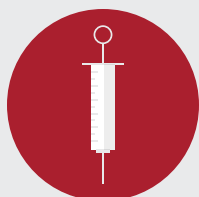




## Addressing the Most Common Reasons for Patient Refusal of Lifesaving Rabies PEP Treatment

Patient refusal of treatment is the most common reason for not administering human rabies immunoglobulin (HRIG) when it is appropriate and reasonable for disease prevention. Here we address the three primary reasons for patient refusal: fear of needles, concerns about plasma-based therapies, and insurance coverage or cost worries.<sup>1</sup>

### Patient refusal based on fears or concerns about:



*Needles*



*Plasma-based therapies*



*Insurance coverage/costs*



### *Needles*

When it comes to rabies, fear of needles can be deadly.<sup>2</sup> During a rabies outbreak in Bali, Indonesia (2008-2011), two patients died because of their refusal of treatment due to fear of needles, according to ProMED, the Program for Monitoring Emerging Diseases. In the first case, a man was bitten by a stray dog in the outbreak area—a clear indication for postexposure prophylaxis (PEP). He received one rabies shot but declined the rest of the postexposure series because of his fear of needles. In the second case, a woman was bitten by both a stray dog and a pet dog, again clear indications of the need for postexposure treatment. However, she also refused treatment because of a fear of needles. Two completely preventable deaths resulted. The decision to forgo treatment because of fear of needles almost certainly cost these people their lives: rabies is preventable with appropriate and timely postexposure treatment.

Contributing to this fear of needles is the misperception that rabies PEP requires multiple painful intra-abdominal injections over a 1-month period. In fact, PEP requires *intramuscular* injections of rabies vaccine plus injection of HRIG into and around the wound area, followed by a series of vaccine doses that depend on previous vaccination history. (Patients who were previously vaccinated require only one more vaccine dose; patients who were never previously vaccinated require three more vaccine doses for a total of 4.) For immunocompromised patients, an additional fifth vaccine dose is recommended.<sup>3</sup> With the availability of a higher concentration HRIG, there is now potential for fewer injections in the delivery of the full HRIG dose.<sup>4</sup>

**For patients who show a fear of needles, it is important to correct any misperceptions they may have and help them understand the risks of refusing PEP care.**



*Plasma-based Therapies*

The anti-vaccine movement is founded on the widely debunked belief that ingredients contained in vaccines are harmful and linked to development of neurodevelopmental disorders such as autism in children. While all medicines embody risk—which should be appropriately communicated to patients—understanding how medicines are made and the safety protocols and procedures in place might help some patients balance these risks with the benefits.

In the case of HRIG, for example, patients may have concerns related to the plasma-based nature of these products and the overall viral safety. Versions of HRIG used before the 1970s were manufactured using horse serum to produce equine RIG. Purified versions as well as the development and availability of HRIG preparations produced using human plasma improved safety over the years.<sup>5</sup> To make HRIG, healthy human donors are professionally immunized with the vaccine against rabies; their plasma is then collected and purified to make the immunoglobulin (see figure).<sup>6</sup>

**HRIG Manufacturing**



*Donor vaccination*



*Plasma donation*



*Plasma*



*Purification*



Epidemiological controls of the donor population and selection of individual donors based on medical screening are also utilized to reduce risk of transmission of pathogens.<sup>4</sup>

HRIG is manufactured using a sophisticated process that significantly reduces product impurities and is subject to the highest quality and safety standards.<sup>4,7</sup> It is a lengthy and complex process that takes up to 12 months from the time of donation until ready for use.<sup>8</sup> Grifols—the maker of HyperRAB<sup>®</sup> (rabies immune globulin [human])—provides a step-by-step overview of the manufacturing process employed in the development of their plasma medicines that is available at <https://www.grifols.com/en/plasma-journey#>. These steps include plasma collection, testing, manufacturing, and formulation before the final product is available to patients.<sup>8</sup>

The manufacturing process incorporates steps with the capacity to inactivate and remove pathogens if present in the starting material. These complex processes incorporate advanced technologies and employ multiple purification and safety steps that contribute to the product's overall quality.<sup>9</sup>

**For patients who exhibit concern about vaccines and plasma-derived products, it is important to reassure them that processes and protocols are in place to maximize safety.**

Plasma-derived products carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. This also applies to unknown or emerging viruses and other pathogens.

