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Rabies Immune Globulin (Human) USP, Heat Treated

Imogam® Rabies – HT

RIG

℞ only

FOR INTRAMUSCULAR USE ONLY

DESCRIPTION

Rabies Immune Globulin (Human) USP, Heat Treated, Imogam® Rabies – HT, is a sterile solution of antirabies immunoglobulin (10-18% protein) for intramuscular administration. Rabies immune globulin (RIG) is prepared by cold alcohol fractionation from pooled venous plasma of individuals immunized with Rabies Vaccine prepared from human diploid cells (HDCV). The product is stabilized with 0.3 M glycine. The globulin solution has a pH of 6.8 ± 0.4 adjusted with sodium hydroxide or hydrochloric acid. No preservatives are added. Imogam® Rabies – HT is a colorless to light opalescent liquid.

A heat-treatment process step (58° to 60°C, 10 hours) to inactivate viruses has been added to further reduce any risk of blood-borne viral transmission. The inactivation and removal of model, laboratory strains of enveloped and non-enveloped viruses during the manufacturing and heat treatment processes for Imogam® Rabies – HT have been validated by spiking experiments. Human immunodeficiency virus, type 1 (HIV-1) and type 2 (HIV-2) were selected as relevant viruses for plasma derived products. Bovine viral diarrhea virus and Sindbis virus were chosen to model hepatitis C virus. Porcine pseudorabies virus was selected to model hepatitis B virus and herpes virus. Avian reovirus was used to model non-enveloped RNA viruses and for its relative resistance to inactivation by chemical and physical methods. Finally, porcine parvovirus was selected to model human parvovirus B19 and its notable resistance to inactivation by heat treatment.

Removal and/or inactivation of the model viruses was demonstrated at the precipitation III stage of manufacturing. In addition, inactivation was demonstrated to occur during the 10-hour (58° to 60°C) heat treatment process for the representative enveloped and non-enveloped viruses.

The product is standardized against the United States (US) Standard Rabies Immune Globulin. The US unit of potency is equivalent to the International Unit (IU) for rabies antibody. The minimal potency is 150 IU/mL.

CLINICAL PHARMACOLOGY

Rabies is a viral infection transmitted in the saliva of infected mammals. Both dog and bat saliva exposures appear to be major contributors (see below) with or without apparent bites. The virus enters the central nervous system of the host, causing an encephalomyelitis that is fatal. After the marked decrease of rabies cases among domestic animals in the US in the 1940s and 1950s, indigenously acquired rabies among humans decreased substantially.[1,2] In 1950, for example, 4,979 cases of rabies were reported among dogs, and 18 cases were reported among humans. Between 1980 and 1997, 95 to 247 cases were reported each year among dogs, and on average only two human cases were reported each year in which rabies was attributable to variants of the virus associated with indigenous dogs.[1,3] Thus, the likelihood of human exposure to a rabid domestic animal in the US has decreased greatly. However, during the same period, 12 cases of human rabies were attributed to variants of the rabies virus associated with dogs from outside the US.[1,4,5] Therefore, international travelers to areas where canine rabies is still endemic have an increased risk of exposure to rabies.[1]

Rabies among wildlife – especially raccoons, skunks, and bats – has become more prevalent since the 1950s, accounting for >85% of all reported cases of animal rabies every year since 1976.[1,2] Rabies among wildlife occurs throughout the continental US; only Hawaii remains consistently rabies-free. Wildlife is the most important potential source of infection for both humans and domestic animals in the US. Since 1980, a total of 21 (58%) of the 36 human cases of rabies diagnosed in the US have been associated with bat variants.[1,3,6,7] In most other countries – including most of Asia, Africa, and Latin America – dogs remain the major species with rabies and the most common source of rabies among humans. Twelve (33%) of the 36 human rabies deaths reported to Centers for Disease Control and Prevention (CDC) from 1980 through 1997 appear to have been related to rabid animals outside the US.[1,3,7]

Although rabies among humans is rare in the US, every year approximately 16,000 to 39,000 persons receive postexposure prophylaxis.[1,8] In order to manage potential human exposures to rabies appropriately, the risk of infection must be accurately assessed. Administration of rabies postexposure prophylaxis is a medical urgency, not a medical emergency, but decisions must not be delayed. Systemic prophylactic treatments occasionally are complicated by adverse reactions, but these reactions are rarely severe.[1,9-13]

Data on the safety, immunogenicity, and efficacy of active and passive rabies immunization have come from both human and animal studies. Although controlled human trials have not been performed, extensive field experience from many areas of the world indicates that postexposure prophylaxis combining local wound treatment, passive immunization, and vaccination is uniformly effective when appropriately applied.[1,14-19]

