

PRODUCT MONOGRAPH
Rabies Immune Globulin [Human]
HYPERRAB™ S/D
Solvent / Detergent Treated
2 mL and 10 mL vials
Injectable Solution
Manufacturer's Standard

THERAPEUTIC CLASSIFICATION

Passive Immunizing Agent

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PRODUCT MONOGRAPH**HYPERRAB™ S/D****Rabies Immune Globulin [Human]*****Solvent/Detergent Treated*****THERAPEUTIC CLASSIFICATION****Passive Immunizing Agent****Injectable Solution****Manufacturer's Standard****ACTION AND CLINICAL PHARMACOLOGY**

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.^{1,2} Similarly, beneficial results were later reported from the U.S.S.R.³ Studies coordinated by WHO helped determine the optimal conditions under which antirabies serum of equine origin and rabies vaccine can be used in man.⁴⁻⁷ These studies showed that 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.⁸ In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin (DEV).^{8,9} 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.

More recently, 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.¹⁰⁻¹⁶ 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.¹⁵

In a clinical study in healthy human adults receiving a 20 IU/kg intramuscular dose of Rabies Immune Globulin (Human) treated with solvent/detergent, Rabies Immune Globulin (Human) - HYPERRAB™ S/D, detectable passive rabies antibody titers were observed in the serum of all subjects by 24 hours post injection and persisted through the 21 day study period. These results are consistent with prior studies^{17,18} with non-solvent/detergent treated product.

INDICATIONS AND CLINICAL USE

Rabies vaccine and Rabies Immune Globulin (Human) - HYPERRAB™ S/D should be given to all persons suspected of exposure to rabies with one exception: persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine. HYPERRAB™ S/D should be administered as promptly as possible after exposure, but can be administered up to the eighth day after the first dose of vaccine is given.

Recommendations for use of passive and active immunization after exposure to an animal suspected of having rabies have been detailed by the Health Canada National Advisory Committee on Immunization¹⁹ and the U.S. Public Health Service Immunization Practices Advisory Committee (ACIP).²⁰

Every exposure to possible rabies infection must be individually evaluated. The following factors should be considered before specific antirabies treatment is initiated:

1. Species of Biting Animal

The animals in Canada most often proven rabid and considered to pose a risk to humans are foxes, skunks, dogs, cats and bats.¹⁹ Carnivorous wild animals (especially skunks, foxes, coyotes, raccoons, and bobcats) and bats are the animals most commonly infected with rabies and have caused most of the indigenous cases of human rabies in the United States since 1960.²¹ Unless the animal is tested and shown not to be rabid, postexposure prophylaxis should be initiated upon bite or nonbite exposure to these animals (see [item 3](#) below). If treatment has been initiated and subsequent testing in a competent laboratory shows the exposing animal is not rabid, treatment can be discontinued.

In Canada and the United States, the likelihood that a domestic dog or cat is infected with rabies varies from region to region; hence, the need for postexposure prophylaxis also varies. However, in most of Asia and all of Africa and Latin America, the dog remains the major source of human exposure; exposures to dogs in such countries represent a special threat. Travelers to those countries should be aware that >50% of the rabies cases among humans in the United States result from exposure to dogs outside the United States.

Rodents (such as squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are rarely found to be infected with rabies and have not been known to cause human rabies in the United States. However, from 1971 through 1988, woodchucks accounted for 70% of the 179 cases of rabies among rodents reported to CDC.²² In these cases, the local health department should be consulted before a decision is made to initiate postexposure antirabies prophylaxis.

2. Circumstances of Biting Incident

An unprovoked attack is more likely to mean that the animal is rabid. (Bites during attempts to feed or handle an apparently healthy animal may generally be regarded as provoked.)

3. Type of Exposure

Rabies is transmitted only when the virus is introduced into open cuts or wounds in skin or mucous membranes. If there has been no exposure (as described in this section), postexposure treatment is not necessary. Thus, the likelihood that rabies infection will result from exposure to a rabid animal varies with the nature and extent of the exposure. Two categories of exposure should be considered:

Bite: any penetration of the skin by teeth. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment.²³

Bat-associated strains of rabies can be transmitted to humans either directly through a bat's bite or indirectly through the bite of an animal previously infected by a bat. Because some bat bites may be less severe, and therefore more difficult to recognize, than bites inflicted by larger mammalian carnivores, rabies postexposure treatment should be considered for any physical contact with bats when bite or mucous membrane contact cannot be excluded.²⁴

Nonbite: scratches, abrasions, open wounds or mucous membranes contaminated with saliva or any potentially infectious material, such as brain tissue, from a rabid animal constitute nonbite exposures. If the material containing the virus is dry, the virus can be considered noninfectious. Casual contact, such as petting a rabid animal and contact with the blood, urine, or feces (e.g., guano) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Instances of airborne rabies have been reported rarely. Adherence to respiratory precautions will minimize the risk of airborne exposure.²⁵

The only documented cases of rabies from human-to-human transmission have occurred in patients who received corneas transplanted from persons who died of rabies undiagnosed at the time of death. Stringent guidelines for acceptance of donor corneas have reduced this risk.

