

# Safety and neutralizing rabies antibody in healthy subjects given a single dose of rabies immune globulin caprylate/chromatography purified

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**Background:** Rabies immune globulin (RIG) and vaccination series are necessary for postexposure prophylaxis. A new formulation of RIG (human) purified by caprylate/chromatography (RIG-C) was evaluated.

**Trial registration:** ClinicalTrials.gov identifier: NCT02139657.

**Materials and methods:** This open-label, single-arm study in healthy subjects evaluated neutralizing rabies antibody concentrations produced from a single 20 IU/kg intramuscular (IM) dose of RIG-C as measured by rapid fluorescent focus inhibition test (50% neutralization endpoint) 1-hour postdose and on days 1, 2, 4, 6, 8, 10, 14, 18, and 21.

**Results:** Twelve subjects were enrolled into the study. No discontinuations, serious adverse events (AEs), or treatment-emergent clinically significant changes in laboratory parameters were observed. All AEs resolved and were mild except 1 moderate AE of oropharyngeal pain. Injection site pain (4 subjects) was most commonly reported. RIG-C produced a rapid increase in neutralizing rabies antibody: mean value 0.113 IU/mL at 24 hours after IM injection, peak on day 4 (0.132 IU/mL), persisting through day 21 (0.116 IU/mL). The mean reciprocal titer was 11.5 by day 2; the peak value of 12.1 was achieved on day 4; and a mean value  $\geq 10.6$  was maintained through day 21.

**Conclusion:** RIG-C was well tolerated and provided neutralizing rabies antibodies, which combined with vaccine series after rabies exposure, should result in effective prophylaxis per World Health Organization/Centers for Disease Control and Prevention guidelines.

**Keywords:** rabies, rabies immune globulin, RIG-C, prophylaxis, rabies neutralizing antibody titers, GTI1301

## Plain language summary

People who have been exposed to potentially rabid animals (ie, bats, foxes, raccoons) need anti-rabies virus antibodies and rabies vaccination to prevent death from rabies infection. This clinical study tested a new formulation of anti-rabies virus antibodies that delivers twice the amount of antibodies per volume as compared to other products currently in the market. Reducing the volume in half offers potentially fewer injections, and doubling the strength allows more antibodies per milliliter to be injected directly into the wound site. To determine whether this medication was safe and well tolerated, 12 healthy volunteers were injected with this new medication and were observed for 21 days. No one withdrew from the study and had serious reactions and any severe reactions from the medication. All reactions were mild, except for a single subject with throat pain, and all reactions disappeared on their own. Most frequently reported was pain at the injection site. This medication was well tolerated and provided enough anti-rabies antibodies, which combined with rabies vaccination, should give effective protection against rabies. The US Food and Drug Administration approved this new formation with the name HyperRAB® (rabies immune globulin [human]) 300 IU/mL.

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## Introduction

Rabies is usually transmitted to humans via the bites of infected animals, resulting in fatal encephalitis. Once human rabies manifests, there is no treatment that mitigates mortality. Thus, the only effective intervention is prevention. Rabies has been known as a scourge through five millennia since the earliest reference to rabies in Mesopotamia around 2300 BCE.<sup>1</sup> From the time of Fracastoro's treatise in 1546, rabies has been referred to as the incurable wound, and Louis Pasteur was the first to break the inexorable chain of transmission. Pasteur successfully immunized 9-year-old Joseph Meister with 13 inoculations of desiccated, infected rabbit spinal cord material after he received a severe bite injury from a rabid dog.<sup>2</sup> Since that time, researchers have diligently sought improvements in postexposure prophylaxis (PEP), yet rabies still causes human mortality at an estimated rate of 26,400 to 61,000 deaths per year worldwide.<sup>3</sup>

Following a bite or nonbite exposure to an animal suspected of rabies infection, PEP requires both passive (rabies immune globulin [RIG]) and active (vaccine) immunization in persons who have not been immunized prior to exposure.<sup>3,4</sup> Human RIG (hRIG) should not be given in the same syringe or at the same anatomical site as the initial dose of rabies vaccine.<sup>4</sup> If anatomically possible, up to the full dose of hRIG (20 IU/kg body weight) must be injected into and around the wound site, enabling the anti-rabies antibodies to infiltrate the tissue surrounding the wound. Any remaining hRIG should be injected intramuscularly (IM) into the deltoid muscle or into the lateral thigh muscle. It is preferable to inject hRIG far from the site of rabies vaccine administration to prevent neutralization of the vaccine. hRIG is generally administered at the same time as the first rabies vaccine dose. If hRIG was not given when vaccination began, it may be administered at any time up to 7 days after the first vaccine dose.

The importance of RIG is multifaceted. Rabies virus neutralization at the wound entry site critically inhibits virus propagation and viral spread via fast axonal transport to the brain. In addition, passive immunization with RIG provides an immunologic bridge until active vaccine-induced immunization produces adequate virus neutralizing antibodies ( $\geq 0.5$  IU/mL) approximately 7–10 days after the first vaccine dose.<sup>5</sup> hRIG is generally preferred over equine RIG due to the possibility of equine RIG-associated serum sickness (in less than 1%–3% of recipients) and the higher dosage requirement for equine RIG, which has a shorter half-life in humans.<sup>3</sup> However in certain geographic locations, equine RIG is utilized in humans because of cost and availability constraints for hRIG.<sup>6,7</sup> Rabies PEP failures are rare among the estimated 20 million people who receive PEP each year.<sup>3</sup>

When rabies PEP fails, it is generally attributed to deviations in standard protocol (eg, late PEP initiation, failure to infiltrate all wounds with RIG, incomplete vaccination series).

hRIG is prepared from pooled plasma of donors who are hyperimmunized with rabies vaccine. Current commercially available hRIG preparations, including Grifols' HyperRAB<sup>®</sup> S/D,<sup>8</sup> Sanofi Pasteur's Imogam<sup>®</sup> Rabies – HT,<sup>9</sup> and Kedrion Biopharma/Kamada's KEDRAB<sup>™</sup> (also known as KamRAB<sup>™</sup>),<sup>10</sup> have a potency of 150 IU/mL.

The new US Food and Drug Administration-approved Grifols product HyperRAB<sup>®</sup> 300 IU/mL [RIG (human)] solution for infiltration and IM injection caprylate/chromatography purified (RIG-C)<sup>11</sup> has twice the potency of currently available hRIG options combined with a low buffer capacity. With its new 300 IU/mL formulation, RIG-C allows for administration of smaller volumes that reach physiologic pH quickly when exposed to body fluids. In addition, RIG-C benefits from state-of-the-art manufacturing techniques similar to those used for commercially available Gamunex<sup>®</sup>-C.<sup>12</sup>

Caprylate/chromatography techniques enhance purity and yield. Because the injection volume of RIG-C is half that of the currently marketed 150 IU/mL hRIG preparations, it may be easier to administer the complete RIG-C dose by infiltrating more RIG-C around the bite wound and injecting less volume IM. Indeed, recently proposed changes to the World Health Organization (WHO) Policy on Rabies Vaccines and Rabies Immunoglobulins recommend local infiltration of as much RIG as possible into and around the wound, as this is the most effective approach in preventing rabies.<sup>13</sup> For example, a 70 kg adult given 300 IU/mL RIG-C at 20 IU/kg dose would require 4.7 mL infiltrated around the wound with any remaining volume injected IM, instead of having to inject twice the volume (9.3 mL) of a 150 IU/mL hRIG product. Considering the typical maximum IM injection volume is 5 mL for a single injection site,<sup>14</sup> the higher RIG-C concentration would minimize the number of IM injections.

