RABIES WATCH
THE COMPREHENSIVE RABIES RESOURCE
FALL 2018 • ISSUE #8

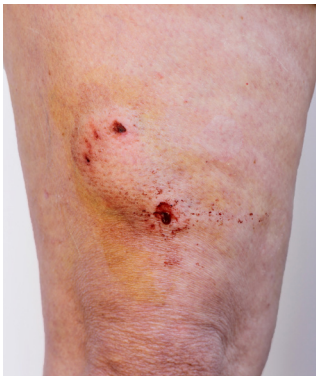
Considerations for Tetanus While Treating an Exposure to Rabies

Since rabies and tetanus are not as common in the United States (US) as they used to be,[1,2] people may not be fully aware of these diseases and their substantial consequences. These people may not know how to respond to potential exposure incidents, which may delay access to care and increase the risk of developing disease.

Q: Can you get tetanus from an animal bite?

A: Yes, people can be exposed to tetanus the same way as with rabies: through a bite or saliva of an infected animal.[1,3]

It is important to know that the bacterium that causes tetanus in humans, *Clostridium tetani*, and its spores, which produce a potent neurotoxin, occur naturally and are widely distributed in our environment.[1] For example, spores from the tetanus bacterium can be found in soil, dust, saliva of many animals, and animal feces.[1,3] Humans can be exposed to the spores of this pathogen through wounds or other breaches of the skin, or through mucous membranes.[1,3,4] Under anaerobic conditions, which may occur with deep puncture wounds, these spores can germinate and produce the potent neurotoxin that causes disease in people.[1,4]



So, stepping on a rusty nail that has been outdoors for a long time and has tetanus spores adhered to it can introduce those spores into a person's body through a skin wound. Or, a person may be exposed to tetanus by having an existing open skin wound or mucous membranes come into contact with soil containing tetanus spores, or through a puncture wound from thorns on a rose bush or, as with rabies, a bite or saliva from an infected animal.[1,3]

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Q: Aren't rabies and tetanus rare diseases nowadays?

A: Both diseases are relatively rare in large part because of successful vaccination programs.[1,2] But rabies and tetanus are still extremely important health risks to the individual people who are exposed to these pathogens each year. Healthcare professionals need to remain vigilant for cases of rabies or tetanus exposure that present for medical attention.

Following the large-scale implementation of rabies vaccination programs targeted at dogs in the middle of the 20th century, transmission of canine-variant rabies virus within this species has been eliminated.[5] However, more than 4400 rabies cases among wild animals, such as bats, raccoons, skunks, and foxes, were reported to the US Centers for Disease Control and Prevention (CDC) in 2016.[6] Humans who may be exposed to these animals continue to be at risk of rabies, as made clear by the 40 confirmed human rabies cases reported in the US and Puerto Rico from 2003 through October 2017.[6]

Tetanus is not as common as it used to be, before universal vaccination programs began in the US in the mid-1940s. However, 462 tetanus cases were reported in the US from 2001 through 2016. In almost all cases, disease developed in people who were either unvaccinated or inadequately vaccinated, or had unknown or uncertain vaccination histories. The CDC reported that the case-fatality ratio (ie, the percentage of fatalities among people reported to have the disease) was 18% from 1998 to 2000 and 8% from 2001 to 2016.[1]

Q: Since potential exposure to sources of either tetanus or rabies may not be considered medical emergencies, won't people be able to wait and see if they develop symptoms before going to a doctor?

A: No. While exposure to sources of tetanus and/or rabies may not be medical emergencies like a heart attack or trauma after a car accident, experts consider them "medical urgencies" and recommend that people seek medical attention as soon as possible after a potential exposure incident.[7,8] This is especially true for people who are the most susceptible to disease, such as those who have never been vaccinated against these diseases and those who have not stayed up to date with tetanus booster doses following completion of an initial tetanus vaccination series in the past, which may include older adults and people without consistent access to medical care, such as immigrant populations.[1,2,4,8] Additionally, the severity/depth and location of wounds associated with potential exposures to rabies and/or

tetanus, as well as the extent of wound contamination (for tetanus risk), are key factors in a clinician's evaluation of the exposure incident, risk of disease, and need for clinical intervention.[1,7] More severe wounds located closer to the central nervous system are associated with higher risks of disease transmission, shorter incubation times, more severe disease, and worse clinical prognosis.[1,4,7,9] Therefore, the sooner postexposure prophylaxis (PEP) is started, the better the chances will be to prevent disease.

