FORMULARY MONOGRAPH

KEDRAB™
Rabies Immune Globulin
(Human)

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

IMPORTANT SAFETY INFORMATION

- 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).
- KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. KEDRAB should be discontinued immediately if there is an allergic or anaphylactic type reaction. In case of shock, standard medical treatment should be implemented. Epinephrine should be available.
- Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.
- Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.
- Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, appropriate laboratory testing should be performed and medical therapy administered as indicated.

- KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. After KEDRAB administration, immunization with measles vaccine should be avoided within 4 months; other live attenuated virus vaccines avoided within 3 months.
- 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 may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).
- KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in KEDRAB.
- In clinical trials, the most common adverse reactions in subjects treated with KEDRAB were injection site pain (33%), headache (15%), muscle pain (9%), and upper respiratory tract infection (9%).

PRODUCT ATTRIBUTES

- Indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, 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]
- 2-mL, 10-mL vial sizes available[1]
- Preservative free, latex free, and pyrogen free[1]
- 20 IU/kg body weight, given at the time of first vaccine dose[1]
- Sterile aqueous solution with a nominal potency of 150 IU/mL[1]
- Ready-to-use solution for wound infiltration and intramuscular injection[1]
- Product may be stored at room temperature not exceeding 25°C (77°F) for up to one month[1]
  - Use within one month after removal from refrigeration. Do not return to refrigeration[1]
- Three specific viral inactivation/removal steps are employed in the manufacture of KEDRAB: solvent/detergent treatment, heat treatment (pasteurization), and nanofiltration[1]
- The manufacturing process reduces the level of thrombogenic activity[1]
  - Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after administration[1]
- KEDRAB has been sold and marketed in various countries outside the US since 2006 as KamRAB[2]

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

IMPORTANT SAFETY INFORMATION

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).

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KEDRAB™
Rabies Immune Globulin (Human)

INTRODUCTION

This formulary monograph provides detailed information about the rabies virus (RABV) and how it damages the nervous system, vectors for infection, and current treatment guidelines. It also outlines a complete description of the efficacy and safety of KEDRAB™ (Rabies Immune Globulin [Human]) and how it should be used in post-exposure prophylaxis (PEP) for rabies. Several of the most important points in the monograph are summarized below.

KEY FACTS ABOUT RABIES AND TREATMENT

Rabies Disease

1. The capacity of rabies to kill 99.9% of the people infected[3] makes it one of the deadliest diseases in the world.[4]

2. Human infection occurs when the virus is transmitted through the saliva of an infected animal by either a bite or scratch.[2] The virus enters muscle cells, evades detection and destruction by the immune system, replicates, and then travels rapidly within axons to reach the central nervous system (CNS). The rabies virus damages neurons and may also kill some of these cells. This results in brain dysfunction that ultimately leads to death.[5]

3. The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, pricking, or burning sensation at the wound site.[6] Other symptoms, including hyperactivity, agitation, hydrophobia (fear of water), hypersalivation, and seizures, emerge after the virus reaches the CNS.[7] Once these symptoms emerge, no treatment is proven to prevent progression to death.[3]

4. Rabies can be transmitted by bites from or the saliva of both wild and domestic animals. Bats constitute the most common source of human rabies cases in the United States.[8]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. KEDRAB should be discontinued immediately if there is an allergic or anaphylactic type reaction. In case of shock, standard medical treatment should be implemented. Epinephrine should be available.

Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.

Rabies Post-exposure Prophylaxis (PEP)

PEP can prevent death due to rabies infection. For every patient not previously vaccinated against rabies, PEP must include both passive immunization with human rabies immune globulin (HRIG) and administration of a series of vaccine injections.[9] Every year, an estimated 40,000 people in the United States receive PEP after contact with a possibly rabid animal.[10]

What Constitutes Proper PEP?

PEP is crucial in preventing rabies

The following 3 components are essential to completely protect patients against rabies.[9] For people exposed or possibly exposed to rabies who have not been vaccinated against the virus, appropriate PEP consists of the following:

1. **Cleansing at the wound site**
   All PEP should begin with immediate and thorough cleansing of all bite wounds with soap and water, including a virucidal agent[1]

2. **Administration of HRIG, such as KEDRAB**
   An HRIG, such as KEDRAB, is administered to previously unvaccinated persons to provide immediate rabies virus-neutralizing antibodies (passive immunization) until the patient responds to the vaccine.[11] KEDRAB should be administered at any time up to and including seven days after the first dose of vaccine[1]

3. **Vaccination against the virus**
   Rabies vaccine stimulates the patient's immune system to produce virus-neutralizing antibodies (active immunization), which occurs approximately 7-10 days after initiation of the vaccine series[9]

KEDRAB

KEDRAB is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine. A large-scale study in 118 healthy volunteers indicated that KEDRAB resulted in a rabies virus neutralizing antibody titer ≥0.5 IU/mL (the World Health Organization [WHO] recommended protective level) in patients, demonstrating noninferiority of KEDRAB to the comparator marketed HRIG.[1]

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

WHAT IS KEDRAB?

KEDRAB™ (Rabies Immune Globulin [Human]) is a sterile, aqueous ready-to-use solution with a nominal potency of 150 IU/mL of anti-rabies immune globulin (human). It is a biologic prepared by chromatographic fractionation from a pool of plasma collected from selected adult human donors who have been immunized with rabies vaccine and have developed high titers of anti-rabies antibody.[2] Three specific viral inactivation/removal steps are employed in the manufacture of KEDRAB.[1]

Viral Inactivation/Removal Steps*

- Solvent/Detergent Treatment
- Heat Treatment (Pasteurization)
- Nanofiltration

*KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.[1]

Kamada Ltd. and Kedrion Biopharma Inc. have a strategic agreement for the clinical development and marketing of KEDRAB in the United States.[12] Kamada has sold more than 1.4 million vials of the product in 9 countries since 2006,[2] demonstrating significant clinical experience with the product.[12]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.

Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, appropriate laboratory testing should be performed and medical therapy administered as indicated.

KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. After KEDRAB administration, immunization with measles vaccine should be avoided within 4 months; other live attenuated virus vaccines avoided within 3 months.

INDICATIONS AND USAGE[1]

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

- Do not administer additional (repeat) doses of KEDRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine
- Do not administer KEDRAB to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer

DOSAGE AND ADMINISTRATION[1]

For wound infiltration and intramuscular use. Do not administer intravenously.

Local Treatment of Wounds prior to KEDRAB Administration

The World Health Organization (WHO) and the U.S. Public Health Service Advisory Committee on Immunization Practices (ACIP) have outlined recommendations for passive and active immunization after exposure to an animal suspected of having rabies. Immediate and thorough cleansing of all bite wounds and scratches with soap and water is an important component of post-exposure prophylaxis (PEP). A virucidal agent (eg, povidone-iodine solution) should be used to irrigate the wounds.

Tetanus prophylaxis and measures to control bacterial infection should be given if medically indicated.

Dosage

Post-exposure prophylaxis consists of a single dose of KEDRAB and a full course of rabies vaccine. The recommended dose of KEDRAB is 20 IU/kg body weight, given at the time of the first vaccine dose. KEDRAB and the first dose of rabies vaccine should be given as soon as possible after exposure, as delays are potentially lethal. However, should a delay occur, KEDRAB should be administered at any time up to and including seven days after the first dose of vaccine. The rabies vaccine should be given according to the manufacturer's instructions. No more than the recommended dose of KEDRAB should be given because KEDRAB partially suppresses active antibody production following vaccination. For the same reason, additional doses of KEDRAB should not be given, even if the antibody response to vaccination is delayed.

Administration

- When the bite site is known and infiltration at the bite site is feasible:
  - Infiltrate as much of the dose as possible into and around any detectable bite wounds. Inject any remaining volume intramuscularly into the upper arm deltoid region or, in small children, into the anterolateral aspect of the thigh. Administer the remaining KEDRAB at site(s) distant from the site of the rabies vaccine
- Avoid administration into the gluteal region, where absorbance is unpredictable (unless the exposure site is in the gluteal region)
- When the bite site is unknown or indeterminate (undetectable) or if infiltration is difficult at the bite site (eg, 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
- If intramuscular administration is contraindicated (eg, in patients with uncorrectable bleeding disorders), administer KEDRAB subcutaneously. However, note that there are no clinical efficacy data to support administration of KEDRAB by the subcutaneous route
- Do not mix with the rabies vaccine or administer in the same syringe with the rabies vaccine
- Do not administer into the same anatomical site(s) as rabies vaccine

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, DO NOT use KEDRAB; contact Kedrion Biopharma Customer Service.

Further Information on Rabies PEP

Consult local or state public health officials if questions arise about the need for rabies prophylaxis.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).

KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in KEDRAB.

In clinical trials, the most common adverse reactions in subjects treated with KEDRAB were injection site pain (33%), headache (15%), muscle pain (9%), and upper respiratory tract infection (9%).

DOSAGE FORMS, HOW SUPPLIED, AND STORAGE[1]

Each carton of KEDRAB contains a single-use vial containing **2 mL or 10 mL** of ready-to-use solution with a nominal potency of 150 IU/mL. The final product is assayed with human rabies immunoglobulin reference standard that is calibrated against the WHO International Standard.

Supplied in Two Vial Sizes

2-mL vial
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

10-mL vial
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

- Store KEDRAB at 2-8°C (36-46°F). Do not freeze
- Keep vial in carton until use
- KEDRAB may be stored at room temperature 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

ORDERING, REIMBURSEMENT, AND MEDICAL INQUIRIES

Please contact Kedrion Biopharma Customer Service by:

Phone:
1-855-353-7466

Fax:
1-855-751-7951

Email:
KedrionCS@ICSConnect.com

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

THE IMPORTANCE OF KEDRAB IN COMBATING THE WORLD'S DEADLIEST DISEASE

Rabies: The Deadliest Infectious Disease

The capacity of rabies to quickly kill its victim—even those treated with modern medicines—has made it one of the deadliest diseases in the world.[4] Death is inevitable following onset of clinical symptoms, and in the developing world, a large number of rabies victims never report to health facilities and are never diagnosed. Although reported deaths due to rabies are rare in the United States, rabies infection associated with dog bites alone kills 160 people every day worldwide (59,000 people per year).[13]

What Makes Rabies So Deadly?

Like many other diseases, a virus causes rabies. The body's immune system effectively detects and destroys a wide range of viruses, but this is not the case for rabies. Given the significant number of people killed by rabies, it is surprising how little is understood regarding the means by which RABV evades the immune system and ultimately kills. It is now known that specific RABV proteins inhibit the innate immune response and permit the virus to survive and replicate in muscle cells. The virus also replicates inside activated T cells and is transported by dendritic cells.[5]

Rabies Kills by Damaging Neuronal Structure and Function

Although RABV infection generally does not kill neurons, it significantly alters their structure, function, and connections between them. The resulting dysfunction in the CNS results in the symptoms of rabies.[5,14] Once patients become symptomatic, no treatment is proven to prevent progression to death.[3]

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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).

Treating Patients Exposed to the Rabies Virus: A Limited Window of Opportunity After Exposure

There is a variable incubation period between exposure to RABV and the appearance of symptoms. This interval typically ranges from 1 to 3 months, however, it may vary from 5 days to >2 years.[9] KEDRAB and the first dose of rabies vaccine should be given as soon as possible, as delays are potentially lethal. However, should a delay occur, KEDRAB should be administered at any time up to and including seven days after the first dose of vaccine.[1] Delivery of prompt and proper PEP as soon as possible after exposure can save the life of the person exposed to rabies.

PEP Is Crucial in Preventing Rabies

In a person exposed to rabies and not previously vaccinated against the virus, prompt and proper PEP consists of the following[9]:

1. Thorough cleansing at the wound site with soap and water

2. Administration of HRIG, such as KEDRAB

3. Vaccination against the virus

These 3 components of treatment are essential to completely protect the exposed person.[9]

The Importance of HRIG Administration

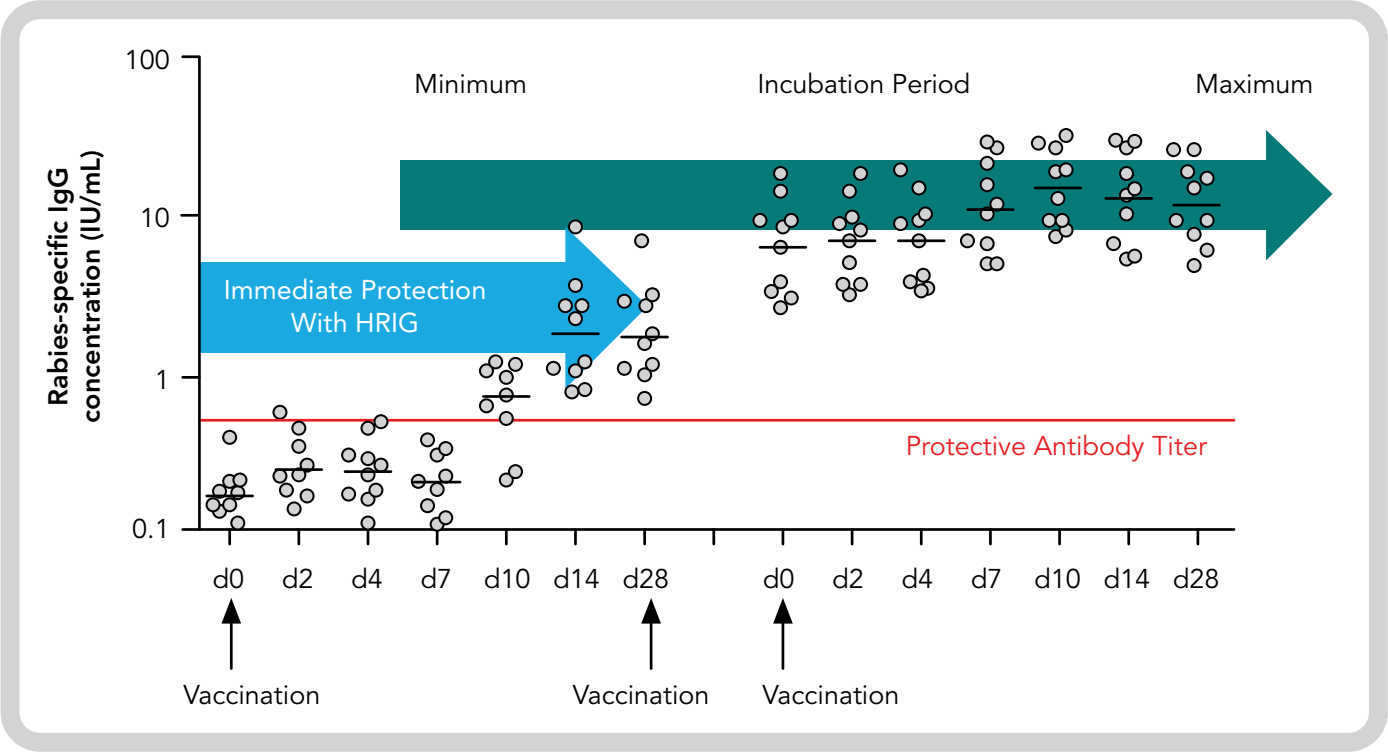
Local administration of HRIG provides immediate anti-rabies antibody at the site of exposure to neutralize remaining RABV. HRIG interferes with viral replication and transport to the CNS during the 7 to 10 days required for the body to develop protective antibody titers (≥0.5 IU/mL) in response to vaccination (Figure 1).[15] Although shorter incubation times tend to be associated with bites on the face, head, and neck, the incubation period for RABV in a given person cannot be readily predicted, and delivering antiviral antibodies as soon as possible after exposure is essential.[16]