The objectives of this study were to characterize the neutralizing rabies antibody levels and to evaluate the safety of a single IM injection in healthy human volunteers. It is important to study passive immunity by RIG-C, as vaccine-induced host immunity is not fully developed during this initial period and local inhibition of axonal viral transport in the first 7–10 days after rabid animal bite is critical for survival.<sup>15,16</sup>

## Materials and methods

This was a single-arm, open-label study conducted at Celerion (Tempe, AZ, USA), a company that conducts studies in healthy volunteers. The study was first registered on May

15, 2014. ClinicalTrials.gov identifier is NCT02139657. The study was designed to assess anti-rabies virus antibody titers as measured by rapid fluorescent focus inhibition test (RFFIT) and to evaluate the safety of a single IM injection of 20 IU/kg RIG-C in 12 healthy subjects (18–65 years old) for up to 21 days after administration. Subjects were required to have no confounding medical conditions, to have adequate renal and hepatic function, to be naïve to rabies vaccine and RIG, and not to be on antiviral treatment at screening. Subjects were excluded if they received corticosteroids, immunosuppressants, or immunomodulators within 6 weeks before screening, or if laboratory results indicated acute or chronic infection with hepatitis A, B, C, human immunodeficiency virus, or parvovirus B19.

During the screening period of up to 21 days, safety assessments and laboratory tests were performed to ascertain eligibility (Figure 1). Subjects were confined at the clinic overnight prior to the “baseline/treatment, study day 0” visit. A single IM dose of RIG-C was administered on day 0, followed by repeated measurements of rabies virus antibody concentrations on days 1, 2, 4, 6, 8, 10, 14, 18, and 21. Oral or topical nonsteroidal anti-inflammatory drugs, acetaminophen, antihypertensive drugs, or antihistamines were not allowed 24 hours before and after RIG-C administration but were otherwise permitted during the study.

## Ethics approval and consent to participate

Standards for Good Clinical Practices were adhered to for all procedures in this study. The investigators ensured that the study was conducted in full conformance with appropriate local laws and regulations and the Declaration of Helsinki. The protocol for this study was prepared in accordance with

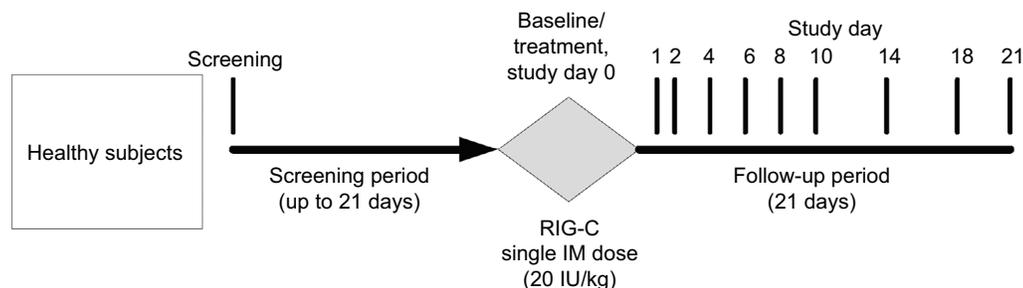
International Conference on Harmonisation Guidelines. The study protocol and site received institutional review board (IRB) approval from Chesapeake IRB. All subjects provided written informed consent for the complete study at the screening visit before any study-specific procedure took place, and the privacy rights of all subjects were observed.

## RIG-C

Grifols Therapeutics developed a manufacturing process that employs caprylate precipitation and depth filtration, caprylate incubation, and chromatographic steps in the immunoglobulin G purification scheme. This is the same process currently used to manufacture Gamunex-C with the final product being more concentrated to a 16.5% protein concentration. The primary differences between RIG-C and Gamunex-C are as follows: 1) RIG-C has antibody specificity against rabies derived from plasma of healthy volunteers vaccinated with rabies vaccine and 2) RIG-C has a higher immune globulin concentration (16.5%) than Gamunex-C (10%).

RIG-C is a sterile solution of anti-RIG stored in glass vials at 2°C–8°C (36°F–46°F). Each vial of RIG-C contains a 16.5% protein solution of human immune globulin with a minimum of 300 IU/mL of rabies antibody as determined by RFFIT. RIG-C was supplied to the study site in 5 mL vials (1500 IU/vial) from a single lot.

Subjects received a single 20 IU/kg dose of RIG-C via IM injection into the lateral thigh muscle. This is the standard dosage based on recommendations by the Centers for Disease Control and Prevention and Advisory Committee on Immunization Practices (ACIP).<sup>5</sup> The volume of RIG-C injected at a single injection site did not exceed 5 mL. If the required volume was in excess of 5 mL, multiple injection sites (ie, both legs) were used.



**Figure 1** Study design.

**Notes:** Written informed consent was obtained from all prospective healthy subjects at the screening visit prior to performing any study procedures. At the screening visit, subjects were screened by physical examination and laboratory assessments. Eligibility for the study was determined by the protocol inclusion and exclusion criteria over a screening period of up to 21 days. Subjects who met all eligibility criteria received a single dose of RIG-C (20 IU/kg) at the baseline/treatment, study day 0 visit. Subjects then entered a postadministration follow-up period of 21 days, with clinic visits on study days 1, 2, 4, 6, 8, 10, 14, 18, and 21. The total duration of study participation for subjects who completed the study was up to 43 days.

**Abbreviations:** IM, intramuscular; RIG-C, rabies immune globulin purified by caprylate/chromatography.

## RFFIT

The primary outcome measure was the anti-rabies virus antibody titers and concentrations (IU/mL) measured by RFFIT. RFFIT is regarded as the standard rabies virus neutralization assay and the benchmark method for measuring rabies-specific antibodies.<sup>4,17</sup> It is also the method used to assign potency to the RIG-C product. Serum samples were obtained during the screening visit, at baseline study day 0 (immediately prior to RIG-C administration), at 1 hour ( $\pm 10$  minutes) postadministration, and on study days 1 (approximately 24 hours), 2, 4, 6, 8, 10, 14, 18, and 21 postadministration. The samples were stored at  $-70^{\circ}\text{C}$  and analyzed at Kansas State Veterinary Diagnostic Laboratory at Kansas State University College of Veterinary Medicine (Manhattan, KS, USA). All samples were assayed in a single batch to avoid test-to-test variability. RFFIT was performed according to standard validated procedures:<sup>18–25</sup> 1) mixing the challenge virus standard 11 (CVS-11) strain of rabies virus with test samples containing neutralizing antibodies and 2) inoculating the reaction mixture into a baby hamster kidney (BHK) cell culture system. After a 20- to 24-hour incubation period, the inoculated BHK cells were examined microscopically for percentage of infectivity. The absence of infectivity constituted a positive neutralization reaction and indicated the presence of virus-specific antibodies in the sample.

