

CONTROL FORM Rh₀(D) Immune Globulin (Human) RhoGAM® Ultra-Filtered PLUS

Hospital _____

ATTENTION LABORATORY

Patient's Name _____

Hospital No. _____ Room No. _____

Patient is Rh negative _____ Date _____

Baby's Rh₀(D) type is positive or unknown
 _____ Date _____

FMH screening test performed, if indicated
 _____ Date _____

LOT NO. OF RhoGAM _____ EXP. DATE _____
 ISSUED _____

Tech. _____

ATTENTION OBSTETRICAL SERVICE

IMPORTANT

1. Establish patient identification before injecting this single dose of RhoGAM intramuscularly.
2. Verify the lot number and expiration date of RhoGAM recorded on this form with the lot number and expiration date printed on the prefilled syringe of RhoGAM.
3. Retain this form for verification of administration of RhoGAM.

Date RhoGAM injected _____

ANTEPARTUM POSTPARTUM

- | | |
|--|---|
| After amniocentesis <input type="checkbox"/> | Abortion <input type="checkbox"/> |
| 28-week prophylaxis <input type="checkbox"/> | Full-term delivery <input type="checkbox"/> |
| Other indication <input type="checkbox"/> | |

(specify) _____ Delivered/Terminated _____ Date _____

Gestational age _____

Attending physician _____

Part 1

CONTROL FORM Rh₀(D) Immune Globulin (Human) RhoGAM[®] Ultra-Filtered PLUS

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Other indication <input type="checkbox"/>	

(specify) _____ Delivered/Terminated _____ Date _____

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Part 2 - LABORATORY RECORD

CONTROL FORM Rh₀(D) Immune Globulin (Human) RhoGAM[®] Ultra-Filtered PLUS

Hospital _____

ATTENTION LABORATORY	ATTENTION OBSTETRICAL SERVICE								
Patient's Name _____ Hospital No. _____ Room No. _____ <input type="checkbox"/> Patient is Rh negative _____ Date _____ <input type="checkbox"/> Baby's Rh ₀ (D) type is positive or unknown _____ Date _____ <input type="checkbox"/> FMH screening test performed, if indicated _____ Date _____ LOT NO. OF RhoGAM ISSUED _____ EXP. DATE _____ Tech. _____	<p>IMPORTANT</p> <ol style="list-style-type: none"> 1. Establish patient identification before injecting this single dose of RhoGAM intramuscularly. 2. Verify the lot number and expiration date of RhoGAM recorded on this form with the lot number and expiration date printed on the prefilled syringe of RhoGAM. 3. Retain this form for verification of administration of RhoGAM. <hr/> Date RhoGAM injected _____ <table border="1"> <thead> <tr> <th>ANTEPARTUM</th> <th>POSTPARTUM</th> </tr> </thead> <tbody> <tr> <td>After amniocentesis <input type="checkbox"/></td> <td>Abortion <input type="checkbox"/></td> </tr> <tr> <td>28-week prophylaxis <input type="checkbox"/></td> <td>Full-term delivery <input type="checkbox"/></td> </tr> <tr> <td>Other indication <input type="checkbox"/></td> <td></td> </tr> </tbody> </table> (specify) _____ Delivered/Terminated _____ Date _____ Gestational age _____ Attending physician _____	ANTEPARTUM	POSTPARTUM	After amniocentesis <input type="checkbox"/>	Abortion <input type="checkbox"/>	28-week prophylaxis <input type="checkbox"/>	Full-term delivery <input type="checkbox"/>	Other indication <input type="checkbox"/>	
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After amniocentesis <input type="checkbox"/>	Abortion <input type="checkbox"/>								
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Other indication <input type="checkbox"/>									

Part 3 - RETURN TO HOSPITAL LABORATORY

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive Du test result. Assess such an individual for a large fetomaternal hemorrhage and adjust the dose of Rho(D) immune globulin accordingly. The presence of passively administered anti Rho(D) in maternal or fetal blood can lead to a positive direct antiglobulin (Coombs') test. If there is an uncertainty about the father's Rh group or immune status, administer Rho(D) immune globulin to the mother.

5.4 Hemolysis

Incompatible blood transfusion

Administration of RhoGAM to patients who are Rh-positive or have received Rh-positive red blood cells may result in signs and symptoms of a hemolytic reaction, including fever, back pain, nausea and vomiting, hypo- or hypertension, hemoglobinuria/emia, elevated bilirubin and creatinine and decreased haptoglobin. Therefore, patients treated for Rh-incompatible transfusion should be monitored by clinical and laboratory means for signs and symptoms of a hemolytic reaction. Alert patients to, and monitor them for, the signs and symptoms of intravascular hemolysis, including back pain, shaking chills, fever, and discolored urine or hematuria. Absence of these signs and/or symptoms of intravascular hemolysis within 8 hours do not indicate intravascular hemolysis cannot occur subsequently.