**Please see Important Safety Information at the end of this article and accompanying full Prescribing Information for HyperRAB<sup>®</sup> (rabies immune globulin [human]).**



### *Insurance Coverage and Costs*

Patients have also expressed concerns about insurance coverage and the costs of PEP. These worries may be based on news stories about uninsured individuals who have received unexpectedly high hospital bills following emergency department (ED) care, treatment, and consultation.<sup>10</sup> Articles and studies have shown discrepancies in ED charges that are so great that patients feel they have no way of knowing how much they can expect to be billed, a somewhat rational fear.<sup>11</sup>

Cost of ED care varies not only across the US depending on region, but also across medical conditions.<sup>11</sup> For example, there is an almost 5-fold variation in charges among the top 10 health conditions that present to the ED, from ~\$700 for an upper respiratory infection to ~\$3500 for a kidney stone.<sup>11\*</sup> Factors such as facility fees, the need for multiple visits, and the need for various consults (eg, plastic surgery) can play a role in ED cost variation. According to the CDC, the cost of rabies PEP treatment—a course of HRIG and four doses of vaccine given over a two-week period—is on the upper end of this cost scale at approximately \$3000.<sup>12</sup>

\*Based on over 8,000 ED encounters across the US, representing more than 76 million visits.

Most insurance plans cover emergency PEP rabies treatment, and some plans with preventive benefits may even cover travel-related vaccinations that are deemed elective.

**For patients who do not have insurance, do not qualify for Medicaid or Medicare, and whose financial resources are strained, assistance programs may be available; see the CDC website at [https://www.cdc.gov/rabies/medical\\_care/programs.html](https://www.cdc.gov/rabies/medical_care/programs.html) or contact the manufacturers of HRIG and rabies vaccine before administering the product to determine if assistance is available.**

**In some states, like New York, Florida, and Texas, state and county health departments help patients regarding costs and may give product to patients at cost or supplement part of the bill that's not covered by insurance.<sup>13</sup>**

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## ***Indication and Usage***

HYPERRAB® (rabies immune globulin [human]) is indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

### Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

## ***Important Safety Information***

### **For infiltration and intramuscular use only.**

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most common adverse reactions in >5% of subjects during clinical trials were injection-site pain, headache, injection-site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

Do not administer repeated doses of HYPERRAB once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.

Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio, or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.

**Please see accompanying full Prescribing Information for HYPERRAB.  
You are encouraged to report negative side effects of prescription drugs to the  
FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**HYPERRAB [rabies immune globulin (human)] solution for infiltration and intramuscular injection**

Initial U.S. Approval: 1974

### INDICATIONS AND USAGE

HYPERRAB® is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies. (1)

#### Limitations of Use

Persons previously immunized with rabies vaccine that have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

### DOSAGE AND ADMINISTRATION

**For infiltration and intramuscular use only.**

**Administer HYPERRAB within 7 days after the first dose of rabies vaccine.**

Postexposure prophylaxis, along with rabies vaccine, after suspected exposure to rabies (2.1)	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight  Single-dose	Administer as soon as possible after exposure, preferably at the time of the first rabies vaccine dose.  Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible.  Inject the remainder, if any, intramuscularly.
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### DOSAGE FORMS AND STRENGTHS

300 IU/mL solution for injection supplied in 1 mL, 3 mL and 5 mL single-dose vials. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Severe hypersensitivity reactions, including anaphylaxis, may occur with HYPERRAB. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- HYPERRAB is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.2)

### ADVERSE REACTIONS

The most common adverse reactions in >5% of subjects in clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- Repeated dosing after administration of rabies vaccine may suppress the immune response to the vaccine. (7)
- Defer live vaccine (measles, mumps, rubella) administration for 4 months. (7)

**See 17 for PATIENT COUNSELING INFORMATION.**

Revised: 1/2021

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**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

HYPERRAB is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.<sup>1,3</sup>

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.<sup>1,3</sup>

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

**2 DOSAGE AND ADMINISTRATION**

**For infiltration and intramuscular use only.**

**The strength of HYPERRAB is 300 IU/mL.**

**2.1 Dose**

Use HYPERRAB in combination with rabies vaccine series to be effective. Do not use HYPERRAB alone for prevention.

Administer HYPERRAB within 7 days after the first dose of rabies vaccine.