The RFFIT neutralization endpoint titer was defined as the highest sample dilution at which 50% of the observed microscopic fields contained at least 1 infected cell. The rabies virus neutralizing antibodies titers (50% neutralization, ED50) were mathematically interpolated using the Reed and Muench formula, and the reciprocal of the 50% endpoint titer was determined (10 to the log power of the 50% endpoint dilution).<sup>26</sup> The endpoint neutralization titer of the test serum was converted into IU/mL values by calibrating from the endpoint neutralization titer of the US Standard Rabies Immune Globulin, Lot R-3, 59 IU (1st WHO International Standard), which was measured in the same assay with an assigned value of 2.0 IU/mL.

The data are reported in both IU/mL and in titer values. Although IU/mL has become a universal reporting standard, it is important to report titer values as well to provide context for historical comparison with prior product. The lower limit of quantification (LLOQ) was determined to be 0.1 IU/mL during validation. However for this study, the limit of detection (LOD) was determined to be 0.05 IU/mL using the 95th percentile method on the baseline (predose) samples. Therefore, the results were reported to a minimum 0.05 IU/mL, and the LOD was determined to be 5 when measured in

reciprocal titer. For the purpose of analyzing results, values below the LOD were reported as 0.05 IU/mL or a titer of 5.

## Safety

Safety was evaluated based on treatment-emergent adverse events (AEs) at all time points; clinical laboratory parameters (chemistry, hematology, urinalysis) at screening, baseline, and day 21; and vital signs at screening, baseline, between 1 and 3 hours after RIG-C injection, and on days 1, 2, 4, 6, 8, 10, 14, 18, and 21.

## Statistical analyses

Rabies virus neutralizing antibody titer and rabies virus neutralizing antibody concentrations (reported in IU/mL) at each visit were summarized. The data for antibody titers were reported as reciprocals. Descriptive statistics and frequency counts were provided for categorical variables. All descriptive statistics were calculated in SAS<sup>®</sup> Version 9.3 or higher. No inferential statistics were performed. A sample size of 12 subjects (to assure 10 completers) was chosen based on previous experience with similar studies and was not based on formal sample size calculations.

## Results

Thirty-two subjects were screened at the Celerion study center. Twelve subjects met eligibility criteria in terms of good health and acceptable laboratory results. There were 20 screen failures for reasons that included abnormal laboratory values ( $n=9$ ), subject decision not to participate ( $n=4$ ), and poor veins/vascular problems ( $n=3$ ). All 12 healthy subjects enrolled and completed the study between March 21, 2014, and May 29, 2014. All 12 subjects were included in the safety population and were evaluated for measurement of rabies antibody levels.

Demographic characteristics are summarized in Table 1. The 12 enrolled subjects were primarily Caucasian ( $n=9$ ) and women ( $n=9$ ) with a median age of 40 years (range 25–53), median weight of 82.6 kg (range 58.7–109.7), and median body mass index of 32.1 kg/m<sup>2</sup>. Three African Americans participated (two men, one woman). All subjects received the full IM dose of 20 IU/kg RIG-C. The total volume administered ranged from 4 mL to 7.3 mL (mean 5.68 mL; median 5.55 mL).

## RFFIT

The activity level of rabies virus neutralizing antibody following the single IM dose of RIG-C on day 0 is depicted in Table 2 and Figure 2. At screening and day 0 predose time points,

**Table 1** Subject demographics

Characteristic	Attribute	Overall (n=12)
Sex	Female	9 (75%)
	Male	3 (25%)
Race	Black or African American	3 (25%)
	White	9 (75%)
Ethnicity	Hispanic or Latino	7 (58%)
	Not Hispanic or Latino	5 (42%)
Age (years)	Mean (SD)	41.0 (9.7)
	Median (range)	40.0 (25–53)
Weight (kg)	Mean (SD)	84.8 (14.9)
	Median (range)	82.6 (58.7–109.7)
Height (cm)	Mean (SD)	167.3 (10.7)
	Median (range)	167.0 (152–185)
Body mass index (kg/m <sup>2</sup> )	Mean (SD)	30.4 (4.9)
	Median (range)	32.1 (20.9–37.9)

**Abbreviation:** SD, standard deviation.

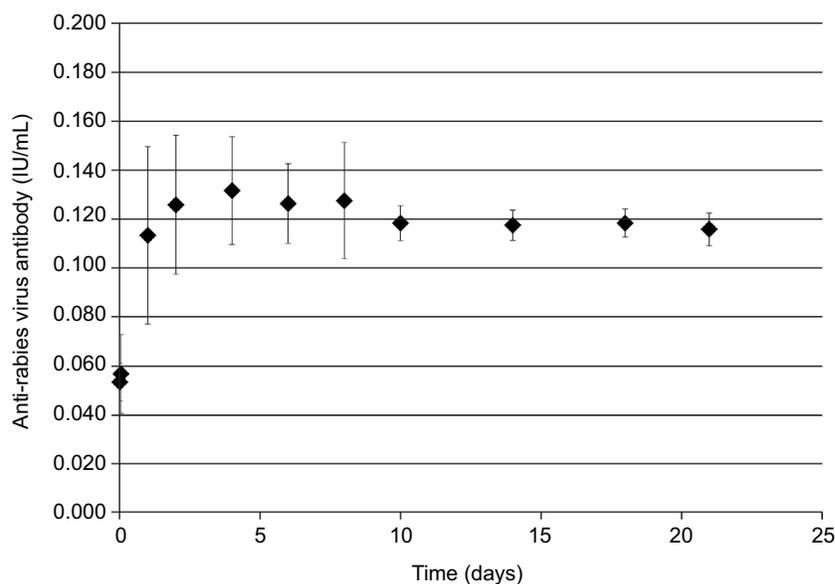
**Table 2** Summary of rabies virus antibody levels (IU/mL) following a single 20 IU/kg dose of RIG-C (n=12)

Time point	Mean (SD)	Median (range)	Geometric mean (SD)
Screening	<0.05	<0.05	<0.05
Day 0 predose	<0.05	<0.05 (<0.05–0.07)	<0.05
Day 0 hour 1	<0.05	<0.05 (<0.05–0.10)	<0.05
Day 1	0.113 (0.038)	0.11 (<0.05–0.21)	0.106 (0.040)
Day 2	0.126 (0.028)	0.12 (0.09–0.21)	0.124 (0.024)
Day 4	0.132 (0.022)	0.12 (0.11–0.19)	0.130 (0.020)
Day 6	0.126 (0.016)	0.12 (0.11–0.17)	0.126 (0.015)
Day 8	0.128 (0.024)	0.12 (0.11–0.18)	0.126 (0.021)
Day 10	0.118 (0.007)	0.12 (0.11–0.13)	0.118 (0.007)
Day 14	0.118 (0.006)	0.12 (0.10–0.12)	0.117 (0.007)
Day 18	0.118 (0.006)	0.12 (0.11–0.13)	0.118 (0.006)
Day 21	0.116 (0.007)	0.12 (0.10–0.12)	0.116 (0.007)

**Abbreviations:** RIG-C, rabies immune globulin purified by caprylate/chromatography; SD, standard deviation.

anti-rabies virus antibody concentrations were all below the LLOQ (range <0.05–0.07 IU/mL). Of the 12 subjects, 2 had levels of <0.05 IU/mL at screening and of 0.07 IU/mL at day 0. It should be noted that the LLOQ was determined to be 0.1 IU/mL during validation, and assay sensitivity below 0.1 IU/mL has some margin of variability. Subsequent to RIG-C administration, rabies virus neutralizing antibody activity increased from  $\leq 0.07$  IU/mL to a median of 0.11 IU/mL on day 1 (24 hours after RIG-C administration), and the median value remained 0.12 IU/mL from days 2 through 21. Mean anti-rabies virus antibody levels were highest on day 2 through 8 (0.126 IU/mL through 0.132 IU/mL); was 0.118 IU/mL at days 10, 14, and 18; and decreased slightly to 0.116 IU/mL on day 21. Geometric mean values followed a similar pattern. It is important to note that, by day 4, antibody levels in all subjects rose higher than 0.10 IU/mL. The 2 subjects with 0.07 IU/mL at day 0 predose (baseline) experienced marked increases to peak values of 0.19 IU/mL and 0.21 IU/mL (respectively), which were the highest levels among all subjects analyzed.