No more than the recommended dose of KEDRAB should be given because KEDRAB partially suppresses active antibody production following vaccination. For the same reason, additional doses of KEDRAB should not be given, even if the antibody response to vaccination is delayed.[1]

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

Figure 1. Providing Complete Protection



Adapted from Blanchard-Rohner 2009.[15]

Consideration of the protection provided by HRIG and the critical importance of combining it with vaccination is underscored by the fact that not all patients will develop protective antibody titers by the end of the 14-day post-exposure regimen (Figure 1).[15]

Results from one cohort of 90 patients who consulted for rabies PEP at the University Hospital in Lausanne, Switzerland, between January 2005 and August 2011 indicated that 6 patients (all without prior vaccination) failed to develop antibody titers ≥0.05 IU/mL between 21 and 29 days after initiation of rabies PEP and after 4 doses of vaccine. All 6 patients developed antibody levels >0.5 IU/mL after additional vaccine doses.[17]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. KEDRAB should be discontinued immediately if there is an allergic or anaphylactic type reaction. In case of shock, standard medical treatment should be implemented. Epinephrine should be available.

Failure of Prophylaxis Administered Without HRIG

An illustrative case report from India[18]

On June 7, 2010, a 30-year-old male was bitten by a dog that was never vaccinated against rabies, that had abnormal behavior on the day of bite, and was killed after the bite incident. The bite resulted in a laceration on the flexor aspect of left middle finger (WHO Class III bite). The wound was not washed with soap and water. The patient was taken to the Primary Health Center of that village and received intramuscular injection of tetanus toxoid and first dose of rabies vaccine and advised to take remaining four doses per Essen regimen.* No HRIG was administered. The patient received the 2nd, 3rd, and 4th doses of cell culture vaccine per schedule. On July 1, 25 days after the bite, the patient had pain at the site of bite as well as headache. The patient was taken to a referral center and additional symptoms indicative of rabies (aerophobia and intolerance to noise) were noted. The patient died of rabies on July 3, 2010, on the 27th day after the dog bite.

*The Essen regimen recommends 5 intramuscular injections of vaccine on days 0, 3, 7, 14, and 28. A sixth injection (on day 90) should be considered optional and should be given to those individuals who are immunologically deficient, are at the extremes of age, and on steroid therapy.[19]

The results in this section indicate that some patients take up to 4 weeks to achieve a protective antibody titer against the rabies virus. These results underscore the importance of administering HRIG to all patients who have not been previously vaccinated in order to provide protection while the body mounts an immunologic response to the vaccine.[17,20] All components of PEP–immediate and thorough wound washing, administration of HRIG, and vaccine–are highly effective in preventing human rabies following exposure.[9]

HRIG should be administered at any time up to and including seven days after the first dose of vaccine. Do not administer additional (repeat) doses of KEDRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.[1]

RABIES VIRUS

OVERVIEW

The virus that causes rabies exists on every continent except Antarctica. RABV is deadly; and every year, an estimated 40,000 people in the United States receive a series of injections known as PEP after contact with a possibly rabid animal.[10] RABV belongs to the order Mononegavirales. These viruses have a genome comprised of nonsegmented, negative-stranded RNA. Within this group, viruses with a distinct "bullet" shape are classified in the *Rhabdoviridae* family, which includes Lyssavirus, Ephemerovirus, and Vesiculovirus. The genus Lyssavirus includes rabies virus, Lagos bat, Mokola virus, Duvenhage virus, European bat virus 1 and 2, and Australian bat virus.[21]

Every year, an estimated 40,000 people in the United States receive a series of injections known as PEP after contact with a possibly rabid animal.[10]

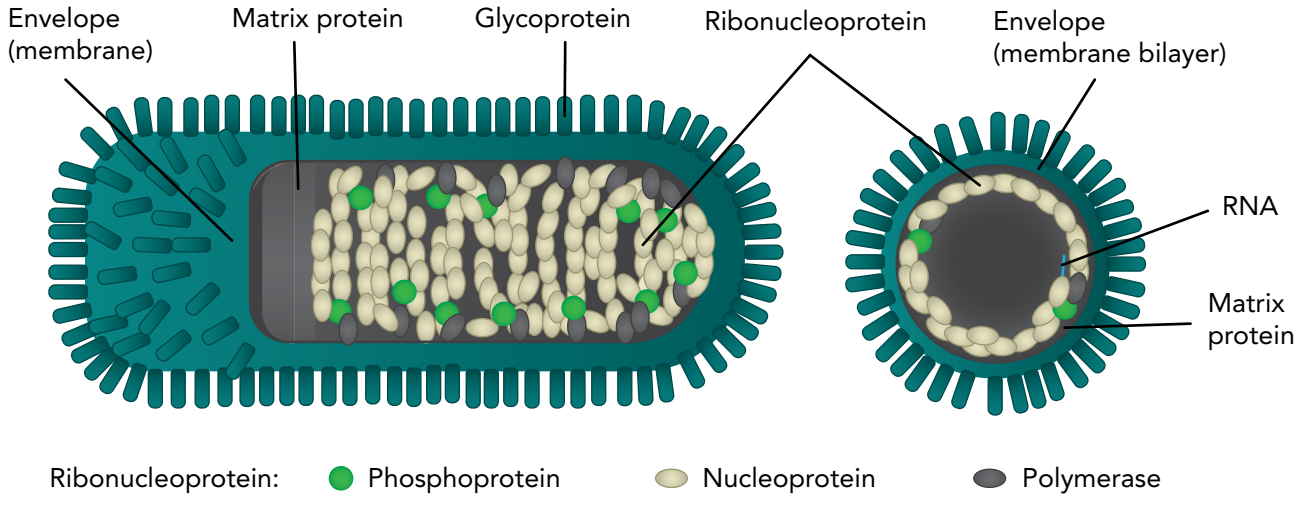
What Is Negative-Stranded RNA?

Negative stranded means that a single-stranded nucleic acid molecule has the opposite sequence to messenger RNA (mRNA) and so cannot be translated into protein until it has been copied. This has important biological implications for viruses with negative-stranded RNA genomes. Since cells have no biochemical mechanism to copy RNA, every negative-stranded RNA virus must carry within the virus particle an RNA-dependent RNA polymerase or the virus cannot replicate once in a host cell.[22]

Viral Structure

Rhabdoviruses are approximately 180 nm long and 75 nm wide (Figure 2) and they have two major structural components: a helical ribonucleoprotein core (RNP) and a surrounding envelope. In the RNP, genomic RNA is tightly encased by the nucleoprotein. Two other viral proteins, the phosphoprotein and the large protein (L-protein or polymerase) are associated with the RNP. The RABV genome encodes 5 proteins: nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and polymerase. The glycoprotein forms approximately 400 trimeric spikes, which are tightly arranged on the surface of the virus.[21]

Figure 2. Structure of RABV

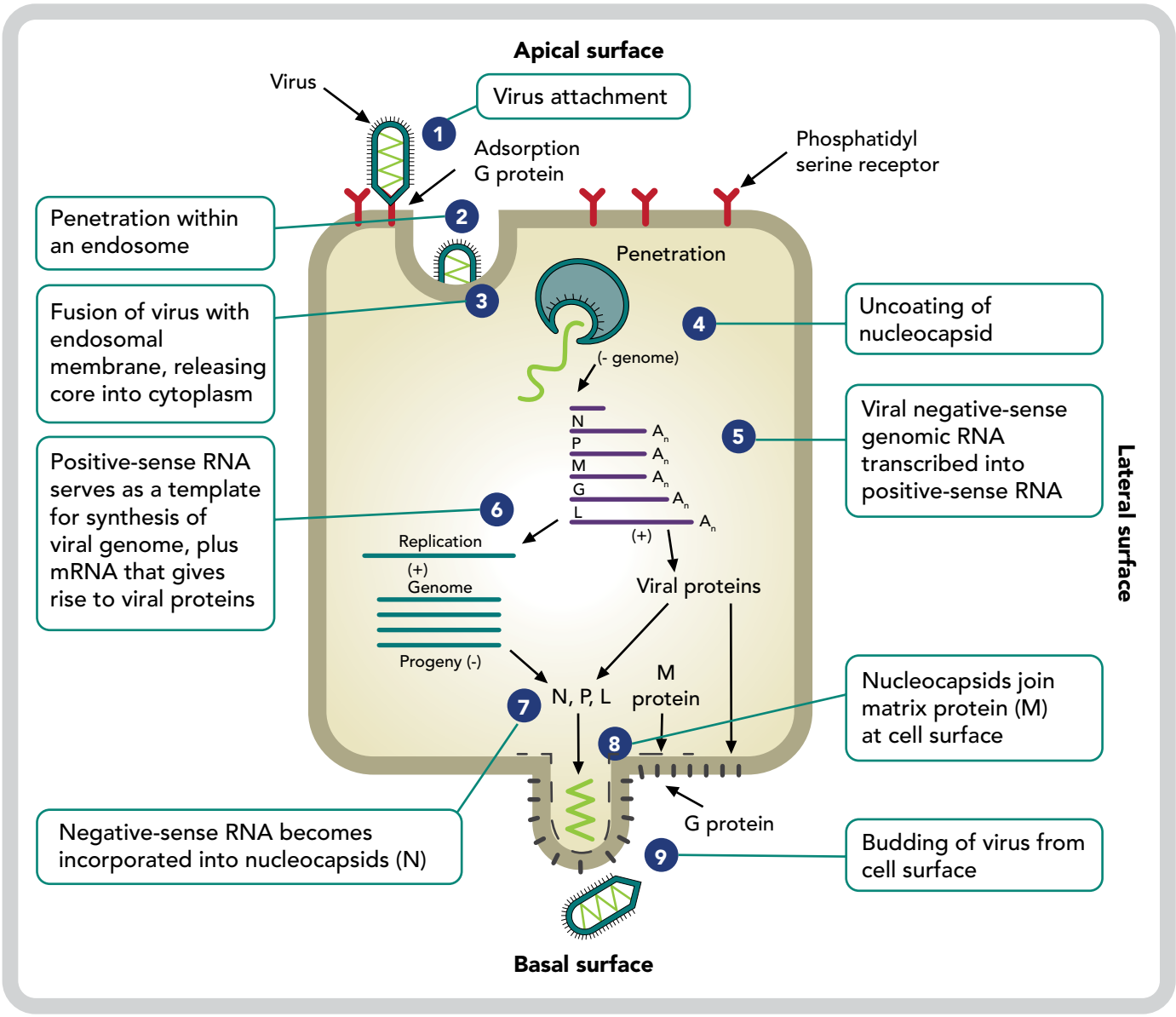


Adapted from Health and Disease Blog 2013.[23]

Replication

The replication of RABV includes multiple steps (Figure 3).

Figure 3. RABV Replication



Adapted from Brooks 2013.[24]

Which Cells Does RABV Use for Replication?

RABV can replicate in both muscle cells and neurons.[25] However, the extent of replication occurs differently in these two cell types. It has been shown that rat myotubes are susceptible to RABV infection and that these cells accumulate viral material over time. However, they do not accumulate infectious virions in the cytoplasm. In contrast, infected neurons accumulate and release large amounts of infectious particles.[26]

> RABV can replicate in both muscle cells and neurons.[25] Infected neurons accumulate and release large amounts of infectious particles.[26]

Escaping Host Immune Responses

The first line of defense against viral infection is the innate immune response, which involves the secretion of type 1 interferons (IFNs), including IFN-α and IFN-β. This response results from activation of pattern recognition receptors, including toll-like receptors. RABV phosphoprotein interferes with the type 1 IFN responses by preventing the phosphorylation of IFN regulatory factor 3 (IRF3). RABV phosphoprotein is critical for prevention of type 1 IFN responses.[27] A second mechanism by which rabies virus evades destruction by the immune system is inducing apoptosis, or internally programmed killing, of T cells.[28]

> RABV uses multiple mechanisms to escape detection and destruction by the immune system.[27,28]

Axonal Transport of RABV and Infection of CNS Neurons

A key step in RABV infection is reaching the CNS. In infected organisms, RABV enters neuronal axons in the area of a bite and exploit the retrograde axonal transport to reach cell bodies (Figure 4).[29] RABV interacts with the p75 neurotrophin receptor (p75NTR) to enter the endings of peripheral nerve axons. The virus then moves via axonal transport in acidic compartments, mostly with p75NTR. RABV is transported faster than nerve growth factor, an endogenous p75NTR ligand. This suggests that RABV not only exploits the neurotrophin transport machinery, but also has a positive influence on transport kinetics, speeding its own arrival in the CNS.[30] RABV continues to sequester the immune response after it reaches the CNS. It induces apoptosis of the relatively small number of infiltrating T cells that respond to the CNS infection,[5] and the blood brain barrier also protects the virus from circulating immune system cells.[31]

