KEDRAB®
Rabies Immune Globulin
(Human)

RABIES AND CHILDREN: PREVALENCE AND CHALLENGES OF HRIG ADMINISTRATION

Highlights from an investigational study comparing pediatric and adult patients receiving human rabies immune globulin (HRIG) in the US*

Reasons for the study:

Children represent a significant number of patients receiving human rabies immune globulin (HRIG) during post-exposure prophylaxis (PEP) following suspected rabies exposures. Despite this, no registered clinical studies for any HRIG had been conducted in this population until recently.[1]

Evidence of pediatric bite wounds in the US[1]:

Up to **80%** of bites involve the head and neck

About **44,000** facial injuries occur each year

33% are severe and mostly affect children under 10

Study overview[1]:

- A comprehensive cross-sectional investigational study of over 100,000 adults and children (aged 14 and under) compared the prevalence of diagnoses and procedures between the two age groups
- For all patients, the most common animal encounter was dog
- Records range from October 2012 to June 2020

Understanding exposure differences by severity and type may help better inform clinical practice and prevent administration errors when treating children[1]

*Findings from Burke RV, et al. Epidemiology of rabies immune globulin use in paediatric and adult patients in the USA. *BMJ Open*. 2022. Study data were queried from the Symphony Integrated Dataverse (IDV), an integrated healthcare database that includes claims (medical, hospital and prescription), point-of-sale prescription, non-retail invoice and demographic data.[1]

INDICATIONS AND USAGE

KEDRAB is a human rabies immune globulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection to persons of all ages when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

SELECTED IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: None.

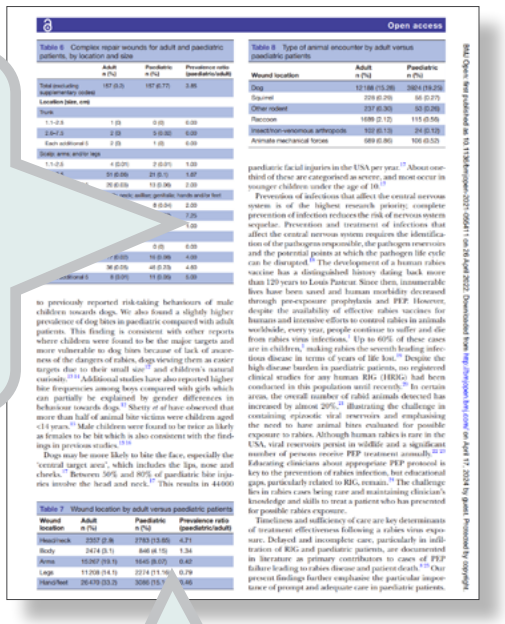
Please see additional Important Safety Information throughout and full Prescribing Information here.

CHILDREN OFTEN SUFFER LARGER AND MORE SEVERE WOUNDS THAN ADULTS[1]

Results are consistent with other studies that found children more likely to sustain bites on the head and face due to their smaller size, lack of awareness, and natural curiosity[1]

Children had more complex wound repairs compared to adults[1]

- Large, complex wounds were 3.83-fold more prevalent
- Of these wounds, the largest difference was for 2.6–7.5 cm wound repairs on the forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet



Children are more likely to suffer wounds on the head, neck, and face[1]

- Nearly 6-fold higher prevalence of "open wounds to the head neck, and trunk"
- Almost 4.5-fold higher prevalence of "open wound of scalp"
- 6.75-fold higher prevalence of "laceration of skin of eyelid and periocular area"

SELECTED IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS: Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis should only receive a booster rabies vaccine without KEDRAB because KEDRAB may interfere with the anamnestic response to the rabies vaccine.

HYPERSENSITIVITY REACTIONS: Hypersensitivity reactions, including anaphylaxis, may occur with KEDRAB. IgA deficient patients with antibodies against IgA are at greater risk. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.

LIVE ATTENUATED VIRUS VACCINES: KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. If feasible, delay immunization with measles vaccine for 4 months, and other live attenuated virus vaccines for 3 months, after KEDRAB administration.

Please see additional Important Safety Information throughout and full Prescribing Information here.

SEVERE WOUNDS CAN CREATE CLINICALLY CHALLENGING SITUATIONS WHEN ADMINISTERING HRIG IN CHILDREN[1]

If HRIG volume is insufficient and wounds cannot be fully infiltrated, a patient will remain at risk of infection and death from the rabies virus[1]

Cases of PEP failure have been reported in children with extensive wounds.[1]

The study authors noted that in previous cases:

- Insufficiency of HRIG or delayed administration compromised protection
- Lack of HRIG volume caused incomplete infiltration of all wounds
- Timeliness and sufficiency of care are key to preventing the rabies virus from spreading throughout the body
- In cases of volume insufficiency, increasing the dose of HRIG is prohibited as dosing higher than 20 IU/kg interferes with vaccine immunogenicity

"Our findings demonstrate that children more frequently sustain larger, more complex wounds compared with adults, increasing the minimum volume of HRIG necessary to fully infiltrate."