Table 3 and Figure 3 illustrate the prompt increase in reciprocal rabies virus antibody titer following RIG-C administration (n=12 subjects). Reciprocal titer results mirrored the data presented in IU/mL and are expressed herein using both modalities for ease of comparison with prior historical results. Briefly, the reciprocal of the anti-rabies virus antibody titer was <5 for all subjects at screening and for 10 subjects at day 0 (predose). Mean anti-rabies virus reciprocal antibody titers increased rapidly in 24 hours (10.3) with peak mean titers occurring at day 4 (12.1). On day 2, the reciprocal titer was 11 in 7 subjects, and 10, 12, and 19 in 1 subject each. The

**Figure 2** Anti-rabies virus antibody concentrations by RFFIT (IU/mL) following a single IM dose of RIG-C (mean  $\pm$  SD).

**Abbreviations:** RFFIT, rapid fluorescent focus inhibition test; IM, intramuscular; RIG-C, rabies immune globulin purified by caprylate/chromatography; SD, standard deviation.

lowest value of 8 occurred in 1 subject, who had a reciprocal titer of 11 on day 1 and 12 on day 4. Thus, 11 of the 12 subjects had a reciprocal titer of  $\geq 10$  on day 2, and all subjects had a reciprocal titer of  $\geq 10$  by day 4. Mean antibody titers decreased slightly after the peak on day 4 but remained  $\geq 10.6$  through day 21. A reciprocal titer  $\geq 9$  was recorded from day 14 through 21 in all subjects.

## Safety

The single dose of RIG-C (20 IU/kg) via IM injection was well tolerated. Table 4 provides a summary of the AEs. Six subjects had no AEs, and 6 subjects (50%) had 15 AEs. All

**Table 3** Summary of reciprocal of rabies virus antibody titers by visit following a single 20 IU/kg dose of RIG-C (n=12)

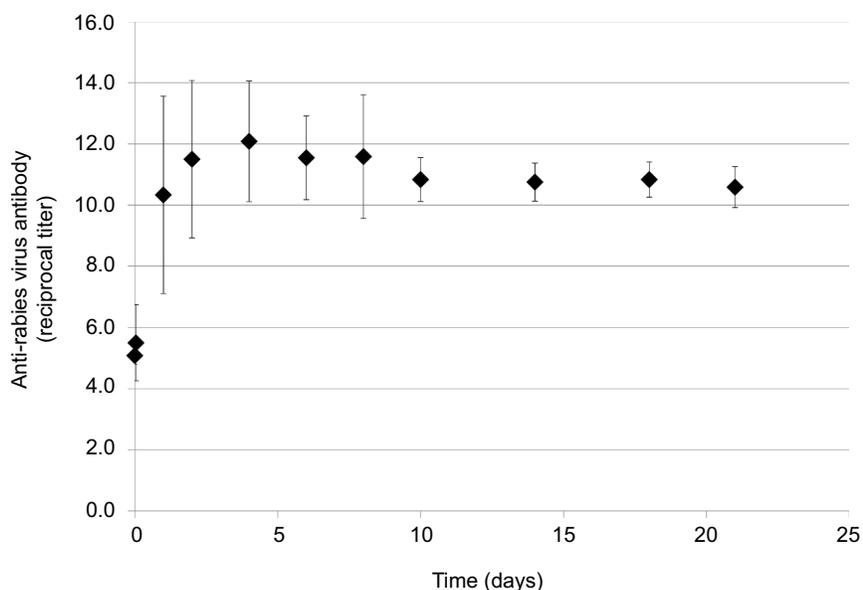
Time point	Mean (SD)	Median (range)	Geometric mean (SD)
Screening	<5	<5	<5
Day 0 predose	<5	<5 (<5–6)	<5
Day 0 hour 1	<5	<5 (<5–9)	<5
Day 1	10.3 (3.39)	10.0 (<5–19)	9.7 (3.41)
Day 2	11.5 (2.58)	11.0 (8–19)	11.3 (2.2)
Day 4	12.1 (1.98)	11.0 (10–17)	12.0 (1.79)
Day 6	11.5 (1.37)	11.0 (10–15)	11.5 (1.32)
Day 8	11.6 (2.02)	11.0 (10–16)	11.4 (1.83)
Day 10	10.8 (0.72)	11.0 (10–12)	10.8 (0.71)
Day 14	10.8 (0.62)	11.0 (9–11)	10.7 (0.66)
Day 18	10.8 (0.58)	11.0 (10–12)	10.8 (0.58)
Day 21	10.6 (0.67)	11.0 (9–11)	10.6 (0.7)

**Abbreviations:** RIG-C, rabies immune globulin purified by caprylate/chromatography; SD, standard deviation.

AEs were mild, except for a single subject with moderate oropharyngeal pain. All AEs resolved without sequelae. All AEs were considered potentially related by the investigator, except for two AEs (procedural dizziness and pain in the extremity) that were unrelated. Four subjects had 10 AEs within 24 hours of RIG-C administration (all related). There were no new AEs between 24 and 72 hours postdose. The AEs occurring >72 hours after IM injection were product-related injection site pain, nasal congestion, and oropharyngeal pain, as well as unrelated procedural dizziness and limb pain in one subject each. There were no deaths, no serious AEs, and no discontinuations due to AEs. Clinical laboratory (chemistry, hematology, and urinalysis) and vital signs data showed no pattern of abnormality posttreatment.

## Discussion

Once encephalitis symptoms appear, rabies is an incurable infectious disease with only 10 known human survivors worldwide.<sup>1</sup> When rabies manifests clinically, there is no treatment that can halt its inexorable progression to death. In the absence of early and adequate PEP, the rabies virus can travel within peripheral nerve axons at a rate of 12–24 mm/day from the wound to central nervous system neurons, causing irrevocable encephalitis that results in inevitable fatality.<sup>27</sup> Rabies PEP requires RIG administration as soon as feasible following exposure (contaminated injury or bite); however, sources and supply are often limited, particularly in resource-poor settings.<sup>15,16</sup>



**Figure 3** Reciprocal of anti-rabies virus antibody titer by RFFIT following a single IM dose of RIG-C (mean  $\pm$  SD).

**Abbreviations:** RFFIT, rapid fluorescent focus inhibition test; IM, intramuscular; RIG-C, rabies immune globulin purified by caprylate/chromatography; SD, standard deviation.