Bite and nonbite exposures from humans with rabies theoretically could transmit rabies, although no cases of rabies acquired this way have been documented.

4. Vaccination Status of Biting Animal

A properly immunized animal has only a minimal chance of developing rabies and transmitting the virus.

5. Presence of Rabies in Region

If adequate laboratory and field records indicate that there is no rabies infection in a domestic species within a given region, local health officials are justified in considering this in making recommendations on antirabies treatment following a bite by that particular species. Such officials should be consulted for current interpretations.

Rabies Postexposure Prophylaxis

The following recommendations are only a guide. In applying them, take into account the animal species involved, the circumstances of the bite or other exposure, the vaccination status of the animal, and presence of rabies in the region. Public health and Food Inspection Agency officials should be consulted if questions arise about the need for rabies prophylaxis.

Local Treatment of Wounds: Immediate and thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies. In experimental animals, simple local wound cleansing has been shown to reduce markedly the likelihood of rabies. Tetanus prophylaxis and measures to control bacterial infection should be given as indicated.

Active Immunization: Active immunization should be initiated as soon as possible after exposure (within 24 hours). Many dosage schedules have been evaluated for the currently available rabies vaccines and their respective manufacturers' literature should be

consulted.

Passive Immunization: A combination of active and passive immunization (vaccine and immune globulin) is considered the acceptable postexposure prophylaxis except for those persons who have been previously immunized with rabies vaccine and who have documented adequate rabies antibody titer. These individuals should receive vaccine only.

For passive immunization, Rabies Immune Globulin (Human) is preferred over antirabies serum, equine.^{16,20} It is recommended both for treatment of all bites by animals suspected of having rabies and for nonbite exposure inflicted by animals suspected of being rabid. Rabies Immune Globulin (Human) should be used in conjunction with rabies vaccine and can be administered through the seventh day after the first dose of vaccine is given. Beyond the seventh day, Rabies Immune Globulin (Human) is not indicated since an antibody response to cell culture vaccine is presumed to have occurred.

Rabies Post-exposure Prophylaxis Guide²⁰		
Animal Species	Condition of animal at time of exposure/attack	Treatment of exposed person [1]
Dog and cat	<p>Healthy and available for 10 days of observation</p> <p>Rabid or suspected rabid</p> <p>Unknown (escaped)</p>	<p>None, unless animal develops rabies [2]</p> <p>1. Local treatment of wound</p> <p>2. RIGH (local and intramuscular) [3] and HDCV</p> <p>Consult public health officials</p>
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck. Includes bat found in room when a person was sleeping unattended.	Regard as rabid unless geographic area is known to be free of rabies or proven negative by laboratory tests [4]	<p>1. Local treatment of wound</p> <p>2. RIGH (local and intramuscular) [3] and HDCV</p>
Livestock, rodents and lagomorphs (rabbits and hares)	Consider individually. Consult appropriate public health and Food Inspection Agency officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares may rarely warrant post-exposure rabies prophylaxis if the	

behaviour of the biting animal was highly unusual.
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- [1] ALL BITES AND WOUNDS SHOULD IMMEDIATELY BE THOROUGHLY CLEANSED WITH SOAP AND WATER. If antirabies treatment is indicated, both Rabies Immune Globulin (Human) [RIGH] and human diploid cell rabies vaccine (HDCV) should be given as soon as possible, REGARDLESS of the interval from exposure.
- [2] During the usual holding period of 10 days, begin treatment with RIGH and vaccine (HDCV) at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.
- [3] If RIGH is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.
- [4] The animal should be killed and the brain be tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

CONTRAINDICATIONS

None known.

WARNINGS

Rabies Immune Globulin (Human) - HYPERRAB™ S/D is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. 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 Talecris Biotherapeutics Ltd. at 1-866-482-5226.

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Rabies Immune Globulin (Human) - HYPERRAB™ S/D should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer HYPERRAB™ S/D to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.²⁶

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

PRECAUTIONS

General

Rabies Immune Globulin (Human) - HYPERRAB™ S/D should **not** be administered intravenously because of the potential for serious reactions. Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactoid symptoms.

Drug Interactions

Repeated doses of HYPERRAB™ S/D should not be administered 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™ S/D preparation may interfere with the response to

live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after HYPERRAB™ S/D administration.

Use in Pregnancy

Animal reproduction studies have not been conducted with HYPERRAB™ S/D. It is also not known whether HYPERRAB™ S/D can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HYPERRAB™ S/D should be given to a pregnant woman only if clearly needed.

Pediatric Use

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

ADVERSE REACTIONS

Soreness at the site of injection and mild temperature elevations may be observed at times. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients. Angioneurotic edema, skin rash, nephrotic syndrome, and anaphylactic shock have rarely been reported after intramuscular injection, so that a causal relationship between immunoglobulin and these reactions is not clear.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Although no data are available, clinical experience with other immunoglobulin preparations suggests that the only manifestations would be pain and tenderness at the injection site.

