CONTROL FORM **Rh$_0$(D) Immune Globulin (Human) RhoGAM® and MICRhoGAM® Ultra-Filtered PLUS**

December 2020 RH-0594-02-2020A

Hospital

ATTENTION LABORATORY

Patient's Name

Hospital No. Room No.

❑ Patient is Rh negative Date

❑ Baby's Rh$_0$(D) type is positive or unknown Date

❑ FMH screening test performed, if indicated Date

Select product administered:

❍ RhoGAM ISSUED LOT NO. EXP. DATE

Or ❍ MICRhoGAM ISSUED

Tech.

ATTENTION OBSTETRICAL SERVICE

IMPORTANT

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

Date RhoGAM or MICRhoGAM injected

ANTEPARTUM		POSTPARTUM	
After amniocentesis	❑	Abortion	❑
28-week prophylaxis	❑	Full-term delivery	❑
Other indication	❑		

(specify) Delivered/Terminated Date

Gestational age

Attending physician

Part 1

CONTROL FORM **Rh$_0$(D) Immune Globulin (Human) RhoGAM® and MICRhoGAM® Ultra-Filtered PLUS**

December 2020 RH-0594-02-2020B

Hospital

ATTENTION LABORATORY

Patient's Name

Hospital No. Room No.

❑ Patient is Rh negative Date

❑ Baby's Rh$_0$(D) type is positive or unknown Date

❑ FMH screening test performed, if indicated Date

Select product administered:

❍ RhoGAM ISSUED LOT NO. EXP. DATE

Or ❍ MICRhoGAM ISSUED

Tech.

ATTENTION OBSTETRICAL SERVICE

IMPORTANT

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

Date RhoGAM or MICRhoGAM injected

ANTEPARTUM		POSTPARTUM	
After amniocentesis	❑	Abortion	❑
28-week prophylaxis	❑	Full-term delivery	❑
Other indication	❑		

(specify) Delivered/Terminated Date

Gestational age

Attending physician

Part 2 - LABORATORY RECORD

CONTROL FORM **Rh$_0$(D) Immune Globulin (Human) RhoGAM® and MICRhoGAM® Ultra-Filtered PLUS**

December 2020 RH-0594-02-2020C

Hospital

ATTENTION LABORATORY

Patient's Name

Hospital No. Room No.

❑ Patient is Rh negative Date

❑ Baby's Rh$_0$(D) type is positive or unknown Date

❑ FMH screening test performed, if indicated Date

Select product administered:

❍ RhoGAM ISSUED LOT NO. EXP. DATE

Or ❍ MICRhoGAM ISSUED

Tech.

ATTENTION OBSTETRICAL SERVICE

IMPORTANT

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

Date RhoGAM or MICRhoGAM injected

ANTEPARTUM		POSTPARTUM	
After amniocentesis	❑	Abortion	❑
28-week prophylaxis	❑	Full-term delivery	❑
Other indication	❑		

(specify) Delivered/Terminated Date

Gestational age

Attending physician

Part 3 - RETURN TO HOSPITAL LABORATORY

Rh_0(D) Immune Globulin (Human)
RhoGAM® Ultra-Filtered PLUS (300 µg) (1500 IU)
MICRhoGAM® Ultra-Filtered PLUS (50 µg) (250 IU)

Rx Only

For Intramuscular Injection Only

Prefilled syringes, preservative-free (thimerosal free), latex-free delivery system

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RhoGAM Ultra-Filtered PLUS (RhoGAM) and MICRhoGAM Ultra-Filtered PLUS (MICRhoGAM) safely and effectively. See full prescribing information for RhoGAM and MICRhoGAM.