**Rabies Postexposure Prophylaxis Schedule\***

Vaccination Status	Treatment	Regiment†
Not previously vaccinated	Wound cleansing	<ul style="list-style-type: none"> <li>Cleanse all wounds immediately and thoroughly with soap and water.</li> <li>Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.</li> </ul>
	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight  Single-dose	<ul style="list-style-type: none"> <li>Administer HYPERRAB as soon as possible after exposure, preferably at the time of the first vaccine dose.</li> <li>Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible. [see Dosage and Administration (2.3)]</li> <li>Inject the remainder, if any, intramuscularly at an anatomical site distant from the site of vaccine administration. [see Dosage and Administration (2.3)]</li> <li>Do not exceed the recommended dose of HYPERRAB, otherwise the active production of rabies antibody may be partially suppressed. [see Drug Interactions (7)]</li> <li>Use separate syringes, needles, and anatomical injection sites for HYPERRAB and for rabies vaccine.</li> </ul>
	Rabies Vaccine	<ul style="list-style-type: none"> <li>Administer rabies vaccine on day 0‡.</li> <li>Complete a rabies vaccination series for previously unvaccinated persons.†</li> </ul>
Previously vaccinated§	Wound cleansing	<ul style="list-style-type: none"> <li>Cleanse all wounds immediately and thoroughly with soap and water.</li> <li>Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.</li> </ul>
	HYPERRAB	<ul style="list-style-type: none"> <li>Do not administer HYPERRAB. [see Indications and Usage (1)]</li> </ul>
	Rabies Vaccine	<ul style="list-style-type: none"> <li>Administer rabies vaccine on day 0‡.</li> <li>Complete a rabies vaccination series for previously vaccinated persons.†</li> </ul>

\* Adapted from reference 1.

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

‡ Day 0 is the day the first dose of vaccine is administered. Refer to vaccine manufacturer’s instructions or to the recommendations of the Advisory Committee on Immunization Practices (ACIP)<sup>1,3</sup> for appropriate rabies vaccine formulations, schedules and dosages.

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



## 2.2 Preparation

- Calculate the volume of HYPERRAB for the recommended dose of 20 IU/kg.
- Ensure the correct strength is used for the calculation. HYPERRAB is formulated with a strength of 300 IU/mL. The predecessor product, HYPERRAB® S/D [rabies immune globulin (human)] was formulated at 150 IU/mL. The volume required of HYPERRAB (300 IU/mL) to achieve the recommended dose of 20 IU/kg is approximately one half of that required for the previous HYPERRAB S/D (150 IU/mL).
- Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. HYPERRAB is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution.
- Do not use HYPERRAB if the product shows any sign of tampering. Notify Grifols Therapeutics LLC immediately [1-800-520-2807].
- Do not freeze. Do not use any solution that has been frozen.
- Discard unused portion.

## 2.3 Administration

- Administer HYPERRAB at the time of the first vaccine dose (day 0), but no later than day 7.<sup>1-3</sup>
- Infiltrate the full dose of HYPERRAB in the area around the wound, if anatomically feasible. Dilute HYPERRAB with an equal volume of dextrose, 5% (D5W), if additional volume is needed to infiltrate the entire wound. Do not dilute with normal saline.
- Inject the remainder, if any, of the HYPERRAB dose intramuscularly into the deltoid muscle of the upper arm or into the lateral thigh muscle, and distant from the site of vaccine administration.
- Do not administer HYPERRAB in the same syringe or needle or in the same anatomic site as vaccine.

## 3 DOSAGE FORMS AND STRENGTHS

HYPERRAB is a sterile, 300 IU/mL solution for injection supplied in 1 mL, 3 mL and 5 mL single-dose vials. The 1 mL vial is sufficient for a child weighing 15 kg. The 3 mL vial is sufficient for a person weighing 45 kg. The 5 mL vial is sufficient for an adult weighing 75 kg.

HYPERRAB is standardized against the U.S. Standard Rabies Immune Globulin to contain a potency of  $\geq 300$  IU/mL. The U.S. unit of potency is equivalent to the international unit (IU) for rabies antibody.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

Patients with isolated immunoglobulin A (IgA) deficiency may develop severe hypersensitivity reactions to HYPERRAB, or subsequently, to the administration of blood products that contain IgA.<sup>4</sup>

### 5.2 Transmissible Infectious Agents

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. HYPERRAB is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the donor population and selection of individual donors by a medical interview and screening of individual donations and plasma pools for viral infection markers; (2) testing of plasma for hepatitis C virus (HCV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), HAV and human parvovirus (B19V) genomic material; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

## 6 ADVERSE REACTIONS

The most common adverse reactions in >5% of subjects during clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

### 6.1 Clinical Trials Experience

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

The new formulation for HYPERRAB is manufactured using caprylate/ chromatography purification and has a rabies antibody concentration of 300 IU/mL. The previous formulation, HYPERRAB S/D, was manufactured using a solvent detergent process and had a rabies antibody concentration of 150 IU/mL. These products were evaluated in 2 clinical trials in a total of 20 healthy subjects using a 20 IU/kg single-dose. The initial study evaluated the original 150 IU/mL HYPERRAB S/D in 8 subjects and the second study evaluated HYPERRAB in 12 subjects. The original study of HYPERRAB S/D reported headache (1/8; 13%).