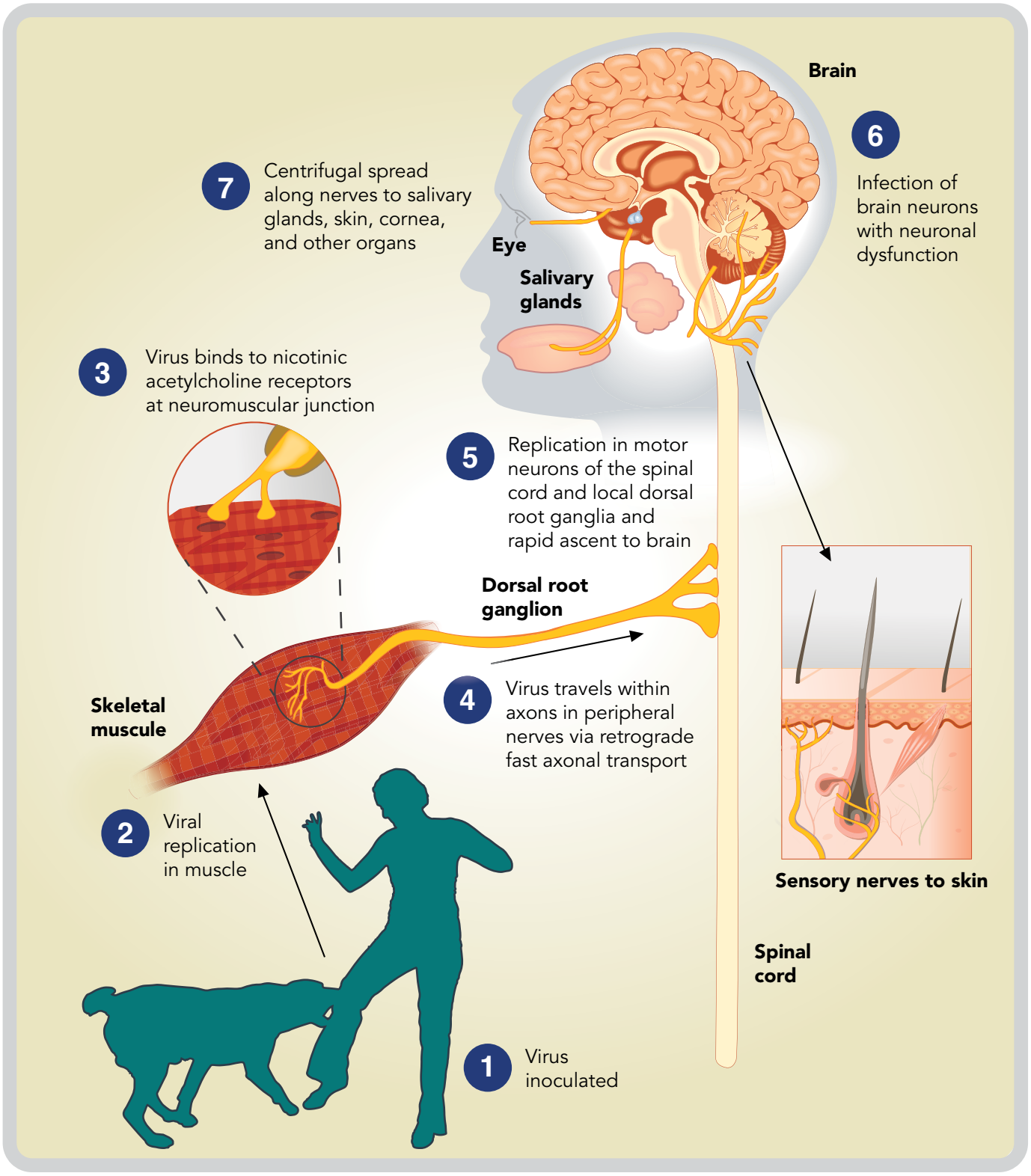
A key step in RABV infection is reaching the CNS. In infected organisms, RABV enters neuronal axons in the area of a bite and reaches cell bodies using retrograde axonal transport.[29]

After infection of the CNS, RABV spreads centrifugally through peripheral nerves to the salivary glands and other tissues. The organ with the highest titers of virus is the submaxillary salivary gland. Other organs where RABV has been found include pancreas, kidney, heart, retina, and cornea.[24]

Effect of RABV on CNS Neurons

Neurotropic viruses, such as RABV, spread between chains of connected neurons. The virus does not typically spread by free diffusion, but rather between tightly connected neurons via synapses or other close cell-cell contacts.[32] The ways in which RABV infection damages the CNS are not fully understood. It has been suggested that apoptotic neuronal cell death underlies the functional changes in the CNS observed in animals and patients infected with the virus. However, RABV infection in some animals does not result in the induction of apoptosis and it causes only limited gross or histopathological lesions in the brains of human patients despite severe clinical neurological signs.[33] Recent work has shown that experimental RABV infection does result in degenerative changes in dendrites and axons of infected neurons. In vitro studies have shown evidence of oxidative stress stimulated by RABV phosphoprotein and that this stress is associated with axonal injury.[34] It has also been shown that the severity of neural damage associated with RABV infection varies with the strain of the virus. Infection of mice with the street RABV strain CNM1101C resulted in severe neuronal dendritic damage, but only mild cell apoptosis, limited T-lymphocyte infiltration, and slight microglial activation. Infection with another street RABV strain, CNM1103C, was characterized by more prominent cell apoptosis, T-lymphocyte infiltration, and microglial activation, as well as dendrite damage.[35]

Figure 4. Transport of RABV to the CNS



Adapted from Jackson 2013.[36]

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

Definitions of RABV Strains[27]

- **Street virus:** an isolate from a naturally infected animal, for example a dog or fox
- **Fixed rabies virus:** a rabies virus that has been passaged in tissue culture or animals. Fixed rabies virus can be pathogenic or nonpathogenic. The term fixed indicates only that the incubation period and virulence have been stabilized and characterized
- **Pathogenic rabies virus:** a strain that typically causes rabies after peripheral inoculation
- **Attenuated rabies virus:** a strain with a greatly reduced ability to cause rabies disease after inoculation into an animal; attenuated viruses are often used in vaccines
- **Neurotropic rabies virus:** a strain that preferentially infects primary neurons or neuronal cell lines
- **Nonneurotropic rabies virus:** a strain that infects neuronal cells at a level less than or equal to other cells types

It is unlikely that immune response-associated inflammation in the brain contributes to the dysfunction associated with RABV infection. No signs of an immune response are detectable in most cases of human rabies at 7 to 10 days after onset of clinical signs.[33] In addition, few individuals have measurable neutralizing antibody on presentation with disease; and when antibody is detected in serum, it rarely appears in cerebrospinal fluid, suggesting limited penetration of antibodies into the CNS.[37] These differences between the pathogenesis of rabies versus most other viral infections are also underscored by the fact that immunosuppression either has no effect or is detrimental to the outcome of RABV infection.[33]

Results from several studies have suggested that rabies infection may disrupt several aspects of normal neuronal function and may also damage or kill neurons.

Results from several studies have suggested that rabies infection may disrupt several aspects of normal neuronal function. It has been shown that expression of intermediate-early response genes is markedly decreased in rabies-infected neurons, resulting in a generalized inhibition of protein synthesis.[38] Other studies have demonstrated that RABV infection results in alterations in synaptic function, including decreased binding of acetylcholine receptor antagonists to relevant receptors and reduced release of and binding of serotonin to its receptors.[39,40] There is also evidence that RABV changes the properties of neurons in ways that interfere with communication among these cells and ultimately result in functional impairment.[14]

Incubation and Clinical Syndromes

The incubation period for rabies is typically 1 to 3 months, but may vary from 5 days to >2 years,[9] depending on factors such as location of rabies entry and rabies viral load.[6] The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, pricking, or burning sensation (paresthesia) at the wound site that is believed to result from damage to the peripheral axons of dorsal root ganglion cells.[6,41] As the virus reaches and then spreads through the CNS, one of two syndromes is observed: furious rabies or paralytic rabies.[6] The progression of rabies is summarized in Figure 5.

The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, pricking, or burning sensation (paresthesia) at the wound site.[6]

Figure 5. Five Clinical Stages of Rabies

	Incubation	Prodrome	Acute Neurological Phase	Coma	Death
Duration[9]	5 days to >2 years	0-10 days	2-7 days	5-14 days	
Symptoms[42]	None	Fever Anorexia Nausea Vomiting Headache Malaise Lethargy Pain or paresthesias at bite site	Hyperventilation Hypoxia Aphasia Lack of coordination CNS signs (paresis, paralysis) Hydrophobia Pharyngeal spasms Confusion Delirium Hallucinations Marked hyperactivity Anxiety Agitation Depression	Pituitary dysfunction Hypoventilation Apnea Hypotension Cardiac arrhythmia Cardiac arrest Coma	Pneumothorax Intravascular thrombosis Secondary infections

Adapted from CDC Advisory Committee on Immunization Practices 2010[9] and Consales 2007.[42]

Furious Rabies

People with furious rabies (~70% of all human cases) exhibit fever, pharyngitis, hyperactivity, agitation, hydrophobia (fear of water), hypersalivation, seizures, and sometimes aerophobia (fear of drafts or of fresh air). Patients eventually fall into a coma, and inspiratory spasms increase. Viral involvement at the sinus or atrioventricular node and myocarditis as well as changes in the cardiac rhythm and function may also occur. Death occurs after a few days due to cardiorespiratory arrest.[6,7,42]

Paralytic Rabies

Paralytic rabies accounts for ~30% of the total number of human cases. This type of rabies has a less dramatic and usually longer course than the furious form. Muscles gradually become paralyzed, starting at the site of the bite or scratch. A coma slowly develops, and eventually death occurs, as described for furious rabies. It has been suggested that the paralytic form of rabies is often misdiagnosed, contributing to the underreporting of the disease.[6]

Analysis of the glycoprotein, nucleoprotein, and phosphoprotein genes of rabies viruses from two human cases, one of furious and one of paralytic rabies, demonstrated only minor nucleotide differences and suggested that clinical manifestations of rabies may not be explained solely by the associated RABV variant.[43] However, it has been demonstrated in dogs naturally infected with RABV that intercellular transport of the virus occurs more rapidly in those with furious symptoms versus those with paralytic symptoms.[44]

Diagnosis of Rabies

Several tests are necessary to diagnose rabies antemortem (before death) in humans; and no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens may be assessed for rabies antigen in the cutaneous nerves at the base of hair follicles.[45] Importantly, none of these tests are widely employed in routine clinical practice.

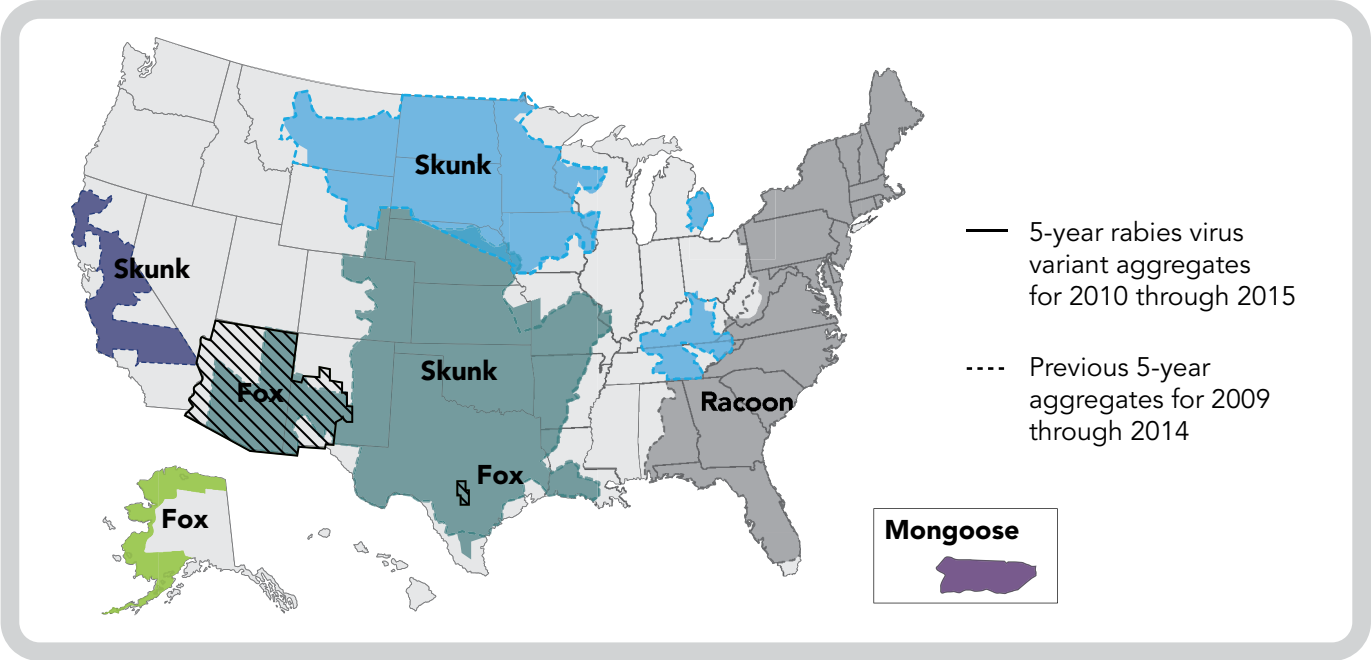
Several tests are necessary to diagnose rabies antemortem (before death) in humans; and no single test is sufficient.[45] Importantly, none of these tests are widely employed in routine clinical practice.