Dosing of HRIG must provide sufficient volume to adequately infiltrate all wounds, as this is the main protective mechanism[1]

SELECTED IMPORTANT SAFETY INFORMATION (CONTINUED)

INTERFERENCE WITH SEROLOGICAL TESTING: A transient rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results of serologic tests after KEDRAB administration. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, and D, may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).

TRANSMISSIBLE INFECTIOUS AGENTS: Because KEDRAB® (Rabies Immune Globulin [Human]) is made from human plasma donors hyper-immunized with rabies vaccine, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion Biopharma Inc. at 1-855-353-7466.

KEDRAB®
Rabies Immune Globulin (Human)

TREATING CHILDREN WITH LARGE AND COMPLEX WOUNDS REQUIRES PROPER HRIG VOLUME[1]

Pediatric patients with lower body weights who sustain larger, more severe wounds often need the maximum HRIG volume allowed[1]

2-mL vial

10-mL vial

KEDRAB, the standard 150 IU/mL HRIG[2]:

- Provides the necessary volume to infiltrate all wounds during HRIG administration
- Is the first and only FDA-approved HRIG studied for safety and effectiveness in children

HRIG VOLUME MATTERS

View the study abstract and choose KEDRAB when treating pediatric patients suspected of a rabies exposure

SELECTED IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS: The most common adverse reactions in adult subjects treated with KEDRAB in clinical trials were injection site pain, headache, muscle pain, joint pain, dizziness, and fatigue. In pediatric subjects treated with KEDRAB and a full course of rabies vaccine, the most common adverse reactions were injection site pain, headache, fever, pain in extremity, bruising (hematoma), fatigue, and vomiting. Less common adverse reactions (≤5%) in pediatric patients were injection site redness (erythema), injection site swelling (edema), muscle pain, oral pain, and wound complication. Insomnia was reported as a less common adverse reaction (<5%) in pediatric patients occurring after 14 days of administration.

DRUG INTERACTIONS: Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis and have a confirmed adequate rabies antibody titer should receive only a booster rabies vaccine (without KEDRAB) because KEDRAB may interfere with the anamnestic response to the vaccine (ACIP). KEDRAB can interfere with the immune response to the rabies vaccine. For this reason, do not exceed the recommended KEDRAB dose or give additional (repeat) doses of KEDRAB once rabies vaccination has been initiated. KEDRAB can inactivate the rabies vaccine. For this reason, do not administer KEDRAB in the same syringe as the rabies vaccine or near the anatomical site of administration of the rabies vaccine.

To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. at 1-855-353-7466 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. Burke RV, Russo P, Sicilia M, et al. Epidemiology of rabies immune globulin use in paediatric and adult patients in the USA: a cross-sectional prevalence study. *BMJ Open.* 2022;12:e055411. doi:10.1136/bmjopen-2021-055411 **2.** KEDRAB [package insert]. Kedrion Biopharma Inc.; 2021.

KEDRAB®
Rabies Immune Globulin (Human)

KEDRION BIOPHARMA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEDRAB safely and effectively. See full prescribing information for KEDRAB.

KEDRAB® Rabies Immune Globulin (Human) solution for wound infiltration and intramuscular injection

Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage (1)	05/2021
Dosage and Administration (2)	05/2021

INDICATIONS AND USAGE

KEDRAB is a human rabies immune globulin (HRIG) indicated for passive, transient post-exposure prophylaxis of rabies infection to persons of all ages when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine. (1)

DOSAGE AND ADMINISTRATION

For wound infiltration and intramuscular use. (2)

Post-exposure prophylaxis: single dose of KEDRAB with a full course of rabies vaccine	20 IU/kg body weight KEDRAB Do not exceed recommended dose. Do not repeat KEDRAB doses once vaccine treatment is initiated.	• Administer as soon as possible after exposure • Infiltrate area around wound with full dose • Inject any remaining KEDRAB intramuscularly, at a site distant from the site of rabies vaccine administration

DOSAGE FORMS AND STRENGTHS

Single-dose vials containing 2 mL or 10 mL ready-to-use solution with a potency of 150 IU/mL.(3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Do not give KEDRAB to persons who have completed rabies pre- or post-exposure prophylaxis because it can interfere with the anamnestic response to the rabies vaccine. (5.1)
- Hypersensitivity reactions, including anaphylaxis, may occur with KEDRAB. IgA deficient patients with antibodies against IgA are at greater risk. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.2)
- Interference with live attenuated virus vaccines. (5.5, 7)
- KEDRAB is made from human plasma, and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.7)