In the study with HYPERRAB at 300 IU/mL, 5 subjects (5/12; 42%) experienced at least 1 adverse reaction. These were: injection site pain (4/12; 33%), injection site nodule (1/12; 8%), abdominal pain (1/12; 8%), diarrhea (1/12; 8%), flatulence (1/12; 8%), headache (1/12; 8%), nasal congestion (1/12; 8%), and oropharyngeal pain (1/12; 8%).

### 6.2 Postmarketing Experience

There are no data on the postmarketing use of HYPERRAB (300 IU/mL). The following adverse reactions have been identified during post approval use of the predecessor formulation, HYPERRAB S/D. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with HYPERRAB S/D, cases of allergic/hypersensitivity reactions including anaphylaxis have been reported. Soreness at the site of injection (injection site pain) may be observed following intramuscular injection of immune globulins. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients.

The following have been identified as the most frequently reported post-marketing adverse reactions:

Immune system disorder	Anaphylactic reaction*, hypersensitivity*
Nervous system disorders	Hypoesthesia
Gastrointestinal disorders	Nausea
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity

\*These reactions have been manifested by dizziness, paresthesia, rash, flushing, dyspnea, tachypnea, oropharyngeal pain, hyperhidrosis, and erythema

## 7 DRUG INTERACTIONS

- Do not administer repeated doses of HYPERRAB® [rabies immune globulin (human)] once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.<sup>1</sup>
- Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.<sup>5</sup>

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no data with HYPERRAB use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with HYPERRAB. It is not known whether HYPERRAB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HYPERRAB should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## 8.2 Lactation

### Risk Summary

There is no information regarding the presence of HYPERRAB in human milk, the effect 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 HYPERRAB and any potential adverse effects on the breastfed infant from HYPERRAB.

## 8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

## 8.5 Geriatric Use

Safety and effectiveness in geriatric population have not been established.

## 10 OVERDOSAGE

Because Rabies Immune Globulin (Human) may partially suppress active production of antibody in response to the rabies vaccine, do not give more than the recommended dose of rabies immune globulin (human).<sup>1</sup>

## 11 DESCRIPTION

HYPERRAB is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution of human antirabies immune globulin for infiltration and intramuscular administration. HYPERRAB is provided in a single-dose vial and contains no preservative. HYPERRAB is prepared from pools of human plasma collected from healthy donors (hyperimmunized with rabies vaccine) by a combination of cold ethanol fractionation, caprylate precipitation and filtration, caprylate incubation, anion-exchange chromatography, nanofiltration and low pH incubation. HYPERRAB consists of 15 to 18% protein at pH 4.1 to 4.8 in 0.16 to 0.26 M glycine. The product is standardized against the U.S. Standard Rabies Immune Globulin to contain a potency value of not less than 300 IU/mL. The U.S. unit of potency is equivalent to the international unit (IU) for rabies antibody.

When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogens.

In the manufacturing process of HYPERRAB, there are several steps with the capacity for virus inactivation or removal.<sup>6</sup> The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Caprylate precipitation/depth filtration
- Caprylate incubation
- Depth filtration
- Column chromatography
- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the HYPERRAB manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious viruses.

The caprylate/chromatography manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD), and Creutzfeldt-Jakob disease (CJD) agents.<sup>6</sup> These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

HYPERRAB provides immediate, passive, rabies virus neutralizing antibody coverage until the previously unvaccinated patient responds to rabies vaccine by actively producing antibodies.<sup>1</sup>

### 12.2 Pharmacodynamics

The usefulness of prophylactic rabies antibody in preventing rabies in humans when administered immediately after exposure was dramatically demonstrated in a group of persons bitten by a rabid wolf in Iran.<sup>7,8</sup> Similarly, beneficial results were later reported from the U.S.S.R.<sup>9</sup> Studies coordinated by WHO (World Health Organization) helped determine the optimal conditions under which antirabies serum of equine origin and rabies vaccine can be used in man.<sup>10-13</sup> These studies showed that antirabies serum can interfere to a variable extent with the active immunity induced by the vaccine, but could be minimized by booster doses of vaccine after the end of the usual dosage series. Preparation of rabies immune globulin of human origin with adequate potency was reported by Cabasso et al.<sup>14</sup> In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin (DEV).<sup>14,15</sup> These studies determined that a human globulin dose of 20 IU/kg of rabies antibody, given simultaneously with the first DEV dose, resulted in amply detectable levels of passive rabies antibody 24 hours after injection in all recipients. The injections produced minimal, if any, interference with the subject's endogenous antibody response to DEV.