UNITED STATES DATA

Surveillance

Since 1980, wildlife has accounted for >90% of all rabid animals reported in the United States. The 5 species considered primary reservoirs include raccoons, bats, skunks, foxes, and mongooses (in Puerto Rico). Although cross-species transmission of rabies does occur (eg, infection of domestic dogs with the raccoon rabies variant), RABV variants are primarily transmitted within a single species that is the reservoir of that variant. RABV variants associated with raccoons, skunks, foxes, and mongooses are distributed in distinct geographic regions (Figure 6). Those associated with bats are broadly distributed across the geographic ranges associated with specific bat species.[46]

Figure 6. Distribution of Major Rabies Virus Variants Among Mesocarnivores in the United States and Puerto Rico for 2014 and 2015



Adapted from Birhane 2017.[46]

During 2015, 50 states and Puerto Rico reported 5508 rabid animals. Three human rabies deaths in the United States were reported to the Centers for Disease Control and Prevention (CDC) in 2015. Of the 5508 cases in the United States of animal rabies, 5088 (92.4%) involved wildlife. Relative contributions by the major animal groups were as follows: 1704 (30.9%) bats, 1619 (29.4%) raccoons, 1365 (24.8%) skunks, 325 (5.9%) foxes, 244 (4.4%) cats, 85 (1.5%) cattle, and 67 (1.2%) dogs.[46]

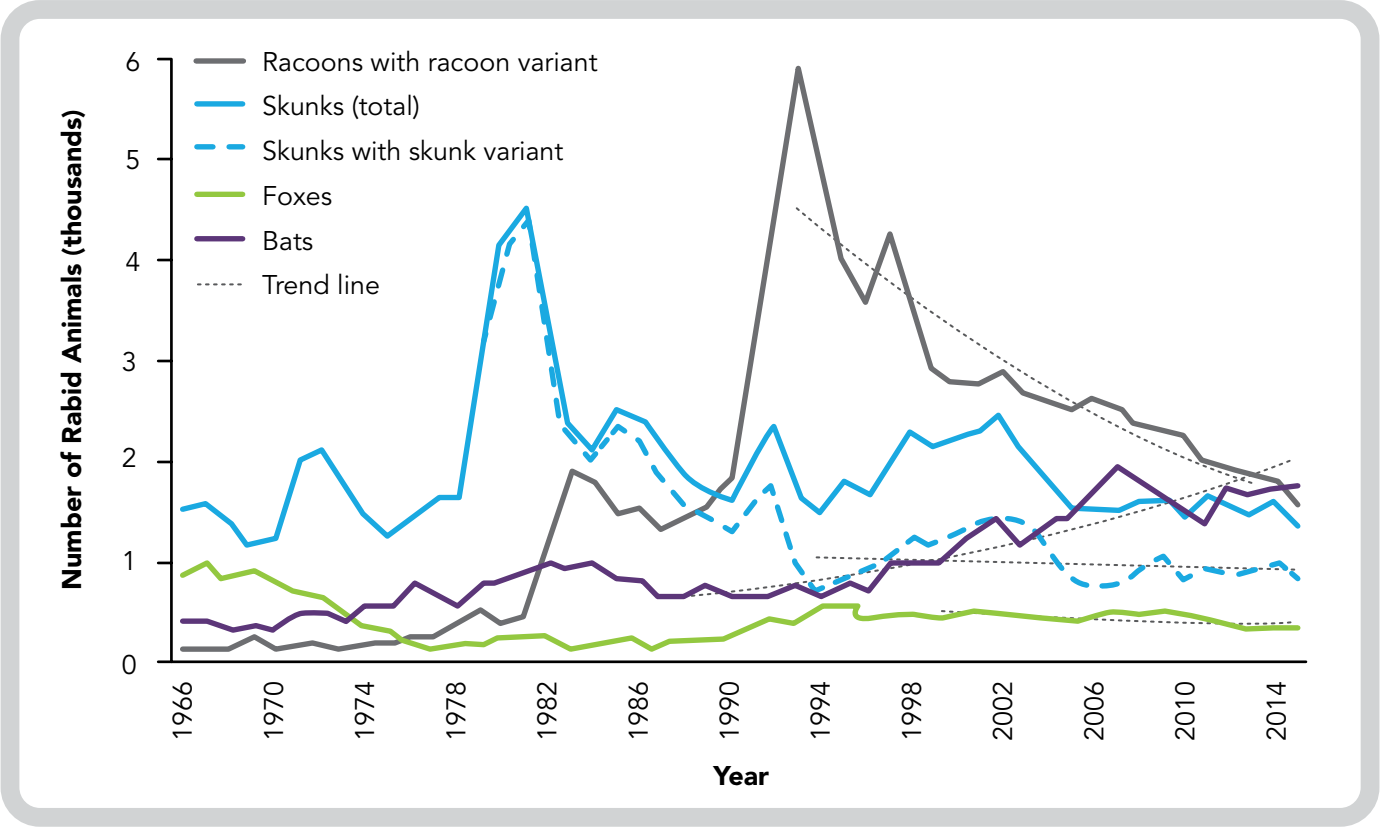
In Figure 6, the diagonal black lines represent fox rabies variants (Arizona gray fox and Texas gray fox). Solid borders represent 5-year rabies virus variant aggregates for 2010 through 2015; dashed borders represent the previous 5-year aggregates for 2009 through 2014.

The CDC has noted that there have been reductions in the prevalence of rabies among wildlife in North America and Europe that have resulted from vaccination programs using orally administered vaccines targeting primarily raccoons, coyotes, and foxes (Figure 7). However, vaccination of bats is not currently feasible. As a result, preventing human infections with bat-associated rabies virus variants relies on secondary intervention methods such as health education, exposure prevention, and PEP.[46]

The results shown in Figure 7 refer to skunk and raccoon variants of the rabies virus. The reservoir species responsible for maintaining the 8 terrestrial rabies virus variants in the United States are raccoons (raccoon variant), skunks (south central, north central, and California skunk variants), gray foxes (Texas and Arizona gray fox variants), arctic foxes (arctic fox variant), and mongooses (dog-mongoose variant in Puerto Rico). In addition to the terrestrial rabies virus variants, there are at least 20 variants associated with bats.[46]

Because there is frequent spillover of the raccoon variant into skunks, trends for skunks with skunk rabies virus variants and for skunks with the raccoon rabies virus variant were analyzed and presented separately in Figure 7.[46]

Figure 7. Cases of Rabies Among Wildlife in the United States, by Year and Species, for 1966 Through 2015



Adapted from Birhane 2017.[46]

Domestic Animals—Livestock

Historically, there has been relatively little concern regarding rabies infection in livestock and individuals working with such animals may not be aware of their risk for exposure.[47] However, domestic animals accounted for 48.7% of all animals submitted for rabies testing in 2015. Of these, 7.6% were positive. A total of 85 rabid cattle, 14 rabid horses and mules, and 7 rabid sheep and goats was reported in 2015 (Table 1).[46]

Table 1. Number of Animals Reported to Be Rabid in the United States and Percentages of Samples Tested for Rabies That Yielded Positive Results for 2015

	Animals	Number of Rabid Animals	Percentage of Samples With Positive Results
Domestic Animals	Cats	244	1.1
	Cattle	85	6.8
	Dogs	67	0.3
	Horses and Mules	14	2.0
	Sheep and Goats	7	1.3
Wildlife	Racoons	1619	13.1
	Bats	1704	6.6
	Skunks	1365	28.1
	Foxes	325	18.8
	All Rabid Animals	5508	5.5
	Rabid Domestic Animals	420	0.9
	Rabid Wildlife	5088	10.3

Adapted from Birhane 2017.[46]

Rabies can be transmitted by bites from or the saliva of domestic livestock. A total of 85 rabid cattle, 14 rabid horses and mules, and 7 rabid sheep and goats were reported in 2015.[46]

Wild Animals

Wild animals accounted for 92.4% of the animal rabies cases reported in 2015. Bats were the most frequently reported rabid animals in the United States (30.9% of all cases), followed by raccoons (29.4%), skunks (24.8%), foxes (5.9%), other wild animals (0.7%), and rodents and lagomorphs (0.6%).[46]

> Bats are the most common source of human rabies in the United States.[8]

It is important to note that bats are the most common source of human rabies in the United States. Among the 19 naturally acquired cases of rabies in humans in the United States from 1997-2006, 17 were associated with bats. In addition, some people, when asleep, may not be aware of the presence of a bat, and may not awaken even from the bite of a bat. Not realizing they have been exposed, they would not report it and not receive proper PEP.[8] Because bats have small teeth, it is possible to be bitten by a bat and not realize it (Figure 8).[48]

Figure 8. Example of a Small, Difficult to Recognize Bat Bite

Adapted from Texas A&M AgriLife Extension Service 2017.[49]

PATIENT MANAGEMENT

Symptomatic Patients

By the time symptoms develop, infection has already been widely established throughout the CNS. Treatment of symptomatic patients is almost uniformly unsuccessful and infection almost always progresses to coma and death.[3,6]

Current diagnostic tools are not suitable for detecting rabies infection before the onset of clinical disease, and unless the rabies-specific signs of hydrophobia or aerophobia are present, clinical diagnosis may be difficult.[6] Rabies should be included in the standard differential diagnosis of all patients presenting with a possible unexplained, acute, progressive viral encephalitis in the emergency room.

> Current diagnostic tools are not suitable for detecting rabies infection before the onset of clinical disease.[6]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.

Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.

Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, appropriate laboratory testing should be performed and medical therapy administered as indicated.

PEP Current Guidance

PEP for Individuals Not Previously Vaccinated Against Rabies

The overall treatment scheme for PEP is summarized in Table 2.

For people who have never been vaccinated against rabies previously, PEP should always include administration of both passive antibody and vaccine.[9]

Table 2. PEP for Rabies

Vaccination Status	Intervention	Regimen*
Not Previously Vaccinated	Wound Cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (eg, povidine-iodine solution) should be used to irrigate the wounds
	Human Rabies Immune Globulin (HRIG)	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because HRIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered. See pages 56-57 for complete information on dosage and administration of KEDRAB
	Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†), 1 each on days 0,‡ 3, 7, and 14
Previously Vaccinated§	Wound Cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds
	Human Rabies Immune Globulin (HRIG)	HRIG should not be administered
	Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area†), 1 each on days 0‡ and 3

*These regimens are applicable for persons in all age groups, including children.
†The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
‡Day 0 is the day dose 1 of vaccine is administered.
§Any person with a history of pre-exposure vaccination with HDCV, PCECV, or rabies vaccine adsorbed (RVA); prior PEP with HDCV, PCECV or RVA; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

NOTE: For persons with immunosuppression, rabies PEP should be administered using all 5 doses of vaccine on days 0, 3, 7, 14, and 28.

Adapted from CDC Advisory Committee on Immunization Practices 2010.[9]

For people who have never been vaccinated against rabies previously, PEP should always include administration of both passive antibody and vaccine. The combination of HRIG and vaccine is recommended for both bite and nonbite exposures, regardless of the interval between exposure and initiation of treatment.[9] The passive administration of HRIG is intended to provide an immediate supply of virus neutralizing antibodies to bridge the gap until the production of active immunity in response to vaccine administration. Use of HRIG provides a rapid, passive immunity that persists for a short time (half-life of approximately 21 days).[11] Concomitant use of an active rabies vaccine assures continuous protection, as the recipient's active antibody levels rise within 7 to 10 days.[9]

Administration of KEDRAB HRIG[1]

When the bite site is known and infiltration at the bite site is feasible: Infiltrate as much of the dose as possible into and around any detectable bite wounds. Inject any remaining volume intramuscularly into the upper arm deltoid region or, in small children, into the anterolateral aspect of the thigh. Administer the remaining KEDRAB at site(s) distant from the site of the rabies vaccine. Avoid administration into the gluteal region, where absorbance is unpredictable (unless the exposure site is in the gluteal region).

When the bite site is unknown or indeterminate (undetectable) or if infiltration is difficult at the bite site (eg, 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. If intramuscular administration is contraindicated (eg, in patients with uncorrectable bleeding disorders), administer KEDRAB subcutaneously. However, note that there are no clinical efficacy data to support administration of KEDRAB by the subcutaneous route.

Do not mix KEDRAB with the rabies vaccine or administer in the same syringe with the rabies vaccine. No more than the recommended dose of KEDRAB should be given because KEDRAB partially suppresses active antibody production following vaccination.

KEDRAB should be administered at a dose of 20 IU/kg body weight. Infiltrate as much of the dose as possible into and around any detectable bite wounds. Inject any remaining volume intramuscularly into the upper arm deltoid region or, in small children, into the anterolateral aspect of the thigh.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. After KEDRAB administration, immunization with measles vaccine should be avoided within 4 months; other live attenuated virus vaccines avoided within 3 months.

Who Should Receive PEP After an Animal Bite?

The decision to start PEP is based on type of exposure and the animal involved, as well as laboratory and surveillance information for the geographic area where the exposure occurred (Table 3).[11]

Table 3. Recommendations for Rabies PEP

Animal Type	Evaluation and Disposition of Animal	PEP Recommendations
Dogs, cats, and ferrets	Healthy and available for 10-day observation	Persons should not begin prophylaxis unless animal develops clinical signs of rabies*
	Rabid or suspected rabid	Immediately begin prophylaxis
	Unknown (eg, escaped)	Consult public health officials
Skunks, racoons, foxes, and most other carnivores; bats†	Regarded as rabid unless animal proven negative by laboratory tests‡	Consider immediate prophylaxis
Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually	Consult public health officials. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require anti-rabies PEP

*During the 10-day observation period, begin PEP at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.
†PEP should be initiated as soon as possible following exposure to such wildlife unless the animal is available for testing and public health authorities are facilitating expenditious laboratory testing or it is already known that brain material from the animal has tested negative. Other factors that might influence the urgency of decision-making regarding initiation of PEP before diagnostic results are known include the species of the animal, the general appearance and behavior of the animal, whether the encounter was provoked by the presence of a human, and the severity and location of bites. Discontinue vaccine if appropriate laboratory diagnostic test (ie, the direct fluorescent antibody test) is negative.
‡The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended.

Adapted from CDC Advisory Committee on Immunization Practices 2008.[11]

Raccoons, skunks, foxes, most other carnivores, and bats should be considered rabid unless proven negative by laboratory tests. PEP—wound cleansing, administration of HRIG, such as KEDRAB, and rabies vaccination—should be initiated immediately, then discontinued if the results of laboratory testing are negative.[11]

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

Domestic Animals: Dogs, Cats, and Ferrets

If animals are healthy and available for 10-day observation, then persons should not begin prophylaxis unless the animal develops clinical signs of rabies during the observation period. If the animal is rabid or suspected of being rabid, PEP should be initiated immediately. If the status of the animal is not known, public health officials should be consulted.[11]

Wild Animals

Raccoons, skunks, foxes, most other carnivores, and bats should be considered rabid unless proven negative by laboratory tests. PEP should be initiated immediately, then discontinued if the results of laboratory testing are negative.[11]

Livestock, Small Rodents, Large Rodents, and Other Mammals

Each of these animals should be considered individually and public health officials should be consulted.[11]

Should PEP Be Delivered if No Bite Is Evident?

It has been suggested that if a person finds that he or she has been sleeping in the same room with a bat, a healthcare professional should be seen as soon as possible. The CDC has provided the following recommendations regarding action to be taken following exposure to a bat[50]:

- Rabies PEP is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies
- PEP should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite, scratch, or mucous membrane exposure did not occur
- In instances in which a bat is found indoors and there is no history of bat–human contact, the likely effectiveness of PEP must be balanced against the low risk such exposures appear to present:
  - PEP can be considered for persons who were in the same room as a bat and who might be unaware that a bite or direct contact had occurred (eg, a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person) and rabies cannot be ruled out by testing the bat
  - PEP would not be warranted for other household members

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).

