HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Rhophylac safely and effectively. See full prescribing information for Rhophylac.

Rhophylac
Rh_0(D) Immune Globulin Intravenous (Human) 1500 IU (300 mcg)
Solution for Intravenous or Intramuscular Injection
Initial US Approval: 2004

WARNING: INTRAVASCULAR HEMOLYSIS IN ITP
See full prescribing information for complete boxed warning. This warning does not apply to Rh_0(D)-negative patients treated for the suppression of Rh isoimmunization.

- **Intravascular hemolysis leading to death has been reported in Rh_0(D)-positive patients treated for immune thrombocytopenic purpura (ITP) with Rh_0(D) Immune Globulin Intravenous (Human) products.[1]**
- **Intravasular hemolysis can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS).**
- **Serious complications, including severe anemia, acute renal insufficiency, renal failure, and disseminated intravascular coagulation (DIC), have also been reported.**
- **Closely monitor patients treated for ITP with Rhophylac in a healthcare setting for at least 8 hours after administration.**

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

• Boxed Warning	09/2010
• Dosage and Administration (2.1)	09/2010
• Warnings and Precautions (5.1.1, 5.3.1)	09/2010

----------INDICATIONS AND USAGE----------
Rhophylac is an Rh_0(D) Immune Globulin Intravenous (Human) indicated for:
Suppression of Rhesus (Rh) Isoimmunization (1.1) in:
- Pregnancy and obstetric conditions in non-sensitized, Rh_0(D)-negative women with an Rh-incompatible pregnancy, including:
  - o Routine antepartum and postpartum Rh prophylaxis
  - o Rh prophylaxis in obstetric complications or invasive procedures
- Incompatible transfusions in Rh_0(D)-negative individuals transfused with blood components containing Rh_0(D)-positive red blood cells (RBCs)

Immune Thrombocytopenic Purpura (ITP) (1.2)
Raising platelet counts in Rh_0(D)-positive, non-splenectomized adults with chronic ITP

----------DOSAGE AND ADMINISTRATION----------
Suppression of Rh Isoimmunization (2.2)
Intravenous or intramuscular administration
- Pregnancy and obstetric conditions
  - o Rh-incompatible pregnancy – 1500 IU (300 mcg) at Week 28-30 of gestation and another 1500 IU (300 mcg) within 72 hours of birth of an Rh_0(D)-positive baby
  - o Obstetric complications/invasive procedures – 1500 IU (300 mcg) within 72 hours of the at-risk event
  - o Excessive fetomaternal hemorrhage – 1500 IU (300 mcg) within 72 hours *plus* 100 IU (20 mcg) per mL fetal RBCs >15 mL (excess transplacental bleeding quantified) **or** another 1500 IU (300 mcg) (excess transplacental bleeding not quantified)
  - o Exposure to >15 mL of Rh_0(D)-positive RBCs (in postpartum prophylaxis and obstetric complications/invasive procedures) – Increase the dose based on guidelines for excessive fetomaternal hemorrhage
- Incompatible transfusions – 100 IU (20 mcg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate within 72 hours of exposure

ITP (2.3)
Intravenous administration only
- Recommended dosage – 250 IU (50 mcg) per kg body weight
- Rate of administration – 2 mL per 15 to 60 seconds

----------DOSAGE FORMS AND STRENGTHS----------
1500 IU (300 mcg) per 2 mL prefilled, ready-to-use glass syringe (3)

----------CONTRAINDICATIONS ----------
- History of anaphylactic or severe systemic reaction to human immune globulin products (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------
Both Indications (5.1)
- IgA deficient patients with known antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions (5.1.1).
- Rhophylac is made from human blood; therefore it may contain infectious agents; e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.1.3).

Suppression of Rh Isoimmunization (5.2)
- For postpartum use following an Rh-incompatible pregnancy, administer Rhophylac to the mother only. Do not administer to the newborn infant (5.2.1).