RhoGAM® Ultra-Filtered PLUS [Rho(D) Immune Globulin (Human)] (300 µg) (1500 IU), prefilled syringe, for intramuscular use

MICRhoGAM® Ultra-Filtered PLUS [Rh_0(D) Immune Globulin (Human)] (50 µg) (250 IU), prefilled syringe, for intramuscular use

Initial U.S. Approval: 1968

----------RECENT MAJOR CHANGES ----------

Indications and Usage, Limitation of Use (1.3)	11/2018
Warnings and Precautions (5)	11/2018
Adverse Reactions (6)	11/2018

---------- INDICATIONS AND USAGE----------

RhoGAM and MICRhoGAM are immune globulins indicated for use in preventing Rh immunization for:

- Pregnancy and other obstetrical conditions in Rh-negative women unless the father or baby are conclusively Rh-negative, e.g. delivery of an Rh-positive baby irrespective of the ABO groups of the mother and baby, any antepartum fetal-maternal hemorrhage (suspected or proven), actual or threatened pregnancy loss at any stage of gestation and ectopic pregnancy. (1.1)
- Prevention of Rh immunization in any Rh-negative person after incompatible transfusion of Rh-positive blood or blood products. (1.2)
- Limitation of use

  Pregnancy and other obstetrical conditions: In the case of postpartum use, RhoGAM and MICRhoGAM are intended for maternal administration. Do not inject the newborn infant. (1.3)

---------- DOSAGE AND ADMINISTRATION----------

For intramuscular use only. (2)

Pregnancy and other obstetrical conditions (2.1)

Dose	Indication	Notes*
RhoGAM (300 µg) (1500 IU)	Postpartum (if the newborn is Rh-positive) Administer within 72 hours of delivery	Additional doses of RhoGAM are indicated when the patient has been exposed to > 15 mL of Rh-positive red blood cells.
	Antepartum: • Prophylaxis at 26 to 28 weeks gestation Administer within 72 hours of suspected or proven exposure to Rh-positive red blood cells • Obstetric complications/ invasive procedures beyond 13 weeks gestation	If antepartum prophylaxis is indicated, it is essential that the mother receive a postpartum dose if the infant is Rh-positive.
MICRhoGAM (50 µg) (250 IU)	Actual or threatened termination of pregnancy (spontaneous or induced) up to and including 12 weeks gestation Administer within 72 hours	RhoGAM may be administered if MICRhoGAM is not available.

*After delivery, obstetric complications, and/or invasive procedures, the volume of the fetal-maternal hemorrhage must be determined to calculate the exact dose of RhoGAM required.

Transfusion of Rh-incompatible blood or blood products (2.1)

Administer within 72 hours of suspected or proven exposure to Rh-positive red blood cells. (2.1)

Dose	Indication	Notes
MICRhoGAM (50 µg) (250 IU)	< 2.5 mL Rh-positive red blood cells	RhoGAM may be administered if MICRhoGAM is not available.
RhoGAM (300 µg) (1500 IU)	≥ 2.5 mL Rh-positive red blood cells	Administer 20 µg of RhoGAM per mL of Rh-positive red blood cell exposure, rounding up to the next whole syringe.

---------- DOSAGE FORMS AND STRENGTHS----------

Rh_0(D) Immune Globulin (Human)

- RhoGAM® Ultra-Filtered PLUS - 300 µg (1500 IU) – Prefilled Syringes (3)
- MICRhoGAM® Ultra-Filtered PLUS - 50 µg (250 IU) – Prefilled Syringes (3)

----------CONTRAINDICATIONS ----------

- Rh-positive individuals. (4)
- Patients with a known history of anaphylactic or severe systemic reactions to the administration of human immune globulin products. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Severe hypersensitivity reactions may occur with the use of RhoGAM and MICRhoGAM. (5.1)
- RhoGAM and MICRhoGAM should be administered in a setting where appropriate equipment, medications such as epinephrine, and personnel trained in the management of hypersensitivity, anaphylaxis, and shock are available. (5.1)
- Products made from human blood may carry a risk of transmitting infectious agents e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.2)
- After administration of Rho(D) immune globulin, a transitory increase of various passively transferred antibodies in the patient's blood may yield positive serological testing results. (5.3)

Incompatible blood transfusion

- Patients treated for Rh-incompatible transfusion should be monitored by clinical and laboratory means for signs and symptoms of a hemolytic reaction. (5.4)

----------ADVERSE REACTIONS ----------

- The most frequently reported adverse reactions in patients receiving Rho(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. (6)
- Severe systemic reactions include allergic reactions and hemolytic reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Kedrion Biopharma Inc. at 1-855-3KDRION (1-855-353-7466) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Outside of the United States, the company distributing these products should be contacted.