WHAT IS KEDRAB?

KEDRAB™ (Rabies Immune Globulin [Human]) is a sterile, aqueous ready-to-use solution with a nominal potency of 150 IU/mL of anti-rabies immune globulin (human).[1] It is prepared by chromatographic fractionation from a pool of plasma collected from selected adult human donors who have been immunized with rabies vaccine and have developed high titers of anti-rabies antibody.[2] KEDRAB has been developed by Kedrion Biopharma and Kamada Ltd. to secure availability in the United States, a market that has experienced inconsistent supply and supply shortages in recent years.[51]

KEDRAB Indication[1]

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

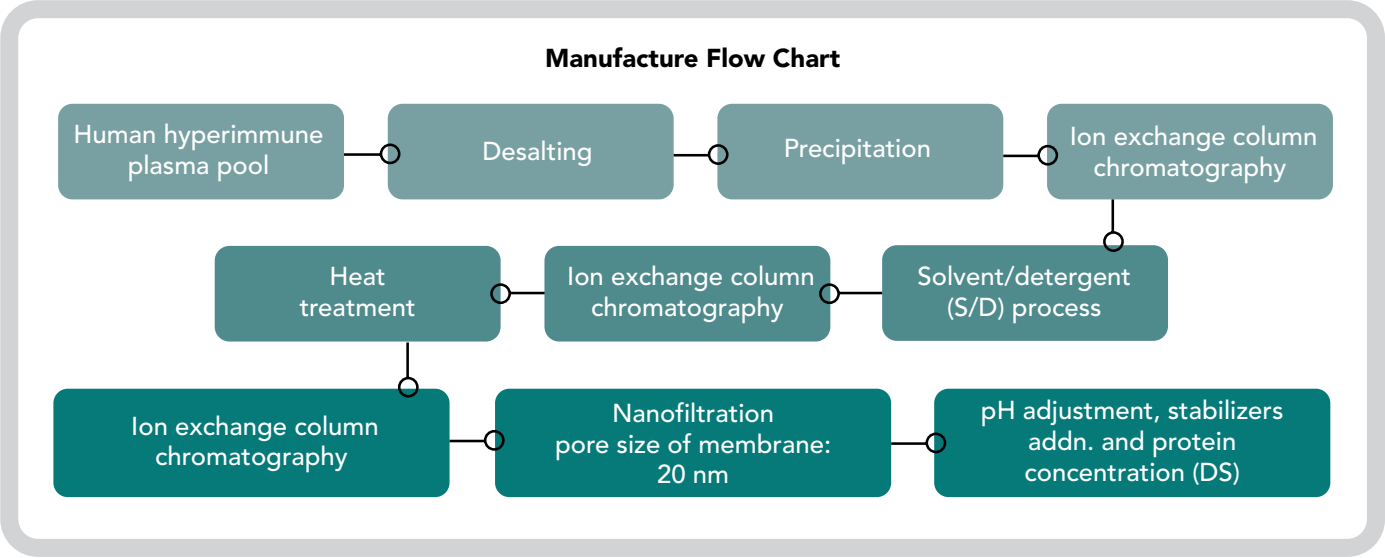
- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

Manufacture of KEDRAB

KEDRAB™ (Rabies Immune Globulin [Human]) is prepared from the plasma of healthy donors who have been immunized with rabies vaccine and have developed high titers of anti-rabies antibody in their blood (hyperimmune plasma). The plasma is processed and purified using a series of ion exchange chromatographic procedures (Figure 9).[2]

Figure 9. Steps in the Manufacture of KEDRAB



Adapted from Data on file. Kedrion Biopharma Inc.[52]

Reducing the Risk for Transmission of Viral Disease

Donor Screening

Prior to donation, the suitability of a donor is determined by a donor questionnaire and physical examination. Donors from high risk categories, such as prostitutes, men who have had sex with men, and intravenous (IV) drug users, are excluded from donating. The risk of including donors in the plasma pool, who might be at risk of potentially transmitting known virus pathogens, or Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt-Jakob Disease (vCJD) by their blood and blood products, is reduced by compliance with the Recommended Donor Deferral Criteria as it appears in the United States Food and Drug Administration Guidance for Industry. Donors are permanently excluded if they have evidence of one of the following viral infections: human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV). In addition to viral infections, having transmissible spongiform encephalopathy (TSE) or a family history of CJD excludes donors.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in KEDRAB.

Plasma Testing

Each unit of plasma is tested for hepatitis B surface antigen (HBsAg) and antibodies to HIV types 1 and 2 (anti HIV-1/2). Because viremia precedes serum conversion to these blood-borne infections by several days to weeks, Nucleic Acid Amplification Technology (NAT) testing is performed to detect early infection within the infectious window period for HIV, HBV, and HAV in source plasma pools. The tests are performed on each donation individually and/or on mini-pools, which enables traceability of a positive result to the individual plasma unit. After the plasma units are pooled, the manufacturing pool is screened and must be nonreactive to HBsAg, anti HIV-1/2, and the level of parvovirus B19 by NAT should be not more than 10^4 IU/mL.[2]

Viral Inactivation Steps

Three specific viral inactivation/removal steps are employed in the manufacture of KEDRAB[2]:

1. Treatment with solvent/detergent (S/D) for inactivation of lipid-enveloped viruses
2. Heat treatment (pasteurization) (58-61˚C for NLT 9.5 hours) for inactivation by denaturation of heat-labile viruses
3. Nanofiltration using Planova™ 20N filters for the size-exclusion of both lipid-enveloped and nonenveloped viruses

The characteristics of the viruses evaluated in the viral inactivation/removal assessment for KEDRAB and reductions in the concentrations of these viruses in experimentally spiked samples are summarized in Tables 4 and 5, respectively. Some of the purification process steps for KEDRAB, such as euglobulin precipitation and ion exchange chromatography, are also known to contribute to virus removal. However, these processes have not been validated for the robustness of virus removal.[2]

Three specific viral inactivation/removal steps are employed in the manufacture of KEDRAB.[1]

Table 4. Viruses Used in Validation Studies for KEDRAB

Virus	Full Name	Family	Rationale	Envelope	Genome	Approx. Size (nm)
BVDV	Bovine viral diarrhea virus	Flaviviridae	Model for hepatitis C virus and WNV	+	RNA	50-70
EMCV	Encephalomyo-carditis virus	Picornaviridae	Model for non-enveloped viruses for which anti-bodies are unlikely to be present and for possible unknown viruses	-	RNA	28-30
HIV-1	Human immunodeficiency virus type 1	Retroviridae	Relevant contaminant and model for other human retroviruses such as HIV-2 and HTLV 2	+	RNA	80-130
PPV	Porcine parvovirus	Parvoviridae	Model for parvovirus B19	-	DNA	18-26
PRV	Pseudorabies virus	Herpesviridae	Model for herpes viruses, which are a potential human contaminant; also employed as a model for other enveloped DNA viruses that cannot be readily assayed (eg, hepatitis B virus)	+	DNA	150-200
WNV	West Nile virus	Flaviviridae	Potential contaminant	+	RNA	40-60

BVDV, bovine viral diarrhea virus; EMCV, encephalomyocarditis; HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus; PPV, porcine parvovirus; PRV, pseudorabies virus; WNV, West Nile virus.

Adapted from Data on file. Kamada Ltd.[2] and Department of Health and Human Services AIGIV BLA 2017.[53]

IMPORTANT SAFETY INFORMATION (CONTINUED)

In clinical trials, the most common adverse reactions in subjects treated with KEDRAB were injection site pain (33%), headache (15%), muscle pain (9%), and upper respiratory tract infection (9%).

Table 5. Log_{10} Virus Reduction During Manufacture of KEDRAB

Process	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

BVDV, bovine viral diarrhea virus; EMCV, encephalomyocarditis virus; HIV, human immunodeficiency virus; PPV, porcine parvovirus; PRV, pseudorabies virus; S/D, solvent/detergent; WNV, West Nile virus.

Adapted from KEDRAB Prescribing Information.[1]

Despite these measures, KEDRAB administration can still potentially transmit infectious diseases. There is also the possibility that unknown infectious agents may be present in KEDRAB.[1]

To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. Customer Service (1-855-353-7466) in the United States. Outside of the United States, the company distributing these products should be contacted. Voluntary reporting of adverse reactions may also be made to the FDA through MedWatch at 1-800-FDA-1088 or at www.fda.gov/medwatch.

Pharmacologic Studies of KEDRAB in Healthy Volunteers

Summary of Studies

KEDRAB™ (Rabies Immune Globulin [Human]) has been evaluated in 3 studies, and the designs and results of these trials are summarized in Table 6.

Table 6. Studies of KEDRAB

Study 23630 (Completed in 2004) Phase 1

Design	Objective	Treatments and Blood Sampling	Number of Subjects	Conclusions
Balanced, randomized, single-dose, two-period, two-treatment, two-sequence, double-blind, crossover study[1]	To compare the PK profile of rabies antibody in the blood of healthy subjects receiving KEDRAB and comparator HRIG in a crossover mode[1]	• 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[1] • Blood samples for determination of plasma levels of rabies antibodies were drawn at screening, at pre-dose, and on days 3, 7,14, 28, 35, and 42 post-dose in each period of the study[2]	26 healthy volunteers (of these, 23 subjects received both products)[2]	• RVNA titer PK parameters were quantitatively similar following treatment with KEDRAB or comparator HRIG[2] • Point estimates of ratios of test to reference geometric LS means for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were within the 80-125% bioequivalence range; however, the lower bound of the 90% CI intervals were less than 80% (the required 90% CI lower limit for bioequivalence)[2]

AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; IM, intramuscular; PK, pharmacokinetic; RVNA, rabies virus neutralizing antibody; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum concentration.

Adapted from KEDRAB Prescribing Information[1] and Data on file. Kamada Ltd.[2]

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

IMPORTANT SAFETY INFORMATION

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).

Table 6.2. Studies of KEDRAB (Continued)

Study 24061 (Completed in 2004) Phase 1[2]

Design	Objective	Treatments and Blood Sampling	Number of Subjects	Conclusions
Balanced, randomized, double-blind, parallel study of KEDRAB injection or placebo plus three injections of active vaccine (Rabipur®) in healthy volunteers	To assess whether KEDRAB interferes with the development of active antibodies when given simultaneously with active rabies vaccine (Rabipur®)	• Subjects were randomly assigned to a single dose of IM KEDRAB injection (20 IU/kg) or placebo (normal saline 0.133 mL/kg) on day 0 and, in addition, 3 IM injections of active vaccine (Rabipur®) on days 0, 7, and 28 • Blood samples for determination of plasma levels of rabies antibodies were drawn at screening, at pre-dose, and 3, 7, 14, 28, 35, and 42 days after KEDRAB/ placebo injection	16 healthy volunteers	• Anti-rabies antibody titer PK parameters C_{max} and $AUC_{0\text{-last}}$ were substantially lower following KEDRAB plus active vaccine (Rabipur®) injections compared with placebo plus active vaccine injections • Subjects who received either KEDRAB or placebo injections had antibody levels <0.5 IU/mL (the WHO recommended minimum titer) until day 14 • On day 14, average titers were above the threshold values in both groups (1.22 IU/mL in the KEDRAB group and 5.05 IU/mL in the placebo group) • This observed lower titer in KEDRAB group is expected and consistent with results of prior studies

AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; IM, intramuscular; PK, pharmacokinetic; RVNA, rabies virus neutralizing antibody; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum concentration.

Adapted from KEDRAB Prescribing Information[1] and Data on file. Kamada Ltd.[2]

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

Table 6.3. Studies of KEDRAB (Continued)

Study 003 (Completed in 2014) Phase 2/3

Design	Objective	Treatments and Blood Sampling	Number of Subjects	Conclusions
Single-center, prospective, randomized, double-blind, parallel-group study of KEDRAB vs comparator HRIG when co-administered with active rabies vaccine in healthy volunteers[1]	To determine whether KEDRAB interferes with the development of self-active antibodies when given simultaneously with rabies vaccine, as compared to comparator HRIG, when coadministered with active rabies vaccine[2]	• Subjects were randomized to receive a single dose of KEDRAB (20 IU/kg) and the first dose of the rabies vaccine (RabAvert®, 1 mL of ≥2.5 IU/mL) on day 0[1] • Subjects subsequently received 4 more doses of rabies vaccine during the treatment period at days 3, 7, 14, and 28[1] • Blood samples for determination of plasma levels of rabies antibodies were collected at days 0, 3, 7, 14, 28, 49, 185, and/or early discontinuation, if applicable[2]	118 healthy volunteers (59 subjects in each group)[1]	• There were no statistically significant differences in plasma RABV neutralizing antibody titer PK parameters (C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, or $t_{1/2}$) between the KEDRAB and comparator HRIG groups[2] • Plasma RABV neutralizing antibody titer-time profiles following IM injection were similar in the KEDRAB and comparator HRIG groups in each time point[1] • For the majority of the PK sampling visits, there was no statistically significant difference reported for the geometric mean of the plasma RABV neutralizing antibody titer between the KEDRAB and comparator HRIG groups; however, the geometric mean RABV neutralizing antibody titer on the day 3 visit was statistically significantly lower in the KEDRAB group vs comparator HRIG group (P=0.0003)[2] • On days 3 and 7, mean and geometric mean RABV neutralizing antibody titers in the KEDRAB and comparator HRIG groups were <0.5 IU/mL; mean RABV antibody titer values in both groups exceeded 0.5 IU/mL on day 14, and at each time point thereafter[2]

AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; IM, intramuscular; PK, pharmacokinetic; RVNA, rabies virus neutralizing antibody; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum concentration.

Adapted from KEDRAB Prescribing Information[1] and Data on file. Kamada Ltd.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin. KEDRAB should be discontinued immediately if there is an allergic or anaphylactic type reaction. In case of shock, standard medical treatment should be implemented. Epinephrine should be available.