Subsequently, human diploid cell rabies vaccines (HDCV) prepared from tissue culture fluids containing rabies virus have received substantial clinical evaluation in Europe and the United States.<sup>14-22</sup> In a study in adult volunteers, the administration of Rabies Immune Globulin (Human) did not interfere with antibody formation induced by HDCV when given in a dose of 20 IU per kilogram body weight simultaneously with the first dose of vaccine.<sup>21</sup>

### 12.3 Pharmacokinetics

In a clinical study of 12 healthy human subjects receiving a 20 IU/kg intramuscular dose of HYPERRAB detectable passive rabies neutralizing antibody was present by 24 hours and persisted through the 21 day follow-up evaluation period. Figure 1 shows the mean levels of rabies virus antibodies in IU/mL across the 21 day evaluation period and indicates that the titer remains stable during this period. This level of passive rabies neutralizing antibody is similar to that reported in the literature for administration of human rabies immune globulin, and is clinically important because it provides interim protection until the host immune response to rabies vaccine produces definitive protective titers of neutralizing rabies antibody (therefore the rabies vaccine series is also essential).<sup>23-24</sup>

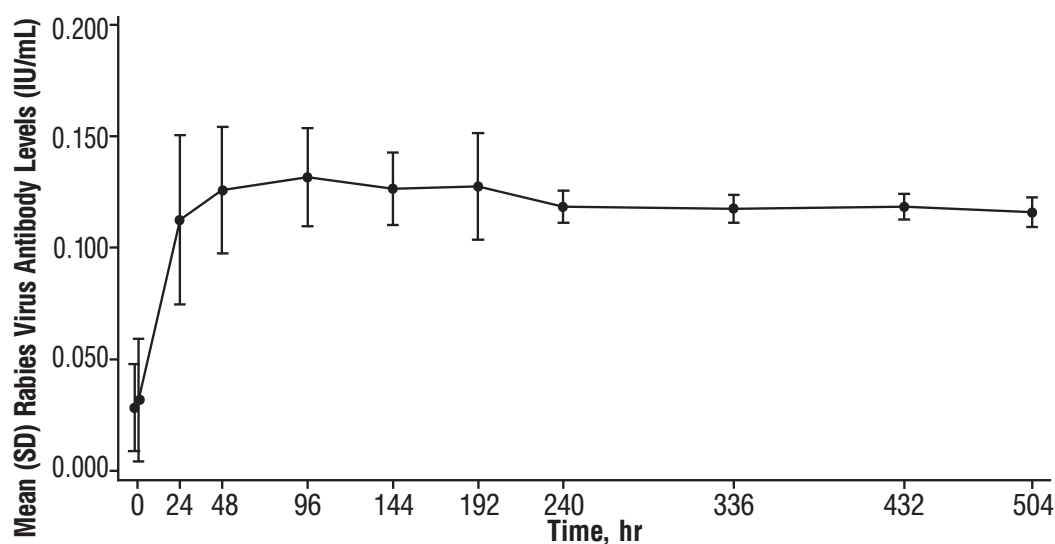
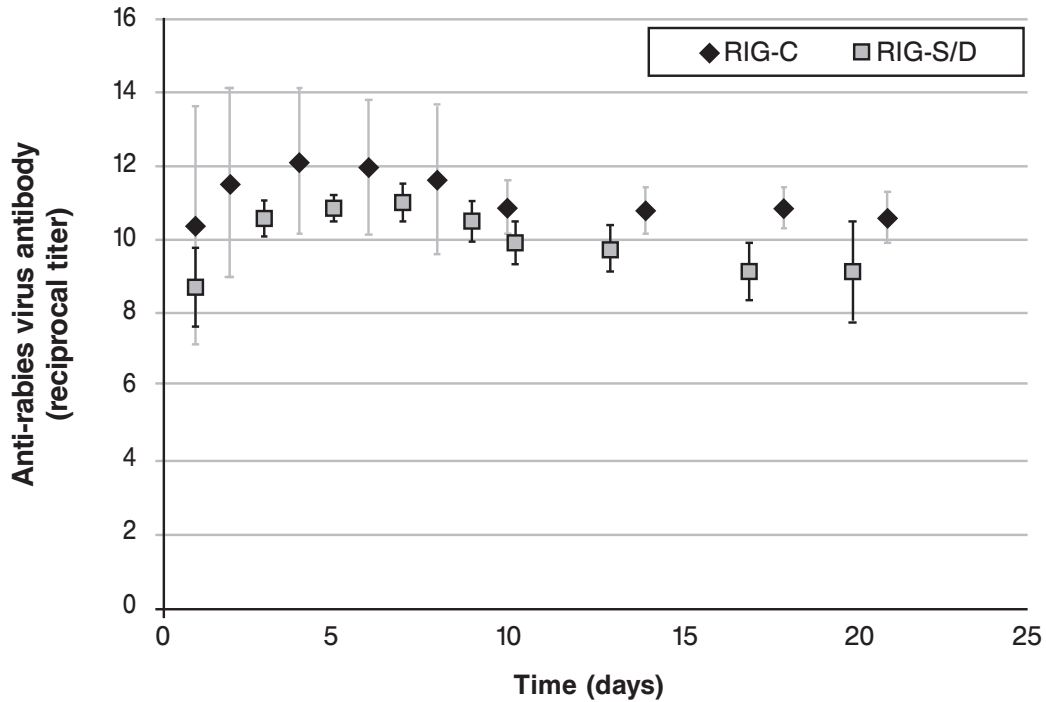


