RHOPHYLAC®

Rh_0(D) Immune Globulin Intravenous (Human)
1500 IU (300 µg)

Rx only
For Intravenous and Intramuscular Injection
Preservative free, ready to use pre-filled syringe

DESCRIPTION

Rhophylac® is a sterile Rh_0(D) Immune Globulin Intravenous (Human) solution in a prefilled, ready to use syringe for either intravenous or intramuscular injection. One syringe contains at least 1500 IU (300 µg) 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 red blood cells[1]. The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard, which is also the US and the European Pharmacopoeia standard[2].

Plasma donations are taken from Rh_0(D)-negative healthy donors who have been immunized with Rh_0(D)-positive red blood cells. The donors' histories have been carefully screened to reduce the risk of receipt of donations containing blood borne pathogens. Each plasma donation used for the manufacture of Rhophylac® is tested for the presence of hepatitis B virus (HBV) surface antigen (HBsAg), human immunodeficiency viruses (HIV) 1/2, and hepatitis C virus (HCV) antibodies as well as elevated alanine aminotransferase (ALT) activity. In addition, plasma used in the manufacture of this product was tested by FDA licensed Nucleic Acid Testing (NAT) for HIV and HCV and found to be negative. An investigational NAT for HBV was 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 has been tested by NAT for hepatitis A virus (HAV) and parvovirus B19.

Rhophylac® is produced by an ion-exchange chromatography isolation procedure[3], using pooled plasma obtained by plasmapheresis of immunized Rh_0(D)-negative US donors. The manufacturing process includes a solvent detergent (S/D) treatment step (using tri-n-butyl phosphate and Triton® X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV. Rhophylac® is nanofiltered using a Planova® 15 nm virus filter which has been validated to be effective in the removal of enveloped as well as non-enveloped viruses. Viral clearance and inactivation data from validation studies are presented below.

The donor selection criteria, testing of donations and manufacturing pools, together with purification steps and specific viral inactivation and removal steps are included to ensure the safety of this product with respect to potential contamination with blood borne pathogens.

Viral Inactivation and Removal

Virus	HIV	BVDV	PRV	MVM
Genome	RNA	RNA	DNA	DNA
Envelope	Yes	Yes	Yes	No
Size	80–100 nm	40–70 nm	120–200 nm	18–24 nm
S/D-treatment	≥ 6.0	≥ 5.4	≥ 5.6	Not tested
Chromatographic process steps	4.5	1.6	≥ 3.9	≥ 2.6
Nanofiltration	≥ 6.3	≥ 5.5	≥ 5.6	3.4
Overall reduction (log_{10} units)	≥ 16.8	≥ 12.5	≥ 15.1	≥ 6.0

HIV: Model for HIV 1 and HIV 2.
BVDV: Bovine viral diarrhea virus, as a model for HCV.
PRV: Pseudorabies virus, as a model for large, enveloped DNA viruses (e.g., herpes virus).
MVM: Minute virus of mice, as a model for parvovirus B19 and other small, non-enveloped DNA viruses.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which Rh_0(D) Immune Globulin suppresses immunization to Rh_0(D)-positive red blood cells is not completely known. In a clinical study with Rh_0(D)-negative healthy male volunteers, both the intravenous and intramuscular administration of Rhophylac® 1500 IU (300 µg) at 24 hours after injection of 15 mL of Rh_0(D)-positive red blood cells resulted in an effective clearance of Rh_0(D)-positive red blood cells. While the intravenous administration of Rhophylac® caused an instant onset of red blood cell disappearance, the onset of elimination of red blood cells following intramuscular administration was delayed as anti-Rh_0(D) IgG had to be released from the injection site into the bloodstream. On average, 99% of injected red cells were cleared within 12 hours after intravenous administration. After intramuscular administration, a similar degree of red cell clearance was measured after 144 hours.[4]