ADVERSE REACTIONS

The most common adverse reactions (>5%) observed in adult subjects were injection site pain, headache, muscle pain, joint pain, dizziness, and fatigue. The most common adverse reactions (>5%) observed in pediatric patients were injection site pain, headache, pyrexia, plain in extremity, bruising, fatigue, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. at 1-855-353-7466 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Do not administer KEDRAB in the same syringe, or into the same anatomical site, as the rabies vaccine. (2,7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KEDRAB is a human rabies immune globulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection to persons of all ages when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

2 DOSAGE AND ADMINISTRATION

For wound infiltration and intramuscular use.

2.1 Dosage

Post-exposure prophylaxis consists of a single 20 IU/kg body weight dose of KEDRAB and a full course of rabies vaccine (See Table 1).

Table 1: Rabies Post-exposure Prophylaxis Schedule*

Vaccination Status	Intervention	Regimen†
Not previously vaccinated	Wound Cleansing	• Cleanse all wounds immediately and thoroughly with soap and water. • Irrigate the wounds with a viricidal agent such as a povidone-iodine solution, if available.
	KEDRAB® 20 IU/kg body weight	• Administer KEDRAB as soon as possible after exposure, preferably at the time of the first rabies vaccine dose. However, should a delay occur, administer KEDRAB at any time up to and including seven days after the first dose of rabies vaccine. • If there is a delay, initiate post-exposure prophylaxis at any time after exposure. • Infiltrate the area around and into the wound(s), if anatomically feasible, with the full dose of KEDRAB. • Inject the remainder, if any, intramuscularly at an anatomical site distant from the site of rabies vaccine administration. • Do not exceed the recommended dose of KEDRAB because this can partially suppress active production of rabies virus antibodies. *[see Drug Interactions (7)]* • Do not administer additional doses of KEDRAB, even if the antibody response to vaccination is delayed. (7) • Use separate syringes, needles, and anatomical injection sites for KEDRAB and for rabies vaccine.
	Rabies Vaccine	• Administer rabies vaccine on Day 0 and on subsequent vaccine administration days‡ at an anatomical site that is distant from the KEDRAB administration site(s). • Complete a rabies vaccination series
Previously vaccinated§	Wound cleansing	• Cleanse all wounds immediately and thoroughly with soap and water. • Irrigate the wounds with a viricidal agent such as povidone-iodine solution if available.
	KEDRAB®	• Do not administer KEDRAB. *[see Warnings and Precautions (5.1)]*
	Rabies Vaccine	• Administer rabies vaccine on Day 0.‡ • Complete a rabies vaccination series for previously vaccinated persons.†
Other Considerations	Tetanus prophylaxis and/or antibiotics	• Provide treatment if medically indicated

* Adapted from reference 1.

† These regimens are applicable for all age groups, including children.

‡ Day 0 is the day the first dose of vaccine is administered. Refer to vaccine manufacturer's instructions or to the recommendations of the Advisory Committee on Immunization Practices (ACIP)[1,2] for appropriate rabies vaccine formulations, schedules, and dosages.

§ Any person with a history of rabies vaccination and a documented history of antibody response to the prior vaccination.

2.2 Administration

Infiltrate as much of the KEDRAB dose as possible into and around any detectable bite wounds if infiltration at the bite site is feasible. Administer any remaining KEDRAB intramuscularly into anatomical site(s) distant from the site of the rabies vaccine.

- When the bite site is unknown or indeterminate (undetectable) or if infiltration is difficult at the bite site (e.g., lips, fingers, knee), administer the full KEDRAB dose by the intramuscular route at a site distant from the site of rabies vaccination.
- If a large intramuscular volume is required (>2 mL for children or >5 mL for adults), administer the total volume in divided doses at different sites.
- Do not mix KEDRAB with the rabies vaccine or administer in the same syringe with the rabies vaccine.
- Discard unused portion of the product in the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if either of these conditions exists, and contact Kedrion Biopharma Inc. at 1-855-353-7466. Do not discard the vial.

3 DOSAGE FORMS AND STRENGTHS

KEDRAB is supplied in single-dose vials containing 2 mL or 10 mL of ready-to-use solution with a nominal potency of 150 IU/mL (Note that more than one vial may be required for a single patient treatment).