For both rabies and tetanus, PEP begins with thorough wound cleansing with soap and water and, if available, a virucidal agent such as povidine-iodine solution for rabies.[2,4] Subsequent management will depend on the clinician's evaluation of several factors, including the exposure type and severity, the patient's immune status and vaccination history, and the disease status of the animal involved in a potential rabies exposure, if available.[1,2,7,10]

Q: Won't it be too late to get shots after being exposed to rabies or tetanus?

A: No, PEP has been developed for exactly this purpose—to prevent the development of symptomatic disease after a person has been exposed to rabies and/or tetanus. The need for rabies and/or tetanus PEP will depend on the type of wound and the patient's prior vaccination status.[1,2,7] The first step in prevention of either infection following potential exposure is appropriate wound management.[2,4]

Wound care for suspected rabies exposure includes cleansing with soap and water. If available, a virucidal agent, such as povidine-iodine solution, can also be used to irrigate the wound. Subsequent management, with administration of rabies vaccine with or without human rabies immune globulin (HRIG), depends on the patient's rabies vaccination history. Patients who have not been previously vaccinated against rabies should receive rabies PEP that includes four 1-mL doses of a rabies vaccine, with the first dose given as soon as possible after the exposure incident (the date of the first dose is defined as day 0 of the rabies PEP regimen). The vaccine doses should be administered intramuscularly into the deltoid area in adults and in the anterolateral aspect of the thigh in children. The remaining 3 subsequent vaccine doses should be administered on days 3, 7, and 14. These patients should also receive a dose of HRIG on day 0. The HRIG dose should be injected into and around all wound areas, with any remaining HRIG volume injected intramuscularly at a site away from the rabies vaccine administration

site to avoid interaction with the vaccine. Patients who have previously been vaccinated with the rabies vaccine should not receive HRIG but should receive additional doses of vaccine. Specifically, these patients should receive two 1-mL doses of vaccine, one on day 0 (day of first vaccine dose), and one on day 3.[2]

Wound care for suspected tetanus exposure is important to minimize to the extent possible the number of *C tetani* spores that may have entered the body through a skin wound. On initial evaluation, the clinician should assess the wound and then clean the area thoroughly, removing dirt, foreign matter, and necrotic tissue. The clinician must then determine whether the wound is "clean and minor" or "dirty." Dirty wounds include deeper puncture or penetrating wounds, such as animal bites, and wounds contaminated with dirt, feces, soil, or saliva. Puncture or penetrating wounds that are contaminated pose a higher risk of tetanus than wounds that are cleaner and superficial.[1,4]

The clinician should then evaluate the patient's vaccination status for tetanus toxoid–containing vaccine. The key question is whether the patient may still have protective levels of antitetanus toxoid antibodies from prior administration of the full 3-dose series of tetanus vaccine plus any booster doses within the past 5 or 10 years.[1]

With that information, the clinician can then follow the Advisory Committee on Immunization Practices (ACIP) recommendations for tetanus prophylaxis, which may include vaccine with or without tetanus immune globulin. The ACIP recommendations are the official, approved guidelines of the CDC.[1]

Q: If rabies and tetanus shots are given at the same time, why do I need both? Wouldn't just one of them help protect me against both diseases?

A: No, these are separate diseases that require separate interventions against rabies (which is caused by infection with the rabies virus) and against tetanus (which is caused by a neurotoxin produced by the bacterium *C tetani*).[1,2] The confusion may come about because PEP against rabies (rabies vaccine + rabies immune globulin) and against tetanus (tetanus vaccine + tetanus immune globulin) may need to be given at the same time to certain people.[7] These people may be at increased risk of developing both rabies and tetanus following incidents that may expose them to both the rabies viruses and the tetanus bacterium (for example, animal bites that puncture the person's skin and expose the person to the animal's saliva).[1,7]

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Important Safety Information

HyperTET® S/D (tetanus immune globulin [human]) is indicated for prophylaxis against tetanus following injury in patients whose immunization is incomplete or uncertain.

HyperTET S/D should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, HyperTET S/D should be given only if the expected benefits outweigh the risks.

Slight soreness at the site of injection and slight temperature elevation may be noted at times. Sensitization to repeated injections of human immunoglobulin is extremely rare. In the course of routine injections of large numbers of persons with immunoglobulin, there have been a few isolated occurrences of angioneurotic edema, nephrotic syndrome, and anaphylactic shock after injection. Administration of live virus vaccines (eg, MMR) should be deferred for approximately 3 months after tetanus immune globulin (human) administration.

