PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

HyperRAB®

Rabies Immunoglobulin [Human]

Injectable Solution, 300 IU per mL

For infiltration and intramuscular injection

Manufacturer's Standard

Passive Immunizing Agent

ATC: J06BB05

Manufactured by:

Grifols Therapeutics LLC
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U.S.A.

Imported and Distributed by:

Grifols Canada Ltd.
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HyperRAB® (Rabies Immunoglobulin [Human]) is indicated for post-exposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies. Persons previously immunized with rabies vaccine that have a confirmed adequate rabies antibody titer should receive only vaccine.

HyperRAB® should be administered as promptly as possible after exposure, but can be administered up to and including 7 days after Day 0 (the day the first dose of vaccine is administered).

Refer to the Canadian Immunization Guide for the most recent recommendations. (see: https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html)

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore Health Canada has not authorized an indication for pediatric use. However, the Canadian Immunization Guide published by the Public Health Agency of Canada, recommends a common dose of rabies immunoglobulin (Human) for all age groups, including children. As such, dosing recommendations for pediatric patients are included in the present Product Monograph.

1.2 Geriatrics

Geriatrics: Safety and effectiveness in geriatric population have not been established.

2 CONTRAINDICATIONS

None known.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- The health professional should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient (see WARNINGS AND PRECAUTIONS: General).
- For intramuscular injection only. Do not give intravenously (see WARNINGS AND PRECAUTIONS: General).
- Products made from human plasma may contain infectious agents such as viruses that can cause disease (see WARNINGS AND PRECAUTIONS: General).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose for HyperRAB® (Rabies Immunoglobulin [Human]) is 20 IU/kg (0.0665 mL/kg) of body weight given preferably at the time of the first rabies vaccine dose. It may also be given through the seventh day after the first dose of rabies vaccine is given.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

If anatomically feasible, the full dose of HyperRAB® should be thoroughly infiltrated in the area around the wound. If the wound covers a large area and the HyperRAB® dose has insufficient volume to infiltrate the entire wound, the HyperRAB® dose may be diluted with an equal volume of dextrose, 5% (D5W) in water. Do not dilute with normal saline. Inject the remainder, if any, intramuscularly, preferably in the deltoid muscle of the upper arm or lateral thigh muscle using a separate syringe and needle. Because of risk of injury to the sciatic nerve, the gluteal region should not be used routinely as an injection site. If the gluteal region is used when very large volumes are to be injected or multiple doses are necessary, the central region MUST be avoided; only the upper, outer quadrant should be used.

HyperRAB® should never be administered in the same syringe or needle or in the same anatomical site as rabies vaccine. Because of interference with active antibody production, the recommended dose should not be exceeded.

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

Table 1: Rabies Post-Exposure Prophylaxis Schedule

Vaccination Status	Treatment	Regimen *
Not previously vaccinated	Wound cleansing	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.
	RIG	Administer 20 IU/kg body weight as soon as possible after exposure. If anatomically feasible, the full dose should be infiltrated around the wound(s) and any remaining volume should be administered IM into the deltoid muscle of the upper arm 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.

	Vaccine	Administer HDCV or PCECV immediately (as soon as possible after exposure) (deltoid area†), on day 0§. Complete a rabies vaccination series for previously unvaccinated persons
Previously vaccinated¶	Wound cleansing	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.
	RIG	RIG should **not** be administered.
	Vaccine	Administer HDCV or PCECV immediately (as soon as possible after exposure) IM (deltoid area†), on day 0§. Complete a rabies vaccination series for previously vaccinated persons

HDCV = human diploid cell vaccine; PCECV = purified chick embryo cell vaccine; RIG = rabies immunoglobulin; 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. Refer to vaccine manufacturer's instructions or to the recommendations of the National Advisory Committee on Immunization (NACI) for appropriate rabies vaccine formulations, schedules and dosages.

¶ Any person with a history of pre-exposure vaccination or prior post-exposure prophylaxis with HDCV, or PCECV; or previous vaccination with other types of rabies vaccine and a documented history of antibody response to the prior vaccination.

5 OVERDOSAGE

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

Because Rabies Immunoglobulin (Human) may partially suppress active production of antibody in response to the rabies vaccine, do not give more than the recommended dose of rabies immunoglobulin (human).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Infiltration and Intramuscular injection	Injectable solution; 15-18% protein, containing not less than 300 IU/mL rabies antibody)	Glycine

HyperRAB® (Rabies Immunoglobulin [Human]) is packaged in 1 mL, 3mL and 5 mL single use vials with an average potency value of 300 international units per mL (IU/mL) based on the U.S. Standard Rabies Immunoglobulin. HyperRAB® contains no preservative and is not made with natural rubber latex. The 1 mL vial contains a total of 300 IU which is sufficient for a child weighing 15 kg. The 3 mL vial contains a total of 900 IU which is sufficient for a person weighing 45 kg. The 5 mL vial contains a total of 1500 IU which is sufficient for a person weighing 75 kg. HyperRAB® is a clear to opalescent, and colorless or pale yellow or pale brown solution.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

HyperRAB® (Rabies Immunoglobulin [Human]) is made from human plasma and may carry a risk of transmitting infectious agents, e.g. such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. 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; (2) screening of individual donations and plasma pools for viral infection markers; 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 health professional or other healthcare provider to Grifols Canada Ltd. at 1-866-482-5226.

