Rhophylac offers protection with her in mind, plus...
Safety and ease of use with you in mind

Using the SAFSITE® Needle-free IV System® with Rhophylac

The Rhophylac glass syringe is compatible with most intravenous (IV) systems. One needle-free connector that has been tested to be compatible with Rhophylac is the SAFSITE® Needle-free IV System.

Close the clamp above the port and/or reset the pump according to manufacturer’s directions for the IV system your hospital uses. Be sure to swab the top of the port, per hospital protocol, and then follow these simple instructions.

1. **This is the SAFSITE® valve.**
2. **This is the SAFSITE® valve blue end cap.**
3. **Using your thumb and forefinger, grasp the syringe.**
4. **Attach the Rhophylac syringe to the SAFSITE® adapter valve by turning the syringe until it is firmly seated on the valve.**
5. **After you’ve administered Rhophylac, remove the SAFSITE® adapter valve, with the syringe still attached, from the IV port. Throw away the adapter valve with the syringe still attached. Open the IV clamp.**

* B. Braun is the manufacturer of the SAFSITE® valve.
If you have any questions regarding the needle-free connector on the IV system you use, please contact the manufacturer directly. CSL Behring does not recommend the use of any one particular needle-free connector.

**Important Safety Information**

Rhophylac is indicated for suppression of rhesus (Rh) isoimmunization in:
- **Pregnancy and obstetric conditions** in non-sensitized, Rh(D)-negative women with an Rh-incompatible pregnancy, including routine antepartum and postpartum Rh prophylaxis and Rh prophylaxis in cases of obstetric complications, invasive procedures during pregnancy, or obstetric manipulative procedures.
- **Incompatible transfusions** in Rh(D)-negative individuals transfused with blood components containing Rh(D)-positive red blood cells.

For suppression of Rh isoimmunization, Rhophylac can be administered IM or IV.
Rhophylac is indicated to raise platelet counts in Rh(D)-positive, non-splenectomized adult patients with chronic immune thrombocytopenic purpura (ITP).

For the treatment of ITP, Rhophylac must be administered IV.
Please see Important Safety Information and enclosed full prescribing information and boxed warning for Rhophylac on the following pages.
Important Safety Information

Rhophylac is indicated for suppression of rhesus (Rh) isoimmunization in:

- Pregnancy and obstetric conditions in non-sensitized, Rh(D)-negative women with an Rh-incompatible pregnancy, including routine antepartum and postpartum Rh prophylaxis and Rh prophylaxis in cases of obstetric complications, invasive procedures during pregnancy, or obstetric manipulative procedures.

- Incompatible transfusions in Rh(D)-negative individuals transfused with blood components containing Rh(D)-positive red blood cells.

For suppression of Rh isoimmunization, Rhophylac can be administered IM or IV.

Rhophylac is indicated to raise platelet counts in Rh(D)-positive, non-splenectomized adult patients with chronic immune thrombocytopenic purpura (ITP). For the treatment of ITP, Rhophylac must be administered IV.

WARNING: INTRAVASCULAR HEMOLYSIS IN ITP

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). 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. See full prescribing information for complete boxed warning.

Rhophylac is contraindicated in individuals with known anaphylactic or severe systemic reaction to human immune globulin products. Rhophylac is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. Allergic or hypersensitivity reactions may occur with Rhophylac; early signs of hypersensitivity include generalized urticaria, chest tightness, wheezing, hypotension, and anaphylaxis.

Rhophylac is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Suppression of Rh Isoimmunization: For postpartum use following an Rh-incompatible pregnancy, Rhophylac should not be given to the newborn infant.

The most common adverse reactions in the suppression of Rh isoimmunization with Rhophylac are nausea, dizziness, headache, injection-site pain, and malaise.