**Table 4** Treatment-emergent adverse event frequency by subject (n=12)

System organ class preferred term	Within 24 hours, n (%)	Overall, n (%)
<b>Number of subjects with any AE</b>	4 (33)	6 (50)
Total number of AEs (number of events)	10 of 15 AEs	15 AEs
<b>Gastrointestinal disorders</b>	1 (8)	1 (8)
Abdominal pain	1 (8)	1 (8)
Diarrhea	1 (8)	1 (8)
Flatulence	1 (8)	1 (8)
<b>General disorders and administration site conditions</b>	4 (33)	5 (42)
Injection site pain	3 (25)	4 (33)
Injection site nodule	1 (8)	1 (8)
<b>Injury, poisoning, and procedural complications</b>	0 (0)	1 (8)
Procedural dizziness <sup>a</sup>	0 (0)	1 (8)
<b>Musculoskeletal and connective tissue disorders</b>	0 (0)	1 (8)
Pain in extremity <sup>a</sup>	0 (0)	1 (8)
<b>Nervous system disorders</b>	1 (8)	1 (8)
Headache	1 (8)	1 (8)
<b>Respiratory, thoracic, and mediastinal disorders</b>	0 (0)	2 (17)
Nasal congestion	0 (0)	1 (8)
Oropharyngeal pain	0 (0)	1 (8)

**Notes:** <sup>a</sup>Indicates unrelated adverse events in 1 patient each. Time frame refers to within 24 hours of RIG-C administration.

**Abbreviations:** AE, adverse events; RIG-C, rabies immune globulin purified by caprylate/chromatography.

Grifols' original hRIG, first licensed in 1974, was the first hRIG product licensed in the US. In 1996, solvent/detergent HyperRAB S/D was introduced with a pH of 6.4–7.2 and an average potency of 150 IU/mL. Recently, Grifols developed a new manufacturing process for RIG-C using caprylate/chromatography purification, which is the same purification process for Gamunex-C, thereby further enhancing purity. Relative to 150 IU/mL of other hRIG products, this new RIG-C preparation has a higher rabies antibody potency of 300 IU/mL, allowing for smaller injection volumes. However, since the RIG-C dose (20 IU/kg) is the same, this new formulation will not interfere with vaccine-induced immunity. Following a rabid animal bite, the full dose of hRIG must be infiltrated into and around the wound with any remaining volume injected IM. Given the 300 IU/mL concentration of RIG-C (twice that of other currently available hRIG products), half the volume is necessary to deliver the standard 20 IU/kg dose of 300 IU/mL RIG-C compared to 150 IU/mL hRIG products. With the typical maximum IM injection volume being 5 mL for a single injection site,<sup>14</sup> the higher RIG-C concentration minimizes the number of IM injections, and maximizes the portion of the dose that can be infiltrated locally into and around the wound. Importantly, rabies vaccine is also administered at a site distant from the hRIG injection site on days 0, 3, 7, and 14 (5th dose on day 28 if required) after rabid animal bite to raise the host protective antibodies high enough for protection against rabies infection.<sup>5</sup>

RIG serves as an essential part of PEP. RIG neutralizes rabies virus and impedes virus propagation when infiltrated around the wound. While adequate antibody titers are not achieved by RIG alone, RIG provides an interim level of passive immunity before vaccine-induced antibodies can be formed. This bridge diminishes the likelihood of prophylaxis failure substantially. About 7–10 days after the first vaccine dose, active immunization produces virus neutralizing antibodies concentrations that peak between day 14 and day 28 (after administration of 4 vaccine doses).<sup>5</sup> Guidelines for rabies immunization practices, including passive immunization, are available through the Centers for Disease Control and Prevention ACIP and the WHO.

For the purposes of defining “adequate immunization” with rabies vaccine, the ACIP recommends complete neutralization of rabies virus at a serum dilution of 1:5 as minimum evidence of circulating rabies virus neutralizing antibodies.<sup>4,5,28</sup> This infers a 100% endpoint titer on RFFIT, which is appropriate when vaccine-induced native humoral response is being assessed in the setting of potentially lethal rabies virus exposure. Generally in virology, considerable over-capacity of neutralizing antibody is required to achieve protection at the time of virus challenge.<sup>29</sup> This is the aim of vaccination. The current study measured the passive transfer of rabies neutralizing antibodies using a 50% endpoint titer, which was chosen intentionally as a lower threshold than the vaccine-induced antibody concentration since the aim was not to interfere with the crucial vaccine response. Thus,

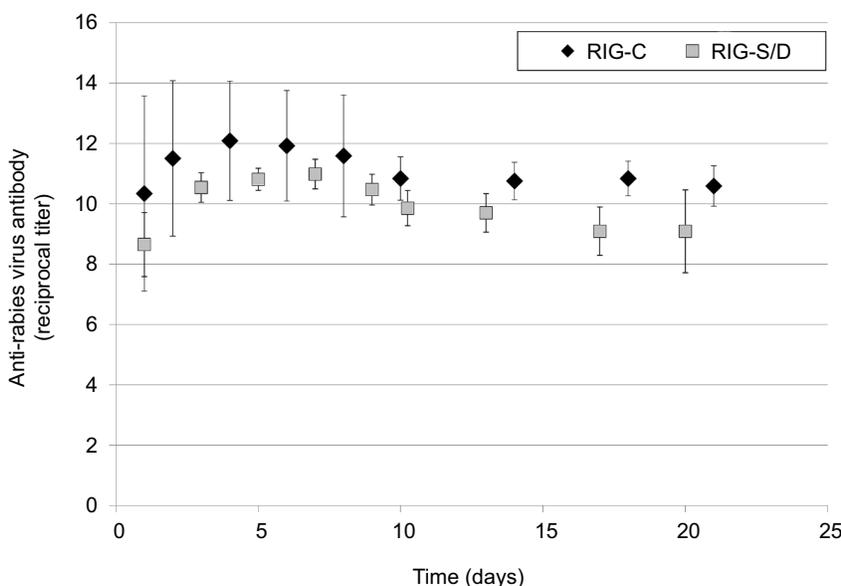
a reciprocal titer of 5 within the confines of this study (50% neutralization endpoint) is not the same as the ACIP vaccine immunization threshold that utilizes a 100% neutralization endpoint at a 1:5 dilution.

RIG has the critical function of providing passive transfer of rabies neutralizing antibody sufficient to allow time for a naïve immune system to respond robustly to vaccination. However, there is delicate equipoise, because RIG passive antibody transfer must be sufficiently low to avoid inhibiting vaccine response. The WHO Expert Committee on Rabies indicated that the seroprotective level of serum rabies virus neutralizing antibodies in persons with exposure to rabies is  $\geq 0.5$  IU/mL.<sup>3</sup> As anticipated in this study, anti-rabies virus antibody concentrations remained below 0.5 IU/mL because rabies vaccine was not administered. This is consistent with the aim of providing interim passive antibody levels sufficient to support, but not impair, intrinsic immune response to vaccine. Excessive amounts of passive antibody administration can interfere with the production of a host's own antibody response. Interference phenomena have been observed in several studies,<sup>30–33</sup> including evaluation of hRIG given at a higher than recommended dosage (eg, 40 IU/kg hRIG in combination with various vaccine regimens). In this study, RIG-C produced a substantial increase in anti-rabies virus antibody concentrations during the time period in which peak values were achieved. Elevated antibody levels and the corresponding reciprocal titers persisted through day 21. Eleva-

tion in rabies antibody level was prompt and demonstrable within 24 hours of administration (mean 0.113 IU/mL and mean titer 10.3 on day 1).