Figure 1: Mean (Standard Deviation) Rabies Virus Neutralizing Antibody Levels (IU/mL) versus Time following a Single 20 IU/kg Dose of HYPERRAB® (300 IU/mL) by Intramuscular Injection

The previous formulation, HYPERRAB® S/D [rabies immune globulin (human)], was studied in 8 healthy subjects over 21 days. As with the new formulation, rabies neutralizing antibody was present by 24 hours and persisted through the 21 day follow up period (Figure 2).



**Figure 2: Reciprocal of Anti-Rabies Virus Neutralizing Antibody Titer Following a Single 20 IU/kg Dose of HYPERRAB® (300 IU/mL; RIG-C) or HYPERRAB® S/D (150 IU/mL; RIG-S/D) Product (mean [standard deviation])**

**14 CLINICAL STUDIES**

HYPERRAB was administered to a total of 20 healthy adult subjects in two clinical trials. [see *Clinical Pharmacology (12.3)*] A single intramuscular dose of 20 IU/kg HYPERRAB (12 subjects) or HYPERRAB S/D (8 subjects) was administered and rabies neutralizing antibody titers were monitored in serum for 21 days. Administration of both HYPERRAB formulations resulted in detectable titers of neutralizing antibodies to the rabies virus that persisted throughout the 21 day study period (Figure 2).

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**16 HOW SUPPLIED/STORAGE AND HANDLING**

HYPERRAB is supplied in 1 mL, 3 mL and 5 mL single-dose vials of ready-to-use solution with a potency value of not less than 300 IU/mL.

HYPERRAB contains no preservative and is not made with natural rubber latex.

<b><u>NDC Number</u></b>	<b><u>Size</u></b>
13533-318-01	1 mL
13533-318-03	3 mL
13533-318-05	5 mL

- Store HYPERRAB at 2 to 8°C (36 to 46°F). Do not freeze.
  - HYPERRAB may be stored at room temperatures not to exceed 25°C (77°F) for up to 6 months.
  - Use within 6 months after removal from refrigeration at any time prior to the expiration date, after which the product must be used or discarded. Do not return to refrigeration.
- Do not use after expiration date printed on the label.
- Discard unused portion.

**17 PATIENT COUNSELING INFORMATION**

Discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient. Inform the patient who is allergic to human immune globulin products that severe, potentially life-threatening allergic reactions could occur. *[see Warnings and Precautions (5.1)]*

Inform the patient who is deficient in IgA the potential for developing anti-IgA antibodies and severe potentially life-threatening allergic reactions. *[see Warnings and Precautions (5.1)]*

Inform the patient that HYPERRAB is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease. While the risk that HYPERRAB can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and including manufacturing steps with the capacity to inactivate and/or remove pathogens, the patient should report any symptoms that concern them. *[see Warnings and Precautions (5.2)]*

# GRIFOLS

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