ITP (5.3)
- Intravascular hemolysis has occurred in a clinical study; monitor patients for signs and symptoms and perform confirmatory laboratory tests (5.3.1).
- In ITP patients with pre-existing anemia, weigh the benefits of Rhophylac vs. the potential risk of increasing the severity of the anemia (5.3.2).

----------ADVERSE REACTIONS----------
Suppression of Rh Isoimmunization
The most common adverse reactions, reported in ≥ 0.5% of subjects, are nausea, dizziness, headache, injection-site pain, and malaise (6.1).

ITP
The most common adverse reactions, reported in > 14% of subjects, are chills, pyrexia/increased body temperature, headache, and mild hemolysis (increased bilirubin, decreased hemoglobin, or decreased haptoglobin) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
Immunoglobulin administration may transiently interfere with the immune response to live virus vaccines, such as measles, mumps and rubella (7.1).

----------USE IN SPECIFIC POPULATIONS----------
ITP
- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 09/2010**

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

CSL Behring

FULL PRESCRIBING INFORMATION

Rhophylac®
Rh_0(D) Immune Globulin Intravenous (Human)

WARNING: INTRAVASCULAR HEMOLYSIS IN ITP

This warning does not apply to Rh_0(D)-negative patients treated for the suppression of Rh isoimmunization.

- **Intravascular hemolysis leading to death has been reported in Rh_0(D)-positive patients treated for immune thrombocytopenic purpura (ITP) with Rh_0(D) Immune Globulin Intravenous (Human) products.[1]**
- **Intravascular hemolysis can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS).**
- **Serious complications, including severe anemia, acute renal insufficiency, renal failure, and disseminated intravascular coagulation (DIC), have also been reported.**
- **Closely monitor patients treated for ITP with Rhophylac in a healthcare setting for at least 8 hours after administration. Perform a dipstick urinalysis at baseline, 2 hours and 4 hours after administration, and prior to the end of the monitoring period. 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 within 8 hours does not indicate IVH cannot occur subsequently. If signs and/or symptoms of intravascular hemolysis are present or suspected after Rhophylac administration, perform post-treatment laboratory tests, including plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect).**

1 INDICATIONS AND USAGE

Rhophylac is an Rh_0(D) Immune Globulin Intravenous (Human) (anti-D) product that is indicated for the suppression of Rh isoimmunization in non-sensitized Rh_0(D)-negative patients and for the treatment of immune thrombocytopenic purpura (ITP) in Rh_0(D)-positive patients.

1.1 Suppression of Rh Isoimmunization

Pregnancy and Obstetric Conditions

Rhophylac is indicated for suppression of rhesus (Rh) isoimmunization in non-sensitized Rh_0(D)-negative women with an Rh-incompatible pregnancy, including:

- Routine antepartum and postpartum Rh prophylaxis
- Rh prophylaxis in cases of:
  - Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage)
  - Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or obstetric manipulative procedures (e.g., external version, abdominal trauma)

An Rh-incompatible pregnancy is assumed if the fetus/baby is either Rh_0(D)-positive or Rh_0(D)-unknown or if the father is either Rh_0(D)-positive or Rh_0(D)-unknown.

Incompatible Transfusions

Rhophylac is indicated for the suppression of Rh isoimmunization in Rh_0(D)-negative individuals transfused with Rh_0(D)-positive red blood cells (RBCs) or blood components containing Rh_0(D)-positive RBCs.

Treatment can be given without a preceding exchange transfusion when the transfused blood represents less than 20% of the total circulating RBCs. If the volume exceeds 20%, an exchange transfusion should be considered prior to administering Rhophylac.

1.2 ITP

Rhophylac is indicated in Rh_0(D)-positive, non-splenectomized adult patients with chronic ITP to raise platelet counts.