The reciprocal titer results from this study are comparable to an earlier open-label, single-center study of Grifols RIG-S/D (Bayer data on file 1996, Report MRR 1321) in 8 subjects given a 20 IU/kg dose IM via two injections (Figure 4). In this previous study of RIG-S/D, peak reciprocal titers of 11 were observed by approximately 48 hours postdose, and individual titers ranged from 6 to 14 during the interval from dosing to day 21. In the current study of RIG-C, a mean reciprocal titer of 11.5 was realized by approximately 48 hours postdose, and peak mean titers occurred at day 4 (mean 12.1) with mean titers ranging from 10.3 to 12.1 during day 1–day 21.

Additionally, these results were comparable to data from the published study<sup>34</sup> by Pasteur Merieux Connaught comparing heat-treated (H-T) hRIG (60°C) and hRIG without pasteurization in 16 subjects per group. Lang et al reported results solely in IU/mL. For those subjects randomized to receive hRIG alone (without vaccination), the maximum geometric mean value was 0.084 IU/mL (95% confidence interval (CI) 0.046–0.155 IU/mL) for H-T hRIG and 0.074 IU/mL (95% CI 0.042–0.152 IU/mL) in the hRIG without pasteurization.<sup>34</sup> The geometric mean values for RIG-C in the current study compare favorably with these data, confirming the effectiveness for passive transfer of rabies neutralizing antibodies. The data for the original Merieux hRIG (when



**Figure 4** Reciprocal of anti-rabies virus antibody titer following a single IM dose of RIG-C or RIG-S/D product (mean  $\pm$  SD).

**Notes:** This graph depicts the mean (SD) RFFIT results for both RIG-C (black diamond) and RIG-S/D (gray square) products. Data for RIG-S/D were derived from the Bayer data on file 1996, Report MRR 1321 of 8 healthy adult subjects who received a 20 IU/kg IM dose of RIG-S/D in two injections.

**Abbreviations:** IM, intramuscular; RIG-C, rabies immune globulin purified by caprylate/chromatography; RIG-S/D, rabies immune globulin purified by solvent/detergent; SD, standard deviation; RFFIT, rapid fluorescent focus inhibition test.

given alone to 16 subjects) produced a geometric mean value of 0.10 IU/mL on day 3, which again was comparable to the geometric mean achieved with RIG-C.<sup>33</sup>

## Limitation

This study included a relatively small sample size of healthy volunteers albeit sufficient to demonstrate detectable neutralizing rabies antibody.

## Conclusion

This study demonstrated that caprylate/chromatography purified hRIG (RIG-C) produced a rapid increase in rabies neutralizing antibodies within 24 hours, peaked on day 4, and maintained through day 21. These results support the conclusion that RIG-C administration provides reproducible passive transfer of neutralizing antibodies commensurate with Grifols HyperRAB S/D product. The single 20 IU/kg IM dose of RIG-C was safe and well tolerated. RIG-C should provide adequate passive adjunctive treatment when combined with vaccination in accordance with guidelines for rabies exposure. This new RIG-C formulation has twice the potency (300 IU/mL) of currently available RIG options (150 IU/mL), offering a greater concentration of anti-rabies virus antibodies within each mL of volume, and for patients, the potential for fewer injections by significantly reducing the injection volume of each dose.

## Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to the fact that the US Food and Drug Administration does not require posting of Phase I data.

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## Author contributions

KH contributed to the conception and design, data acquisition, analysis and interpretation of the data. MCC contributed to the analysis and interpretation of the RFFIT data. EM was the medical monitor of this study from July 1, 2014 to study completion, contributed to the interpretation of

all data, and drafted the first version of the manuscript. EC contributed to the study design and data acquisition, and managed the study conduct. PV contributed to analysis and interpretation of the RFFIT data. All authors made substantive contributions to revising the manuscript critically for important intellectual content, gave final approval to the version to be published, had full access to the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis.

## Disclosure

All the authors are employees of Grifols and report personal fees from Grifols during the conduct of the study. The authors report no other conflicts of interest in this work.

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use HYPERRAB® safely and effectively. See full prescribing information for HYPERRAB.

**HYPERRAB [rabies immune globulin (human)] solution for infiltration and intramuscular injection**

Initial U.S. Approval: 1974

**INDICATIONS AND USAGE**

HYPERRAB is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies. (1)

Limitations of Use:

Persons previously immunized with rabies vaccine that have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of post-exposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

**DOSAGE AND ADMINISTRATION**

**For infiltration and intramuscular use only.**  
Administer HYPERRAB within 7 days after the first dose of rabies vaccine.

Postexposure prophylaxis, along with rabies vaccine, after suspected exposure to rabies (2.1)	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight  Single dose	<ul style="list-style-type: none"> <li>Administer as soon as possible after exposure, preferably at the time of the first rabies vaccine dose.</li> <li>Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible.</li> <li>Inject the remainder, if any, intramuscularly.</li> </ul>
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**DOSAGE FORMS AND STRENGTHS**

300 IU/mL solution for injection supplied in 1 mL and 5 mL single-dose vials. (3)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

- Severe hypersensitivity reactions, including anaphylaxis, may occur with HYPERRAB. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- HYPERRAB is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.2)

**ADVERSE REACTIONS**

The most common adverse reactions in > 5% of subjects in clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Repeated dosing after administration of rabies vaccine may suppress the immune response to the vaccine. (7)
- Defer live vaccine (measles, mumps, rubella) administration for 4 months. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2018

<b>FULL PRESCRIBING INFORMATION: CONTENTS*</b>	<b>6</b>	<b>ADVERSE REACTIONS</b>	<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>
<b>1 INDICATIONS AND USAGE</b>		6.1 Clinical Trials Experience		12.1 Mechanism of Action
<b>2 DOSAGE AND ADMINISTRATION</b>	<b>7</b>	6.2 Postmarketing Experience		12.2 Pharmacodynamics
2.1 Dose		<b>8 DRUG INTERACTIONS</b>		12.3 Pharmacokinetics
2.2 Preparation		<b>8 USE IN SPECIFIC POPULATIONS</b>	<b>14 CLINICAL STUDIES</b>	
2.3 Administration		8.1 Pregnancy	<b>15 REFERENCES</b>	
<b>3 DOSAGE FORMS AND STRENGTHS</b>		8.2 Lactation	<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>	
<b>4 CONTRAINDICATIONS</b>		8.4 Pediatric Use	<b>17 PATIENT COUNSELING INFORMATION</b>	
<b>5 WARNINGS AND PRECAUTIONS</b>	<b>11</b>	8.5 Geriatric Use		
5.1 Hypersensitivity Reactions		<b>10 OVERDOSAGE</b>		
5.2 Transmissible Infectious Agents		<b>11 DESCRIPTION</b>		

\*Sections or subsections omitted from the Full Prescribing Information are not listed.

**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

HYPERRAB is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.<sup>1-3</sup>

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of post-exposure prophylaxis.<sup>1-3</sup>

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

**2 DOSAGE AND ADMINISTRATION**

**For infiltration and intramuscular use only.**

**The strength of HYPERRAB is 300 IU/mL.**

**2.1 Dose**

Use HYPERRAB in combination with rabies vaccine series to be effective. Do not use HYPERRAB alone for prevention.

Administer HYPERRAB within 7 days after the first dose of rabies vaccine.

