Warning: Intravascular Hemolysis in ITP

See full prescribing information for complete boxed warning. This warning does not apply to Rh(D)-negative patients treated for the suppression of Rh isoimmunization.

• Intravascular hemolysis leading to death has been reported in Rh(D)-positive patients treated for immune thrombocytopenic purpura (ITP) with Rh (D) Immune Globulin Intravenous (Human) products.

• Intravascular hemolysis can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS); acute renal insufficiency, renal failure, and disseminated intravascular coagulation (DIC) have been reported.

• Monitor patients for signs and symptoms of intravascular hemolysis in a healthcare setting for at least 8 hours after administration.

---

Dosage and Administration (2.2) 05/2016

Warnings and Precautions (5.1.1) 05/2016

---

Indications and Usage

Rhophylac is an Rh(D) Immune Globulin Intravenous (Human) indicated for:

• Suppression of Rh isoimmunization (1.1) in:
  - Pregnancy and obstetric conditions in non-sensitized, Rh0(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 Rh0(D)-negative individuals transfused with blood components containing Rh(D)-positive red blood cells (RBCs)

Immune Thrombocytopenic Purpura (ITP) (1.2)

• Raising platelet counts in Rh(D)-positive, non-splenectomized adults with chronic ITP

Dosage and Administration

Suppression of Rh isoimmunization (2.2) (IV or IM administration only.)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Timing</th>
<th>Dose* (IV or IM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh-incompatible pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine antepartum prophylaxis</td>
<td>At Week 28-30 of gestation</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Postpartum prophylaxis</td>
<td>Within 72 hours of birth</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Obstetric complications/invasive</td>
<td>Within 72 hours of</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>procedures</td>
<td>complication/procedure</td>
<td></td>
</tr>
</tbody>
</table>

---

Adverse Reactions

Excessive fetomaternal hemorrhage (>15 mL) Within 72 hours of complication 1500 IU (300 mcg) plus: 100 IU (20 mcg) per mL of fetal RBCs in excess of 15 mL if excess transplacental bleeding is quantified, OR An additional 1500 IU (300 mcg) 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

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Anticipated Adverse Reactions

6.1 Clinical Studies Experience
6.2 Postmarketing Experience

---

Full Prescribing Information: Contents*

1 Indications and Usage
   1.1 Suppression of Rh Isoimmunization
   1.2 ITP

2 Dosage and Administration
   2.1 Preparation and Handling
   2.2 Suppression of Rh Isoimmunization
   2.3 ITP

3 Dosage Forms and Strengths

4 Contraindications

5 Warnings and Precautions
   5.1 Both Indications
   5.1.1 Hypersensitivity
   5.1.2 Interference With Laboratory Tests
   5.1.3 Transmissible Infectious Agents
   5.2 ITP
   5.2.1 Intravascular Hemolysis
   5.2.2 Pre-existing Anemia

6 Adverse Reactions
   6.1 Clinical Studies Experience
   6.2 Postmarketing Experience

7 Drug Interactions
   7.1 Live Virus Vaccines

8 Use in Specific Populations
   8.1 Pregnancy
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use

9 Overdose

11 Description

12 Clinical Pharmacology
   12.1 Mechanism of Action
   12.3 Pharmacokinetics

14 Clinical Studies
   14.1 Suppression of Rh Isoimmunization
   14.2 ITP

15 References

16 How Supplied/Storage and Handling

17 Patient Counseling Information

* Sections or subsections omitted from the full prescribing information are not listed.
Rhophylac®
Rh0(D) Immune Globulin Intravenous (Human)

**WARNING: INTRAVASCULAR HEMOLYSIS IN ITP**
This warning does not apply to Rh0(D)-negative patients treated for the suppression of Rh isoimmunization.

- Intravascular hemolysis leading to death has been reported in Rh0(D)-positive patients for immune thrombocytopenic purpura (ITP) with Rh0(D) Immune Globulin Intravenous (Human) products.
- Intravascular hemolysis can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS); acute renal insufficiency, renal failure, and disseminated intravascular coagulation (DIC) have been reported.
- Monitor patients treated for signs and symptoms of hemolysis 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, back pain, shaking chills, fever, and discoloration of 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 Rh0(D) Immune Globulin Intravenous (Human) (anti-D) product that is indicated for the suppression of Rh isoimmunization in non-sensitized Rh0(D)-negative patients and for the treatment of immune thrombocytopenic purpura (ITP) in Rh0(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 Rh0(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 Rh0(D)-positive or Rh0(D)-unknown or if the father is either Rh0(D)-positive or Rh0(D)-unknown.

**Incompatible Transfusions**

Rhophylac is indicated for the suppression of Rh isoimmunization in Rh0(D)-negative individuals transfused with Rh0(D)-positive red blood cells (RBCs) or blood components containing Rh0(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 Rh0(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.