- The 2 mL vial contains a total of 300 IU, which is sufficient for a child weighing 15 kg (33 lb)
- The 10 mL vial contains a total of 1500 IU, which is sufficient for an adult weighing 75 kg (165 lb)

The final product is assayed with human rabies immunoglobulin reference standard that is calibrated against the WHO International Standard.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Previous Rabies Vaccination

Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis should only receive a booster rabies vaccine without KEDRAB because KEDRAB may interfere with the anamnestic response to the vaccine (ACIP)[1].

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, may occur with KEDRAB. History of prior systemic allergic reactions to human immunoglobulin preparations places patients at greater risk. Have epinephrine available for treatment of acute allergic symptoms. Patients with isolated immunoglobulin A (IgA) deficiency may develop severe hypersensitivity reactions to KEDRAB or, subsequently, to the administration of blood products that contain IgA.

5.5 Live Attenuated Virus Vaccines

KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. If feasible, delay immunization with measles vaccine for 4 months, and other live attenuated virus vaccines for 3 months, after KEDRAB administration.

5.6 Interference with Serologic Testing

- A transient rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results of serologic tests after KEDRAB administration.
- Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, and D, may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).

5.7 Transmissible Infectious Agents

Because KEDRAB is made from human plasma donors hyper-immunized with rabies vaccine, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion Biopharma Inc. at 1-855-353-7466.

6 ADVERSE REACTIONS

The most common adverse reactions (>5%) observed in adult subjects were injection site pain, headache, muscle pain, joint pain, dizziness, and fatigue.

The most common adverse reactions (>5%) observed in pediatric patients were injection site pain, headache, pyrexia, plain in extremity, bruising, fatigue and vomiting.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates of adverse reactions in clinical trials of another drug and may not reflect the rates observed in clinical practice.

KEDRAB was evaluated in three single-center, controlled clinical trials in adults. Subjects in these clinical studies of KEDRAB were healthy adults, primarily white, and ranged in age from 18 to 72 years. A total of 160 adult subjects were treated in these three studies, including 91 subjects who received single intramuscular doses of KEDRAB (20 IU/kg) with or without rabies vaccine.

Table 2 summarizes adverse reactions occurring in >3% of adult subjects in the clinical trials of KEDRAB. (Table 2).

Table 2: Adverse Reactions Occurring in >3% of Subjects in All Combined Studies in Adults

	All KEDRAB **(N=91)**	All Comparator HRIG **(N=84)**	Saline Placebo+Vaccine **(N=8)**
Injection site pain	30 (33%)	26 (31%)	2 (25%)
Headache	14 (15%)	11 (13%)	3 (38%)
Muscle pain	8 (9%)	6 (7%)	0 (0%)
Joint Pain	5 (6%)	0 (0%)	1 (13%)
Dizziness	5 (6%)	3 (4%)	0 (0%)
Fatigue	5 (6%)	2 (2%)	0 (0%)
Abdominal pain	4 (4%)	1 (1%)	0 (0%)
Blood in urine (Hematuria)	4 (4%)	2 (2%)	0 (0%)
Nausea	4 (4%)	3 (4%)	0 (0%)
Feeling faint	4 (4%)	1 (1%)	0 (0%)

Data are presented as number of subjects (% of subjects).

Less frequent adverse reactions (≤3%) in adult subjects were diarrhea, vomiting, decreased appetite, musculoskeletal stiffness, malaise, weakness (asthenia), fainting (syncope), itching (pruritis), tingling sensation (paresthesia), rash, sunburn and elevation in liver function.

KEDRAB was also evaluated in a two-center, open-label clinical trial in 30 pediatric patients exposed or possibly exposed to rabies virus. They ranged in age from 0.5 to 14.9 years. Study treatment included a single dose of KEDRAB (20 IU/kg) and active rabies vaccine on Days 0, 3, 7 and 14 administered as per ACIP[1] recommendations for rabies post-exposure prophylaxis.

Twelve pediatric patients (40%) experienced adverse reactions within 14 days of receipt of KEDRAB and first dose of rabies vaccine. There were no serious adverse reactions. Table 3 summarizes the adverse reactions that occurred in >5% of patients in the pediatric clinical trial within 14 days of receipt of KEDRAB and the first dose of the rabies vaccine.

Table 3: Adverse Reactions Occurring in >5% of Pediatric Patients within 14 Days of Post-exposure Prophylaxis with KEDRAB and Active Rabies Vaccine

	KEDRAB + Rabies Vaccine N = 30
Injection site pain	8 (27%)
Headache	4 (13%)
Fever (Pyrexia)	4 (13%)
Pain in extremity	3 (10%)
Bruising (hematoma)	2 (7%)
Fatigue	2 (7%)
Vomiting	2 (7%)

Data are presented as number of patients (% of patients).