Immune Thrombocytopenic Purpura: The most serious adverse reactions in patients receiving Rh(D) immune globulin have been observed in the treatment of ITP. ITP patients being treated with Rhophylac should be monitored for signs and symptoms of intravascular hemolysis, including back pain, shaking chills, fever, and hemoglobinuria. Potentially serious complications of intravascular hemolysis include clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation, and death.

The most common adverse reactions observed in the treatment of ITP are chills, pyrexia/increased body temperature, and headache. Mild extravascular hemolysis has also been observed. In patients with preexisting anemia, weigh the benefits of Rhophylac against the potential risk of increasing the severity of the anemia.

Immunoglobulin administration may transiently interfere with the immune response to live virus vaccines, such as measles, mumps and rubella.

Please see full prescribing information for Rhophylac.
### Incompatible transfusions in Rh0(D)-negative individuals transfused with blood

- Raising platelet counts in Rh0(D)-positive, non-splenectomized adults with chronic ITP

### Immune Thrombocytopenic Purpura (ITP) (1.2)

- Pregnancy and obstetric conditions in non-sensitized, Rh0(D)-negative women with

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### RHOPHYLAC

**Rh(D) Immune Globulin Intravenous (Human) 1500 IU (300 mcg)**

**Solution for Intravenous (IV) or Intramuscular (IM) Injection**

**Warnings and Precautions (5.1.1) 05/2016**

**Dosage and Administration (2.2) 05/2016**

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### RECENT MAJOR CHANGES

**Dosage and Administration (2.2) 05/2016**

**Warnings and Precautions (5.1.1) 05/2016**

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### INDICATIONS AND USAGE

- **Suppression of Rhesus (Rh) Isoimmunization (1.1) in:**
  - Pregnancy and obstetric conditions in non-sensitized, Rh(D)-negative women with an Rh-incompatible pregnancy, including:
    - Routine antepartum and postpartum Rh prophylaxis
    - Rh prophylaxis in obstetric complications or invasive procedures
    - Incompatible transfusions in Rh(D)-positive individuals transfused with blood components containing Rh(D)-positive red blood cells (RBCs)
- **Rhophylac is an Rh(D) Immune Globulin Intravenous (Human) product.**
- **Monitor patients for signs and symptoms of intravascular hemolysis in a healthcare setting for at least 8 hours after administration.**

### Dosage and Administration

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

### ADVERSE REACTIONS

- **Minor adverse reactions:**
  - ITP
  - Both indications
  - 1.2.1 Interference With Laboratory Tests
  - 1.2.2 Pre-existing Anemia

### DRUG INTERACTIONS

- 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) if excess transplacental bleeding cannot be quantified
- Incompatible transfusions
  - Within 72 hours of exposure
  - 100 IU (20 mcg) per mL transfused blood or per 1 mL erythrocyte concentrate

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### PATIENT COUNSELING INFORMATION

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

## 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.

### Incompatible Transfusions

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

### Dosage and Administration

#### 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)

**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.

#### 2. ITP

Rhophylac is indicated for the treatment of immune thrombocytopenic purpura (ITP) to raise platelet counts. Rhophylac should be administered at a rate of 2 mL per 15 to 60 seconds.

### 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.

### Dosage Forms and Strengths

- 1500 IU (300 mcg)†
- 1500 IU (300 mcg) per mL fetal RBCs
- 1500 IU (300 mcg) per 2 mL transfused
- 1500 IU (300 mcg) per mL fetal RBCs

### Administration

- **Intravenous (IV) Administration:**
  - For the suppression of Rh isoimmunization,
  - For immune thrombocytopenic purpura (ITP)

- **Intramuscular (IM) Administration:**
  - Do not administer intramuscularly

### Monitoring

- 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 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).