6 ADVERSE REACTIONS

The most frequently reported adverse reactions in patients receiving Rh_o(D) Immune Globulin (Human) products are injection site reactions, such as swelling, induration, redness and mild pain or warmth. Possible systemic reactions are skin rash, body aches or a slight elevation in temperature. Severe systemic reactions include allergic reactions and hemolytic reactions (see *Warnings and Precautions [5.2]*).

There have been no reported fatalities due to anaphylaxis or any other cause related to RhoGAM administration.

6.1 Clinical Studies Experience

Because clinical studies are conducted under different protocols and widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

No clinical studies with RhoGAM have been conducted under the current Good Clinical Practices (GCP) Guidelines.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to Rho(D) Immune Globulin (Human) products.

The following adverse reactions have been reported during post-approval use of RhoGAM: hypersensitivity reactions, including cases of anaphylactic shock or anaphylactoid reactions, skin rash, erythema, pruritus, chill, pyrexia, malaise, and back pain. Transient injection-site irritation and pain have been reported following intramuscular administration.

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

Immune globulin preparations including Rho(D) Immune Globulin (Human) may impair the efficacy of live vaccines such as measles, mumps and varicella. Administration of live vaccines should generally be delayed until 12 weeks after the final dose of immune globulin. If an immune globulin is administered within 14 days after administration of a live vaccine, the immune response to the vaccination may be inhibited.⁵

Because of the importance of rubella immunity among women of childbearing age, the postpartum vaccination of rubella-susceptible women with rubella or MMR vaccine should not be delayed because of the receipt of Rho(D) Immune Globulin (Human) during the last trimester of pregnancy or at delivery. Vaccination should occur immediately after delivery and if possible, testing should be performed after 3 or more months to ensure immunity to rubella and if necessary, to measles.⁵

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

RhoGAM is used in pregnant women for the suppression or Rh isoimmunization. The available evidence suggests that Rh_o(D) Immune Globulin (Human) does not harm the fetus or affect future pregnancies or reproduction capacity when given to pregnant Rh_o(D)-negative women for suppression of Rh isoimmunization.⁶

Animal reproduction studies have not been conducted with RhoGAM.

8.2 Lactation

Risk Summary

RhoGAM can be used during breastfeeding. Immunoglobulins are excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No clinical studies have been performed in geriatric subjects.

10 OVERDOSAGE

There are no reports of known overdoses in patients being treated with RhoGAM.

11 DESCRIPTION

RhoGAM Rho(D) Immune Globulin (Human) is a sterile solutions containing immunoglobulin G (IgG) anti-D (anti-Rh) for use in preventing Rh immunization. It is manufactured from human plasma containing anti-D from Rh-negative donors immunized with Rh-positive red blood cells. A single dose of RhoGAM contains sufficient anti-D (300 µg or 1500 IU) to suppress the immune response to up to 15 mL of Rh-positive red blood cells.⁷ The anti-D dose is measured by comparison to the RhoGAM in-house reference standard, the potency of which is established relative to the U.S./World Health Organization/European Pharmacopoeia Standard Anti-D Immunoglobulin Rho(D) Immune Globulin (Human).⁸

Plasma for RhoGAM is typically sourced from a donor center owned and operated by KEDPlasma LLC., US Lic. No. 1876. All donors are carefully screened by history and laboratory testing to reduce the risk of transmitting blood-borne pathogens from infected donors. Each plasma donation is tested and found to be non-reactive for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C (HCV) and human immunodeficiency viruses (HIV) 1 and 2. Additionally, plasma is tested by FDA licensed Nucleic Acid Testing (NAT) for hepatitis B virus (HBV), HCV and HIV-1. Each plasma unit must be negative (non-reactive) in all tests. Plasma is tested by in-process NAT procedures for hepatitis A virus (HAV) and parvovirus B19 (B19) in a minipool format. Only plasma that has passed virus screening is used for production. The NAT procedure for B19 detects all three genotypes based upon sequence alignment of known virus isolates. The limit of B19 DNA in the manufacturing pool is set not to exceed 10⁴ IU per mL.

Fractionation of the plasma is performed by a modification of the cold alcohol procedure that has been shown to significantly lower viral titers.³ Following plasma fractionation, a viral clearance filtration step and a viral inactivation step are performed. The viral filtration step removes both enveloped and non-enveloped viruses as small as approximately 20 nm via a size-exclusion mechanism.

