107.4.26 驗收

Rabies Immune Globulin (Human)

HyperRAB® S/D

Solvent/Detergent Treated

08941118 (Rev. September 2012)

DESCRIPTION

Rabies Immune Globulin (Human) — Hyper**RAB**® S/D treated with solvent/detergent is a colorless to pale yellow or pink sterile solution of antirabies immune globulin for intramuscular administration; it is preservative-free and latex-free. Hyper**RAB** 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. Hyper**RAB** 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. Hyper**RAB** S/D is then incubated in the final container for 21–28 days at 20–27°C. The product is standardized against the U.S. Standard Rabies Immune Globulin to contain an average potency value of 150 IU/mL. The U.S. unit of potency is equivalent to the international unit (IU) for rabies antibody.

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for Hyper**RAB** 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 Human Herpes viruses and other large enveloped DNA 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 achieved at two steps in the Cohn fractionation process leading to the collection of Cohn Fraction II: the precipitation and removal of Fraction III in the processing of Fraction II + IIIW suspension to Effluent III and the filtration step in the processing of Effluent III to Filtrate III. Significant inactivation of enveloped viruses is achieved at the time of treatment of solubilized Cohn Fraction II with TNBP/sodium cholate.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[27-30] Studies of the Hyper**RAB** S/D manufacturing process demonstrate that TSE clearance is achieved during the Pooled Plasma to Effluent III Fractionation Process (6.7 $\log_{10}$). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

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 (World Health Organization) 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 eight healthy human adults receiving a 20 IU/kg intramuscular dose of Rabies Immune Globulin (Human) treated with solvent/detergent, Hyper**RAB** 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 USAGE

Rabies vaccine and Hyper**RAB** 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. Hyper**RAB** 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 U.S. Public Health Service Advisory Committee on Immunization Practices (ACIP).[19]

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

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.[20] 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 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.[21] In these cases, the state or 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.[22]

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 can go completely undetected, unlike bites inflicted by larger animals, especially mammalian carnivores, rabies postexposure treatment should be considered for any physical contact with bats when bite or mucous membrane contact cannot be excluded.[23]

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.[24]

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. Local or state public health 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.[16,19] 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 Postexposure Prophylaxis Guide[19]

Animal species	Condition of animal at time of exposure/attack	Treatment of exposed person [1]
Dog and cat	Healthy and available for 10 days of observation	None, unless animal develops rabies [2]
	Rabid or suspected rabid	RIGH [3] and HDCV
	Unknown (escaped)	Consult public health officials
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck	Regard as rabid unless animal proven negative by laboratory tests [4]	RIGH [3] and HDCV
Livestock, rodents, and lagomorphs (rabbits and hares)	Consider individually. Local and state public health officials should be consulted on questions about the need for rabies prophylaxis. In most geographical areas bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.	

[1] ALL POSTEXPOSURE PROPHYLAXIS SHOULD BEGIN WITH IMMEDIATE THOROUGH CLEANSING OF THE WOUND (IF ONE CAN BE DETECTED) 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 postexposure prophylaxis at first sign of rabies in a dog or cat that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized 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 euthanized and 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, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent 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 Grifols Therapeutics Inc. [1-800-520-2807].**

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

Hyper**RAB** 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 Hyper**RAB** 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.[25]

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

PRECAUTIONS

General

Hyper**RAB** 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 Hyper**RAB** 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 Hyper**RAB** 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 Hyper**RAB** S/D administration.

Pregnancy Category C

Animal reproduction studies have not been conducted with Hyper**RAB** S/D. It is also not known whether Hyper**RAB** S/D can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyper**RAB** 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.

DOSAGE AND ADMINISTRATION

The recommended dose for Hyper**RAB** 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 the full dose of Hyper**RAB** S/D should be thoroughly infiltrated in the area around the wound and the rest should be administered intramuscularly in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve.[26] Hyper**RAB** S/D should never be administered in the same syringe or needle or in the same anatomical site as vaccine.

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

Rabies postexposure prophylaxis schedule—United States, 1999 [19]

Vaccination status	Treatment	Regimen*
Not previously vaccinated	Wound cleansing	All postexposure 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.
	RIG	Administer 20 IU/kg body weight. If anatomically feasible, **the full dose** should be infiltrated around the wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0§, 3, 7, 14, and 28.
Previously vaccinated¶	Wound cleansing	All postexposure 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.
	RIG	RIG should **not** be administered.
	Vaccine	HDCV, RVA, or PCEC 1.0 mL, IM (deltoid area†), one each on days 0§ and 3.