Less common adverse reactions (≤5%) in pediatric patients were injection site redness (erythema), injection site swelling (edema), muscle pain, oral pain, and wound complication.

Insomnia was reported as a less common adverse reactions (<5%) in pediatric patients occurring after 14 days of administration.

7 DRUG INTERACTIONS

- Patients who can document previous complete rabies pre-exposure prophylaxis or complete post-exposure prophylaxis and have a confirmed adequate rabies antibody titer should receive only a booster rabies vaccine (without KEDRAB) because KEDRAB may interfere with the anamnestic response to the vaccine (ACIP)[1].
- KEDRAB can interfere with the immune response to the rabies vaccine. For this reason, do not exceed the recommended KEDRAB dose or give additional (repeat) doses of KEDRAB once rabies vaccination has been initiated.
- KEDRAB can inactivate the rabies vaccine. For this reason, do not administer KEDRAB in the same syringe as the rabies vaccine or near the anatomical site of administration of the rabies vaccine.
- KEDRAB contains other antibodies that may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Avoid immunization with live virus vaccines within 3 months after KEDRAB administration, or in the case of measles vaccine, within 4 months after KEDRAB administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

KEDRAB has not been studied in pregnant women. Therefore, the risk of major birth defects and miscarriage in pregnant women who are exposed to KEDRAB is unknown. Animal developmental or reproduction toxicity studies have not been conducted with KEDRAB. It is not known whether KEDRAB can cause harm to the fetus when administered to a pregnant woman or whether KEDRAB can affect reproductive capacity. In the U.S. general population, the estimated background of major birth defects occurs in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KEDRAB in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KEDRAB and any potential adverse effects on the breastfed infant from KEDRAB or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness have been established in children. In a pediatric study of 30 patients ranging in age from 0.5 to 14.9 years, KEDRAB presented no serious adverse reactions through day 84. Of the 30 patients, 28 (93.3%) achieved a Day-14 RVNA titer ≥0.5 IU/mL, the WHO recommended level. None of the patients who were followed until the end of the study (28/30 patients) developed rabies infection through day 84. [see Clinical Trials (14)]

Adverse reactions that occurred in ≥3.3% of patients within the first 14 days of KEDRAB and the first rabies vaccination administration are listed in Section 6.1.

The clinical trial conducted in the pediatric population is described in Section 14.

Additional evidence to support the use of KEDRAB in children comes from Real World Evidence. Based on claims data, 172 U.S. children (≤17 years) were treated with KEDRAB between 2018-2020. Based on Center for Disease Control data, no children in the U.S. treated with post-exposure prophylaxis have been reported to have had rabies between 2018-April 2021.

8.5 Geriatric Use

Clinical studies of KEDRAB did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Clinical experience with HRIG products has not identified differences in effectiveness between elderly and younger patients (ACIP)[1].

11 DESCRIPTION

KEDRAB is a sterile, non-pyrogenic aqueous solution of anti-rabies immunoglobulin (≥95% protein as IgG). The product is stabilized with 0.3 M glycine and has a pH of 5.5 ± 0.5. It does not contain preservatives and the vial stopper is not made with natural rubber latex. KEDRAB is a clear to opalescent liquid.

KEDRAB is prepared from human plasma from donors hyper-immunized with rabies vaccine. Individual plasma units are tested using FDA-licensed serologic assays for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as by FDA-licensed Nucleic Acid Testing (NAT) for hepatitis B virus (HBV), HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is also tested by in-process NAT procedures for HAV and parvovirus B19. Each plasma unit must be non-reactive to HAV, while the limit in the manufacturing pool is set not to exceed 10^4 IU per mL for parvovirus B19. The KEDRAB manufacturing process includes three validated and effective viral elimination steps:

- Solvent/detergent (S/D) treatment - inactivates enveloped viral agents
- Heat inactivation (pasteurization) - inactivates both enveloped and non-enveloped viruses
- Nanofiltration (NF) - physically removes viruses

The effectiveness of the S/D treatment, pasteurization and nanofiltration procedures for reducing viral content has been assessed using a series of viruses with a range of physico-chemical characteristics. The results of the viral challenge studies are summarized in Table 4.