---------- DRUG INTERACTIONS ----------

- 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 administered within 14 days after administration of a live vaccine, the efficacy of the vaccination may be impaired. (7)
- 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). (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pregnancy and other obstetrical conditions

RhoGAM and MICRhoGAM are indicated for administration to Rh-negative women not previously sensitized to the Rho(D) factor, unless the father or baby are conclusively Rh-negative, in case of:

- Delivery of an Rh-positive baby irrespective of the ABO groups of the mother and baby
- Antepartum prophylaxis at 26 to 28 weeks gestation
- Antepartum fetal-maternal hemorrhage (suspected or proven) as a result of placenta previa, amniocentesis, chorionic villus sampling, percutaneous umbilical blood sampling, other obstetrical manipulative procedure (e.g., version) or abdominal trauma
- Actual or threatened pregnancy loss at any stage of gestation
- Ectopic pregnancy

1.2 Transfusion of Rh-incompatible blood or blood products

RhoGAM and MICRhoGAM are indicated for prevention of Rh immunization in any Rh-negative person after incompatible transfusion of Rh-positive blood or blood products (e.g., red blood cells, platelet concentrates, granulocyte concentrates).

1.3 Limitation of use

Pregnancy and other obstetrical conditions

In the case of postpartum use, RhoGAM and MICRhoGAM are intended for maternal administration. Do not inject the newborn infant.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only.

2.1 Dose

Pregnancy and other obstetrical conditions

Dose	Indication	Notes*
RhoGAM (300 µg) (1500 IU)	Postpartum (if the newborn is Rh-positive) Administer within 72 hours of delivery.	Additional doses of RhoGAM are indicated when the patient has been exposed to > 15 mL of Rh-positive red blood cells. This may be determined by use of qualitative or quantitative tests for fetal-maternal hemorrhage.
	Antepartum: • Prophylaxis at 26 to 28 weeks gestation Administer within 72 hours of suspected or proven exposure to Rh-positive red blood cells resulting from: • Amniocentesis, chorionic villus sampling (CVS) and percutaneous umbilical blood sampling (PUBS) • Abdominal trauma or obstetrical manipulation • Ectopic pregnancy • Threatened pregnancy loss after 12 weeks gestation with continuation of pregnancy • Pregnancy termination (spontaneous or induced) beyond 12 weeks gestation	If antepartum prophylaxis is indicated, it is essential that the mother receive a postpartum dose if the infant is Rh-positive. If RhoGAM is administered early in pregnancy (before 26 to 28 weeks), there is an obligation to maintain a level of passively acquired anti-D by administration of RhoGAM at 12-week intervals.
MICRhoGAM (50 µg) (250 IU)	Actual or threatened termination of pregnancy (spontaneous or induced) up to and including 12 weeks gestation Administer within 72 hours	RhoGAM may be administered if MICRhoGAM is not available.

*After delivery, obstetric complications, and/or invasive procedures, the volume of the fetal-maternal hemorrhage must be determined to calculate the exact dose of RhoGAM required.

- Administer RhoGAM every 12 weeks starting from first injection to maintain a level of passively acquired anti-D.
- If delivery occurs within three weeks after the last antepartum dose, the postpartum dose may be withheld, but a test for fetal-maternal hemorrhage should be performed to determine if exposure to > 15 mL of red blood cells has occurred.
- If delivery of the baby does not occur 12 weeks after the administration of the standard antepartum dose (at 26 to 28 weeks), a second dose is recommended to maximize protection antepartum.

RhoGAM dosage

Each single dose prefilled syringe of RhoGAM contains 300 µg (1500 IU) of Rh_0(D) Immune Globulin (Human). This is the dose for the indications associated with pregnancy at or beyond 13 weeks unless there is clinical or laboratory evidence of a fetal-maternal hemorrhage (FMH) in excess of 15 mL of Rh-positive red blood cells.