HDCV=human diploid cell vaccine; PCEC=purified chick embryo cell vaccine; RIG=rabies immune globulin; RVA=rabies vaccine adsorbed; 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 preexposure vaccination with HDCV, RVA, or PCEC; prior postexposure prophylaxis with HDCV, RVA, or PCEC; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

HOW SUPPLIED

Hyper**RAB** S/D is packaged in 2 mL and 10 mL single dose vials with an average potency value of 150 international units per mL (IU/mL). 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. Hyper**RAB** S/D is preservative-free and latex-free.

NDC Number	Size
13533-618-02	2 mL vial
13533-618-10	10 mL vial

STORAGE

Hyper**RAB** S/D should be stored under refrigeration (2–8°C, 36–46°F). Solution that has been frozen should not be used.

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

LIMITED WARRANTY

A number of factors 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 labeling, 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.

REFERENCES

1. Baltazard M, Bahmanyar M, Ghodssi M, et al: Essai pratique du sérum antirabique chez les mordus par loups enragés. *Bull WHO* 13:747-72, 1955.
2. Habel K, Koprowski H: Laboratory data supporting the clinical trial of antirabies serum in persons bitten by a rabid wolf. *Bull WHO* 13:773-9, 1955.
3. Selimov M, Boltucij L, Semenova E, et al: [The use of antirabies gamma globulin in subjects severely bitten by rabid wolves or other animals.] *J Hyg Epidemiol Microbiol Immunol (Praha)* 3:168-80, 1959.
4. Atanasiu P, Bahmanyar M, Baltazard M, et al: Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. *Bull WHO* 14:593-611, 1956.
5. Atanasiu P, Bahmanyar M, Baltazard M, et al: Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part II. *Bull WHO* 17:911-32, 1957.
6. Atanasiu P, Cannon DA, Dean DJ, et al: Rabies neutralizing antibody response to different schedules of serum and vaccine innoculations in non-exposed persons: Part 3. *Bull WHO* 25:103-14, 1961.
7. Atanasiu P, Dean DJ, Habel K, et al: Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part 4. *Bull WHO* 36:361-5, 1967.
8. Cabasso VJ, Loofbourow JC, Roby RE, et al: Rabies immune globulin of human origin: preparation and dosage determination in non-exposed volunteer subjects. *Bull WHO* 45:303-15, 1971.
9. Loofbourow JC, Cabasso VJ, Roby RE, et al: Rabies immune globulin (human): clinical trials and dose determination. *JAMA* 217(13): 1825-31, 1971.
10. Plotkin SA: New rabies vaccine halts disease — without severe reactions. *Mod Med* 45(20):45-8, 1977.
11. Plotkin SA, Wiktor TJ, Koprowski H, et al: Immunization schedules for the new human diploid cell vaccine against rabies. *Am J Epidemiol* 103(1):75-80, 1976.
12. Hafkin B, Hattwick MA, Smith JS, et al: A comparison of a WI-38 vaccine and duck embryo vaccine for preexposure rabies prophylaxis. *Am J Epidemiol* 107(5):439-43, 1978.
13. Kuwert EK, Marcus I, Höher PG: Neutralizing and complement-fixing antibody responses in pre- and post-exposure vaccinees to a rabies vaccine produced in human diploid cells. *J Biol Stand* 4(4):249-62, 1976.
14. Grandien M: Evaluation of tests for rabies antibody and analysis of serum responses after administration of three different types of rabies vaccines. *J Clin Microbiol* 5(3):263-7, 1977.
15. Kuwert EK, Marcus I, Werner J, et al: Postexpositionelle Schutzimpfung des Menschen gegen Tollwut mit einer neu-entwickelten Gewebekulturvakzine (HDCS-Impfstoff). *Zentralbl Bakteriol [A]* 239(4):437-58, 1977.
16. Bahmanyar M, Fayaz A, Nour-Salehi S, et al: Successful protection of humans exposed to rabies infection: postexposure treatment with the new human diploid cell rabies vaccine and antirabies serum. *JAMA* 236(24):2751-4, 1976.
17. American Hospital Formulary Service. Drug Information. Section 80:04. Rabies immune globulin. Bethesda, American Society for Health-Systems Pharmacy, 1997, p. 2545-7.
18. Rubin RH, Sikes RK, Gregg MB: Human rabies immune globulin. Clinical trials and effects on serum anti-globulins. *JAMA* 224:871-4, 1973.
19. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Rabies prevention—United States, 1999. *MMWR* 48 (RR-1):1-21, 1999.
20. Reid-Sanden FL, Dobbins JG, Smith JS, et al: Rabies surveillance in the United States during 1989. *J Am Vet Med Assoc* 197(12):1571-83, 1990.
21. Fishbein DB, Belotto AJ, Pacer RE, et al: Rabies in rodents and lagomorphs in the United States, 1971-1984: increased cases in the woodchuck (*Marmota monax*) in mid-Atlantic states. *J Wildl Dis* 22(2):151-5, 1986.
22. Hattwick MAW: Human rabies. *Public Health Rev* 3(3):229-74, 1974.
23. Epidemiologic Notes and Reports: Human Rabies—California, 1994. *MMWR* 43(25):455-457, 1994.
24. Garner JS, Simmons BP: Guideline for isolation precautions in hospitals. *Infect Control* 4(4 Suppl):245-325, 1983.
25. Fudenberg HH: Sensitization to immunoglobulins and hazards of gamma globulin therapy. In: Merler E (ed.): Immunoglobulins: biologic aspects and clinical uses. Washington, DC, Nat Acad Sci, 1970, pp 211-20.
26. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP): General recommendations on immunization. *MMWR* 2002: 51(RR02), 1-36.
27. Stenland CJ, Lee DC, Brown P, et al. Partitioning of human and sheep forms of the pathogenic prion protein during the purification of therapeutic proteins from human plasma. *Transfusion* 2002. 42(11):1497-500.
28. Lee DC, Stenland CJ, Miller JL, et al. A direct relationship between the partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. *Transfusion* 2001. 41(4):449-55.
29. Lee DC, Stenland CJ, Hartwell RC, et al. Monitoring plasma processing steps with a sensitive Western blot assay for the detection of the prion protein. *J Virol Methods* 2000. 84(1):77-89.
30. Cai K, Miller JL, Stenland CJ, et al. Solvent-dependent precipitation of prion protein. *Biochim Biophys Acta* 2002. 1597(1):28-35.