Table 4: Log_{10} Virus Reduction during Manufacture of KEDRAB

Process Step	**Enveloped Viruses**				**Non-enveloped Viruses**	
	HIV-1	**BVDV**	**PRV**	**WNV**	**EMCV**	**PPV**
S/D treatment	>4.99	>5.70	>4.38	>5.46	Not tested	Not tested
Heat treatment	>6.21	>5.67	Not tested	>6.33	3.30	Not tested
Nanofiltration	Not tested	Not tested	>6.58	Not tested	>7.66	3.41
Global Log_{10} Reduction Factor	**>11.20**	**>11.37**	**>10.96**	**>11.79**	**>10.96**	**3.41**

Abbreviations: BVDV: bovine viral diarrhea virus; EMCV: encephalomyocarditis virus; HIV-1: human immunodeficiency virus 1; HRIG: human rabies immune globulin; PPV: Porcine parvovirus; PRV: Pseudorabies virus; S/D: solvent/detergent; WNV: West Nile Virus.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rabies is a zoonotic disease caused by RNA viruses in the family Rhabdoviridae, genus *Lyssavirus*. Virus is typically present in the saliva of rabid mammals and is transmitted primarily through a bite. KEDRAB is infiltrated into the inoculation site(s) in previously unvaccinated

persons, to provide immediate passive rabies virus neutralizing antibody protection until the patient's immune system responds to vaccination by actively producing antibodies.

12.2 Pharmacodynamics

A protective threshold for rabies virus neutralizing activity (RVNA) has never been established. However, the WHO has generally accepted a RVNA of at least 0.5 IU/mL measured 14 days after initiation of post-exposure prophylaxis as protective.

12.3 Pharmacokinetics

A randomized, single-dose, two-period, two-treatment, two-sequence, double-blind, crossover study assessed the pharmacokinetics of KEDRAB. Twenty-six healthy volunteer subjects were randomized to receive a single IM injection of 20 IU/kg HRIG on two separate occasions (KEDRAB or Comparator HRIG). Subjects received the second treatment (A or B) following the 42-day test period and a 21-day washout period. Single dose IM injection of KEDRAB resulted in maximum plasma RVNA levels of 0.25 IU/mL. The median T_{max} was 7 days (range: 3-14 days). The elimination half-life was approximately 17.9 days. A statistical analysis of the pharmacokinetic parameters showed that KEDRAB was not bioequivalent to the Comparator HRIG (Table 5).

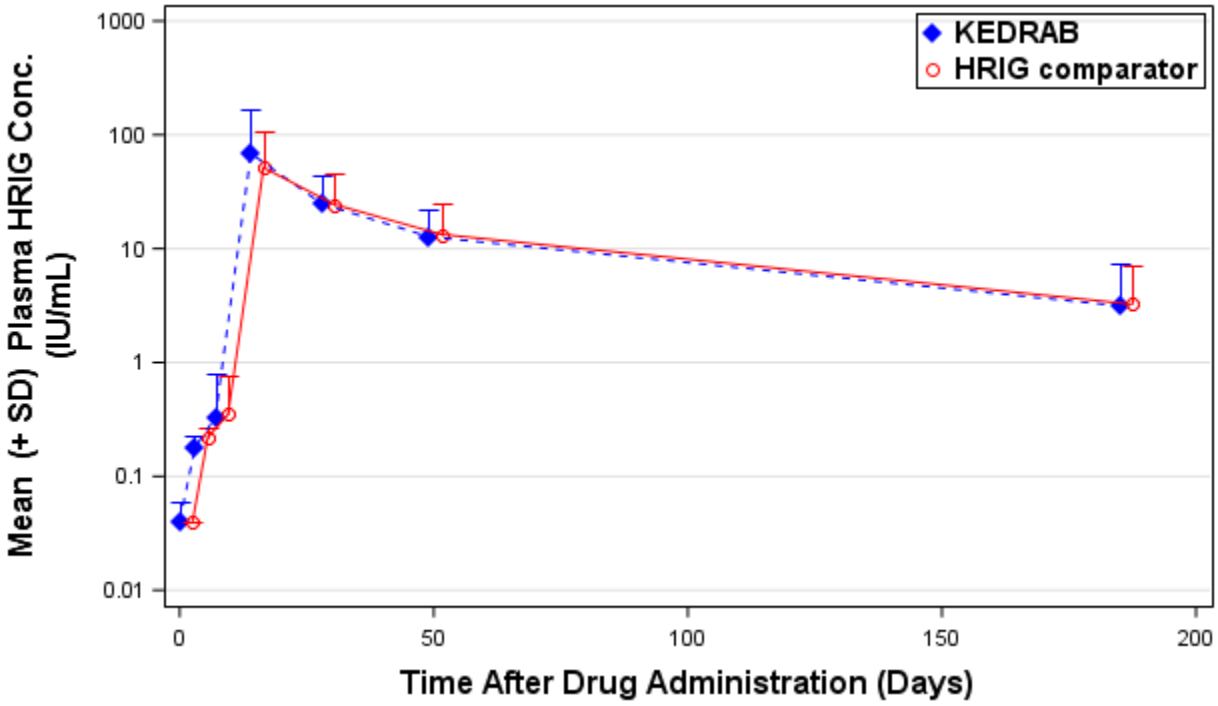
Table 5: Statistical Analysis of Rabies Virus Neutralizing Antibody Pharmacokinetic Parameters - Crossover Study of KEDRAB