DOSAGE AND ADMINISTRATION

For intramuscular injection. Do not give intravenously. The recommended dose for Rabies Immune Globulin (Human) - HYPERRAB™ S/D is 20 IU/kg (0.133 mL/kg) of body weight given preferably at the time of the first vaccine dose.^{8,9} It may also be given through the seventh day after the first dose of vaccine is given. If anatomically feasible, up to one-half the dose of HYPERRAB™ S/D should be thoroughly infiltrated in the area around the

wound and the rest should be administered intramuscularly in the gluteal area or lateral thigh muscle using a separate syringe and needle. Because of risk of injury to the sciatic nerve, the central region of the gluteal area MUST be avoided; only the upper, outer quadrant should be used.²⁷ HYPERRAB™ S/D should never be administered in the same syringe or needle or in the same anatomical site as vaccine. Because of interference with active antibody production, the recommended dose should not be exceeded.¹⁹

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Rabies Post-Exposure Prophylaxis Schedule^{19,20}

Vaccination Status	Treatment	Regimen *
Not previously vaccinated	Wound cleansing RIG Vaccine	<p>All post-exposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds.</p> <p>Administer 20 IU/kg body weight as soon as possible after exposure. If anatomically feasible, up to one-half the dose should be infiltrated around the wound(s) and any remaining volume should be administered IM into the gluteal area (upper outer quadrant only) or lateral thigh muscle (because of the large volume to be injected). When more than one wound exists, each should be locally infiltrated with a portion of the RIG. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of the antibody, no more than the recommended dose should be given.</p> <p>HDCV started immediately (as soon as possible after exposure) 1.0 mL, IM (deltoid area†), one each on days 0§, 3, 7, 14, and 28.</p>
Previously vaccinated¶	Wound cleansing RIG Vaccine	<p>All post-exposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as a povidone-iodine solution should be used to irrigate the wounds.</p> <p>RIG should not be administered.</p> <p>HDCV started immediately (as soon as possible after exposure) 1.0 mL, IM (deltoid area†), one each on days 0§ and 3.</p>

HDCV = human diploid cell vaccine; RIG = rabies immune globulin; IM = intramuscular

* These regimens are applicable for 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 the first dose of vaccine is administered.

¶ Any person with a history of pre-exposure vaccination with HDCV; prior post-exposure prophylaxis with HDCV; or previous vaccination with other types of rabies vaccine or with HDCV according to unapproved schedules but in whom neutralizing rabies antibody is demonstrated in serum.

PHARMACEUTICAL INFORMATION

Rabies Immune Globulin (Human) - HYPERRAB™ S/D treated with solvent/detergent is a sterile solution of antirabies immune globulin for intramuscular administration; it contains no preservative. HYPERRAB™ S/D is prepared by cold ethanol fractionation from the plasma of donors hyperimmunized with rabies vaccine. The immune globulin is isolated from solubilized Cohn fraction II. The fraction II solution is adjusted to a final concentration of 0.3% tri-n-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration and finally ultrafiltration and diafiltration. HYPERRAB™ S/D is formulated as a 15–18% protein solution at a pH of 6.4–7.2 in 0.21–0.32 M glycine. The pH is adjusted with sodium carbonate. HYPERRAB™ S/D is then incubated in the final container for 21–28 days at 20–27°C.

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for HYPERRAB™ S/D has been validated in laboratory studies. Human Immunodeficiency Virus, Type 1 (HIV-1), was chosen as the relevant virus for blood products; Bovine Viral Diarrhea Virus (BVDV) was chosen to model Hepatitis C virus; Pseudorabies virus (PRV) was chosen to model Hepatitis B virus and the Herpes viruses; and Reo virus type 3 (Reo) was chosen to model non-enveloped viruses and for its resistance to physical and chemical inactivation. Significant removal of model enveloped and non-enveloped viruses is seen in the Fraction II + IIIW to Effluent III step and significant removal of PRV and Reo virus is also seen in the Effluent III to Filtrate III step. Significant inactivation of enveloped viruses is achieved at the time of treatment of solubilized Cohn Fraction II with solvent/detergent.

STORAGE

HYPERRAB™ S/D should be stored under refrigeration (2–8°C, 36–46°F). Do not freeze. Solution that has been frozen should not be used. Do not use beyond the expiration date. The vials are single use. Once entered, discard any unused contents.

AVAILABILITY OF DOSAGE FORMS

Rabies Immune Globulin (Human)- HYPERRAB™ S/D is packaged in 2 mL and 10 mL single use vials with an average potency value of 150 international units per mL (IU/mL) based on the U.S. Standard Rabies Immune Globulin. The 2 mL vial contains a total of 300 IU which is sufficient for a child weighing 15 kg. The 10 mL vial contains a total of 1500 IU which is sufficient for an adult weighing 75 kg.

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

No warranty, express or implied, including any warranty of merchantability or fitness is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labelling, including the package insert for this product, except by printed notice from the Company's headquarters. The prescriber and user of this product must accept the terms hereof.

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