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

Date:

To: To File, BLA 125613/76

From: Evi Struble, Ph.D., Research Pharmacology, PDB, DPPT, OTAT

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Applicant: Kamada Ltd.

Product: Rabies Immune Globulin (human), KEDRAB

Subject: Preclinical Pharm-Tox Review

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Introduction

KEDRAB is a [redacted] 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. It was approved in the US in August 2017 for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and concurrently with a full course of rabies vaccine. The current application is a Prior Approval Supplement (PAS) containing a clinical study in pediatric patients exposed or possibly exposed to rabies virus. The study fulfils a postmarketing commitment the sponsor agreed to as a condition of the BLA approval.

Pharmacology and Toxicology

There is no new animal pharmacology and toxicology studies submitted with this PAS. Studies submitted with the original BLA are supportive of this application. Briefly, 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 demonstrating that the clinical dose of KEDRAB is likely to be safe, including in the pediatric population.

Formulation and Impurities

A list of selected constituents of KEDRAB, including active, inactive ingredients and impurities, is shown in Table 1.

Based on these specifications, a dose of 20 IU/kg corresponds to an administered volume of ~0.13 mL/kg (20 IU/kg ÷150 IU/mL) and calculated exposure to total protein, glycine, Triton X-100 and TnBP as shown in Table 2. These exposures are smaller than a product with a history of safe use, including in pediatric population, Gammagard® SD (Baxalta, initial approval 1994). Thus, when used in the pediatric population, the formulation and impurity profile of KEDRAB is expected to be safe.

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[1]	(b) (4)	100 mg/mL	
	(b) (4)	400 mg/kg	(b) (4)
Glycine[2]	(b) (4)	NMT 600 mmol/L	
	(b) (4)	(b) (4)	(b) (4)
Residual Triton X-100 [2] and Residual TnBP[2]	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	(b) (4)

[1]Exposure was calculated by multiplying the upper bound of the specification with the administered volume

[2]Dose volume for Gammagard SD was calculated using the typical dose and the product concentration: 400 mg/kg ÷ 100 mg/mL=4 mL/kg

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

Recommendation

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