Parameter	Units	Geometric LS Mean Values		Test/Reference (%)	90% Confidence Interval (%)
		KEDRAB	Comparator HRIG		
C_{max}	IU/mL	0.24	0.30	81.71	75.34-88.62
$AUC_{0\text{-last}}$	Day*IU/mL	5.08	6.17	82.35	77.39-87.63
$AUC_{0\text{-inf}}$	Day*IU/mL	6.64	7.86	84.44	78.63-90.68

Abbreviations: AUC: area under the concentration-time curve; C_{max}: maximum concentration; inf: infinity; IU: international units; mL: milliliter; PK: Pharmacokinetic; RVNA: rabies virus neutralizing antibody

A plot of plasma rabies virus neutralizing antibody titer concentration versus time (Figure 1) demonstrated that, in both treatment groups, plasma rabies virus neutralizing antibody concentrations declined in a biphasic manner after the absorption phase was complete.

Figure 1: **Plasma HRIG Concentrations [Mean (±SD)] at Scheduled PK Sampling Days (Semi-log Scale), Phase 2/3 Study, Pharmacokinetic Analysis**



Additionally, a prospective, randomized, double-blind, non-inferiority, study evaluated the pharmacokinetics, safety, and effectiveness of simulated post-exposure prophylaxis with KEDRAB with co-administration of active rabies vaccine in 118 healthy subjects. Subjects were randomized into two treatment groups (59 per treatment group) to receive intramuscular KEDRAB or comparator HRIG at a dose of 20 IU/kg on Day 0, and rabies vaccine on Days 0, 3, 7, 14 and 28. The peak plasma RVNA was 71.9 IU/mL and 53.9 IU/mL for KEDRAB and comparator HRIG respectively. For both treatment groups, the median T_{max} was 14 days (range: 14-49 days). The half-lives were 48.6 hours and 52.7 hours for KEDRAB and comparator HRIG respectively.

Bioequivalent assessment showed that KEDRAB was not bioequivalent to the comparator HRIG when co-administered with a five-dose rabies vaccine regimen (Table 6). Furthermore, the RVNA on Day 3 was lower in the KEDRAB with rabies vaccine group relative to the comparator HRIG with vaccine group (0.188+0.051 vs 0.229+0.054, P=0.0005). However, these pharmacokinetic differences are not expected to affect clinical outcomes.

Table 6: Pharmacokinetic Comparison of Rabies Virus Neutralizing Antibody between KEDRAB and a Comparator HRIG Administered with Rabies Vaccine

Parameter	Units	Geometric LS Mean Values		Test/Reference (%)	90% Confidence Interval (%)
		KEDRAB (Test)	Comparator HRIG (Reference)		
C_{max}	IU/mL	44.87	36.02	124.59	90.62-171.28
$AUC_{0\text{-last}}$	Day*IU/mL	1741.40	1686.03	103.28	79.03-134.98
$AUC_{0\text{-inf}}$	Day*IU/mL	2045.87	1916.90	106.73	80.48-141.54

Abbreviations: AUC: area under the concentration-time curve; C_{max}: maximum concentration; inf: infinity; IU: international units; mL: milliliter; RVNA: rabies virus neutralizing antibody

Please see *Clinical Studies (14)* section for clinical efficacy.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Intramuscular administration of a single dose of KEDRAB to rats at 60 and 120 IU/kg (3-fold and 6-fold higher than the recommended human dose of 20 IU/kg) did not result in any signs of toxicity.

14 CLINICAL STUDIES

The efficacy of KEDRAB administered concurrently with rabies vaccine was studied in a single-center, randomized, comparator HRIG-controlled clinical study in adults. Study subjects were healthy adults 18 to 72 years of age who were without significant acute or chronic illness. A total of 118 subjects (59 per treatment group) received intramuscular KEDRAB or comparator HRIG at a dose of 20 IU/kg on Day 0, and rabies vaccine on Days 0, 3, 7, 14 and 28. The mean age of study subjects was 45 years; subjects were, predominantly white (93%), and 64% were women. The efficacy variable was RVNA, as assessed by Rapid Fluorescent Focus Inhibition Test (RFFIT), on Day 14. Efficacy analyses were performed on the As-Treated Population, which comprised the 116 study subjects who received KEDRAB or comparator HRIG and at least 3 of the 5 doses of rabies vaccine before Day 14.