Pharmacokinetics

In a clinical study of fourteen Rh_0(D)-negative women, a single injection of Rhophylac® 1500 IU (300 µg) was administered either intravenously or intramuscularly at week 28 of gestation and anti-Rh_0(D) IgG serum levels were measured until 11 weeks. Six women received Rhophylac® intravenously and eight women received Rhophylac® intramuscularly.
Following intravenous injection in pregnant Rh_0(D)-negative women, peak serum levels ranged from 62 to 84 ng/mL after one day. The mean systemic clearance was 0.20 ± 0.03 mL/min and half-life was 16 ± 4 days.
Following intramuscular injection, peak serum concentrations of anti-Rh_0(D) IgG ranged from 7 to 46 ng/mL and were achieved between two and seven days. The mean apparent clearance was 0.29±0.12 mL/min and half-life was 18±5 days. The absolute bioavailability of intramuscular administration was 69%.
Regardless of the route of administration, anti-D IgG titers were measurable in all women up to at least nine weeks following administration of Rhophylac®.

INDICATIONS AND USAGE

Pregnancy and Obstetrical Conditions

Rhophylac® is recommended:

1. for the suppression of Rh isoimmunization in non-sensitized Rh_0(D)-negative (D-negative) women.
   The criteria for an Rh-incompatible pregnancy requiring administration of Rhophylac® at 28 to 30 weeks of gestation and within 72 hours after delivery are:
   - the mother must be Rh_0(D)-negative,
   - the mother is carrying a child whose father is either Rh_0(D)-positive or Rh_0(D) unknown,
   - the baby is either Rh_0(D)-positive or Rh_0(D) unknown, and the mother must not be previously sensitized to the Rh_0(D) factor.
2. for Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage.
3. for Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma.

Incompatible Transfusions

Rhophylac® Rh_0(D) Immune Globulin Intravenous (Human), is recommended for the suppression of Rh isoimmunization in Rh_0(D)-negative individuals transfused with Rh_0(D)-positive RBCs or blood components containing Rh_0(D)-positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh_0(D)-positive blood represents less than 20% of the total circulating red cells. A 1500 IU (300 µg) dose will suppress the immunizing potential of approximately 15 mL of Rh_0(D)-positive RBCs.

CLINICAL STUDIES

The efficacy, safety, tolerability and pharmacokinetics of Rhophylac® are supported by the results of two clinical studies in 446 Rh_0(D)-negative pregnant women[5,6]. In both studies, Rh_0(D)-negative women received Rhophylac® 1500 IU (300 µg) intravenously or intramuscularly in the 28th week of pregnancy. Mothers who gave birth to a Rh_0(D)-positive child received a further dose of Rhophylac® 1500 IU (300 µg) within 72 hours after the birth.
Eight out of 14 pregnant women from the above mentioned pharmacokinetic study gave birth to a Rh_0(D)-positive child and received Rhophylac® 1500 IU (300 µg) postpartum as well. The antibody tests performed 6 to 8 months later were negative for all mothers, which suggest that no Rh_0(D) immunization occurred.
In a second study at 22 centres in the United Kingdom and the USA, 432 pregnant women received Rhophylac® 1500 IU (300 µg) for antepartum rhesus prophylaxis. Two randomized groups of 216 women each received Rhophylac® 1500 IU (300 µg), either as an intravenous or intramuscular injection. Rhophylac® 1500 IU (300 µg) was also injected if there was a risk of fetomaternal hemorrhage between routine antepartum rhesus prophylaxis in the 28th week of pregnancy and birth, or if extensive fetomaternal hemorrhage was measured after birth. Of the 432 women who received Rhophylac® 1500 IU (300 µg) in the 28th week of pregnancy, 270 women delivered Rh_0(D)-positive children. 248 women were available for the investigation of Rh_0(D) immunization 6 to 11.5 months postpartum. None of those women developed antibodies against the Rh_0(D) antigen as assessed by the absence of anti-D antibodies.

CONTRAINDICATIONS

Rhophylac® is contraindicated in persons with hypersensitivity to human globulin.
The concentration of IgA in Rhophylac® was found to be below the detection limit of 5 µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although anti-D immunoglobulin has been used to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risk of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

WARNINGS

Rhophylac® is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing. The Rhophylac® 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 HBV, HCV, and HIV[7,8]. Rhophylac® is nanofiltered using a Planova® 15 nm virus filter that is effective in reducing the level of enveloped as well as non enveloped viruses[3]. These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and non enveloped viruses, respectively. Despite these measures, these products could still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have

been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Bioplasma Inc. at (866) 244 2952. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

For postpartum use, Rhophylac® is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh_0(D)-positive individuals. Patients should be observed for at least 20 minutes after administration.