HyperTET S/D is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease. There is also the possibility that unknown infectious agents may be present in such products.

Please see accompanying full Prescribing Information for HyperTET S/D.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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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, or call 1-800-FDA-1088.

REFERENCES

1. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2018;67(2):1-44. **2.** Rupprecht CE, Briggs D, Brown CM, et al; Centers for Disease Control and Prevention (CDC). Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2010;59(RR-2):1-9. **3.** Iannelli V. 5 myths about tetanus and tetanus shots. https://vaxopedia.org/2017/04/12/5-myths-about-tetanus-and-tetanus-shots/. Accessed June 26, 2018. **4.** Centers for Disease Control and Prevention. Tetanus: for clinicians. https://www.cdc.gov/tetanus/clinicians.html. Updated May 31, 2018. Accessed June 26, 2018. **5.** Centers for Disease Control and Prevention. US declared canine-rabies free. 2007. http://www.cdc.gov/media/pressrel/2007/r070907.htm. Updated May 20, 2014. Accessed June 19, 2018. **6.** Ma X, Monroe BP, Cleaton JM, et al. Rabies surveillance in the United States during 2016. *J Am Vet Med Assoc.* 2018;252(8):945-957. **7.** Manning SE, Rupprecht CE, Fishbein D, et al; Advisory Committee on Immunization Practices Centers for Disease Control and Prevention (CDC). Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2008;57(RR-3):1-28. **8.** Immunization Action Coalition. Ask the experts: diphtheria, tetanus, pertussis. http://www.immunize.org/askexperts/experts_per.asp. Updated June 18, 2018. Accessed June 26, 2018. **9.** Tetanus. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book®: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:793-798. **10.** World Health Organization. *WHO Expert Consultation on Rabies: Third Report.* WHO Technical Report Series 1012. Geneva, Switzerland: World Health Organization; 2018.

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.

---------- 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.

---------- 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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

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.[1-3]

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.[1-3]

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	Regimen†
Not previously vaccinated	Wound cleansing	• Cleanse all wounds immediately and thoroughly with soap and water. • Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.
	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight Single-dose	• Administer HYPERRAB as soon as possible after exposure, preferably at the time of the first vaccine dose. • 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)]* • Inject the remainder, if any, intramuscularly at an anatomical site distant from the site of vaccine administration. *[see Dosage and Administration (2.3)]* • Do not exceed the recommended dose of HYPERRAB, otherwise the active production of rabies antibody may be partially suppressed. *[see Drug Interactions (7)]* • Use separate syringes, needles, and anatomical injection sites for HYPERRAB and for rabies vaccine.
	Rabies Vaccine	• Administer rabies vaccine on day 0‡. • Complete a rabies vaccination series for previously unvaccinated persons.†
Previously vaccinated§	Wound cleansing	• Cleanse all wounds immediately and thoroughly with soap and water. • Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.
	HYPERRAB	• Do not administer HYPERRAB. *[see Indications and Usage (1)]*
	Rabies Vaccine	• Administer rabies vaccine on day 0‡. • Complete a rabies vaccination series for previously vaccinated persons.†

* Adapted from reference 1.

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

‡ Day 0 is the day the first dose of vaccine is administered. Refer to vaccine manufacturer's instructions or to the recommendations of the Advisory Committee on Immunization Practices (ACIP)[1,3] 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.[1-3]
- 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 ≥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.[4]

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.[1]
- 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.[5]

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 backgrounds 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).[1]

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.[6] 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.[6] 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.[1]

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.[7,8] Similarly, beneficial results were later reported from the U.S.S.R.[9] 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.[10-13] 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.[14] In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin (DEV).[14,15] 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.[14-22] 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.[21]

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).[23-24]

