

HYPERRAB S/D - human rabies virus immune globulin injection
GRIFOLS USA, LLC

Rabies Immune Globulin (Human)
HyperRAB[®] S/D
Solvent/Detergent Treated

DESCRIPTION

Rabies Immune Globulin (Human) — HyperRAB[®] 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. 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. HyperRAB 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 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 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 HyperRAB S/D manufacturing process demonstrate that TSE clearance is achieved during the Pooled Plasma to Effluent III Fractionation Process (6.7 log₁₀). 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, 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 USAGE

Rabies vaccine and 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 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*
Dog and cat	Healthy and available for 10 days of observation Rabid or suspected rabid Unknown (escaped)	None, unless animal develops rabies [†] RIGH [‡] and HDCV Consult public health officials
Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck	Regard as rabid unless animal proven negative by laboratory tests [§]	RIGH [‡] and HDCV
Livestock, rodents, and lagomorphs	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, (rabbits and gerbils, chipmunks, rats, mice, other rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.	

* 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.

[†] 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.

[‡] If RIGH is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage.

[§] 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

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* 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.

<u>NDC Number</u>	<u>Size</u>
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

Rx 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.

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Grifols Therapeutics Inc.

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

08941118

(Rev. September 2012)

PACKAGE LABEL

Rabies Immune Globulin (Human)

HyperRAB[®]S/D

Solvent/Detergent Treated

Preservative-free, latex-free

150 IU/mL Suitable for use with Rabies Vaccine

10 mL

NDC 13533-618-10

The patient and physician should discuss the risks and benefits of this product.

One Single Dose Vial

FOR INTRAMUSCULAR INJECTION ONLY. DO NOT GIVE INTRAVENOUSLY.

For complete dosage and administration information, read enclosed package insert.

Store at 2–8°C (36–46°F).

Do not freeze.

If the shrink band is absent or shows any sign of tampering, do not use the product and notify Grifols Therapeutics Inc. immediately.

Not returnable for credit or exchange.

Rx only

CAUTION: U.S. federal law prohibits dispensing without prescription.

Rabies Immune Globulin (Human) is a sterile solution of immunoglobulin containing 15%–18% protein stabilized with 0.21–0.32 M glycine. The pH is adjusted with sodium carbonate.

The potency of each vial is 150 IU/mL based on the U.S. Standard Rabies Immune Globulin.

Grifols Therapeutics Inc.

Research Triangle Park, NC 27709 USA

U.S. License No. 1871

Carton: 08940719



10 mL
Rabies Immune Globulin (Human)
NDC 13533-618-10

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The potency of each vial is 150 IU/mL based on the U.S. Standard Rabies Immune Globulin.

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

10 mL 10 mL 10 mL

10 mL 10 mL

10 mL 10 mL

10 mL 10 mL 10 mL

Rabies Immune Globulin (Human)

HyperRAB® S/D

Solvent/Detergent Treated

Preservative-free, latex-free

150 IU/mL
Suitable for use with Rabies Vaccine

10 mL

NDC 13533-618-10

GRIFOLS

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Not returnable for credit or exchange.

Rx only

CAUTION: U.S. federal law prohibits dispensing without prescription.



(01)003 13533 618100

Carton: 08940719

NDC 13533-618-11

Rabies Immune Globulin (Human)

Hyper**RAB**® S/D 10 mL

Solvent/Detergent Treated

Grifols Therapeutics, Inc.
RTP, NC 27709 USA
U.S. License No. 1871

The patient and physician should discuss the risks and benefits of this product.

One Single Dose Vial

150 IU/mL

Do not give intravenously.

Dosage: 20 IU/kg in conjunction with Rabies Vaccine.

See directions before using.

Rx only

08940696

Lot

Exp.

08940696

Lot Exp. (01)003 13533 618117

NDC 13533-618-11
Rabies Immune Globulin (Human)
HyperRAB® S/D 10 mL
Solvent/Detergent Treated
Grifols Therapeutics, Inc.
RTP, NC 27709 USA
U.S. License No. 1871

One Single Dose Vial
150 IU/mL
Do not give intravenously.
Dosage: 20 IU/kg in conjunction with Rabies Vaccine.
See directions before using.
Rx only

The patient and physician should discuss the risks and benefits of this product.

HYPERRAB S/D

human rabies virus immune globulin injection

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:13533-618
Route of Administration	INTRAMUSCULAR	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Human Rabies Virus Immune Globulin (Human Rabies Virus Immune Globulin)	Human Rabies Virus Immune Globulin	150 [iU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycine	

Product Characteristics

Color	YELLOW (Clear liquid, colorless to pale yellow)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-618-02	1 in 1 CARTON		
1	NDC:13533-618-20	2 mL in 1 VIAL, GLASS; Combination Product Type = C112160		
2	NDC:13533-618-10	1 in 1 CARTON		
2	NDC:13533-618-11	10 mL in 1 VIAL; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA101144	08/14/1996	

Labeler - GRIFOLS USA, LLC (048987452)**Establishment**

Name	Address	ID/FEI	Business Operations
Grifols Therapeutics Inc.		6 110 19 113	MANUFACTURE(13533-618)

Revised: 9/2012

GRIFOLS USA, LLC