller than after single dose administration of Gammagard® SD. There are no expected toxicities from such an exposure, and the formulation is considered safe.

The pH of KEDRAB final formulation is 5.0-6.0. This range of pH is comparable to other IG products intended for subcutaneous injection such as Hizentra (CSLB, pH 4.6-5.2) and Hyqvia (Baxalta, pH 4.6-5.1). In addition, this pH is within the range of other marketed preparations intended for IM administration, such numerous antibiotic preparations (Handbook on Injectable Drugs™ - 19th Ed., American Society of Health-System Pharmacists, Inc., 2017). Thus there is no uncommon local toxicity expected following IM administration of KEDRAB.

Review of the Label

The reviewer recommends these changes to the label, section 13.

13.1

Carcinogenesis, Mutagenesis, Impairment of Fertility

~~Because immunoglobulins are naturally occurring molecules in humans, no long term studies in animals~~
No animal studies were conducted to evaluate carcinogenesis, mutagenesis or impairment of fertility ~~were conducted.~~

13.2

Animal Toxicology and/or Pharmacology

~~Acute i~~~~Intramuscular single dose administration of Kamada HRIG~~ **a single dose of Kedrab** to rats at ~~two~~
~~dose levels, 60 and 120 IU/kg (3-fold and 6-fold of the human dose of 20 IU/kg, respectively), did not~~
result in any signs of toxicity.