MICRhoGAM dosage

Each single dose prefilled syringe of MICRhoGAM contains 50 µg (250 IU) of Rho(D) Immune Globulin (Human). This dose will suppress the immune response to up to 2.5 mL of Rh-positive red blood cells. MICRhoGAM is indicated within 72 hours after termination of pregnancy up to and including 12 weeks gestation. At or beyond 13 weeks gestation, RhoGAM should be administered instead of MICRhoGAM.

Multiple Dosage

Multiple doses of RhoGAM are required if a FMH exceeds 15 mL, an event that is possible but unlikely prior to the third trimester of pregnancy and is most likely at delivery. Patients known or suspected to be at increased risk of FMH should be tested for FMH by qualitative or quantitative methods.[3] In efficacy studies, RhoGAM was shown to suppress Rh immunization in all subjects when given at a dose of > 20 µg per mL of Rh-positive red blood cells. Thus, a single dose of RhoGAM will suppress the immune response after exposure to < 15 mL of Rh-positive red blood cells. However, in clinical practice, laboratory methods used to determine the amount of exposure (volume of transfusion or FMH) to Rh-positive red blood cells are imprecise. Therefore, administration of more than 20 µg of RhoGAM per mL of Rh-positive red blood cells should be considered whenever a large FMH or red blood cell exposure is suspected or documented. Multiple doses may be administered at the same time or at spaced intervals, as long as the total dose is administered within three days of exposure.[1]

Transfusion of Rh-incompatible blood or blood products

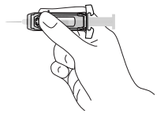
Administer within 72 hours of suspected or proven exposure to Rh-positive red blood cells.

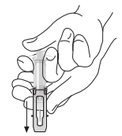
Dose	Indication	Notes
MICRhoGAM (50 µg) (250 IU)	< 2.5 mL Rh-positive red blood cells	RhoGAM may be administered if MICRhoGAM is not available.
RhoGAM (300 µg) (1500 IU)	2.5 - 15.0 mL Rh-positive red blood cells	
RhoGAM (300 µg) (1500 IU) (multiple syringes)	> 15.0 mL Rh-positive red blood cells	Additional doses of RhoGAM are indicated when the patient has been exposed to > 15 mL of Rh-positive red blood cells. Administer 20 µg of RhoGAM per mL of Rh-positive red blood cell exposure, rounding up to the next whole syringe. Multiple doses may be administered at the same time or at spaced intervals, as long as the total dose is administered within three days of exposure.

2.2 Administration

- Visually inspect RhoGAM and MICRhoGAM for particulate matter, discoloration and syringe damage prior to administration.
- Do not use if particulate matter is observed.
- RhoGAM and MICRhoGAM are clear or slightly opalescent. Do not use if discolored.
- Administer injection per standard protocol.

Note: When administering RhoGAM intramuscularly, place fingers in contact with glass syringe barrel through windows in shield to prevent possible premature activation of safety guard.





After injection, to engage the safety guard, use free hand to slide safety guard over needle. An audible "click" indicates proper activation. Keep hands behind needle at all times. Dispose of the syringe in accordance with local regulations.

As with all blood products, patients should be observed for at least 20 minutes following administration of RhoGAM or MICRhoGAM.

3 DOSAGE FORMS AND STRENGTHS

- RhoGAM® Ultra-Filtered PLUS - 300 µg (1500 IU)* – Prefilled Syringes
- MICRhoGAM® Ultra-Filtered PLUS - 50 µg (250 IU)* – Prefilled Syringes

*The anti-D content of RhoGAM / MICRhoGAM is expressed as µg per dose or as International Units (IU) per dose. The conversion factor is 1 µg = 5 IU.[2]

4 CONTRAINDICATIONS

The use of RhoGAM and MICRhoGAM is contraindicated in the following:

- Rh-positive individuals
- Patients with a known history of anaphylactic or severe systemic reactions to the administration of human immune globulin products.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur with the use of RhoGAM/MICRhoGAM, even in patients who have tolerated previous administrations.