### Adverse Reactions

- Intravascular hemolysis can lead to clinically compromising anemia and intravascular coagulation (DIC) have been reported.
- Rhophylac is contraindicated in patients treated for immune thrombocytopenic purpura (ITP)

### Dosage Table

<table>
<thead>
<tr>
<th>Indication</th>
<th>Timing of Administration</th>
<th>Dose* (Administer by Intravenous or Intramuscular Injection)</th>
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<tr>
<td>Postpartum prophylaxis (required only if the newborn is Rh0(D)-positive)</td>
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<td>1500 IU (300 mcg)†</td>
</tr>
<tr>
<td>Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage)</td>
<td>Within 72 hours of complication</td>
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</tr>
<tr>
<td>Excessive fetomaternal hemorrhage (&gt;15 mL)</td>
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</tr>
</tbody>
</table>

* 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.

### Additional Information

- 1500 IU (300 mcg) per mL fetal RBCs
- 1500 IU (300 mcg) per 2 mL transfused
- 1500 IU (300 mcg) per mL fetal RBCs

### Instructions for Use

- Do not administer Rhophylac postpartum.

### CSL BEHRING

**FULL PRESCRIBING INFORMATION**

**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 treated 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 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).

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Timing of Administration</th>
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<td>Excessive fetomaternal hemorrhage (&gt;15 mL)</td>
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</tr>
</tbody>
</table>

IL, international units; mcg, micrograms.
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 (11.1)]. 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.3 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)].3 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 chill, 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.

Suppression of Rh Isoimmunization

In two clinical studies, 447 Rh(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(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(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.

Sixty-nine (70.4%) subjects had 186 adverse events. Within 24 hours of dosing, 73 (74.5%) subjects experienced 183 Treament-Emgergent Adverse Events, and 66 (67%) subjects experienced 156 adverse reactions.

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 adverse reactions observed in the clinical study.

<table>
<thead>
<tr>
<th>TEAR</th>
<th>Number of Subjects (%) With a TEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>34 (34.7%)</td>
</tr>
<tr>
<td>Pyrexia / Increased body temperature</td>
<td>30 (30.6%)</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>21 (21.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (11.2%)</td>
</tr>
</tbody>
</table>

Serious adverse reactions (SARs) were reported in 4 (4.1%) subjects. SARs 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, diarrhoea and back pain have been reported. Transient injection-site irritation and pain have been observed following intramuscular administration.

There have been reports of lack of effect in patients with a body mass index ≥30 when administration via the intramuscular route was attempted [see Dosing and Administration (2.2)].

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)]. Do not immunize with live vaccines within 3 months after the final dose of Rhophylac. If Rhophylac is administered within 14 days after administration of a live vaccine, the immune response to the vaccination may be inhibited.3

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Suppression of Rh Isoimmunization

Rhophylac is used in pregnant women for the 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 Rh0(D)-negative women for suppression of Rh isoimmunization.4

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.

If 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 Rh0(D) immune globulin should be monitored because of the potential risk for hemolysis.

11 DESCRIPTION

Rhophylac is a sterile Rh(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 Rh0(D) in a 2 mL solution, in a ready-to-use prefilled glass syringe for intravenous or intramuscular injection. No undesirable effects on a nursing infant are expected during breastfeeding.

Rhophylac has not been evaluated in nursing mothers with ITP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Suppression of Rh Isoimmunization

The mechanism by which Rh0(D) immune globulin suppresses immunization to Rh(D)-positive RBCs is not completely known. In a clinical study of Rh(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(D)-positive RBCs resulted in a effective clearance of Rh(D)-positive RBCs. On average, 99% of injected RBCs were cleared within 12 hours following intravenous administration and within 144 hours following intramuscular administration.

Rhophylac has been shown to increase platelet counts and to reduce bleeding in non-splenectomized Rh0(D)-positive subjects with chronic ITP. The mechanism of action is thought to involve the formation of Rh(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.

12.3 Pharmacokinetics

Suppression of Rh Isoimmunization

In a clinical study comparing the pharmacokinetics of intravenous versus intramuscular administration, 15 Rh0(D)-negative pregnant women received a single 1500 IU (300 mcg) dose of Rhophylac at Week 28 of gestation. Following intravenous administration, peak serum levels of Rh(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(D) immune globulin titer were detected in all women up to at least 9 weeks following administration of Rhophylac.