Following viral filtration, quality control tests are performed on the 20 nm filtration membrane to insure filter integrity. The viral inactivation step (Solvent/Detergent treatment) utilizes Triton X-100 and tri-n-butyl phosphate (TNBP) to inactivate enveloped viruses such as HCV, HIV, HBV and West Nile Virus (WNV).^{3,9-11}

The donor selection process, the fractionation process, the viral filtration step, the viral inactivation process and other manufacturing process steps increase product safety by reducing the virus load potentially present in the starting material and thus reducing the risk of transmission of enveloped and non-enveloped viruses. Rho(D) Immune Globulin (Human) intended for intramuscular use and prepared by cold alcohol fractionation has not been shown to transmit hepatitis or other infectious diseases.¹² There have been no documented cases of infectious disease transmission by RhoGAM.

Laboratory spiking studies, performed in accordance with good laboratory practices³ have shown that the cumulative viral removal and inactivation capability of the RhoGAM manufacturing process is as follows:

Virus	HIV	BVDV	PRV	PPV	EMCV
Lipid Enveloped	Yes	Yes	Yes	No	No
Size (nm)	80-120	40-70	120-200	18-24	25-30
Genome	ss-RNA	ss-RNA	ds-DNA	ss-DNA	ss-RNA
Step					
Methanol precipitation	5.16	4.46	4.95	4.02	4.57
Depth filtration	≥ 4.95	2.53	2.34	3.83	Not Significant (< 1 Log)
Viral Grade Filtration (Nanofiltration)	> 3.64 (> 5.13) ¹	> 2.93 (> 5.31) ¹	> 6.02	4.52	> 4.61
Solvent/Detergent treatment	≥ 5.08	≥ 4.47	≥ 4.05	N/A	N/A
Total Viral Reduction	≥ 18.83	≥ 14.39	≥ 17.36	12.37	> 9.18

¹The lower factor reduction value (corresponding to the removal mechanism only) was used for the calculation of the Total Viral Reduction (log10), instead of the total reduction value which derives from both removal and inactivation mechanisms (value in brackets).

Units = log10 reduction

HIV Human Immunodeficiency Virus, Relevant virus for HIV-1 and 2 and model virus for Human T-cell Lymphotropic Virus (HTLV) 1 and 2

BVDV Bovine Viral Diarrhea Virus, Model for Hepatitis C Virus and West Nile Virus (WNV)

PRV Pseudorabies Virus, Model for large, enveloped DNA viruses such as Herpes Viruses and Hepatitis B Virus

PPV Porcine Parvovirus, Model for Parvovirus B19

EMCV Encephalomyocarditis Virus, Model for Hepatitis A Virus

N/A Not Applicable

The safety of Rh_o(D) Immune Globulin (Human) has been further shown in an empirical study of viral marker rates in female blood donors in the United States.¹³ This study revealed that Rh-negative donors, of whom an estimated 55-60% had received Rho(D) Immune Globulin (Human) for pregnancy-related indications, had prevalence and incidence viral marker rates similar to those of Rh-positive female donors who had not received Rho(D) Immune Globulin (Human).

The final product contains 5 ± 1% IgG, 2.9 mg/mL sodium chloride, 0.01% Polysorbate 80 (non-animal derived) and 15 mg/mL glycine. Small amounts of IgA, typically less than 15 µg per dose, are present.³ The pH range is 6.20 - 7.00 and IgG purity is > 98%. The product contains no added human serum albumin (HSA), no thimerosal or other preservatives and utilizes a latex-free delivery system.

RhoGAM Ultra-Filtered PLUS is manufactured by Kedrion Biopharma Inc., 155 Duryea Road, Melville, NY 11747 USA.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

RhoGAM acts by suppressing the immune response of Rh-negative individuals to Rh-positive red blood cells. The mechanism of action is unknown. RhoGAM and other Rho(D) Immune Globulin (Human) products are not effective in altering the course or consequences of Rh immunization once it has occurred.

12.2 Pharmacodynamics

Use after Rh-Incompatible Transfusion

An Rh-negative individual transfused with one unit of Rh-positive red blood cells has about an 80% likelihood of producing anti-D. However, Rh immunization can occur after exposure to < 1 mL of Rh-positive red blood cells. Protection from Rh immunization is accomplished by administering > 20 µg of RhoGAM per mL of Rh-positive red blood cells within 72 hours of transfusion of incompatible red blood cells.¹⁴⁻¹⁶

12.3 Pharmacokinetics

Pharmacokinetic studies after intramuscular injection were performed on sixteen Rh-negative subjects receiving a single dose of (368 µg or 1840 IU) RhoGAM.³ Plasma anti-D levels were monitored for thirteen weeks using a validated Automated Quantitative Hemagglutination method with sensitivity of approximately 1 ng/mL. The following mean pharmacokinetic parameters were obtained from data collected over the first ten weeks of a thirteen-week study:

Parameter	Mean	SD	Units
Maximum plasma concentration obtained (Cmax)	54.0	13.0	ng/mL
Time to attain Cmax (Tmax)	4		days
Elimination half-life (T1/2)	30.9	13.8	days
Volume of distribution (Vd)	7.3	1.5	liters
Clearance (CL)	150.4	53.3	mL/day

14 CLINICAL STUDIES

Rho(D) Immune Globulin (Human) administered at 28 weeks, as well as within 72 hours of delivery, has been shown to reduce the Rh immunization rate to about 0.1-0.2%.^{15,16} Clinical studies demonstrated that administration of Rh immune globulin within three hours following pregnancy termination was 100% effective in preventing Rh immunization.¹⁷

Multiple studies have been performed that prove the safety and efficacy of RhoGAM in both the obstetrical and post transfusion settings.

Pollack, Gorman and colleagues¹⁸ studied the efficacy of RhoGAM in the postpartum setting in a randomized, controlled study completed in 1967. The control group received no immunoglobulin therapy after delivery, while the test group received 300 µg of RhoGAM intramuscularly within 72 hours of delivery of an Rh-positive infant. Six months after delivery, the incidence of Rh immunization in the control group was 6.4% (32/499) versus 0.13% (1/781) in the RhoGAM group (p < 0.001).

Pollack et al. performed two randomized, placebo-controlled studies in the post transfusion setting that were designed to establish the dose response relationship of RhoGAM. In the first study,⁷ 178 (176 males, 2 females) Rh-negative volunteers received varying volumes of Rh-positive red cells; 92 subjects then received RhoGAM. A single dose of RhoGAM (1.1 mL @ 267 µg/mL) was shown to suppress anti-D formation after injection of up to 15.1 mL of Rh-positive red cells. In a companion study, Pollack administered 500 mL of Rh-positive whole blood to 44 Rh-negative male volunteers. Twenty-two (22) subjects received 20 µg RhoGAM per mL of Rh-positive red cells and 22 received no RhoGAM. None of the RhoGAM-treated subjects developed anti-D; 18/22 control arm subjects developed anti-D (p < 0.0001)¹⁵

A study was conducted in 1985 using the low protein formulation of RhoGAM. None of the 30 Rh negative male volunteers who received RhoGAM after injection of 15 ml of Rh positive red cells developed anti-D.

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16 HOW SUPPLIED / STORAGE AND HANDLING

The following presentations of RhoGAM are available:

Presentation	Product description/ package sizes	Carton NDC number	Primary container NDC number
RhoGAM® Ultra-Filtered PLUS (300 µg) (1500 IU) – Carton of 1 syringe	1 prefilled single-dose syringe in a pouch, 1 package insert, 1 control form, 1 patient identification card	NDC 0562-7805-01	
RhoGAM® Ultra-Filtered PLUS (300 µg) (1500 IU) – Carton of 5 syringes	5 prefilled single-dose syringe in a pouch, 5 package insert, 5 control form, 5 patient identification card	NDC 0562-7805-05	prefilled single-dose syringe NDC 0562-7805-00
RhoGAM® Ultra-Filtered PLUS (300 µg) (1500 IU) – Carton of 25 syringes	25 prefilled single-dose syringe in a pouch, 25 package insert, 25 control form, 25 patient identification card	NDC 0562-7805-25	

Store at 2 to 8°C. Do not store frozen.

Do not use after the expiration date printed on the syringe.

17 PATIENT COUNSELING INFORMATION

Please inform patients of the following:

- The risks and benefits of RhoGAM.
- The most common adverse reactions are local reactions including swelling, induration, redness and mild pain at the site of injection, and a small number of patients have noted a slight elevation in temperature.
- Allergic reactions to RhoGAM may occur. Patients should be observed for at least 20 minutes after administration. Signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis.
- RhoGAM may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella). Instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations.
- RhoGAM is prepared from human plasma and may contain infectious agents that can cause disease. Numerous tests have been applied in the plasma collection process and specific viral inactivation steps have been added to the manufacturing process to minimize the risk of transmission of diseases, but all risk cannot be eliminated.
- Retain the RhoGAM Patient Identification Card and advise the patient to retain the card and present it to other health care providers when appropriate.

<p>SUMMARY OF REVISIONS</p> <p>The PI was amended to update the nanofilter used for manufacturing and eliminate Ortho Clinical Diagnostics, Inc as a manufacturer. As a result, all information related to Viresolve filter has been replaced with nanofilter, the viral clearance table revised, and Ortho Clinical Diagnostics, Inc has been deleted. The technical-scientific information related to nanofilter has been revised from the following section: Description (11)</p>

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