Study 23630

Objectives

This phase 1, randomized, single-dose, double-blind, two-period, crossover PK study comparing KEDRAB™ (Rabies Immune Globulin [Human]) with HyperRAB® had two objectives[2]:

1. To evaluate the PK of rabies antibody in the blood of healthy subjects receiving KEDRAB injection (without previous immunization)
2. To evaluate any adverse events after administration of a 20 IU/kg, single IM injection of KEDRAB

Number of Subjects

The study included 26 male and female subjects between 18 and 45 years of age, likely to receive pre-exposure rabies immunization due to their occupation, and not previously vaccinated. All subjects were negative for rabies antibodies by the rapid fluorescent focus inhibition test (RFFIT).[2]

In a standard noninferiority study, plasma anti-rabies antibody titers achieved with KEDRAB were comparable to those observed with HyperRAB®.[2]

Rapid Fluorescent Focus Inhibition Test

The RFFIT is regarded as the standard rabies virus neutralization assay in diagnostic laboratories, vaccine and biotherapeutic characterization, and rabies-related clinical studies. The RFFIT procedure is used to measure the level of rabies virus neutralizing antibody activity against the challenge virus standard 11 (CVS-11) strain of rabies virus in human serum samples.[54]

Treatment and Blood Sampling

On day 0, all subjects received IM doses of not more than 5 mL per site of either KEDRAB or HyperRAB®, and the PK of anti-rabies antibodies was subsequently measured in the subjects' blood. Blood samples were taken on days 0, 3, 7, 14, 28, 35, and 42 for measurement of rabies antibodies by RFFIT. This was followed by a washout period ≥21 days, after which the alternative product, was injected followed by repeat sampling as above.[2]

Key PK Results

PK parameters for the two treatments are summarized in Table 7 and time versus concentration curves for plasma anti-rabies antibodies for the two treatments are shown in Figure 10.

Table 7. Median Anti-Rabies Antibody Titer PK Findings for Each Dose Administered

Treatment	C_{max} (IU/mL)	T_{max} (days)	AUC_T (days•IU/mL)	AUC_I (days•IU/mL)	$T_{1/2}$ (days)
KEDRAB 20 IU/kg	0.249 (0.063)	7.0 (3-14)	5.2 (1.3)	6.7 (1.27)	17.9 (6.37)
HyperRAB® 20 IU/kg	0.302 (0.068)	3.0 (3-14)	6.3 (1.24)	8.0 (1.36)	17.8 (6.74)

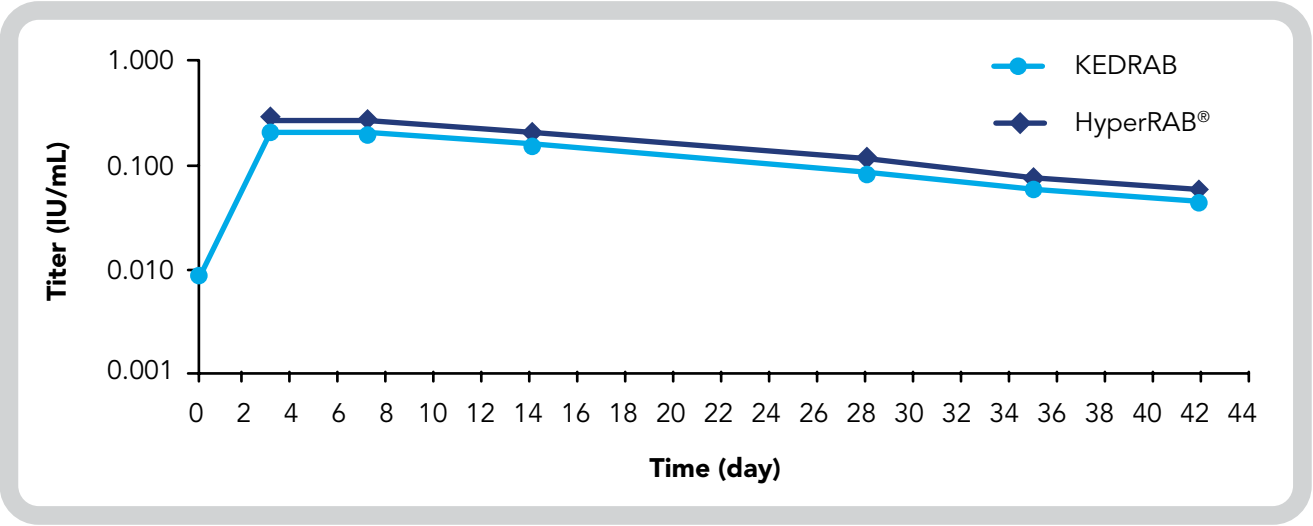
All values in parentheses are mean and standard deviation except T_{max} which is median (range).
AUC, area under the concentration-time curve; C_{max}, maximum concentration; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum concentration.

Adapted from Data on file. Kamada Ltd.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity. KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.

Figure 10. Mean Plasma Anti-Rabies Antibody Titer Concentrations Versus Time Profile (Log Scale Following the Administration of IM KEDRAB 20 IU/kg and IM HyperRAB® 20 IU/kg)



Adapted from Data on file. Kamada Ltd.[2]

Summary of Study Results[2]

- The point estimate for the ratio of anti-rabies antibody titer AUC_T values of the KEDRAB and HyperRAB® was 82.3 (90% CI, 77.4%-87.64%)
- The point estimate for the ratio of anti-rabies antibody titer AUC_I values of KEDRAB and HyperRAB® was 84.4 (90% CI, 78.6%-90.7%)
- There was no statistically significant difference (*P*=0.4491) in anti-rabies antibody titer T_{max} between KEDRAB and HyperRAB®
- There is a marginally statistically significant sequence effect seen in C_{max} (*P*=0.0415) and AUC_T (*P*=0.0329). While this indicates a slight difference between the two products, it is apparently due to a treatment by period interaction
- Overall, plasma anti-rabies antibody titers achieved with KEDRAB were comparable to those observed with HyperRAB®

Study 24061

Objectives

This phase 1, double-blind, one-period, single-dose study that evaluated the PK of KEDRAB when administered with 3 doses of rabies vaccine (Rabipur®) had two objectives[2]:

1. To assess whether KEDRAB interfered with the development of active antibodies when given simultaneously with the active rabies vaccine
2. To monitor the subjects for safety and adverse events after the coadministration of a single IM injection of KEDRAB and repeated injections of an active rabies vaccine

Number of Subjects

The study included 16 male and female subjects between 18 and 45 years of age, likely to receive pre-exposure rabies immunization due to their occupation, and not previously vaccinated. All subjects were negative at baseline for rabies antibodies by the RFFIT.[2]

Treatment and Blood Sampling

On day 0, subjects (n=8 in each group) received an IM dose of 20 IU/kg of KEDRAB or a saline placebo. All subjects also received IM injections of Rabipur® on days 0, 7, and 28. Blood samples were drawn on days 0, 3, 7, 14, 28, 35, and 42 for measurement of rabies antibodies by RFFIT.[2]

Key PK Results

PK parameters for anti-rabies antibodies for the KEDRAB and saline treatment groups are summarized in Table 8, and time versus concentration curves for plasma anti-rabies antibodies for the two treatments are shown in Figure 11.

Table 8. Median Anti-Rabies Antibody Titer Pharmacokinetic Findings for Each Dose Administered

Treatment	C_{max} (IU/mL)	T_{max} (days)	AUC_T (days*IU/mL)
KEDRAB 20 IU/kg	9.4 (10.72)	42 (42-42)	85.2 (92.2)
Saline Placebo	24.0 (21.1)	42 (14-42)	276.3 (204.7)

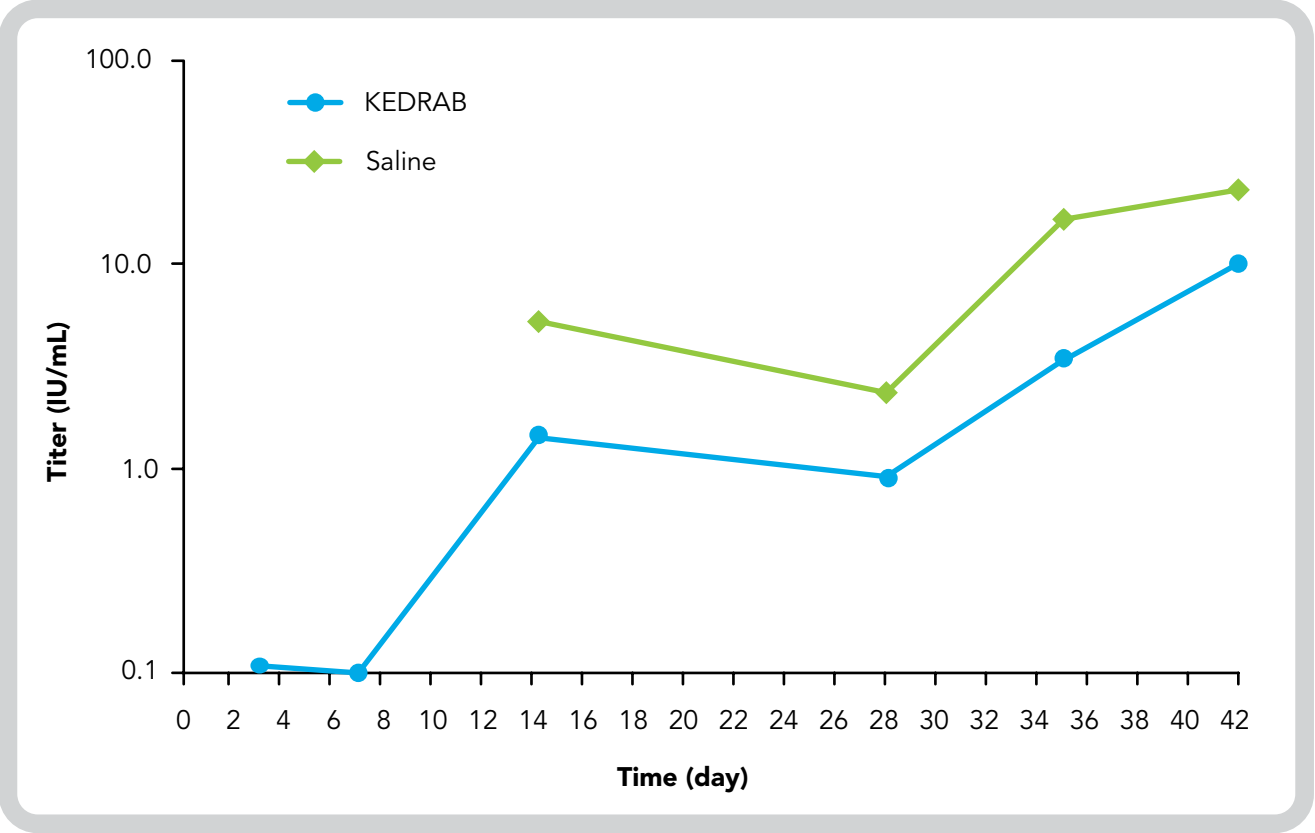
All values in parentheses are mean and standard deviation except T_{max} which is median (range).
AUC, area under the concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration.

Adapted from Data on file. Kamada Ltd.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.

Figure 11. Mean Plasma Anti-Rabies Antibody Titer Concentrations Versus Time Profile (Semi-Log Scale) Following Administration of IM KEDRAB 20 IU/kg or Saline With Three Doses of Rabipur®



Adapted from Data on file. Kamada Ltd.[2]

Summary of Study Results

- The C_{max} for rabies antibodies for KEDRAB™ (Rabies Immune Globulin [Human]) plus vaccine appeared to be substantially lower than the C_{max} for placebo plus vaccine (42.9%). However, there was no statistically significant difference between values due to the high variability in the data[2]
- The mean AUC_T or KEDRAB plus vaccination was statistically significantly lower than mean AUC_T for placebo plus vaccine[2]
- Both of these findings are consistent with the known antibody titer-dampening effect of administering a passive antibody and vaccine concurrently[55,56]

Study 003

Objectives

This phase 2/3, single-center, prospective, randomized, double-blind, parallel-group study that evaluated the safety and effectiveness of KEDRAB versus HyperRAB® when coadministered with rabies vaccine (RabAvert®) had two objectives[2]:

1. To evaluate the safety and tolerability of KEDRAB versus HyperRAB®
2. To determine whether KEDRAB interferes with the development of active anti-rabies antibodies when given simultaneously with active rabies vaccine, as compared to HyperRAB®, also given simultaneously with the active rabies vaccine

A phase 2/3 study of 118 healthy volunteers indicated that KEDRAB, administered with rabies vaccine, resulted in an anti-rabies virus neutralizing antibody titer ≥0.5 IU/mL (the WHO recommended protective level) in 98.2% of patients.[1]

Number of Subjects

The study included 118 healthy adult male and female subjects who were not previously immunized against rabies, exposed to rabies, or recipients of HRIG. Subjects received a single IM dose of 20 IU/kg body weight of KEDRAB or HyperRAB® on day 0 plus IM 1.0-mL doses of rabies vaccine on days 0, 3, 7, 14, and 28. Serum samples for rabies antibody titer by RFFIT were collected on days 0, 3, 7, 14, 28, 49, and 185, and/or at early discontinuation, if applicable. Serum samples for immunogenicity markers were collected at screening, day 0 (prior to drug administration), and days 14, 49, or 185, and/or early discontinuation, if applicable.[52]

IMPORTANT SAFETY INFORMATION (CONTINUED)

Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, appropriate laboratory testing should be performed and medical therapy administered as indicated.