Although no postexposure vaccine failures have occurred in the US since cell culture vaccines have been routinely used, failures have occurred abroad when some deviation was made from the recommended postexposure treatment protocol or when less than the currently recommended amount of antirabies sera was administered.[1,20-23] Specifically, patients who contracted rabies after postexposure prophylaxis did not have their wounds cleansed with soap and water, did not receive their rabies vaccine injections in the deltoid area (ie, vaccine was administered in the gluteal area), or did not receive Rabies Immune Globulin (RIG) around the wound site.[1]

Rabies antibody provides passive protection when given immediately to individuals exposed to rabies virus.[24] In a clinical study, Rabies Immune Globulin (Human) [RIG(H)] of adequate potency[25] was used in conjunction with Rabies Vaccine of duck embryo origin.[25,26] When a Rabies Immune Globulin (Human) dose of 20 IU/kg of rabies antibody was given simultaneously with the first dose of vaccine, levels of passive rabies antibody were detected 24 hours after injection in all individuals. There was minimal or no interference with the immune response to the initial and subsequent doses of vaccine, including booster doses.

Studies of Rabies Immune Globulin (Human),[27] Imogam® Rabies, given with the first of five doses of Sanofi Pasteur SA HDCV[1] confirmed that passive immunization with 20 IU/kg of Rabies Immune Globulin (Human) provides maximum circulating antibody with minimum interference of active immunization by HDCV.

A double-blind randomized trial[28] was conducted to compare the safety and antibody levels achieved following intramuscular injection of Imogam® Rabies – HT (heat treated) and Rabies Immune Globulin (Human), Imogam® Rabies (non-heat treated). Each Rabies Immune Globulin (Human) was administered on day 0, either alone or in combination with the human diploid cell Rabies Vaccine (Imovax® Rabies) using the standard postexposure prophylactic schedule of day 0, 3, 7, 14, and 28.

Sixty-four healthy veterinary student volunteers were randomized into four parallel groups of 16 each to receive the following Rabies Immune Globulin (Human) and vaccine regimens:

Imogam® Rabies – HT	+	Imovax®
Imogam® Rabies	+	Imovax®
Imogam® Rabies – HT	+	placebo
Imogam® Rabies	+	placebo

The treatment of both Rabies Immune Globulin (Human) and vaccine corresponded to the postexposure recommended dose of 20 IU/kg of Rabies Immune Globulin (Human) and was administered in three, equally divided IM injections of under 5 mL in either gluteus. Serum rabies antibody levels were assessed before treatment and on days 3, 7, 14, 28, 35, and 42 by the Rabies Fluorescent Focus Inhibition Test (RFFIT).

Serum antibody levels were similar in the Imogam® Rabies – HT and Imogam® Rabies groups. By day three, 60% of each group had detectable antibody titers of ≥ 0.05 IU/mL. By day 14, the geometric mean titers (with 95% confidence interval) were 19 IU/mL (11-38) in the Imogam® Rabies – HT + vaccine group and 31 IU/mL (20 to 48) in the Imogam® Rabies + vaccine group. These differences were not statistically different.

Two subjects reported severe headaches, one in the Imogam® Rabies – HT + placebo group and one in the Imogam® Rabies + Imovax® Rabies group. One third of the volunteers had moderate systemic (headache and malaise) reactions. These were equally distributed among the 4 treatment groups with no significant differences between the groups.

Both Imogam® Rabies – HT and Imogam® Rabies were safe and without serious adverse events or allergic reactions. The safety profile did not differ between groups, although Imogam® Rabies – HT produced fewer and milder local reactions such as pain or tenderness at the injection site.

INDICATIONS AND USAGE

Rabies Immune Globulin (Human) Heat Treated, Imogam® Rabies – HT, is indicated for individuals suspected of exposure to rabies, particularly severe exposure, with one exception: persons who have been previously immunized with Rabies Vaccine prepared from human diploid cells (HDCV) in a pre-exposure or postexposure treatment series should receive only vaccine. Persons who have been previously immunized with Rabies Vaccines other than HDCV, RVA (Rabies Vaccine Adsorbed), or PCEC (Purified Chick Embryo Cell Vaccine) vaccines should have confirmed adequate rabies antibody titers if they are to receive only vaccine.[1]

Imogam® Rabies – HT should be injected as promptly as possible after exposure along with the first dose of vaccine. If initiation of treatment is delayed for any reason, Imogam® Rabies – HT and the first dose of vaccine should still be given, regardless of the interval between exposure and treatment. Imogam® Rabies – HT may be given up to eight days after the first dose of vaccine was given.

Rabies virus is usually transmitted by the bite of a rabid animal (dog, bat, etc.) but can occasionally penetrate abraded skin contaminated with the saliva of infected animals. Progress of the virus after exposure is believed to follow a neural pathway and the time between exposure and clinical rabies is a function of the proximity of the bite (or abrasion) to the central nervous system and the dose of virus injected. The incubation is usually 2 to 6 weeks but can be longer. After severe bites about the face and neck and arms, it may be as short as 10 days. After initiation of the vaccine series (human diploid cell origin), it takes approximately one week for development of immunity to rabies; therefore, the value of immediate passive immunization with rabies antibodies in the form of Rabies Immune Globulin (Human) cannot be overemphasized.