2 DOSAGE AND ADMINISTRATION

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

2.1 Preparation and Handling

- Rhophylac is a clear or slightly opalescent, colorless to pale yellow solution. Inspect Rhophylac visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates.
- Prior to intravenous use, ensure that the needle-free intravenous administration system is compatible with the tip of the Rhophylac glass syringe.
- Do not freeze.
- Bring Rhophylac to room temperature before use.
- Rhophylac is for single use only. Dispose of any unused product or waste material in accordance with local requirements.

2.2 Suppression of Rh Isoimmunization

Rhophylac should be administered by intravenous or intramuscular injection. If large doses (greater than 5 mL) are required and intramuscular injection is chosen, it is advisable to administer Rhophylac in divided doses at different sites.

Table 1 provides dosing guidelines based on the condition being treated.

Table 1: Dosing Guidelines for Suppression of Rh Isoimmunization

Indication	Timing of Administration	Dose* (Administer by Intravenous or Intramuscular Injection)
Rh-incompatible pregnancy		
Routine antepartum prophylaxis	At Week 28-30 of gestation	1500 IU (300 mcg)
Postpartum prophylaxis (required only if the newborn is Rh_0(D)-positive)	Within 72 hours of birth	1500 IU (300 mcg)†
Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage)	Within 72 hours of complication	1500 IU (300 mcg)†
Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or obstetric manipulative procedures (e.g., external version, abdominal trauma)	Within 72 hours of procedure	1500 IU (300 mcg)†
Excessive fetomaternal hemorrhage (>15 mL)	Within 72 hours of complication	1500 IU (300 mcg) *plus:* • 100 IU (20 mcg) per mL fetal RBCs in excess of 15 mL if excess transplacental bleeding is quantified *or* • An additional 1500 IU (300 mcg) dose if excess transplacental bleeding cannot be quantified
Incompatible transfusions	Within 72 hours of exposure	100 IU (20 mcg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate

IU, international units; mcg, micrograms.

* A 1500 IU (300 mcg) dose of Rhophylac will suppress the immunizing potential of ≥15 mL of Rh_0(D)-positive RBCs.[2]

† The dose of Rhophylac must be increased if the patient is exposed to >15 mL of Rh_0(D)-positive RBCs; in this case, follow the dosing guidelines for excessive fetomaternal hemorrhage.

2.3 ITP

For treatment of ITP, **ADMINISTER RHOPHYLAC BY THE INTRAVENOUS ROUTE ONLY** *(see Preparation and Handling [2.1])*. **Do not administer intramuscularly**.

A 250 IU (50 mcg) per kg body weight dose of Rhophylac is recommended for patients with ITP. The following formula can be used to calculate the recommended amount of Rhophylac to administer:

Dose (IU) x body weight (kg) = Total IU / 1500 IU per syringe = Number of syringes

Rhophylac should be administered at a rate of 2 mL per 15 to 60 seconds.

3 DOSAGE FORMS AND STRENGTHS

1500 IU (300 mcg) per 2 mL prefilled, ready-to-use, glass syringe

4 CONTRAINDICATIONS

- Rhophylac is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Rhophylac is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Both Indications

5.1.1 Hypersensitivity

Severe hypersensitivity reactions may occur. If symptoms of allergic or early signs of hypersensitivity reactions (including generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) occur, discontinue Rhophylac administration

immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.
Rhophylac contains trace amounts of IgA (less than 5 mcg/mL) (*see Description [11]*). Patients with known antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Rhophylac is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reactions (*see Contraindications [4]*).

5.1.2 Interference with Laboratory Tests

The administration of Rh_0(D) immune globulin may affect the results of blood typing, the antibody screening test, and the direct antiglobulin (Coombs') test. Antepartum administration of Rh_0(D) immune globulin to the mother can also affect these tests in the newborn infant.
Rhophylac can contain antibodies to other Rh antigens (e.g., anti-C antibodies), which might be detected by sensitive serological tests following administration.