RhoGAM / MICRhoGAM contain a small quantity of IgA[3]. There is a potential risk of hypersensitivity in IgA deficient individuals. Although high doses of intravenous immune globulin containing IgA at levels of 270-720 µg/mL have been given without incident during treatment of patients with high-titer antibodies to IgA[4], the attending physician must weigh the benefit against the potential risks of hypersensitivity reactions.

RhoGAM / MICRhoGAM should be administered in a setting where appropriate equipment, medications such as epinephrine, and personnel trained in the management of hypersensitivity, anaphylaxis, and shock are available.

5.2 Transmissible Infectious Agents

Because RhoGAM and MICRhoGAM are made from human blood, they may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

All infections thought by a physician possibly to have been transmitted by these products should be reported by the physician or other healthcare provider in the United States to Kedrion Biopharma Inc. at 1-855-3KDRION (1-855-353-7466). Outside the United States, the company distributing these products should be contacted. The physician should discuss the risks and benefits of these products with the patient.

5.3 Interference with Laboratory Tests

After administration of Rho(D) immune globulin, a transitory increase of various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, C and E) and other blood group antibodies may cause a positive direct or indirect antiglobulin (Coombs') test.

Recovery of anti-D in plasma or serum after injection of RhoGAM or other Rho(D) Immune Globulin (Human) products is highly variable among individuals. Anti-D detection in a patient's plasma is dependent on assay sensitivity and time of sample collection post-injection. Currently there are no requirements or practice standards to test for the presence of anti-D in order to determine adequacy or efficacy of dose following an injection of RhoGAM.

The presence of passively acquired anti-D antibodies in the maternal serum may cause a positive antibody screening test. This does not preclude further antepartum or postpartum prophylaxis.

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 / MICRhoGAM 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_0(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 or MICRhoGAM 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 and MICRhoGAM 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/MICRhoGAM: 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 and/or MICRhoGAM is used in pregnant women for the suppression or Rh isoimmunization. The available evidence suggests that Rh_0(D) Immune Globulin (Human) does not harm the fetus or affect future pregnancies or reproduction capacity when given to pregnant Rh0(D)-negative women for suppression of Rh isoimmunization.[6]

Animal reproduction studies have not been conducted with RhoGAM or MICRhoGAM.

8.2 Lactation

Risk Summary

RhoGAM or MICRhoGAM 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 or MICRhoGAM.

11 DESCRIPTION

RhoGAM and MICRhoGAM Rho(D) Immune Globulin (Human) are sterile solutions containing immunoglobulin G (IgG) anti-D (anti-Rh) for use in preventing Rh immunization. They are 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] A single dose of MICRhoGAM contains sufficient anti-D (50 µg or 250 IU) to suppress the immune response to up to 2.5 mL of Rh-positive red blood cells. 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) CBER Lot 4: NIBSC Lot 01/572 (285 IU/ampoule).[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 10^4 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 patented viral clearance filtration step and a patented viral inactivation step are performed. The viral filtration step removes viruses via a size-exclusion mechanism utilizing a patented Viresolve 180 ultrafiltration membrane with defined pore-size distribution of 12-18 nanometers to remove enveloped and non-enveloped viruses.

Following viral filtration, quality control tests (CorrTest and diffusion test) are performed on the Viresolve 180 ultrafiltration membrane to insure filter integrity.[8] The viral inactivation step utilizes Triton X-100 and tri-n-butyl phosphate (TNBP) to inactivate enveloped viruses such as HCV, HIV and West Nile Virus (WNV).[3,9]

The donor selection process, the fractionation process, the viral filtration step and the viral inactivation process increase product safety by 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.[10] There have been no documented cases of infectious disease transmission by RhoGAM or MICRhoGAM.

