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 contains no bacterial endotoxins. 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% to 0.6% (w/v) thymus-based (TNBP) and 0.2% sodium cholate. After addition of solvent/detergent (S/D), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reagents are removed by precipitation, filtration and final ultrafiltration and dialfiltration. HyperRAB® S/D is formulated as a 15-16% protein solution at pH 6.4-7.2 in 0.21-0.32 M glycine. HyperRAB® S/D is then inactivated 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 shown as the relevant blood-borne virus. 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 in 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 + WW suspension to Effluent II 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.21,22

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/VGJD 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.2,12 Similarly, beneficial results were later reported from the U.S.23-25 Studies coordinated by WHO demonstrated that health officials 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.4 In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of equine origin and rabies vaccine can be used in man. 4-7 These studies show 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.

In a clinical study in eight healthy human adults receiving a 20 IU 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 studies13-15 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).

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

1. Species of Biting Animal
Caribous with wild animals (especially skunks, foxes, coyotes, raccoons, and bobcats) and bats are the most likely to come in contact with humans 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). If rabies has been identified 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, so 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 such countries should be aware that >50% of the rabies cases occurring in 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. However, from 1989 to 1998, woodchucks and squirrels were identified as the source of the 179 cases of rabies among rodents reported to CDC.22 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. There has been no documented case of transmission by inhalation, so aerosol transmission 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.21

Bat-assocated 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 unrecognized 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.20

Nonbite: scratches, abrasions, open mucous membranes contaminated with saliva or any potentially infectious material, such as brain tissue, from a rabid animal constitute nonbite exposures. Even if the material containing the virus is dry, the virus can be considered noninfectious. Casual contact, such as petting a rabid animal, can result in contact with the blood, saliva, or tears (e.g., saliva) of a rabid animal, does not constitute an exposure and is not an indication for prophylaxis. Instances of airborne rabies have been reported rarely. Aderosity 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 corneal transplants from persons who died of rabies undiagnosed at the time of death. Stringent guidelines for acceptance of cornea and organ grafts 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 cleaning has been shown to reduce the risk of rabies.10-16 In a study in dogs, postexposure prophylaxis was begun 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 appropriate postexposure prophylaxis regimen 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 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 together in 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

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Condition of animal</th>
<th>At time of exposure/threat</th>
<th>Treatment of exposed person [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog and cat</td>
<td>Healthy and available for 10 days of observation</td>
<td>Rabid or suspected rabid</td>
<td>RIG [3] and HDCV</td>
</tr>
<tr>
<td>Skunk, bat, fox, coyote, raccoon, bobcat, and other carnivores; woodchuck</td>
<td>Regard as rabid unless animal proven negative by laboratory tests [4]</td>
<td></td>
<td>RIG [3] and HDCV</td>
</tr>
<tr>
<td>Livestock, rodents, and lagomorphs (rabbits, and hares)</td>
<td>Consider individually. Local and state public health officials should be consulted on questions about the need for prophylaxis.</td>
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reactions to subsequent administration of blood products that contain IgA. 25

Vaccination status Treatm ent Regim en* 
The physician should discuss the risks and benefits of this product w ith the patient, before prescribing

Hyper

HDC V= hum an diploid cell vaccine; PCE C = purified chick em bryo cell vaccine; RIG= rabies im m une
globulin. RVA= rabies vaccine absorbed; IM, intramuscular.

† The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children,

‡ Any person with a history of pree xposure vaccination with HDC V, RVA, or PCE C; prior postexposure prophylaxis with HDC V, RIG, or PCE C; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.

§ The use of antirabies globulin in subjects severely

¶ Any person with a history of antibody response to the prior vaccination.

Drug Interactions

Repeated doses of Hyper

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Pediatric Use

Soreness at the site of injection and m ild tem perature elevations m ay be observed at tim es. Sensitization to

repeated injections has occurred occasionally in im m unoglobulin-deficient patients. Angioneurotic edem a,
skin rash, nephrotic syndrom e, and anaphylactic shock have rarely been reported after intramuscular

injection, so that a causal relationship betw een im m unoglobulin and these reactions is not clear.

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HOW  SUPPLIED

Hyper

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