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.

14 CLINICAL STUDIES

14.1 Suppression of Rh Isoimmunization

In two clinical studies, 447 Rh0(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(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(D)-positive baby and received the postpartum dose of 1500 IU (300 mcg) of Rhophylac. Antibody tests performed 6 to 8 months later were negative for all women. This suggests that no Rh(D) immunization occurred.

• Study 2 (Pivotal Study) – In an open-label, single-arm clinical study at 22 centers in the United States and 14 centers in Latin America, 432 pregnant Rh0(D)-negative pregnant women were given the antepartum dose of 1500 IU (300 mcg) of Rhophylac. Subjects received a additional 1500 IU (300 mcg) dose if an obstetric complication occurred between the routine antepartum dose and birth or if excessive fetomaternal hemorrhage was measured after birth. Of the 270 women who gave birth to an Rh(D)-positive baby, 248 women were evaluated for Rh(D) immunization 6 to 11.5 months postpartum. None of these women developed antibodies against the Rh(D) antigen.

14.2 ITP

In an open-label, single-arm, multicenter study, 98 Rh0(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 ≥ 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>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>PRV</th>
<th>BVDV</th>
<th>MVV</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>
</tbody>
</table>

Table 3: Virus Inactivation and Removal in Rhophylac

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>PRV</th>
<th>BVDV</th>
<th>MVV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
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<td>DNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>Yes</td>
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<tr>
<td>Size (nm)</td>
<td>80-100</td>
<td>120-200</td>
<td>40-70</td>
<td>18-24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacturing step</th>
<th>Mean LRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent/detergent treatment</td>
<td>±6.0</td>
</tr>
<tr>
<td>Chromatographic process steps</td>
<td>4.5</td>
</tr>
<tr>
<td>Virus filtration</td>
<td>±6.0</td>
</tr>
<tr>
<td>Overall reduction (log10 units)</td>
<td>±16.8</td>
</tr>
</tbody>
</table>

HIV, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a model for large, enveloped DNA viruses (e.g., herpes viruses); BVDV, bovine viral diarrhea virus, a model for HIV and West Nile virus; MVV, minute virus of mice, a model for B19V and other small, non-enveloped DNA viruses.
Table 4: Primary Response Rates (ITT and PP Populations)

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>No. Subjects</th>
<th>No. Responders</th>
<th>Primary Response Rate at Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Responders</td>
</tr>
<tr>
<td>ITT</td>
<td>98</td>
<td>65</td>
<td>66.3%</td>
</tr>
<tr>
<td>PP</td>
<td>92</td>
<td>62</td>
<td>67.4%</td>
</tr>
</tbody>
</table>

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 10^9/L)</th>
<th>Total No. Subjects</th>
<th>No. (%) Subjects Achieving a Platelet Count of ≥30 x 10^9/L and an Increase of &gt;20 x 10^9/L</th>
<th>No. (%) Subjects With an Increase in Platelet Counts to ≥50 x 10^9/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 (100.0)</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 10^9/L at screening but <30 x 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

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, 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:

- Presentation
- Carton NDC Number
- Components

<table>
<thead>
<tr>
<th>1500 IU (300 mcg)</th>
<th>44206-300-01</th>
<th>Single-use, prefilled 2 mL syringe (NDC 44206-300-90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 IU (300 mcg)</td>
<td>44206-300-10</td>
<td>Ten single-use, prefilled 2 mL syringes (NDC 44206-300-90)</td>
</tr>
<tr>
<td>Multipack</td>
<td></td>
<td>Ten SafetyGlide needles</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 (5.1.1)].
- 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 (5.1.3)].
- 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, shakiness, fever, discolorated urine, decreased urine output, sudden weight gain, edema, and/or shortness of breath [see Warnings and Precautions (5.2.1)].

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Bern, Switzerland
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Kankakee, IL 60901 USA

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