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

HyperRAB® should not be administered intravenously because of the potential for serious reactions (see Hypersensitivity Reactions).

Hematologic

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

Hypersensitivity Reactions

HyperRAB® (Rabies Immunoglobulin [Human]) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations. Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactoid symptoms, should they occur.

Weigh the benefits of administering HyperRAB® to persons with isolated immunoglobulin A (IgA) deficiency 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.

Reproductive Health: Female and Male Potential

See 7.1.1 Pregnant Women

7.1 Special Populations

7.1.1 Pregnant Women

There are no data with HyperRAB® use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with HyperRAB® . It is also 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.

7.1.2 Breast-feeding

It is unknown if HyperRAB® is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. 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®.

7.1.3 Pediatrics

Pediatrics (<18 years): Safety and effectiveness in the pediatric population have not been established. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See also 1.1 INDICATIONS: Pediatrics.

7.1.4 Geriatrics

Safety and effectiveness in geriatric population have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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. The most common adverse reactions in clinical studies were injection site pain and headache.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3: Adverse Drug Reactions from Clinical Studies of Healthy Subjects administered a single dose of HyperRAB® or HyperRAB® S/D (20 IU/kg)

	HyperRAB® Study #1: N = 12** n (%)	HyperRAB® S/D* Study #2: N = 8 n (%)
Gastrointestinal Disorders		
Abdominal Pain	1 (8%)	0
Diarrhea	1 (8%)	0
Flatulence	1 (8%)	0
General Disorders and Administration Site Conditions		
Injection site pain	4 (33%)	0
Injection site nodule	1 (8%)	0
Nervous System Disorders		
Headache	1 (8%)	1 (13%)
Respiratory, Thoracic and Mediastinal Disorders		
nasal congestion	1 (8%)	0
oropharyngeal pain	1 (8%)	0

* original 150 IU/mL HyperRAB® S/D (solvent/detergent treated)

** a total of 5 subjects experienced at least one adverse reaction in this study

No subject discontinued study due to adverse reaction in either study. All adverse reactions were mild except for moderate oropharyngeal pain in the HyperRAB® study.

8.5 Post-Market Adverse Reactions

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 immunoglobulins. 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 disorders	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.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Repeated doses of HyperRAB® (Rabies Immunoglobulin [Human]) 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® preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, defer immunization with live vaccines for 3 months after HyperRAB® administration.

Do not dilute HyperRAB® with normal saline. Use dextrose, 5% (D5W) in water to dilute HyperRAB®.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Rabies Immunoglobulin [Human] provides immediate, passive, rabies virus neutralizing antibody coverage until the previously unvaccinated patient responds to rabies vaccine by actively producing antibodies.

10.2 Pharmacodynamics

See Section 10.1.

10.3 Pharmacokinetics

In a clinical study of 12 healthy human subjects receiving a 20 IU/kg intramuscular dose of HyperRAB® (Rabies Immunoglobulin [Human]) detectable passive rabies neutralizing antibody was present by the second day and persisted through the 21 day follow-up evaluation period. Rabies immunoglobulin (Human) for intramuscular administration is bioavailable in the recipient's circulation after a delay of 1-2 days. Rabies immunoglobulin (Human) has a half-life of about 3-4 weeks. This half-life may vary from patient to patient.

11 STORAGE, STABILITY AND DISPOSAL

HyperRAB® (Rabies Immunoglobulin [Human]) should be stored at 2–8°C. Do not freeze. Solution that has been frozen should not be used.

During the shelf-life, HyperRAB® may also be stored at room temperature (not more than 25ºC) for a period of up to 6 months. After being stored at room temperature, the product must either be used or discarded, and should not be returned to the refrigerator.

Do not use beyond the expiration date printed on the label.

The vials are single use. Once entered, discard any unused contents.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: HyperRAB®

Common name: Rabies Immunoglobulin [Human]

Product Characteristics:

HyperRAB® (Rabies Immunoglobulin [Human]) is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution of human antirabies immunoglobulin for 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 Immunoglobulin 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.

Viral Inactivation

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 viral inactivation or removal. 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. 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.