GRIFOLS

Grifols Therapeutics Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

08941118
(Rev. September 2012)

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

3047927

----------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 post-exposure 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 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 Inc. 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: 2/2018**

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 post-exposure 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 post-exposure 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 Inc. immediately [1-800-520-2807].
- Do not freeze. Do not use any solution that has been frozen.

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 and 5 mL single- dose vials. The 1 mL vial is sufficient for a child weighing 15 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.

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 Inc. [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 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® [rabies immune globulin (human)] 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 globin (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 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]

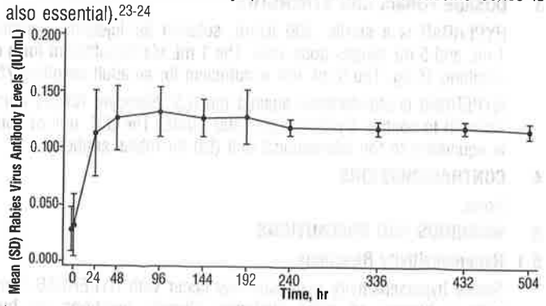

Figure 1: Mean (Standard Deviation) Rabies Virus Neutralizing Antibody Levels (IU/mL) versus Time following a Single 20 IU/kg Dose of HYPERRAB (300 IU/mL) by Intramuscular Injection

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).

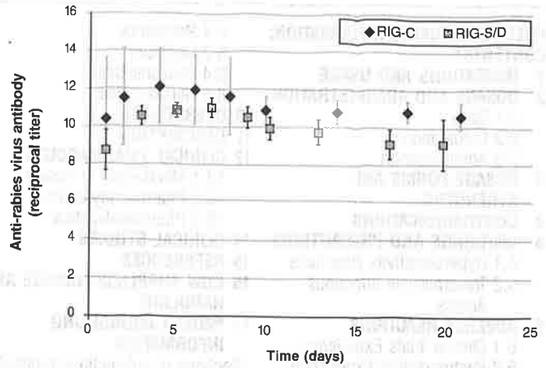

Figure 2: Reciprocal of Anti-Rabies Virus Neutralizing Antibody Titer Following a Single 20 IU/kg Dose of HYPERRAB (300 IU/mL; RIG-C) or HYPERRAB S/D (150 IU/mL; RIG-S/D) Product (mean [standard deviation])

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).