Recommendations for passive and/or active immunization after exposure to an animal suspected of having rabies have been outlined by the WHO[29] and by the United States Public Health Service Advisory Committee on Immunization Practices (ACIP).[1]

Each exposure to possible rabies infection must be individually evaluated. Local or state public health officials should be consulted if questions arise about the need for rabies prophylaxis.

I. Rationale of Treatment

In the United States and Canada the following factors should be considered before specific antirabies treatment is indicated:

1. Species of Biting Animal

Carnivorous animals (especially skunks, foxes, coyotes, raccoons, dogs, bobcats, and cats) and bats are more likely to be infected with rabies than other animals. Rats, mice, squirrels, hamsters, guinea pigs, gerbils, chipmunks and other rodents or rabbits and hares are rarely infected with rabies and have not been known to cause human rabies in the United States. Their bites almost never call for antirabies prophylaxis; therefore, before initiating antirabies prophylaxis, the local or state health department should be consulted.

Because some bat bites may be less severe, and therefore more difficult to recognize, rabies postexposure treatment should be considered for any physical contact with bats when bite or mucous membrane contact cannot be excluded.[1,20,30]

2. Circumstances of Biting Incident
An UNPROVOKED attack is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as PROVOKED.

3. Type of Exposure
Rabies is commonly transmitted by inoculation with infectious saliva. 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.

Nonbite: Scratches, abrasions, open wounds or mucous membranes contaminated with saliva or other potentially infectious material such as brain tissue from a rabid animal.

In addition, two cases of rabies have been attributed to airborne exposures in laboratories and two cases of rabies have been attributed to probable exposures to a bat-infested cave (Frio Cave, Texas).[1,31-33] Casual contact with a rabid animal, such as petting the animal (without a bite or nonbite exposure as described above) does not constitute an exposure and is not an indication for prophylaxis.

The only documented cases of rabies due to human-to-human transmission occurred in patients who received corneas transplanted from persons who died of rabies undiagnosed at the time of death.[1,34]

4. Vaccination Status of Biting Animal
A properly immunized animal has a minimal chance of developing rabies and transmitting the virus.

II. Postexposure Treatment of Rabies
1. Local Treatment of Wounds
Immediate and thorough local treatment of all bite wounds and scratches is perhaps the most effective preventive measure. The wound should be thoroughly cleansed immediately with soap and water. Tetanus prophylaxis and measures to control bacterial infection should be given as indicated.

2. Specific Treatment
Postexposure antirabies vaccination with rabies vaccine should be accompanied by administration of Rabies Immune Globulin (RIG). However, persons who have previously received complete vaccination regimens (pre-exposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers should receive vaccine alone.[1] The combination of Rabies Immune Globulin (RIG) and vaccine is recommended for both bite exposures and nonbite exposures (see **Rationale of Treatment**), regardless of the interval between exposure and initiation of treatment.

3. Postexposure Treatment Guide
The following recommendations are only a guide. They should be applied in conjunction with knowledge of the animal species involved, circumstances of the bite or other exposure, vaccination status of the animal, and presence of rabies in the region. Local and state public health officials should be consulted if questions arise about the need for rabies prophylaxis.

TABLE 1 [1] **RABIES POSTEXPOSURE PROPHYLAXIS GUIDE, UNITED STATES, 1999**

Animal Type	Evaluation and Disposition of Animal	Postexposure Prophylaxis Recommendations
Dogs, cats, and ferrets	Healthy and available for 10 days observation	Persons should not begin prophylaxis unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediately vaccinate.
	Unknown (eg escaped)	Consult public health officials.
Skunks, raccoons, foxes, and most other carnivores; bats	Regarded as rabid unless animal proven negative by laboratory tests†	Consider immediate vaccination.
Livestock, small rodents, lagomorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis.

* During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.
† 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
Imogam® Rabies – HT should NOT be administered in repeated doses once vaccine treatment has been initiated. Repeating the dose may interfere with maximum active immunity expected from the vaccine.

WARNINGS
Rabies Immune Globulin (Human) USP, Heat Treated, Imogam® Rabies – HT, is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, eg, viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. 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. An alcohol fractionation procedure used to purify the immunoglobulin component removes and/or inactivates both enveloped and non-enveloped viruses to a certain extent. An added heat treatment process (60°C, 10 hours) further inactivates both enveloped and non-enveloped viruses. Despite these measures, it is still theoretically possible that known or unknown infectious agents may be present. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other health-care provider to the Pharmacovigilance Department, Sanofi Pasteur Inc., telephone 1-800-822-2463. The physician should discuss the risks and benefits of this product with the patient.