5.1.3 Transmissible Infectious Agents

Because Rhophylac is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Rhophylac.
Report any infections thought to be possibly transmitted by Rhophylac to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.2 Suppression of Rh Isoimmunization

5.2.1 Postpartum Use Following an Rh-incompatible Pregnancy

Administer Rhophylac to the mother only. Do not administer to the newborn infant (*see Pediatric Use [8.4]*).

5.3 ITP

5.3.1 Intravascular Hemolysis

Intravascular hemolysis has occurred in a clinical study with Rhophylac. All cases resolved completely. However, as reported in the literature, some Rh_0(D)-positive patients treated with Rh_0(D) Immune Globulin Intravenous (Human) for ITP developed clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation (DIC) and death.[1] **Note**: This warning does not apply to Rh_0(D)-negative patients treated for the suppression of Rh isoimmunization.
Closely monitor patients in a healthcare setting for at least 8 hours after administration of Rhophylac. Perform a dipstick urinalysis at baseline, 2 hours and 4 hours after administration, and prior to the end of the monitoring period.
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.
If signs and/or symptoms of intravascular hemolysis are present or suspected after Rhophylac administration, perform post-treatment laboratory tests, including plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect). DIC may be difficult to detect in the ITP population; the diagnosis is dependent mainly on laboratory testing.
If patients who develop hemolysis with clinically compromising anemia after receiving Rhophylac are to be transfused, Rh_0(D)-negative packed RBCs should be used to avoid exacerbating ongoing hemolysis.

5.3.2 Pre-existing Anemia

The safety of Rhophylac in the treatment of ITP has not been established in patients with pre-existing anemia. The physician must weigh the benefits of Rhophylac against the potential risk of increasing the severity of the anemia.

6 ADVERSE REACTIONS

The most serious adverse reactions in patients receiving Rh_0(D) Immune Globulin Intravenous (Human) have been observed in the treatment of ITP and include intravascular hemolysis, clinically compromising anemia, acute renal insufficiency, and, very rarely, DIC and death (*see Boxed Warning, Warnings and Precautions [5.3.1]*).[1]
The most common adverse reactions observed in the use of Rhophylac for suppression of Rh isoimmunization (≥0.5% of subjects) are nausea, dizziness, headache, injection-site pain, and malaise.
The most common adverse reactions observed in the treatment of ITP (>14% of subjects) are chills, pyrexia/increased body temperature, and headache. Mild hemolysis (manifested by an increase in bilirubin, a decrease in hemoglobin, or a decrease in haptoglobin) was also observed.

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.

Suppression of Rh Isoimmunization

In two clinical studies, 447 Rh_0(D)-negative pregnant women received either an intravenous or intramuscular injection of Rhophylac 1500 IU (300 mcg) at Week 28 of gestation. A second 1500 IU (300 mcg) dose was administered to 267 (9 in Study 1 and 258 in Study 2) of these women within 72 hours of the birth of an Rh_0(D)-positive baby. In addition, 30 women in Study 2 received at least one extra antepartum 1500 IU (300 mcg) dose due to obstetric complications (*see Clinical Studies [14.1]*).
The most common adverse reactions in study subjects were nausea (0.7%), dizziness (0.5%), headache (0.5%), injection-site pain (0.5%), and malaise (0.5%). A laboratory finding of a transient positive anti-C antibody test was observed in 0.9% of subjects.

ITP

In a clinical study, 98 Rh_0(D)-positive adult subjects with chronic ITP received an intravenous dose of Rhophylac 250 IU (50 mcg) per kg body weight (*see Clinical Studies [14.2]*). Premedication to alleviate infusion-related side effects was not used except in a single subject who received acetaminophen and diphenhydramine.
Eighty-four (85.7%) subjects experienced 392 treatment-emergent adverse events (TEAEs). Sixty-nine (70.4%) subjects had 186 drug-related TEAEs (defined as TEAEs with a probable, possible, definite, or unknown relationship to the study drug). Within 24 hours of dosing, 73 (74.5%) subjects experienced 183 TEAEs, and 66 (67%) subjects experienced 156 drug-related TEAEs.
Mild hemolysis (manifested as an increase in bilirubin, a decrease in hemoglobin, or a decrease in haptoglobin) was observed. An increase in blood bilirubin was seen in 21% of subjects. The median decrease in hemoglobin was greatest (0.8 g/dL) at Day 6 and Day 8 following administration of Rhophylac.
Table 2 shows the most common TEAEs observed in the clinical study.