**Rabies Postexposure Prophylaxis Schedule\***

<b>Vaccination Status</b>	<b>Treatment</b>	<b>Regiment†</b>
Not previously vaccinated	Wound cleansing	<ul style="list-style-type: none"> <li>• Cleanse all wounds immediately and thoroughly with soap and water.</li> <li>• Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.</li> </ul>
	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight  Single dose	<ul style="list-style-type: none"> <li>• Administer HYPERRAB as soon as possible after exposure, preferably at the time of the first vaccine dose.</li> <li>• Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible. [see <i>Dosage and Administration (2.3)</i>]</li> <li>• Inject the remainder, if any, intramuscularly at an anatomical site distant from the site of vaccine administration. [see <i>Dosage and Administration (2.3)</i>]</li> <li>• Do not exceed the recommended dose of HYPERRAB, otherwise the active production of rabies antibody may be partially suppressed. [see <i>Drug Interactions (7)</i>]</li> <li>• Use separate syringes, needles, and anatomical injection sites for HYPERRAB and for rabies vaccine.</li> </ul>
	Rabies Vaccine	<ul style="list-style-type: none"> <li>• Administer rabies vaccine on day 0‡.</li> <li>• Complete a rabies vaccination series for previously unvaccinated persons.</li> </ul>

Vaccination Status	Treatment	Regiment†
Previously vaccinated§	Wound cleansing	<ul style="list-style-type: none"> <li>• Cleanse all wounds immediately and thoroughly with soap and water.</li> <li>• Irrigate the wounds with a virucidal agent such as a povidone-iodine solution, if available.</li> </ul>
	HYPERRAB	<ul style="list-style-type: none"> <li>• Do not administer HYPERRAB. [see <i>Indications and Usage (1)</i>]</li> </ul>
	Rabies Vaccine	<ul style="list-style-type: none"> <li>• Administer rabies vaccine on day 0‡.</li> <li>• Complete a rabies vaccination series for previously vaccinated persons.†</li> </ul>

\* Adapted from reference 1.

† These regimens are applicable for all age groups, including children.

‡ Day 0 is the day the first dose of vaccine is administered. Refer to vaccine manufacturer's instructions or to the recommendations of the Advisory Committee on Immunization Practices (ACIP)<sup>1,3</sup> for appropriate rabies vaccine formulations, schedules and dosages.

§ Any person with a history of rabies vaccination and a documented history of antibody response to the prior vaccination.

## 2.2 Preparation

- Calculate the volume of HYPERRAB for the recommended dose of 20 IU/kg.
- Ensure the correct strength is used for the calculation. HYPERRAB is formulated with a strength of 300 IU/mL. The predecessor product, HYPERRAB® S/D [rabies immune globulin (human)] was formulated at 150 IU/mL. The volume required of HYPERRAB (300 IU/mL) to achieve the recommended dose of 20 IU/kg is approximately one half of that required for the previous HYPERRAB S/D (150 IU/mL).
- Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. HYPERRAB is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution.
- Do not use HYPERRAB if the product shows any sign of tampering. Notify Grifols Therapeutics LLC immediately [1-800-520-2807].
- Do not freeze. Do not use any solution that has been frozen.

## 2.3 Administration

- Administer HYPERRAB at the time of the first vaccine dose (day 0), but no later than day 7.<sup>1-3</sup>
- Infiltrate the full dose of HYPERRAB in the area around the wound, if anatomically feasible. Dilute HYPERRAB with an equal volume of dextrose, 5% (D5W), if additional volume is needed to infiltrate the entire wound. Do not dilute with normal saline.
- Inject the remainder, if any, of the HYPERRAB dose intramuscularly into the deltoid muscle of the upper arm or into the lateral thigh muscle, and distant from the site of vaccine administration.
- Do not administer HYPERRAB in the same syringe or needle or in the same anatomic site as vaccine.

## 3 DOSAGE FORMS AND STRENGTHS

HYPERRAB is a sterile, 300 IU/mL solution for injection supplied in 1 mL and 5 mL single-dose vials. The 1 mL vial is sufficient for a child weighing 15 kg. The 5 mL vial is sufficient for an adult weighing 75 kg.

HYPERRAB is standardized against the U.S. Standard Rabies Immune Globulin to contain a potency of  $\geq 300$  IU/mL. The U.S. unit of potency is equivalent to the international unit (IU) for rabies antibody.

## 4 CONTRAINDICATIONS

None.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hypersensitivity Reactions**

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

Patients with isolated immunoglobulin A (IgA) deficiency may develop severe hypersensitivity reactions to HYPERRAB, or subsequently, to the administration of blood products that contain IgA.

### **5.2 Transmissible Infectious Agents**

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. HYPERRAB is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the donor population and selection of individual donors by a medical interview and screening of individual donations and plasma pools for viral infection markers; (2) testing of plasma for hepatitis C virus (HCV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), HAV and human parvovirus (B19V) genomic material; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

## **6 ADVERSE REACTIONS**

The most common adverse reactions in >5% of subjects during clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The new formulation for HYPERRAB is manufactured using caprylate/ chromatography purification and has a rabies antibody concentration of 300 IU/mL. The previous formulation, HYPERRAB S/D, was manufactured using a solvent detergent process and had a rabies antibody concentration of 150 IU/mL. These products were evaluated in 2 clinical trials in a total of 20 healthy subjects using a 20 IU/kg single dose. The initial study evaluated the original 150 IU/mL HYPERRAB S/D in 8 subjects and the second study evaluated HYPERRAB in 12 subjects. The original study of HYPERRAB S/D reported headache (1/8; 13%).

In the study with HYPERRAB at 300 IU/mL, 5 subjects (5/12; 42%) experienced at least 1 adverse reaction. These were: injection site pain (4/12; 33%), injection site nodule (1/12; 8%), abdominal pain (1/12; 8%), diarrhea (1/12; 8%), flatulence (1/12; 8%), headache (1/12; 8%), nasal congestion (1/12; 8%), and oropharyngeal pain (1/12; 8%).

## 6.2 Postmarketing Experience

There are no data on the postmarketing use of HYPERRAB (300 IU/mL). The following adverse reactions have been identified during post approval use of the predecessor formulation, HYPERRAB S/D. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with HYPERRAB S/D, cases of allergic/hypersensitivity reactions including anaphylaxis have been reported. Soreness at the site of injection (injection site pain) may be observed following intramuscular injection of immune globulins. Sensitization to repeated injections has occurred occasionally in immunoglobulin-deficient patients.

The following have been identified as the most frequently reported post-marketing adverse reactions:

Immune system disorder	Anaphylactic reaction*, hypersensitivity*
Nervous system disorders	Hypoesthesia
Gastrointestinal disorders	Nausea
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, pain in extremity

\*These reactions have been manifested by dizziness, paresthesia, rash, flushing, dyspnea, tachypnea, oropharyngeal pain, hyperhidrosis, and erythema

## 7 DRUG INTERACTIONS

- Do not administer repeated doses of HYPERRAB once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.<sup>1</sup>
- Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.<sup>5</sup>

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no data with HYPERRAB® [rabies immune globulin (human)] use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with HYPERRAB. It is not known whether HYPERRAB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HYPERRAB should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated backgrounds risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### 8.2 Lactation

#### Risk Summary

There is no information regarding the presence of HYPERRAB in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HYPERRAB and any potential adverse effects on the breastfed infant from HYPERRAB.