Laboratory spiking studies[3,11] have shown that the cumulative viral removal and inactivation capability of the RhoGAM / MICRhoGAM manufacturing process is as follows:

Virus	HIV	BVDV	PRV	PPV	EMC	WNV	HAV
Lipid Enveloped	Yes	Yes	Yes	No	No	Yes	No
Size (nm)	80-120	40-70	120-200	18-24	25-30	40-60	27-32
Genome	SS-RNA	SS-RNA	DS-DNA	SS-DNA	SS-RNA	SS-RNA	SS-RNA
Fractionation	≥ 7.98	7.29	≥ 11.74	8.30	ND	ND	ND
Viral Filtration	≥ 5.60	5.40	≥ 6.20	3.30	4.16	ND	≥ 5.07
Viral Inactivation	≥ 4.28	≥ 4.90	≥ 5.58	N/A	N/A	≥ 7.05	N/A
Total Viral Reduction	≥ 17.86	≥ 17.59	≥ 23.52	11.60	4.16	≥ 7.05	≥ 5.07

Units = $\log_{10}$ reduction

HIV Human Immunodeficiency Virus, Model for HIV-1 and 2 and Human T-cell Lymphotropic Virus (HTLV) 1 and 2
BVDV Bovine Viral Diarrhea Virus, Model for Hepatitis C Virus
PRV Pseudorabies Virus, Model for Herpes Viruses
PPV Porcine Parvovirus, Model for Parvovirus B19
EMC Encephalomyocarditis Virus, Model for Hepatitis A Virus
WNV West Nile Virus
HAV Hepatitis A Virus
ND Not Determined
N/A Not Applicable

The safety of Rh_0(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 and MICRhoGAM Ultra-Filtered PLUS are manufactured for Kedrion Biopharma Inc., 155 Duryea Road, Melville, NY 11747 USA, by Ortho-Clinical Diagnostics, Inc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

RhoGAM and MICRhoGAM act by suppressing the immune response of Rh-negative individuals to Rh-positive red blood cells. The mechanism of action is unknown. RhoGAM, MICRhoGAM 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 or MICRhoGAM per mL of Rh-positive red blood cells within 72 hours of transfusion of incompatible red blood cells.[14,15,16]

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 MICRhoGAM 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.

Freda, Gorman and colleagues[18] 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 ($p < 0.0001$).

Human clinical studies[3] were subsequently performed to prove the efficacy of MICRhoGAM and the low protein (5%) formulations. In the MICRhoGAM study, 81 Rh-negative male volunteers received an initial injection of 2.5 mL Rh-positive red cells, followed by a booster injection (0.1 mL) of red cells at 26 weeks; 40 subjects received an injection of MICRhoGAM after the initial red cell injection. None of the subjects who received MICRhoGAM developed anti-D, both before and after the booster red cell injection. A similar study was performed 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	prefilled single-dose syringe NDC 0562-7805-00
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	
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	

The following presentations of MICRhoGAM are available:

Presentation	Product description/ package sizes	Carton NDC number	Primary container NDC number
MICRhoGAM Ultra-Filtered PLUS (50 µg) (250 IU) – Carton of **1** syringe	1 prefilled single-dose syringe in a pouch, 1 package insert, 1 control form, 1 patient identification card	NDC 0562-7806-01	prefilled single-dose syringe NDC 0562-7806-00
MICRhoGAM Ultra-Filtered PLUS (50 µg) (250 IU) – Carton of **5** syringes	5 prefilled single-dose syringe in a pouch, 5 package insert, 5 control form, 5 patient identification card	NDC 0562-7806-05	
MICRhoGAM Ultra-Filtered PLUS (50 µg) (250 IU) – Carton of **25** syringes	25 prefilled single-dose syringe in a pouch, 25 package insert, 25 control form, 25 patient identification card	NDC 0562-7806-25	

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 and MICRhoGAM.
- 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 and MICRhoGAM 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 and MICRhoGAM 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 and MICRhoGAM are 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.

SUMMARY OF REVISIONS

Replaced all instances of Kedrion Melville Inc. with Kedrion Biopharma Inc.
Replaced Kedrion Group with KEDPlasma LLC., US Lic. No. 1876 in section 11 DESCRIPTION.

US LICENSE 1906

Kedrion Biopharma Inc., 155 Duryea Road, Melville, NY 11747 USA
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