Ensure the site of administration will allow the injection to reach the muscle if Rhophylac is administered intramuscularly. Consider intravenous administration if reaching the muscle is of concern [see Adverse Reactions (6.2)]. Do not administer Rhophylac subcutaneously into the fatty tissue.

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

**Table 1: Dosing Guidelines for Suppression of Rh Isoimmunization**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Timing of Administration</th>
<th>Dose* (Administer by Intravenous or Intramuscular Injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh-incompatible pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine antepartum prophylaxis</td>
<td>At Week 28-30 of gestation</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Postpartum prophylaxis (required only if the newborn is Rh0(D)-positive)</td>
<td>Within 72 hours of birth</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Obstetric complications</td>
<td>Within 72 hours of complication</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or obstetric manipulative procedures (e.g., external version, abdominal trauma)</td>
<td>Within 72 hours of procedure</td>
<td>1500 IU (300 mcg)</td>
</tr>
<tr>
<td>Excessive fetomaternal hemorrhage (&gt;15 mL)</td>
<td>Within 72 hours of complication</td>
<td>1500 IU (300 mcg) plus:</td>
</tr>
</tbody>
</table>

- 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

**IL**, international units; mcg, micrograms.

* A 1500 IU (300 mcg) dose of Rhophylac will suppress the immunizing potential of ≤15 mL of Rh0(D)-positive RBCs.
† The dose of Rhophylac must be increased if the patient is exposed to >15 mL of Rh0(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 Dosage and Administration (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:

\[
\text{Dose (IU)} = \text{body weight (kg)}\times \text{IU per kg body weight (50 mcg/kg)}
\]

In a 70 kg adult patient, the dose would be:

\[
\text{Dose (IU)} = 70\times 50 = 3500 \text{ IU}
\]

**DOSE FORMS AND STRENGTHS**

1500 IU (300 mcg) per 2 mL prefilled, ready-to-use, glass syringe for IV or IM use.

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 to Rhophylac or any of its components.
- Do not administer Rhophylac to the newborn infant of a mother that received Rhophylac postpartum.
5 WARNINGS AND PRECAUTIONS

5.1 Both Indications

5.1.1 Hypersensitivity

Severe hypersensitivity reactions may occur even in patients who have tolerated previous administrations. 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 to Rhophylac or any of its components.

Rhophylac contains trace amounts of IgA (less than 5 mcg/mL) [see Description (11)]. Patients with known antibodies to IgA have a 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(D) immune globulin may affect the results of blood typing, the antibody screening test, and the direct antiglobulin (Coombs') test. Antepartum administration of Rh(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 ITP

5.2.1 Intravascular Hemolysis

Serious intravascular hemolysis has occurred in a clinical study with Rhophylac. All cases resolved completely. However, as reported in the literature, some Rh(D)-positive patients treated with Rh(D) Immune Globulin Intravenous (Human) for ITP developed clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation (DIC) and death.² Note: This warning does not apply to Rh(D)-negative patients treated for the suppression of Rh isoimmunization.

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(D)-negative packed RBCs should be used to avoid exacerbating ongoing hemolysis.

5.2.2 Pre-existing Anemia

The safety of Rhophylac in the treatment of ITP has not been established in patients with pre-existing anemia. Rhophylac may increase the severity of anemia.

6 ADVERSE REACTIONS

The most serious adverse reactions in patients receiving Rh(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, and Warnings and Precautions (5.3.1)].² 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. 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.

5 WARNINGS AND PRECAUTIONS

5.1 Both Indications

5.1.1 Hypersensitivity

Serious intravascular hemolysis has occurred in a clinical study with Rhophylac. All cases resolved completely. However, as reported in the literature, some Rh(D)-positive patients treated with Rh(D) Immune Globulin Intravenous (Human) for ITP developed clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation (DIC) and death.² Note: This warning does not apply to Rh(D)-negative patients treated for the suppression of Rh isoimmunization.

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(D)-negative packed RBCs should be used to avoid exacerbating ongoing hemolysis.

5.2 ITP

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Serious intravascular hemolysis has occurred in a clinical study with Rhophylac. All cases resolved completely. However, as reported in the literature, some Rh(D)-positive patients treated with Rh(D) Immune Globulin Intravenous (Human) for ITP developed clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation (DIC) and death.² Note: This warning does not apply to Rh(D)-negative patients treated for the suppression of Rh isoimmunization.

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(D)-negative packed RBCs should be used to avoid exacerbating ongoing hemolysis.

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The safety of Rhophylac in the treatment of ITP has not been established in patients with pre-existing anemia. Rhophylac may increase the severity of anemia.

6 ADVERSE REACTIONS

The most serious adverse reactions in patients receiving Rh(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, and Warnings and Precautions (5.3.1)].² 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. 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.
pregnancies or reproduction capacity when given to pregnant Rh_{0}(D)-negative women for suppression of Rh isoimmunization.\textsuperscript{a}

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.