### 8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

### 8.5 Geriatric Use

Safety and effectiveness in geriatric population have not been established.

**10 OVERDOSAGE**

Because Rabies Immune Globulin (Human) may partially suppress active production of antibody in response to the rabies vaccine, do not give more than the recommended dose of rabies immune globulin (human).<sup>1</sup>

**11 DESCRIPTION**

HYPERRAB is a clear or slightly opalescent, and colorless or pale yellow or light brown sterile solution of human antirabies immune globulin for infiltration and intramuscular administration. HYPERRAB contains no preservative. HYPERRAB is prepared from pools of human plasma collected from healthy donors (hyperimmunized with rabies vaccine) by a combination of cold ethanol fractionation, caprylate precipitation and filtration, caprylate incubation, anion-exchange chromatography, nanofiltration and low pH incubation. HYPERRAB consists of 15 to 18% protein at pH 4.1 to 4.8 in 0.16 to 0.26 M glycine. The product is standardized against the U.S. Standard Rabies Immune Globulin to contain a potency value of not less than 300 IU/mL. The U.S. unit of potency is equivalent to the international unit (IU) for rabies antibody.

When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogens.

In the manufacturing process of HYPERRAB, there are several steps with the capacity for virus inactivation or removal.<sup>6</sup> 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.<sup>6</sup> These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

**12 CLINICAL PHARMACOLOGY****12.1 Mechanism of Action**

HYPERRAB provides immediate, passive, rabies virus neutralizing antibody coverage until the previously unvaccinated patient responds to rabies vaccine by actively producing antibodies.<sup>1</sup>

## 12.2 Pharmacodynamics

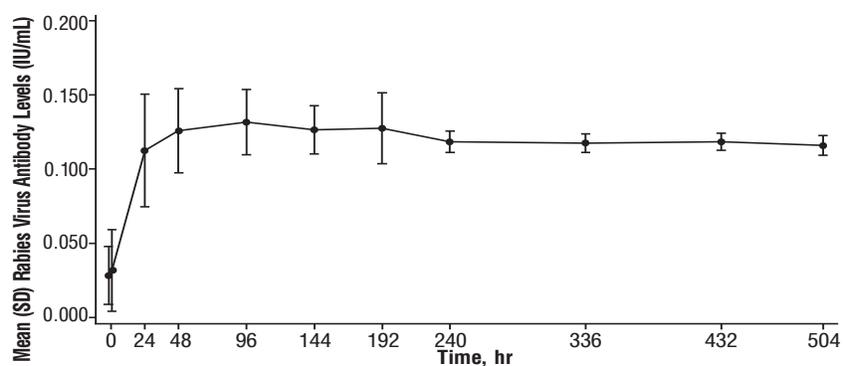
The usefulness of prophylactic rabies antibody in preventing rabies in humans when administered immediately after exposure was dramatically demonstrated in a group of persons bitten by a rabid wolf in Iran.<sup>7,8</sup> Similarly, beneficial results were later reported from the U.S.S.R.<sup>9</sup> 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.<sup>10-13</sup> These studies showed that antirabies serum can interfere to a variable extent with the active immunity induced by the vaccine, but could be minimized by booster doses of vaccine after the end of the usual dosage series.

Preparation of rabies immune globulin of human origin with adequate potency was reported by Cabasso et al.<sup>14</sup> In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin (DEV).<sup>14,15</sup> These studies determined that a human globulin dose of 20 IU/kg of rabies antibody, given simultaneously with the first DEV dose, resulted in amply detectable levels of passive rabies antibody 24 hours after injection in all recipients. The injections produced minimal, if any, interference with the subject's endogenous antibody response to DEV.

Subsequently, human diploid cell rabies vaccines (HDCV) prepared from tissue culture fluids containing rabies virus have received substantial clinical evaluation in Europe and the United States.<sup>14-22</sup> 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.<sup>21</sup>

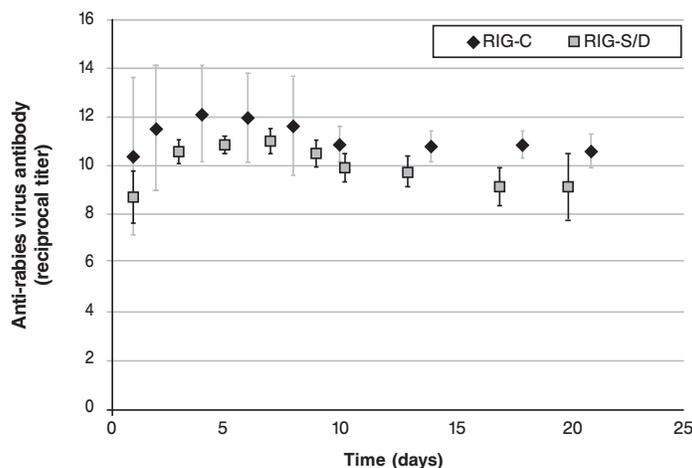
## 12.3 Pharmacokinetics

In a clinical study of 12 healthy human subjects receiving a 20 IU/kg intramuscular dose of HYPERRAB detectable passive rabies neutralizing antibody was present by 24 hours and persisted through the 21 day follow-up evaluation period. Figure 1 shows the mean levels of rabies virus antibodies in IU/mL across the 21 day evaluation period and indicates that the titer remains stable during this period. This level of passive rabies neutralizing antibody is similar to that reported in the literature for administration of human rabies immune globulin, and is clinically important because it provides interim protection until the host immune response to rabies vaccine produces definitive protective titers of neutralizing rabies antibody (therefore the rabies vaccine series is also essential).<sup>23-24</sup>



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

The previous formulation, HYPERRAB® S/D [rabies immune globulin (human)], was studied in 8 healthy subjects over 21 days. As with the new formulation, rabies neutralizing antibody was present by 24 hours and persisted through the 21 day follow up period (Figure 2).



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

#### 14 CLINICAL STUDIES

HYPERRAB was administered to a total of 20 healthy adult subjects in two clinical trials. [see *Clinical Pharmacology (12.3)*] A single intramuscular dose of 20 IU/kg HYPERRAB (12 subjects) or HYPERRAB S/D (8 subjects) was administered and rabies neutralizing antibody titers were monitored in serum for 21 days. Administration of both HYPERRAB formulations resulted in detectable titers of neutralizing antibodies to the rabies virus that persisted throughout the 21 day study period (Figure 2).

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**16 HOW SUPPLIED/STORAGE AND HANDLING**

HYPERRAB is supplied in 1 mL and 5 mL single dose vials with a potency value of not less than 300 IU/mL.

HYPERRAB contains no preservative and is not made with natural rubber latex.

<u>NDC Number</u>	<u>Size</u>
13533-318-01	1 mL
13533-318-05	5 ml

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

**17 PATIENT COUNSELING INFORMATION**

Discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Inform the patient who is allergic to human immune globulin products that severe, potentially life-threatening allergic reactions could occur. *[see Warnings and Precautions (5.1)]*

Inform the patient who is deficient in IgA the potential for developing anti-IgA antibodies and severe potentially life threatening allergic reactions. *[see Warnings and Precautions (5.1)]*

Inform the patient that HYPERRAB is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease. While the risk that HYPERRAB can transmit an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and including manufacturing steps with the capacity to inactivate and/or remove pathogens, the patient should report any symptoms that concern them. *[see Warnings and Precautions (5.2)]*

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