Table 2: Most Common Treatment-Emergent Adverse Events (TEAEs) in Subjects with ITP

TEAE	Number of Subjects (%) With a TEAE n=98	Number of Subjects (%) With a Drug-Related TEAE* n=98
Chills	34 (34.7%)	34 (34.7%)
Pyrexia/ Increased body temperature	32 (32.6%)	30 (30.6%)
Increased blood bilirubin	21 (21.4%)	21 (21.4%)
Headache	14 (14.3%)	11 (11.2%)

* Defined as TEAEs with a possible, probable, definite, or unknown relationship to the study drug.

Serious adverse events (SAEs) were reported in 10 (10.2%) subjects. SAEs considered to be drug-related were intravascular hemolytic reaction (hypotension, nausea, chills and headache, and a decrease in haptoglobin and hemoglobin) in two subjects; headache, dizziness, nausea, pallor, shivering, and weakness requiring hospitalization in one subject; and an increase in blood pressure and severe headache in one subject. All four subjects recovered completely.

6.2 Postmarketing Experience

Because postmarketing adverse 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 product exposure. The following adverse reactions have been identified during post-approval use of Rhophylac:

Suppression of Rh Isoimmunization

Hypersensitivity reactions, including rare cases of anaphylactic shock or anaphylactoid reactions, headache, dizziness, vertigo, hypotension, tachycardia, dyspnea, nausea, vomiting, rash, erythema, pruritus, chills, pyrexia, malaise, diarrhea and back pain have been reported. Transient injection-site irritation and pain have been observed following intramuscular administration.

ITP

Transient hemoglobinuria has been reported in a patient being treated with Rhophylac for ITP.

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps, rubella, and varicella (*see Patient Counseling Information [17.1]*).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Rhophylac.

Suppression of Rh Isoimmunization

The available evidence suggests that Rhophylac does not harm the fetus or affect future pregnancies or reproduction capacity when given to pregnant Rh_0(D)-negative women for suppression of Rh isoimmunization.[3]

ITP

Rhophylac has not been evaluated in pregnant women with ITP.

8.3 Nursing Mothers

Suppression of Rh Isoimmunization

Rhophylac is used in nursing mothers for the suppression of Rh isoimmunization. No undesirable effects on a nursing infant are expected during breastfeeding.

ITP

Rhophylac has not been evaluated in nursing mothers with ITP.

8.4 Pediatric Use

Suppression of Rh Isoimmunization in Incompatible Transfusions

The safety and effectiveness of Rhophylac have not been established in pediatric subjects being treated for an incompatible transfusion. The physician should weigh the potential risks against the benefits of Rhophylac, particularly in girls whose later pregnancies may be affected if Rh isoimmunization occurs.

8.5 Geriatric Use

Suppression of Rh Isoimmunization in Incompatible Transfusions

Rhophylac has not been evaluated for treating incompatible transfusions in subjects 65 years of age and older.

ITP

Of the 98 subjects evaluated in the clinical study of Rhophylac for treatment of ITP (*see Clinical Studies [14.2]*), 19% were 65 years of age and older. No overall differences in effectiveness or safety were observed between these subjects and younger subjects.

10 OVERDOSAGE

There are no reports of known overdoses in patients being treated for suppression of Rh isoimmunization or ITP. Patients with incompatible transfusion or ITP who receive an overdose of Rh_0(D) immune globulin should be monitored because of the potential risk for hemolysis.