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.

Chronic ITP

The safety and effectiveness of Rhophylac have not been established in pediatric subjects with chronic ITP. Dosing in the treatment of children with chronic ITP is expected to be similar to adults.

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.

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.\textsuperscript{3} The product potency is expressed in IU by comparison to the World Health Organization (WHO) standard, which is also the US and the European Pharmacopoeia standard.

Rhophylac is produced by an ion-exchange chromatography isolation procedure,\textsuperscript{4} using pooled plasma obtained by plasmapheresis of immunized Rh_{0}(D)-negative US donors. 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 HBV, HCV, and HIV-1 and found to be negative. 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,\textsuperscript{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 HCV, HIV, and HBV.\textsuperscript{5,6} Rhophylac is filtered using a Planova\textsuperscript{®} 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_{2} reduction factor (LRF).

Table 3: Virus Inactivation and Removal in Rhophylac

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>PRV</th>
<th>BVDV</th>
<th>MVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Size (nm)</td>
<td>80-100</td>
<td>120-200</td>
<td>40-70</td>
<td>18-24</td>
</tr>
<tr>
<td>Manufacturing step</td>
<td>Mean LRF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvent/detergent treatment</td>
<td>≥6.0</td>
<td>≥5.6</td>
<td>≥5.4</td>
<td>Not tested</td>
</tr>
<tr>
<td>Chromatographic process steps</td>
<td>4.5</td>
<td>≥3.9</td>
<td>1.6</td>
<td>≥2.6</td>
</tr>
<tr>
<td>Virus filtration</td>
<td>≥6.3</td>
<td>≥5.6</td>
<td>≥5.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Overall reduction (log_{2} units)</td>
<td>≥16.8</td>
<td>≥15.1</td>
<td>≥12.5</td>
<td>≥6.0</td>
</tr>
</tbody>
</table>

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.\textsuperscript{a}

12.2 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.\textsuperscript{9}

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.\textsuperscript{10}

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.\textsuperscript{9} 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).\textsuperscript{11} Subjects received an additional 1500 IU (300 mcg) dose if an obstetric complication occurred between the routine antepartum dose and birth of if excessive 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.
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)

<table>
<thead>
<tr>
<th>Baseline Platelet Count (x 10⁹/L)</th>
<th>Total No. Subjects</th>
<th>No. (%) Subjects Achieving a Platelet Count of ≥30 x 10⁹/L and an Increase of &gt;20 x 10⁹/L</th>
<th>No. (%) Subjects With an Increase in Platelet Counts to ≥50 x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>38</td>
<td>15 (39.5)</td>
<td>10 (26.3)</td>
</tr>
<tr>
<td>&gt;10 to 20</td>
<td>28</td>
<td>22 (78.6)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>&gt;20 to 30</td>
<td>27</td>
<td>24 (88.9)</td>
<td>22 (81.5)</td>
</tr>
<tr>
<td>&gt;30*</td>
<td>5</td>
<td>4 (80.0)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Overall (all subjects)</td>
<td>98</td>
<td>65 (66.3)</td>
<td>54 (55.1)</td>
</tr>
</tbody>
</table>

* Reflects subjects with a platelet count of ≥30 x 10⁹/L at screening but >30 x 10⁹/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


2. Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia or hemoglobinuria following Rh(0D) immune globulin intravenous administration for immune thrombocytopenic purpura. Blood. 2005;106:1532-1537.


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- Rhophylac 1500 IU (300 mcg) is supplied in packages of one or ten (10) prefilled, ready-to-use, glass syringes(s), each containing 2 mL liquid for injection. Each syringe is accompanied by a SafetyGlide™ needle for intravenous or intramuscular use.

Each product presentation includes a package insert and the following components:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Carton NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 IU (300 mcg)</td>
<td>44206-300-01</td>
<td>Single-use, prefilled 2 mL syringe [NDC 44206-300-90]</td>
</tr>
<tr>
<td>1500 IU (300 mcg) Multipack</td>
<td>44206-300-10</td>
<td>Ten single-use, prefilled 2 mL syringes [NDC 44206-300-90]</td>
</tr>
</tbody>
</table>

16.2 Storage and Handling

- DO NOT FREEZE.
- Rhophylac contains no preservatives; do not store at room temperature.
- 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 prefilled Rhophylac syringe is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Both Indications

- Inform patients to immediately report the following signs and symptoms to their physician: hives, chest tightness, wheezing, hypotension, and anaphylaxis [see Warnings and Precautions (5.1)].

- 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 [see Warnings and Precautions (5.1)].
- 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.

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.

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 [see Warnings and Precautions (5.2.1)].

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Kankakee, IL 60901 USA

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