Efficacy, considered when RVNA titer is 0.5 IU/mL or higher on Day 14 (as established by the WHO), was met by 56/57 subjects (98.2%) in the KEDRAB group and 59/59 subjects in the comparator HRIG group (Table 7). The lower limit of the 90% CI was greater than the pre-specified non-inferiority margin of -10%; thus, KEDRAB was non-inferior to comparator HRIG.

Table 7: Subjects with Geometric Mean RVNA ≥0.5 IU/mL on Day 14 (As-Treated Population)

	KEDRAB with Rabies Vaccine (N=57)	Comparator HRIG with Rabies Vaccine (N=59)
Rabies virus neutralizing antibody titer ≥0.5 IU/mL, n (%)	56 (98.2)	59 (100)
Exact 95% CI for proportion (%)	(90.6, 100)	(93.9, 100)
Difference (Pa-Pb)[a] (%)	-1.8	
Exact 90% CI for difference[b] (%)	(-8.1, 3.0)	

[a] 'Pa' and 'Pb' are the proportion of participants with IgG antibody titer ≥0.5 IU/mL on Day 14 in Groups A and B, respectively. Group A = KEDRAB +Rabies Vaccine, Group B = Control HyperRAB®+Rabies Vaccine.
[b] based on Farrington-Manning score statistic.
Abbreviations: CI: confidence interval; HRIG: human rabies immune globulin; IU: international units; mL: milliliter

Additional efficacy analyses in adult subjects included pharmacokinetics [see *Clinical Pharmacology (12)*].

KEDRAB was also evaluated in a two-center, open-label clinical trial in 30 pediatric patients exposed or possibly exposed to rabies virus for whom post-exposure prophylaxis was indicated. The patients were treated with KEDRAB at a dose of 20 IU/kg on Day 0 and active rabies vaccine on Days 0, 3, 7, and 14 as per ACIP[1] recommendations for rabies post-exposure prophylaxis. The patients ranged in age from 0.5 to 14.9 years, 46.7% were females, 6.7% were Asian, 23.3% were Black and 70% were White, 10% were Latino. The efficacy variables were RVNA as assessed by RFFIT on Day 14 and occurrence of rabies disease through Day 84 after administration of KEDRAB. Efficacy analyses were performed on the As-Treated Population, which comprised all 30 study patients.

In the As-Treated Population, the geometric mean (SD) Day-14 RVNA titer was 18.89 (31.61) IU/mL and the median Day-14 RVNA titer was 8.81 (range 0.21 – 153.62) IU/mL. Of the 30 treated pediatric patients, 28 patients (93.3%) had a Day-14 RVNA titer ≥ 0.5 IU/mL, the WHO recommended level. None of the 28/30 patients who were followed for the duration of the study developed rabies infection through day 84.

15 REFERENCES

1. Centers for Disease Control and Prevention. Human rabies prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008;57 (No. RR-3).
2. Use of a Reduced (4-Dose) Vaccine schedule for postexposure prophylaxis to prevent human rabies: Recommendations of the Advisory Committee on Immunization Practices. MMWR 2010;59 (No. RR-2).
3. WHO 2018, Expert Consultation on Rabies. Third Report. Geneva: WHO Press. Technical Report Series (No. 1012).

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each package of KEDRAB contains a single-dose vial containing 2 mL or 10 mL of ready-to-use solution with a potency of 150 IU/mL (Note that more than one vial may be required for a single patient treatment).
- The 2-mL vial contains a total of 300 IU which is sufficient for a child weighing 15 kg (33 lb). (NDC 76125-150-02). The 10-mL vial contains a total of 1500 IU which is sufficient for an adult weighing 75 kg (165 lb). (NDC 76125-150-10)
- Keep vial in package until use.
- Store KEDRAB at 2-8 °C (36-46 °F). DO NOT FREEZE.
- KEDRAB may be stored at room temperatures not exceeding 25 °C (77 °F) for up to one month.
- Use within one month after removal from refrigeration. Do not return to refrigeration.
- Do not use after the expiration date printed on the label.

17 PATIENT COUNSELING INFORMATION

- Inform patients that KEDRAB is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Symptoms of a possible viral infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice. Patients should contact their healthcare provider if any of these symptoms develop. [see *Warnings and Precautions (5.7)*].
- Remind patients that it is necessary to complete the rabies vaccine series.

Distributed by:
Kedrion Biopharma Inc.
Parker Plaza, 400 Kelby St.
Fort Lee, NJ 07024
United States

Manufactured by:
Kamada Ltd.
Beit Kama
MP Negev 8532500
Israel

US License No. 1826