11 DESCRIPTION

Rhophylac is a sterile Rh_0(D) Immune Globulin Intravenous (Human) (anti-D) solution in a ready-to-use prefilled glass syringe for intravenous or intramuscular injection. One syringe contains at least 1500 IU (300 mcg) of IgG antibodies to Rh_0(D) in a 2 mL solution, sufficient to suppress the immune response to at least 15 mL of Rh-positive RBCs.[1] The product potency is expressed in IUs by comparison to the World Health Organization (WHO) standard, which is also the US and the European Pharmacopoeia standard.

Plasma is obtained from healthy Rh_0(D)-negative donors who have been immunized with Rh_0(D)-positive RBCs. The donors are screened carefully to reduce the risk of receiving donations containing blood-borne pathogens. Each plasma donation used in the manufacture of Rhophylac is tested for the presence of HBV surface antigen (HBsAg), HIV-1/2, and HCV antibodies. In addition, plasma used in the manufacture of Rhophylac is tested by FDA-licensed Nucleic Acid Testing (NAT) for HIV and HCV and found to be negative. An investigational NAT for HBV is also performed on all source plasma used and found to be negative; however, the significance of a negative result has not been established. The source plasma is also tested by NAT for hepatitis A virus (HAV) and B19 virus (B19V).

Rhophylac is produced by an ion-exchange chromatography isolation procedure[4], using pooled plasma obtained by plasmapheresis of immunized Rh_0(D)-negative US donors. The manufacturing process includes a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton™ X-100) that is effective in inactivating enveloped viruses such as HIV, HCV, and HBV.[5,6] Rhophylac is filtered using a Planova® 15 nanometer (nm) virus filter that has been validated to be effective in removing both enveloped and non-enveloped viruses. Table 3 presents viral clearance and inactivation data from validation studies, expressed as the mean $\log_{10}$ reduction factor (LRF).

Table 3: Virus Inactivation and Removal in Rhophylac

	HIV	PRV	BVDV	MVM
Virus property				
Genome	RNA	DNA	RNA	DNA
Envelope	Yes	Yes	Yes	No
Size (nm)	80-100	120-200	40-70	18-24
Manufacturing step	**Mean LRF**			
Solvent/detergent treatment	≥6.0	≥5.6	≥5.4	Not tested
Chromatographic process steps	4.5	≥3.9	1.6	≥2.6
Virus filtration	≥6.3	≥5.6	≥5.5	3.4
Overall reduction ($\log_{10}$ units)	**≥16.8**	**≥15.1**	**≥12.5**	**≥6.0**

HIV, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a model for large, enveloped DNA viruses (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for HCV and West Nile virus; MVM, minute virus of mice, a model for B19V and other small, non-enveloped DNA viruses.

Rhophylac contains a maximum of 30 mg/mL of human plasma proteins, 10 mg/mL of which is human albumin added as a stabilizer. Prior to the addition of the stabilizer, Rhophylac has a purity greater than 95% IgG. Rhophylac contains less than 5 mcg/mL of IgA, which is the limit of detection. Additional excipients are approximately 20 mg/mL of glycine and up to 0.25 M of sodium chloride. Rhophylac contains no preservative. Human albumin is manufactured from pooled plasma of US donors by cold ethanol fractionation, followed by pasteurization.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Suppression of Rh Isoimmunization

The mechanism by which Rh_0(D) immune globulin suppresses immunization to Rh_0(D)-positive RBCs is not completely known.

In a clinical study of Rh_0(D)-negative healthy male volunteers, both the intravenous and intramuscular administration of a 1500 IU (300 mcg) dose of Rhophylac 24 hours after injection of 15 mL of Rh_0(D)-positive RBCs resulted in an effective clearance of Rh_0(D)-positive RBCs. On average, 99% of injected RBCs were cleared within 12 hours following intravenous administration and within 144 hours following intramuscular administration.