As with all pharmaceutical agents, allergic responses may occur. If symptoms of allergic or anaphylactic type reactions occur, immediately discontinue administration. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. If necessary, the current medical standards for shock treatment should be observed.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Drug Interactions

Active immunization with live virus vaccines (e.g., measles, mumps, rubella or varicella) should be postponed until 3 months after the last administration of immunoglobulin products, as the efficacy of the live virus vaccine may be impaired. If immunoglobulin needs to be administered within 2–4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

The results of blood typing and antibody testing in neonates, including the Coombs or antiglobulin test, may be affected by the administration of anti-D immunoglobulin.

Rhophylac® can contain antibodies to other Rh antigens, e.g., anti-C antibodies, which might be detected by sensitive serological test methods following administration of the product.

Pregnancy Category C

This medicinal product is used in pregnancy. Animal reproduction studies have not been conducted with Rhophylac®. The available evidence suggests that Rhophylac® does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient.

Rh_0(D) Immune Globulin is not secreted in breast milk. No hazards are expected during breast-feeding.

ADVERSE REACTIONS

When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.

Mild and transient fever, malaise, headache, cutaneous reactions and chills occur occasionally. In rare cases, nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reactions, including dyspnea and shock are reported, even when the patient has shown no hypersensitivity to previous administration.

No data are available on overdosage. Patients with incompatible transfusion who receive an overdose of anti-D immunoglobulin should be monitored clinically and by biological parameters because of the risk of hemolytic reaction. In other Rh_0(D)-negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

DOSAGE AND ADMINISTRATION

Indication	Dose (administer IM or IV)
Pregnancy	
Routine antepartum prevention (at 28 to 30 weeks of gestation)	1500 IU (300 µg)
Postpartum prevention (within 72 hrs)	1500 IU (300 µg)
Obstetric conditions	
Obstetric complications e.g. miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage	1500 IU (300 µg)
Invasive procedures during pregnancy e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma	1500 IU (300 µg)
Incompatible transfusions	100 IU (20 µg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate

In case of known or suspected excessive feto-maternal hemorrhage, the number of fetal red blood cells in the maternal circulation should be determined. If excess transplacental bleeding is measured, extra anti-D immunoglobulin [100 IU (20 µg) for each 1 mL of fetal red blood cells] should be administered, preferably by the intravenous route. If testing is not feasible and an excessive feto-maternal hemorrhage cannot be excluded, a further 1500 IU (300 µg) should be administered. A 1500 IU (300 µg) dose will suppress the immunizing potential of at least 15 mL of Rh_0(D)-positive red blood cells[1].

Rhophylac® should be administered by intravenous or intramuscular injection as soon as possible within 72 hours of delivery, or of the at-risk event, in cases of obstetric complications or invasive procedures.

For incompatible transfusions, the recommended dose is 100 IU (20 µg) anti-D IgG per 2 mL of transfused Rh_0(D)-positive blood or per 1 mL of Rh_0(D)-positive erythrocyte concentrate.

Rhophylac® should be brought to room or body temperature before use. Rhophylac® should be administered by slow intravenous or by intramuscular injection. If large doses (> 5 mL) are required and intramuscular injection is chosen, it is advisable to administer them in divided doses at different sites. Rhophylac® is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED

Rhophylac®, Rh_0(D) Immune Globulin Intravenous (Human) 1500 IU (300 µg) is available in packages containing one or ten pre-filled 2 mL syringes.

STORAGE

Store at 2 °C to 8 °C (36 °F to 46 °F). If stored at this temperature, Rhophylac® has a shelf life of 36 months. Do not freeze. Protect from light. The preparation should not be used after the expiration date printed on the label.

REFERENCES

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Manufactured by:
ZLB Bioplasma AG
Wankdorfstrasse 10, 3000 Berne 22
Switzerland
US License No. 1598

Distributed by:
ZLB Bioplasma Inc.
Glendale, California 91203, USA

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