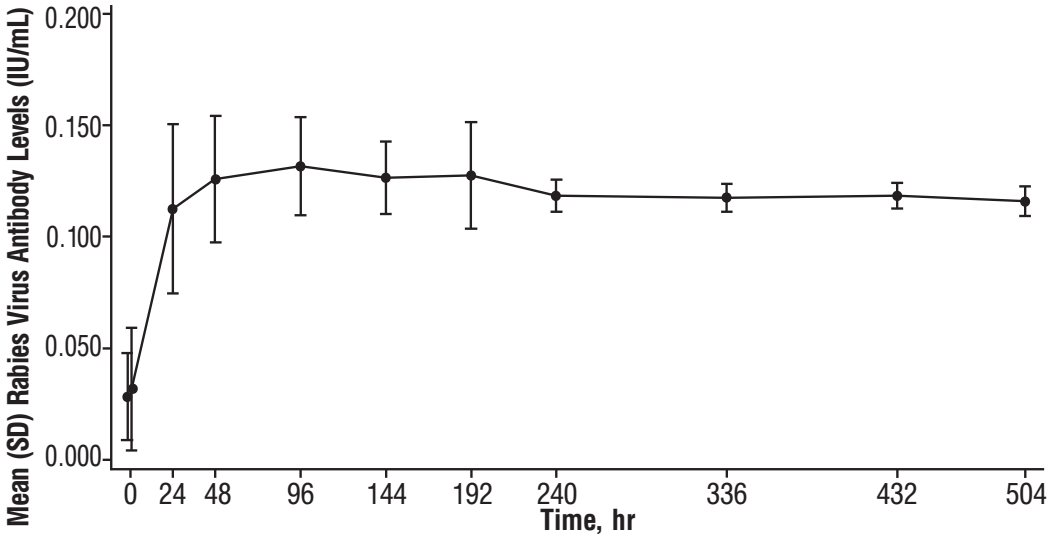

Figure 1: Mean (Standard Deviation) Rabies Virus Neutralizing Antibody Levels (IU/mL) versus Time following a Single 20 IU/kg Dose of HYPERRAB® (300 IU/mL) by Intramuscular Injection

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).

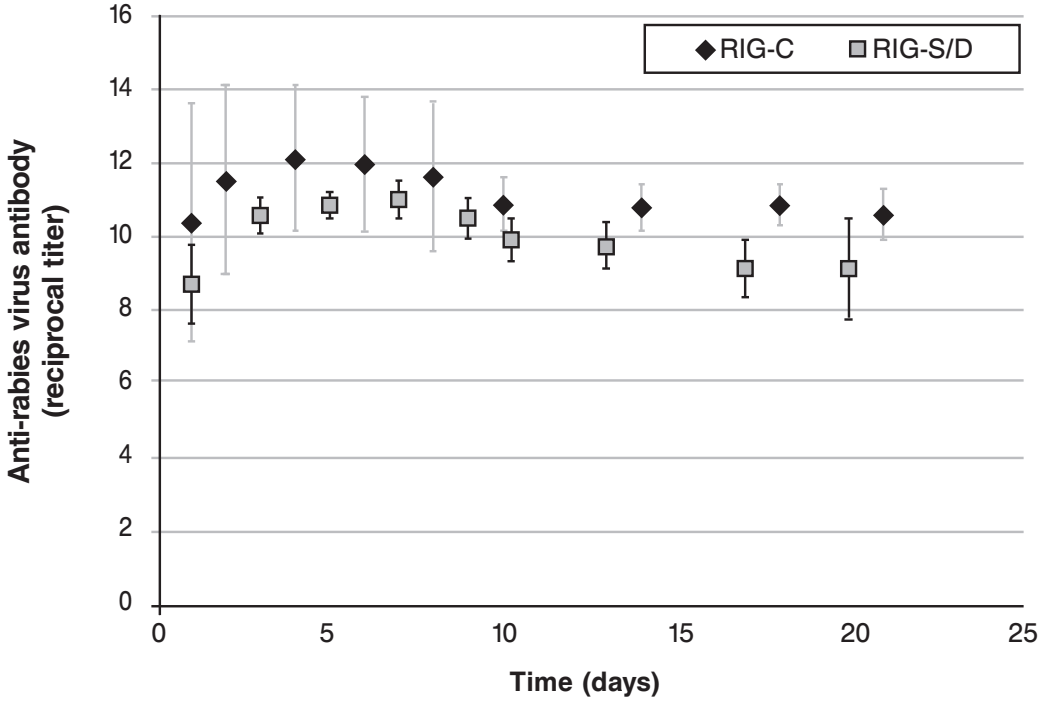

Figure 2: Reciprocal of Anti-Rabies Virus Neutralizing Antibody Titer Following a Single 20 IU/kg Dose of HYPERRAB® (300 IU/mL; RIG-C) or HYPERRAB® S/D (150 IU/mL; RIG-S/D) Product (mean [standard deviation])

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.

NDC Number	Size
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)]*

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Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License Number 1871

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