Key Efficacy Results

Nearly all subjects in the KEDRAB™ (Rabies Immune Globulin [Human]) group (55 of 56 subjects; 98.2%) and all subjects in the HyperRAB® group had an anti-rabies antibody titer by RFFIT of ≥0.5 IU/mL on day 14 (Table 9).[1]

Table 9. Subjects With Mean Anti-Rabies Antibody Titer ≥0.5 IU/mL on Day 14, Phase 2/3 Study

	KEDRAB With Rabies Vaccine (N=57)	HyperRAB® 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 (KEDRAB - HyperRAB®) (%)	-1.8	
Exact 90% CI for difference* (%)	(-8.1, 3.0)	

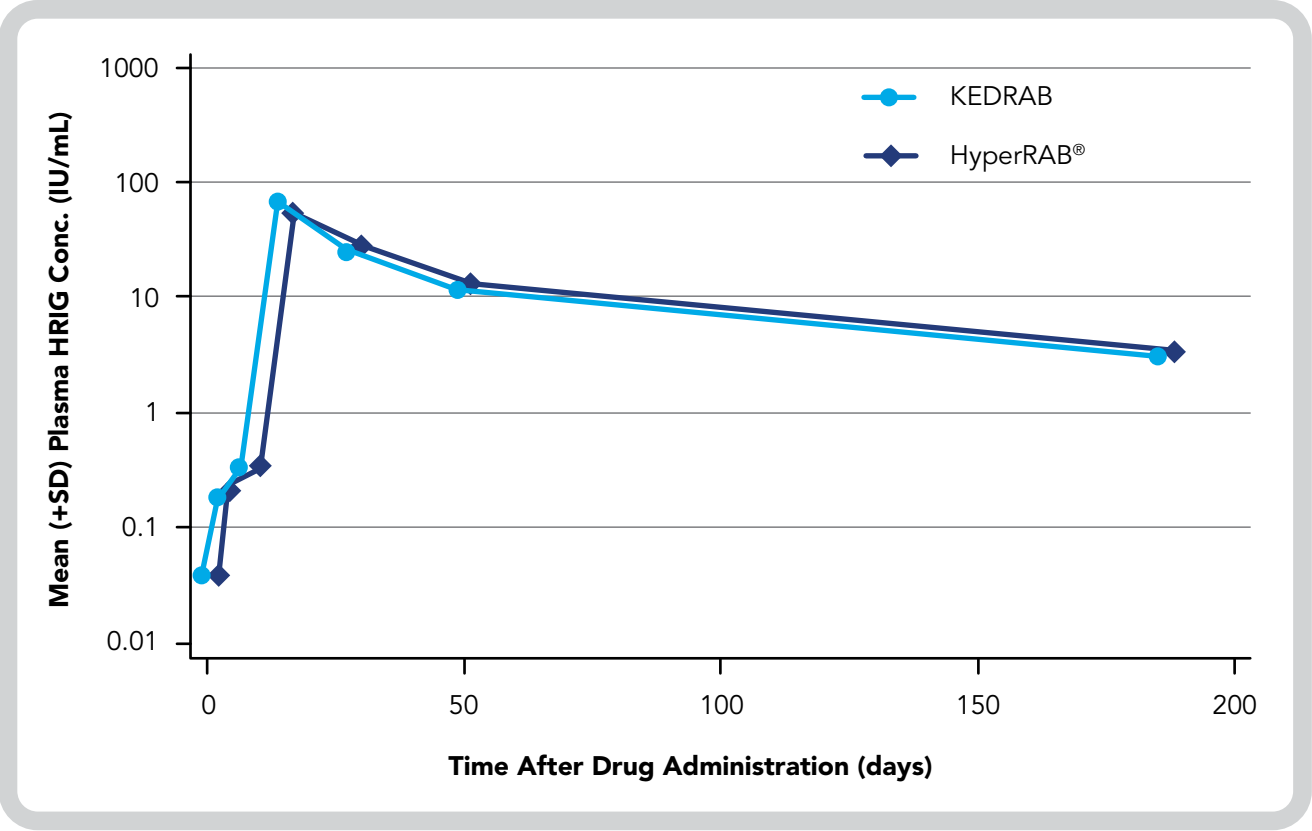
*Based on Farrington-Manning score statistic.
CI, confidence interval.

Adapted from KEDRAB Prescribing Information.[1]

The difference between the proportion of subjects with an anti-rabies antibody titer ≥0.5 IU/mL on day 14 in the KEDRAB and HyperRAB® was -1.8% (90% CI, -8.1 to 3.0). The lower limit of the 90% CI was greater than the prespecified noninferiority margin of -10%, thus demonstrating that KEDRAB was noninferior to HyperRAB® for the primary end point.[52] It should be noted that results from the data from the Kansas State College of Veterinary Medicine, Veterinary Diagnostic Laboratory have indicated that over a 10-year period of assessing patients treated with HRIG and anti-rabies vaccine, ≥1.3% of patients did not achieve an antibody titer of 0.5 IU/mL by day 14. Thus, the data for KEDRAB are consistent with those obtained for other HRIG products (Susan M. Moore, PhD, Personal Communication, 2017).

Mean HRIG concentrations for the KEDRAB and HyperRAB® groups are shown in Figure 12, and PK parameters are summarized in Table 10.

Figure 12. Mean (+SD) Plasma HRIG Concentrations for KEDRAB and HyperRAB®



Adapted from Data on file. Kamada Ltd.[2]

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines. After KEDRAB administration, immunization with measles vaccine should be avoided within 4 months; other live attenuated virus vaccines avoided within 3 months.

Key PK Results

Table 10. PK Comparison of Rabies Virus Neutralizing Antibody Between KEDRAB and HyperRAB® Administered With Rabies Vaccine

Parameter	Units	Geometric LS Mean Values		Test/Reference (%)	90% Confidence Interval (%)
		KEDRAB (Test)	HyperRAB® (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

AUC, area under the concentration-time curve; C_{max}, maximum concentration; inf, infinity.

Adapted from KEDRAB Prescribing Information.[1]

Summary of Study Results[2]

- The rabies virus neutralizing activity (RVNA) on day 3 was lower in the KEDRAB with rabies vaccine group relative to the HyperRAB® 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
- The peak plasma RVNA was 71.9 IU/mL for KEDRAB and 53.9 IU/mL for HyperRAB®. For both treatment groups, the median T_{max} was 14 days
- The half-lives were 48.6 hours and 52.7 hours for KEDRAB and HyperRAB®, respectively
- No statistically significant differences in plasma HRIG PK parameters (C_{max}, $AUC_{0\text{-last}}$, or $AUC_{0\text{-}\infty}$) were observed between the KEDRAB and HyperRAB® groups

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

KEDRAB Safety[1]

Contraindications

None.

Warnings and Precautions

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).

Anaphylactic Shock

- KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin
- Discontinue KEDRAB injection immediately if there is an allergic or anaphylactic type reaction. In case of shock, implement standard medical treatment. Epinephrine should be available for treatment of acute anaphylactic symptoms

Hypersensitivity

- Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity
- KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test).

Thrombosis

- Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration
- Patients at increased risk of thrombosis include patients with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and hyperviscosity syndromes (including cryoglobulinemias, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies)
- Consider measurement of baseline blood viscosity in patients at risk for hyperviscosity

Hemolysis

- Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Patients at increased risk include those with non-O blood group types, those with underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days
- Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, perform appropriate laboratory testing and administer medical therapy as indicated

Live Attenuated Virus Vaccines

- KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines
  - Avoid immunization with measles vaccine within 4 months after KEDRAB administration
  - Avoid immunization with other live attenuated virus vaccines within 3 months after KEDRAB administration

Please see additional KEDRAB Important Safety Information throughout and Full Prescribing Information on pages 64-76.

KEDRAB™
Rabies Immune Globulin (Human)

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, eg, A, B, and D, may interfere with serologic tests for red cell antibodies such as the antiglobulin test (Coombs' test)

Transmissible Infectious Agents

- KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- The risk of transmitting an infectious agent has been minimized by
  - Screening plasma donors for prior exposure to certain viruses
  - Testing for certain viral infections
  - Inactivating and removing certain viruses during the manufacturing process

Despite these measures, KEDRAB administration can still potentially transmit infectious diseases. There is also the possibility that unknown infectious agents may be present in KEDRAB.

Any infection considered to have possibly been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion Biopharma Inc. Customer Service (1-855-353-7466) or FDA at 1-800-FDA-1088.

Adverse Reactions

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. Subjects in the clinical studies of KEDRAB were healthy adults, primarily white and ranged in age from 18 to 72 years. A total of 160 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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in KEDRAB.

Table 11 summarizes adverse events (assessed by the investigator as related or unrelated to study treatment) occurring in >3% of subjects in the clinical trials of KEDRAB. The most frequent adverse events in the KEDRAB group (>6%) were injection site pain, headache, muscle pain, and upper respiratory tract infection (Table 11).[1]

Table 11. Adverse Events Occurring in >3% of Subjects in All Studies Combined

Adverse Reaction	KEDRAB N=91	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)
Upper respiratory tract infection	8 (9)	8 (10)	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	4 (4)	2 (2)	0 (0)
Nausea	4 (4)	3 (4)	0 (0)
Feeling faint	4 (4)	1 (1)	0 (0)
Bruising	3 (3)	1 (1)	0 (0)
Sunburn	3 (3)	0 (0)	0 (0)
White blood cells in urine	3 (3)	4 (5)	0 (0)

Data are represented as the number of subjects (% of subjects).

Adapted from KEDRAB Prescribing Information.[1]

Less common adverse events were joint pain, dizziness, fatigue, abdominal pain, blood in urine, nausea, feeling faint, bruising, sunburn, and white blood cells in urine.

Drug Interactions

- Do not administer additional (repeat) doses of KEDRAB once vaccination has been initiated, since additional doses of KEDRAB may interfere with the immune response to the vaccine

- Do not administer KEDRAB into the same anatomical site(s) as 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

Use in Specific Populations

Pregnancy: 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.

Lactation: 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.

Pediatric Use: The safety and effectiveness of KEDRAB in the pediatric population have not been established.

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).

Patient Counseling Information

The KEDRAB manufacturing process includes three valid and effective viral elimination steps. In addition, the process allows the removal of thrombogenic activity. Inform patients that KEDRAB is made from human plasma and may contain infectious agents that can cause disease (eg, viruses and, theoretically, the CJD agent). Explain that the risk of KEDRAB transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing. Inform patients of symptoms of a possible viral infection, including headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice.

IMPORTANT SAFETY INFORMATION (CONTINUED)

In clinical trials, the most common adverse reactions in subjects treated with KEDRAB were injection site pain (33%), headache (15%), muscle pain (9%), and upper respiratory tract infection (9%).

Dosage and Administration[1]

For wound infiltration and intramuscular use. Do not administer intravenously.

Local Treatment of Wounds prior to KEDRAB Administration

The World Health Organization (WHO) and the U.S. Public Health Service Advisory Committee on Immunization Practices (ACIP) have outlined recommendations for passive and active immunization after exposure to an animal suspected of having rabies. Immediate and thorough cleansing of all bite wounds and scratches with soap and water is an important component of post-exposure prophylaxis (PEP). A virucidal agent (eg, povidone-iodine solution) should be used to irrigate the wounds.

Tetanus prophylaxis and measures to control bacterial infection should be given if medically indicated.

Dosage[1]

Post-exposure prophylaxis consists of a single dose of KEDRAB and a full course of rabies vaccine. The recommended dose of KEDRAB is 20 IU/kg body weight, given at the time of the first vaccine dose. KEDRAB and the first dose of rabies vaccine should be given as soon as possible after exposure, as delays are potentially lethal. However, should a delay occur, KEDRAB should be administered at any time up to and including seven days after the first dose of vaccine. The rabies vaccine should be given according to the manufacturer's instructions.

No more than the recommended dose of KEDRAB should be given because KEDRAB partially suppresses active antibody production following vaccination. For the same reason, additional doses of KEDRAB should not be given, even if the antibody response to vaccination is delayed.

Administration[1]

When the bite site is known and infiltration at the bite site is feasible: Infiltrate as much of the dose as possible into and around any detectable bite wounds. Inject any remaining volume intramuscularly into the upper arm deltoid region or, in small children, into the anterolateral aspect of the thigh. Administer the remaining KEDRAB at site(s) distant from the site of the rabies vaccine. Avoid administration into the gluteal region, where absorbance is unpredictable (unless the exposure site is in the gluteal region).

When the bite site is unknown or indeterminate (undetectable) or if infiltration is difficult at the bite site (eg, 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. If intramuscular administration is contraindicated (eg, in patients with uncorrectable bleeding disorders), administer KEDRAB subcutaneously. However, note that there are no clinical efficacy data to support administration of KEDRAB by the subcutaneous route.

- Do not mix with the rabies vaccine or administer in the same syringe with the rabies vaccine
- Do not administer into the same anatomical site(s) as rabies vaccine

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, DO NOT use KEDRAB; contact Kedrion Biopharma Customer Service.

Further Information on Rabies Post-Exposure Prophylaxis

Consult local or state public health officials if questions arise about the need for rabies prophylaxis.

Dosage Form, How Supplied, and Storage[1]

Each carton of KEDRAB contains a single-use vial containing **2 mL or 10 mL** of ready-to-use solution with a nominal potency of 150 IU/mL. The final product is assayed with human rabies immunoglobulin reference standard that is calibrated against the WHO International Standard.

Supplied in Two Vial Sizes

- Store KEDRAB at 2-8°C (36-46°F). Do not freeze
- Keep vial in carton until use
- KEDRAB may be stored at room temperature 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

2-mL vial
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

10-mL vial
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

INDICATIONS AND USAGE

KEDRAB™ (Rabies Immune Globulin [Human]) is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal. KEDRAB should be administered concurrently with a full course of rabies vaccine.

- Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- KEDRAB should not be administered to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.

IMPORTANT SAFETY INFORMATION

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).

CONCLUSIONS

Every year, an estimated 40,000 people in the United States receive post-exposure prophylaxis (PEP) after contact with a possibly rabid animal.[10] If the bite or other exposure is indeed from a rabid animal and PEP is not carried out, rabies is almost invariably fatal. For people who have never been vaccinated against rabies previously, PEP should always include wound cleansing and administration of both human rabies immune globulin (HRIG) and vaccine.[9] KEDRAB™ (Rabies Immune Globulin [Human]) is a highly purified rabies immune globulin which provides protective titers of anti-rabies antibodies in healthy volunteers and does not interfere with the immune response to rabies vaccine.[2] It is manufactured by Kamada, a biopharmaceutical company headquartered in Israel, and marketed by Kedrion Biopharma to secure availability of an essential therapy in the United States, a market that has experienced inconsistent supply and supply shortages in recent years.[51]

For people who have never been vaccinated against rabies previously, PEP should always include wound cleansing and administration of both HRIG and vaccine.[9]

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Visit www.KEDRAB.com for additional information.

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 intramuscular injection
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

KEDRAB is a human rabies immunoglobulin (HRIG) indicated for passive, transient post-exposure prophylaxis of rabies infection, 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).

- Do not administer additional (repeat) doses of KEDRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine (1).
- Do not administer KEDRAB to persons with a history of a complete pre-exposure or post-exposure rabies vaccination and confirmed adequate rabies antibody titer (1).