ITP

Rhophylac has been shown to increase platelet counts and to reduce bleeding in non-splenectomized Rh_0(D)-positive subjects with chronic ITP. The mechanism of action is thought to involve the formation of Rh_0(D) immune globulin RBC complexes, which are preferentially removed by the reticuloendothelial system, particularly the spleen. This results in Fc receptor blockade, thus sparing antibody-coated platelets.[7]

12.3 Pharmacokinetics

Suppression of Rh Isoimmunization

In a clinical study comparing the pharmacokinetics of intravenous versus intramuscular administration, 15 Rh_0(D)-negative pregnant women received a single 1500 IU (300 mcg) dose of Rhophylac at Week 28 of gestation.[8]

Following intravenous administration, peak serum levels of Rh_0(D) immune globulin ranged from 62 to 84 ng/mL after 1 day (i.e., the time the first blood sample was taken following the antepartum dose). Mean systemic clearance was 0.20 ± 0.03 mL/min, and half-life was 16 ± 4 days.

Following intramuscular administration, peak serum levels ranged from 7 to 46 ng/mL and were achieved between 2 and 7 days. Mean apparent clearance was 0.29 ± 0.12 mL/min, and half-life was 18 ± 5 days. The absolute bioavailability of Rhophylac was 69%.

Regardless of the route of administration, Rh_0(D) immune globulin titers were detected in all women up to at least 9 weeks following administration of Rhophylac.

ITP

Pharmacokinetic studies with Rhophylac were not performed in Rh_0(D)-positive subjects with ITP. Rh_0(D) immune globulin binds rapidly to Rh_0(D)-positive erythrocytes.[9]

14 CLINICAL STUDIES

14.1 Suppression of Rh Isoimmunization

In two clinical studies, 447 Rh_0(D)-negative pregnant women received a 1500 IU (300 mcg) dose of Rhophylac during Week 28 of gestation. The women who gave birth to an Rh_0(D)-positive baby received a second 1500 IU (300 mcg) dose within 72 hours of birth.

- Study 1 (Pharmacokinetic Study) – Eight of the women who participated in the pharmacokinetic study (*see Clinical Pharmacology [12.3]*) gave birth to an Rh_0(D)-positive baby and received the postpartum dose of 1500 IU (300 mcg) of Rhophylac.[8] Antibody tests performed 6 to 8 months later were negative for all women. This suggests that no Rh_0(D) immunization occurred.
- Study 2 (Pivotal Study) – In an open-label, single-arm clinical study at 22 centers in the US and United Kingdom, 432 pregnant women received the antepartum dose of 1500 IU (300 mcg) of Rhophylac either as an intravenous or intramuscular injection (two randomized groups of 216 women each).[10] Subjects received an additional 1500 IU (300 mcg) dose if an obstetric complication occurred between the routine antepartum dose and birth or if extensive fetomaternal hemorrhage was measured after birth. Of the 270 women who gave birth to an Rh_0(D)-positive baby, 248 women were evaluated for Rh_0(D) immunization 6 to 11.5 months postpartum. None of these women developed antibodies against the Rh_0(D) antigen.

14.2 ITP

In an open-label, single-arm, multicenter study, 98 Rh_0(D)-positive adult subjects with chronic ITP and a platelet count of 30 x 10^9/L or less were treated with Rhophylac. Subjects received a single intravenous dose of 250 IU (50 mcg) per kg body weight.

The primary efficacy endpoint was the response rate defined as achieving a platelet count of ≥30 x 10^9/L as well as an increase of >20 x 10^9/L within 15 days after treatment with Rhophylac. Secondary efficacy endpoints included the response rate defined as an increase in platelet counts to ≥50 x 10^9/L within 15 days after treatment and, in subjects who had bleeding at baseline, the regression of hemorrhage defined as any decrease from baseline in the severity of overall bleeding status.

Table 4 presents the primary response rates for the intent-to-treat (ITT) and per-protocol (PP) populations.