Imogam® Rabies – HT should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immune globulin.

Persons with specific IgA deficiency have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products containing IgA.[35,36]

PRECAUTIONS
GENERAL
Care is to be taken by the health-care provider for the safe and effective use of this product.

EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THIS PRODUCT.

Imogam® Rabies – HT should not be administered intravenously because of the potential for serious reactions. Injection should be made intramuscularly (see **DOSAGE AND ADMINISTRATION** section for injection procedure) and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel. Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactoid reactions. As with all preparations given intramuscularly, bleeding complications may be encountered in patients with bleeding disorders.

Rabies Immune Globulin (Human) (RIGH) should never be administered in the same syringe or into the same anatomical site as vaccine. Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.[1,27]

A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of according to biohazard waste guidelines.

INFORMATION FOR PATIENT
Patients, parents or guardians should be fully informed by their health-care provider of the benefits and risks of administration of Imogam® Rabies – HT.

Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

DRUG INTERACTIONS
Live virus vaccine such as measles vaccines should not be given close to the time of Imogam® Rabies – HT administration because antibodies in the globulin preparation may interfere with the immune response to the vaccination. Immunization with live vaccines should not be given within three months after Imogam® Rabies – HT administration.

PREGNANCY CATEGORY C
Animal reproduction studies have not been conducted with Imogam® Rabies – HT. It is also not known whether Imogam® Rabies – HT can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Imogam® Rabies – HT should be given to a pregnant woman only if clearly needed.

Because of the potential consequences of inadequately treated rabies exposure and limited data that indicate that fetal abnormalities have not been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis.[1,39] If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may also be indicated during pregnancy.[1]

ADVERSE REACTIONS
In a recent clinical trial involving 16 volunteers in 4 treatment groups, two subjects reported severe headaches, one in the Imogam® Rabies – HT + placebo group and one in the Imogam® Rabies + Imovax® Rabies group, and one third of the volunteers reported moderate systemic (headache and malaise) reactions. These were equally distributed among the 4 treatment groups with no significant differences between the groups.[28]

Local adverse reactions such as tenderness, pain, soreness or stiffness of the muscles may occur at the injection site and may persist for several hours after injection. These may be treated symptomatically. Mild systemic adverse reactions to the globulin after intramuscular injection are uncommon.[28,37,38]

Although not reported specifically for HRIG, angioneurotic edema, nephrotic syndrome, and anaphylaxis have been reported after injection of immune globulin (IG), a product similar in biochemical composition but without antirabies activity. These reactions occur so rarely that a causal relationship between IG and these reactions has not been established.[1]

Reporting of Adverse Events

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine.[40-42]

Reporting by patients, parents or guardians of all adverse events occurring after HRIG administration should be encouraged. Adverse events following treatment with HRIG should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[40-42]

The health-care provider also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the vaccine should not be administered.

Imogam® Rabies – HT should be used in conjunction with Rabies Vaccine such as Rabies Vaccine Imovax® Rabies, for intramuscular immunization, vaccine prepared from human diploid cell cultures. The recommended dose of Imogam® Rabies – HT is 20 IU/kg (0.133 mL/kg) or 9 IU/lb (0.06 mL/lb) of body weight administered at time of the first vaccine dose.[25,26,43] The gluteal area should never be used for HDCV, RVA (Rabies Vaccine Adsorbed), or PCEC (Purified Chick Embryo Cell Vaccine) injections because administration of HDCV in this area results in lower neutralizing antibody titers.[1,43,44] *If anatomically feasible, the full dose of Rabies Immune Globulin (Human) (RIGH) should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly, using a separate needle, at a site distant from vaccine administration.*[1,44]

Rabies Immune Globulin (Human) (RIGH) should never be administered in the same syringe or into the same anatomical site as vaccine. Because HRIG may partially suppress active production of antibody, no more than the recommended dose should be given.[1,27]

HOW SUPPLIED

Imogam® Rabies – HT is supplied in 2 mL and 10 mL vials with minimal potency of 150 International Units per milliliter (IU/mL).
Vial, 2 mL contains 300 IU which is sufficient for a child weighing 15 kg (33 lb). Product No. 49281-190-20.
Vial, 10 mL contains a total of 1,500 IU which is sufficient for an adult weighing 75 kg (165 lb). Product No. 49281-190-10.

CPT® Code: **90376**

STORAGE

Imogam® Rabies – HT should be stored in the refrigerator at 2° to 8°C (35° to 46°F). DO NOT FREEZE.

Imogam® Rabies – HT CONTAINS NO PRESERVATIVE AND UNUSED PORTION MUST BE DISCARDED IMMEDIATELY.

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Product Information as of December 2005

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