15 REFERENCES

1. Centers for Disease Control and Prevention. Human rabies prevention — United States, 2008: Recommendations of the Advisory Committee on Immunization Practices. MMWR. 2008;57(RR03):1-26, 28.
2. World Health Organization. WHO Expert Consultation on Rabies: Second report. 2013. WHO technical report series, No. 982.
3. Centers for Disease Control and Prevention. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies. Recommendations of the Advisory Committee on Immunization Practices. MMWR. 2010;59(RR02):1-9. Erratum in: MMWR 2010;59(16):493.
4. Fudenberg HH. Sensitization to immunoglobulins and hazards of gamma globulin therapy. In: Merler E (editor). Immunoglobulins: biologic aspects and clinical uses. Washington, DC: National Academy of Science; 1970, p. 211-20.
5. Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2011;60(RR02):1-61. Erratum in: MMWR 2011;60(29):993.
6. Barnette D, Roth NJ, Hotta J, et al. Pathogen safety profile of a 10% IgG preparation manufactured using a depth filtration-modified process. Biologicals. 2012;40:247-53.
7. Baltazard M, Bahmanyar M, Ghodssi M, et al. Essai pratique du sérum antirabique chez les mordus par loups enragés. [Practical test of anti-rabies serum in bites by rabid wolves]. Bull WHO. 1955;13:747-72.
8. Habel K, Koprowski H. Laboratory data supporting the clinical trial of antirabies serum in persons bitten by a rabid wolf. Bull WHO. 1955;13:773-9.
9. Selimov M, Boltucij L, Semenova E, et al. [The use of antirabies gamma globulin in subjects severely bitten by rabid wolves or other animals.] J Hyg Epidemiol Microbiol Immunol (Praha). 1959;3:168-80.
10. Atanasiu P, Bahmanyar M, Baltazard M, et al. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons. Bull WHO. 1956;14:593-611.
11. Atanasiu P, Bahmanyar M, Baltazard M, et al. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part II. Bull WHO. 1957;17:911-32.
12. Atanasiu P, Cannon DA, Dean DJ, et al. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part 3. Bull WHO. 1961;25:103-14.
13. Atanasiu P, Dean DJ, Habel K, et al. Rabies neutralizing antibody response to different schedules of serum and vaccine inoculations in non-exposed persons: Part 4. Bull WHO. 1967;36:361-5.
14. Cabasso VJ, Loofbourow JC, Roby RE, et al. Rabies immune globulin of human origin: preparation and dosage determination in non-exposed volunteer subjects. Bull WHO. 1971;45:303-15.
15. Loofbourow JC, CabassVJ, Roby RE, et al. Rabies immune globin (human): clinical trials and dose determination. JAMA. 1971;217(13):1825-31.
16. Plotkin SA. New rabies vaccine halts disease — without severe reactions. Mod Med. 1977;45(20):45-8.
17. Plotkin SA, Wiktor TJ, Koprowski H, et al. Immunization schedules for the new human diploid cell vaccine against rabies. Am J Epidemiol. 1976;103(1):75-80.
18. Hafkin B, Hattwick MA, Smith JS, et al. A comparison of a WI-38 vaccine and duck embryo vaccine for preexposure rabies prophylaxis. Am J Epidemiol. 1978;107(5):439-43.
19. Kuwert EK, Marcus I, Höher PG. Neutralizing and complement-fixing antibody responses in pre- and post-exposure vaccinees to a rabies vaccine produced in human diploid cells. J Biol Stand. 1976;4(4):249-62.
20. Grandien M. Evaluation of tests for rabies antibody and analysis of serum responses after administration of three different types of rabies vaccines. J Clin Microbiol. 1977;5(3):263-7.
21. Kuwert EK, Marcus I, Werner J, et al. Postexpositionelle Schutzimpfung des Menschen gegen Tollwut mit einer neu-entwickelten Gewebekulturvakzine (HDCS-Impfstoff). [Post exposure use of human diploid cell culture rabies vaccine (author's transl)]. Zentralbl Bakteriol [A]. 1977;239(4):437-58.
22. Bahmanyar M, Fayaz A, Nour-Salehi S, et al. Successful protection of humans exposed to rabies infection: postexposure treatment with the new human diploid cell rabies vaccine and antirabies serum. JAMA. 1976;236(24):2751-4.
23. Helmick CG, Johnston C, Sumner J, et al. A clinical study of Merieux human rabies immune globulin. J Biol Stand. 1982;(10):357-67.
24. Lang J, Gravenstein S, Briggs D. Evaluation of the safety and immunogenicity of a new, heat-treated human rabies immune globulin using a sham, post-exposure prophylaxis of rabies. Biologicals 1998;(26):7-15.

16 HOW SUPPLIED/STORAGE AND HANDLING

HYPERRAB is supplied in 1 mL and 5 mL single dose vials 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
13533-318-05	5 ml

- Store HYPERRAB at (2 to 8°C, 36 to 46°F).
- Do not freeze.
- Do not use after expiration date.

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

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

3047927