Table 4: Primary Response Rates (ITT and PP Populations)

Analysis Population	No. Subjects	No. Responders	Primary Response Rate at Day 15	
			% Responders	95% Confidence Interval (CI)
ITT	98	65	66.3%	56.5%, 74.9%
PP	92	62	67.4%	57.3%, 76.1%

The primary efficacy response rate (ITT population) demonstrated a clinically relevant response to treatment, i.e., the lower bound of the 95% confidence interval (CI) was greater than the predefined response rate of 50%. The median time to platelet response was 3 days, and the median duration of platelet response was 22 days.

Table 5 presents the response rates by baseline platelet count for subjects in the ITT population.

Table 5: Response Rates By Baseline Platelet Count (ITT Population)

		Response Rates at Day 15	
Baseline Platelet count (x 10^9/L)	Total No. Subjects	No. (%) Subjects Achieving a Platelet Count of ≥30 x 10^9/L and an Increase of >20 x 10^9/L	No. (%) Subjects With an Increase in Platelet Counts to ≥50 x 10^9/L
≤10	38	15 (39.5)	10 (26.3)
>10 to 20	28	22 (78.6)	17 (60.7)
>20 to 30	27	24 (88.9)	22 (81.5)
>30*	5	4 (80.0)	5 (100.0)
Overall (all subjects)	98	65 (66.3)	54 (55.1)

* Reflects subjects with a platelet count of ≤30 × 10^9/L at screening but >30 × 10^9/L immediately before treatment.

During the study, an overall regression of hemorrhage was seen in 44 (88%, 95% CI: 76% to 94%) of the 50 subjects with bleeding at baseline. The percentage of subjects showing a regression of hemorrhage increased from 20% at Day 2 to 64% at Day 15. There was no evidence of an association between the overall hemorrhage regression rate and baseline platelet count.

Approximately half of the 98 subjects in the ITT population had evidence of bleeding at baseline. Post-baseline, the percentage of subjects without bleeding increased to a maximum of 70.4% at Day 8.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

- Rhophylac 1500 IU (300 mcg) is supplied in packages of one or ten (10) prefilled, ready-to-use, glass syringe(s), each containing 2 mL liquid for injection. Each syringe is accompanied by a SafetyGlide™ needle for intravenous or intramuscular use.
- Rhophylac contains no preservatives.
- The prefilled Rhophylac syringe contains no latex.
- DO NOT FREEZE.
- Store at 2 to 8°C (36 to 46°F) for a shelf life of 36 months from the date of manufacture, as indicated by the expiration date printed on the outer carton and syringe label.
- Keep Rhophylac in its original carton to protect it from light.

The following presentations of Rhophylac are available:

NDC Number	Product Description
44206-300-01	1 prefilled 2 mL syringe
44206-300-10	10 prefilled 2 mL syringes

17 PATIENT COUNSELING INFORMATION

17.1 Both Indications

- Inform patients to immediately report the following signs and symptoms to their physician: hives, chest tightness, wheezing, hypotension, and anaphylaxis.
- Inform patients that Rhophylac is made from human blood and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk Rhophylac may transmit an infectious agent has been reduced by screening all plasma donors, by testing the donated plasma for certain viruses, and by inactivating and/or removing certain viruses during manufacturing. Advise patients to report any symptoms that concern them and that may be related to viral infections.
- Inform patients that Rhophylac may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella), and instruct them to notify their healthcare professional of this potential interaction when they are receiving vaccinations.

17.2 Suppression of Rh Isoimmunization

- Inform patients receiving the antepartum dose of Rhophylac for suppression of Rh isoimmunization that they will need a second dose within 72 hours of birth if the baby's blood type is Rh-positive.

17.3 ITP

- Instruct patients being treated with Rhophylac for ITP to immediately report symptoms of intravascular hemolysis, including back pain, shaking chills, fever, discolored urine, decreased urine output, sudden weight gain, edema, and/or shortness of breath.

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