DOSAGE AND ADMINISTRATION

- **For wound infiltration and intramuscular use** (2).
- Post-exposure prophylaxis consists of a single dose of KEDRAB and a full course of rabies vaccine. Administer KEDRAB and the rabies vaccine as soon as possible after exposure (2.1).
- Dosage: 20 IU/kg body weight (2.1).
- Infiltrate as much of the dose as possible into and around the exposure site (if visible); administer the remainder intramuscularly at sites distant from the site of vaccination (2.2).

DOSAGE FORMS AND STRENGTHS

- Single-use 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

- KEDRAB should not be administered to individuals who have documented previous vaccination against rabies (5.1).
- Shock or anaphylactic reaction may occur following administration of KEDRAB (5.2).
- Individuals with IgA-deficiency and antibodies against IgA may develop hypersensitivity reactions to KEDRAB (5.3).
- Individuals with increased risk of thrombosis and thrombotic complications should be monitored following KEDRAB administration (5.4).
- Individuals receiving KEDRAB, particularly those at increased risk for hemolysis, should be monitored following KEDRAB administration (5.5).
- KEDRAB administration may interfere with development of an immune response to live attenuated viral vaccines (5.6).
- KEDRAB may interfere with serologic tests (5.7).
- KEDRAB may carry a risk of transmitting infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically the Creutzfeldt-Jakob disease (CJD) agent, despite manufacturing steps designed to minimize the risk of viral transmission (5.8, 11).

ADVERSE REACTIONS

The most frequent adverse events in subjects treated with KEDRAB in clinical trials were injection site pain, headache, muscle pain, and upper respiratory tract infection (6).
To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. Customer Service (1-855-353-7466) in the United States. Outside of the United States, the company distributing these products should be contacted. Voluntary reporting of adverse reactions may also be made to the FDA through MedWatch at 1-800-FDA-1088 or on the Internet at www.fda.gov/medwatch. 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).
- Immunization with live vaccines: KEDRAB 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 (7).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2017

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

- Do not administer additional (repeat) doses of KEDRAB once vaccine treatment has been initiated, since this may interfere with the immune response to the rabies vaccine.
- Do not administer KEDRAB to patients with a history of a complete pre-exposure or post-exposure vaccination regimen and confirmed adequate rabies antibody titer.[1]

2 DOSAGE AND ADMINISTRATION

- **For wound infiltration and intramuscular use. Do not administer intravenously.**

Local Treatment of Wounds prior to KEDRAB Administration

The World Health Organization (WHO) and the U.S. Public Health Service Advisory Committee on Immunization Practices (ACIP) have outlined recommendations for passive and active immunization after exposure to an animal suspected of having rabies.[1,2,3] Immediate and thorough cleansing of all bite wounds and scratches with soap and water is an important component of post-exposure prophylaxis (PEP). A virucidal agent (e.g., povidone-iodine solution) should be used to irrigate the wounds.

Tetanus prophylaxis and measures to control bacterial infection should be given if medically indicated.

2.1 Dosage

Post-exposure prophylaxis consists of a single dose of KEDRAB and a full course of rabies vaccine. The recommended dose of KEDRAB is 20 IU/kg body weight, given at the time of the first vaccine dose. KEDRAB and the first dose of rabies vaccine should be given as soon as possible after exposure, as delays are potentially lethal. However, should a delay occur, KEDRAB should be administered at any time up to and including seven days after the first dose of vaccine. The rabies vaccine should be given according to the manufacturer's instructions.

No more than the recommended dose of KEDRAB should be given because KEDRAB partially suppresses active antibody production following vaccination. For the same reason, additional doses of KEDRAB should not be given, even if the antibody response to vaccination is delayed.

2.2 Administration

- When the bite site is known and infiltration at the bite site is feasible:

  - Infiltrate as much of the dose as possible into and around any detectable bite wounds. Inject any remaining volume intramuscularly into the upper arm deltoid region or, in small children, into the anterolateral aspect of the thigh. Administer the remaining KEDRAB at site(s) distant from the site of the rabies vaccine.

- Avoid administration into the gluteal region, where absorbance is unpredictable (unless the exposure site is in the gluteal region):
- 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.
- If intramuscular administration is contraindicated (e.g., in patients with uncorrectable bleeding disorders), administer KEDRAB subcutaneously. However, note that there are no clinical efficacy data to support administration of KEDRAB by the subcutaneous route.
- Do not mix with the rabies vaccine or administer in the same syringe with the rabies vaccine.
- Do not administer into the same anatomical site(s) as rabies vaccine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, DO NOT use KEDRAB; discard the vial.

Further Information on Rabies Post-Exposure Prophylaxis

Consult local or state public health officials if questions arise about the need for rabies prophylaxis.

3 DOSAGE FORMS AND STRENGTHS

KEDRAB is supplied in single-use vials containing 2 mL or 10 mL of ready-to-use solution with a nominal potency of 150 IU/mL.

The 2-mL vial contains a total of 300 IU and the 10-mL vial contains a total of 1,500 IU. 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 Anaphylactic Shock

- KEDRAB should not be injected into a blood vessel because of the risk of severe allergic or hypersensitivity reactions, including anaphylactic shock. KEDRAB can induce a fall in blood pressure associated with an anaphylactic reaction, even in patients who tolerated previous treatment with human immunoglobulin.
- Discontinue KEDRAB injection immediately if there is an allergic or anaphylactic type reaction. In case of shock, implement standard medical treatment. Epinephrine should be available for treatment of acute anaphylactic symptoms.

5.3 Hypersensitivity

- Patients with a history of prior systemic allergic reactions following administration of human immune globulin preparations should be monitored for hypersensitivity.
- KEDRAB contains a small quantity of IgA. Patients who are deficient in IgA have the potential to develop IgA antibodies and may have anaphylactic reactions following administration of blood components containing IgA. The healthcare provider should assess the risks of this reaction against the benefits of administering KEDRAB.

5.4 Thrombosis

- Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.
- Patients at increased risk of thrombosis include patients with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and hyperviscosity syndromes (including cryoglobulinemias, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies).
- Consider measurement of baseline blood viscosity in patients at risk for hyperviscosity.

5.5 Hemolysis

- Hemolysis may occur in patients receiving immune globulin products, particularly those who are determined to be at increased risk. Patients at increased risk include those with non-O blood group types, those with underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days.

- Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If any of these occur, perform appropriate laboratory testing and administer medical therapy as indicated.

5.6 Live Attenuated Virus Vaccines

- KEDRAB administration may interfere with the development of an immune response to live attenuated virus vaccines.
    - Avoid immunization with measles vaccine within 4 months after KEDRAB administration.
    - Avoid immunization with other live attenuated virus vaccines within 3 months after KEDRAB administration.

5.7 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).

5.8 Transmissible Infectious Agents

- KEDRAB is derived from human plasma; therefore, the potential exists that KEDRAB administration may transmit infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- The risk of transmitting an infectious agent has been minimized by
    - Screening plasma donors for prior exposure to certain viruses
    - Testing for certain viral infections
    - Inactivating and removing certain viruses during the manufacturing process [see Description (11)].

Despite these measures, KEDRAB administration can still potentially transmit infectious diseases. There is also the possibility that unknown infectious agents may be present in KEDRAB.

Any infection considered to have possibly been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion Biopharma Inc. Customer Service (1-855-353-7466) or FDA at 1-800-FDA-1088.

6 ADVERSE REACTIONS

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. Subjects in the clinical studies of KEDRAB were healthy adults, primarily white and ranged in age from 18 to 72 years. A total of 160 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 1 summarizes adverse events (assessed by the investigator as related or unrelated to study treatment) occurring in >3% of subjects in the clinical trials of KEDRAB. The most frequent adverse events in the KEDRAB group (>6%) were injection site pain, headache, muscle pain, and upper respiratory tract infection (Table 1).

Table 1: Adverse Events Occurring in >3% of Subjects in All Studies Combined

	KEDRAB N = 91	**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)
Upper respiratory tract infection	8 (9)	8 (10)	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	4 (4)	2 (2)	0 (0)
Nausea	4 (4)	3 (4)	0 (0)
Feeling faint	4 (4)	1 (1)	0 (0)
Bruising	3 (3)	1 (1)	0 (0)
Sunburn	3 (3)	0 (0)	0 (0)
White blood cells in urine	3 (3)	4 (5)	0 (0)

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

Less common adverse events were joint pain, dizziness, fatigue, abdominal pain, blood in urine, nausea, feeling faint, bruising, sunburn, and white blood cells in urine.

7 DRUG INTERACTIONS

- Do not administer additional (repeat) doses of KEDRAB once vaccination has been initiated, since additional doses of KEDRAB may interfere with the immune response to the vaccine.
- Do not administer KEDRAB into the same anatomical site(s) as 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 *[see Warnings and Precautions (5.5)]*.

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

The safety and effectiveness of KEDRAB in the pediatric population have not been established.

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 104 IU per mL for parvovirus B19.

To reduce the risk of viral transmission further, the manufacturing process for KEDRAB includes three steps specifically designed to remove or inactivate viruses. The first of these is solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TnBP) and Octynoxol 9, which inactivates enveloped viral agents such as HIV, HBV and HCV. The second and third are heat-treatment (pasteurization) steps, which can inactivate both enveloped and non–enveloped viruses, and a nanofiltration (NF) step which removes viruses on the basis of size. 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 2.

Table 2: 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 (i.e., at the beginning of anti-rabies PEP) to 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 PEP as protective. By comparison, the ACIP recommends complete neutralization of rabies virus at a 1:5 serum dilution by a rapid fluorescent focus inhibition test

(RFFIT) from 1 to 2 weeks after prophylaxis; this corresponds to RVNA ~0.1-0.2 IU/mL. In support of these recommendations, there has been almost no documented clinical disease when the current rabies PEP regimen is administered appropriately (ACIP) [1].

KEDRAB has the potential to attenuate the patient's immune response to rabies vaccine. This was evaluated in a double-blind, randomized study where 16 healthy subjects were administered either KEDRAB (20 IU/kg IM) or saline placebo followed by three doses of a rabies vaccine (Table 3). Lower RVNA levels were seen in the KEDRAB + vaccine group compared to the placebo + vaccine group at all time-points beginning on Day 14, confirming that KEDRAB interferes with the host immune response to rabies vaccine.

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 Tmax 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 3).

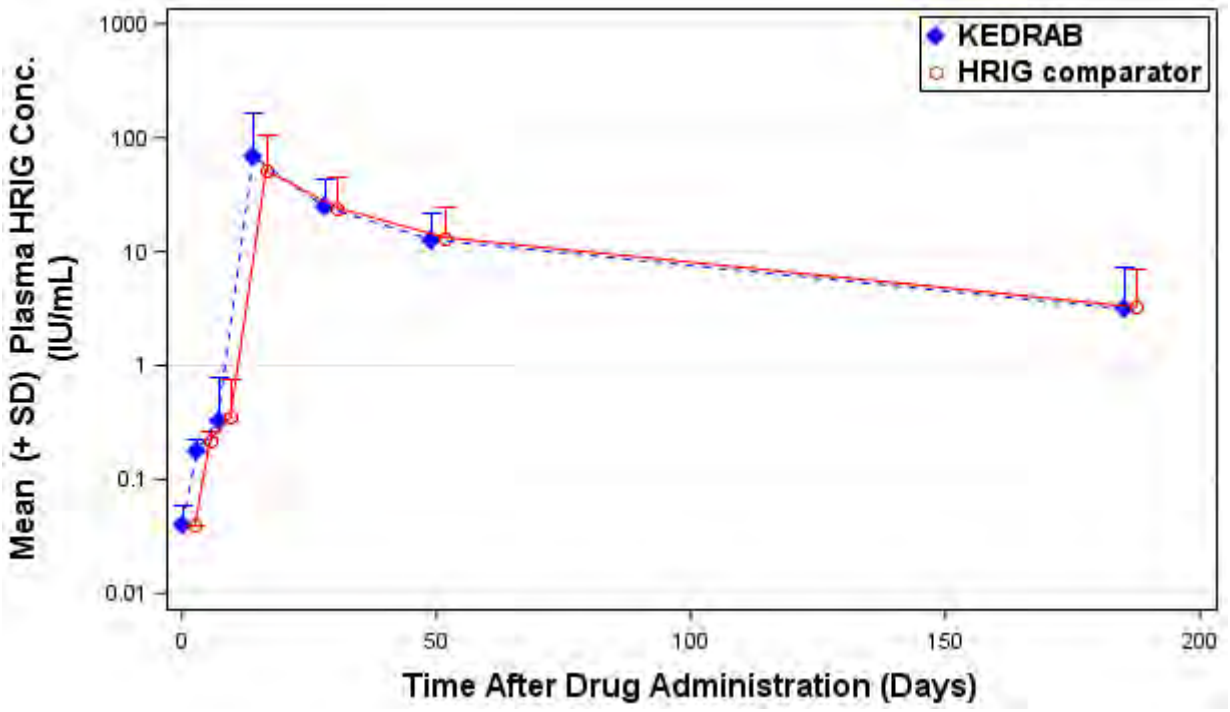
Table 3: Statistical Analysis of Rabies Virus Neutralizing Antibody Pharmacokinetic Parameters - Crossover Study of KEDRAB

Parameter	Units	Geometric LS Mean Values		Test/Reference (%)	90% Confidence Interval (%)
		KEDRAB	Comparator HRIG		
Cmax	IU/mL	0.24	0.30	81.71	75.34-88.62
AUC0-last	Day*IU/m	5.08	6.17	82.35	77.39-87.63
AUC0-inf	Day*IU/m	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 Tmax 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 4). 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 4: 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)		
Cmax	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. 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 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 5). 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 5: 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 included pharmacokinetics *[see Clinical Pharmacology (12)]*.

15 REFERENCES

1. 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 2013, Expert Consultation on Rabies. Second Report. Geneva: WHO Press. Technical Report Series (No. 982).

16 HOW SUPPLIED/STORAGE AND HANDLING

- Each carton of KEDRAB contains a single-use vial containing 2 mL or 10 mL of ready-to-use solution with a potency of 150 IU/mL.
- 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)
- Store KEDRAB at 2-8 °C (36-46 °F). Do not freeze.
- Keep vial in carton until use.
- 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

The KEDRAB manufacturing process includes three valid and effective viral elimination steps. In addition, the process allows the removal of thrombogenic activity.

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). Explain that the risk of KEDRAB transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing [see *Warnings and Precautions (5.7)*]. Inform patients of symptoms of a possible viral infection, including headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice.

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