14 CLINICAL TRIALS

HyperRAB® was administered to a total of 12 healthy adult subjects in one clinical trial. In this study a single intramuscular of dose of 20 IU/kg HyperRAB® was administered and passive rabies antibody titers were monitored in serum for 21 days. The product was well-tolerated and resulted in detectable titers of antibodies to the rabies virus that persisted throughout the 21 day study period.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether HyperRAB® affects fertility in males or females. No long-term studies have been undertaken to evaluate immunogenicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

HyperRAB®

(Rabies Immunoglobulin [Human])

Read this carefully before you start taking **HyperRAB®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **HyperRAB®**.

Serious Warnings and Precautions

- Your healthcare professional should discuss the risks and benefits of this product with you before prescribing or administering it to you.
- This product must only be administered by intramuscular injection. It must not be given intravenously.
- This product is made from human plasma may theoretically contain infectious agents such as viruses that can cause disease

What is HyperRAB® used for?

In combination with a vaccine **HyperRAB®** is used to help prevent rabies in people who may have been exposed to rabies through contact with an infected animal.

How does HyperRAB® work?

Vaccines work by stimulating your immune system to produce antibodies against a particular disease. Because vaccines require this immune response, they take time to work and are not immediately effective. **HyperRAB®** is made from the blood of people who have already been vaccinated against rabies and therefore already contains rabies antibodies. It starts working immediately after being injected and helps to protect you from getting rabies until your body starts producing its own antibodies in response to the vaccine.

What are the ingredients in HyperRAB®?

Medicinal ingredients: Human Rabies Immunoglobulin

Non-medicinal ingredients: Glycine

HyperRAB® comes in the following dosage forms:

Single use vials with an average potency value of 300 international units per mL (IU/mL)

- 1 mL vial (containing 300 IU)
- 3 mL vial (containing 900 IU)
- 5 mL vial (containing 1500 IU)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HyperRAB®. Talk about any health conditions or problems you may have, including if you:

- have previously had a reaction to any immunoglobulin product like **HyperRAB®** and/or if you have an immunoglobulin A (IgA) deficiency
- have been diagnosed with thrombocytopenia or any other bleeding disorder
- have received rabies vaccine in the past
- are pregnant or breastfeeding

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HyperRAB®:

- Certain types of vaccines such as measles, mumps, polio or rubella. **HyperRAB®** could interfere with the effectiveness of certain vaccines, and you should avoid being vaccinated with these until 3 months after your treatment with **HyperRAB®**.
- If your doctor needs to dilute **HyperRAB®** to treat a larger bite, they should only use a 5% dextrose solution. **HyperRAB®** should not be diluted with saline.

How to take HyperRAB®:

- Your healthcare professional will administer **HyperRAB®**. If possible, the full dose should be injected all around the bite wound. If your healthcare professional needs to dilute **HyperRAB®** to treat a larger bite, they should only use a 5% dextrose solution. **HyperRAB®** should not be diluted with saline.
- If not possible to administer the full dose around the wound, any left-over **HyperRAB®** should be given as an intramuscular injection into the upper part of the arm, or the side of the thigh. The gluteal region (buttocks) should not routinely be used to administer **HyperRAB®**, and it should not be given in the same location as your injection of rabies vaccine.

Usual dose:

The recommended dose for **HyperRAB®** is 20 IU/kg (or 0.0665 mL/kg) based on body weight. It should preferably be given at the same time as the first dose of rabies vaccine, but can also be given up to a week after the first dose of rabies vaccine.

Overdose:

There is no data regarding what to expect in case of a **HyperRAB®** overdose, although experience with similar products suggests that the only issues might include pain and tenderness at the injection site.

If you think you, or a person you are caring for, have received too much **HyperRAB®**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using HyperRAB®?

These are not all the possible side effects you may have when taking HyperRAB®. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects reported in two small clinical studies of **HyperRAB®** were pain at the injection site and headache. Other reported side effects (each reported only once in the studies) were stomach pain, diarrhea, flatulence/gas, a bump at the injection site, nasal congestion, and pain in the mouth/throat.

Other side effects that have been reported following use of **HyperRAB®**, include a reduced sense of touch, nausea, joint and muscle pain, hypersensitivity reactions, and allergic reactions.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Anaphylaxis (serious allergic reaction with symptoms that can include dizziness, numbness or tingling, rash, flushing or reddening of the skin, difficult or rapid breathing, pain in the mouth or throat, and excessive sweating)	**-**	**YES**	**YES**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

HyperRAB® should be stored at (2–8°C), and should never be frozen. **HyperRAB®** may also be stored at room temperature (not more than 25°C), for a period of up to 6 months anytime before the product expiry date. After being stored at room temperature, it must either be used or discarded, and should not be returned to the refrigerator. Do not use past the expiry date printed on the product label.

Keep out of reach and sight of children.

If you want more information about HyperRAB®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-482-5226.

This leaflet was prepared by Grifols Therapeutics LLC.

Last Revised [TBD]