Product Information

Rhophylac®

Australia

NAME OF THE MEDICINE

Human Anti-D (Rh_0) Immunoglobulin solution for injection in pre-filled syringe.

DESCRIPTION

Rhophylac® is a solution containing 750 IU (150 µg) per mL Human anti-D immunoglobulin corresponding to 1500 IU (300 µg)/2 mL. The solution also contains glycine, sodium chloride and human albumin.

The product contains a maximum of 30 mg/mL of human plasma proteins of which 10 mg/mL is human albumin as stabiliser. At least 95% of the other plasma proteins are IgG. Rhophylac® contains not more than 5 µg/mL IgA.

Rhophylac® is a sterile, pyrogen-free liquid solution for intravenous and intramuscular administration. It is purified by means of an ion exchange chromatography isolation procedure resulting in high recovery of anti-D and a high specificity of the product. Solvent-detergent treatment and virus filtration clearance steps included in the manufacturing process ensure the viral safety of the product.

PHARMACOLOGY

Rhophylac® contains specific IgG antibodies against the Rh(D) antigen of human red blood cells.

During pregnancy, and especially at the time of childbirth, foetal red blood cells may enter the maternal circulation. When the woman is Rh(D)-negative and the foetus Rh(D)-positive, the woman might become immunised to the Rh(D) antigen and may produce anti-Rh(D) antibodies which cross the placenta and may cause haemolytic disease of the newborn. Passive immunisation with anti-D immunoglobulin prevents Rh(D) immunisation in more than 99% of cases provided that a sufficient dose of anti-D immunoglobulin is administered early enough after exposure to Rh(D)-positive foetal red blood cells.

The mechanism by which anti-D immunoglobulin suppresses immunisation to Rh(D)-positive red blood cells is not known. Suppression may be related to the clearance of the red blood cells from the circulation before they reach immunocompetent sites or, it may

be due to more complex mechanisms involving recognition of foreign antigen and antigen presentation by the appropriate cells at the appropriate sites in the presence or absence of antibody.

Pharmacodynamic properties

In a clinical study of Rh(D)-negative healthy male volunteers, both the intravenous and intramuscular administration of a 1000 IU (200 µg) dose of Rhophylac® 24 hours after injection of 15 mL of Rh(D)-positive red blood cells resulted in an effective clearance of Rh(D)-positive red blood cells. On average, 99% of injected red blood cells were cleared within 60 hours following intravenous administration and within 144 hours following intramuscular administration.

Pharmacokinetic properties

In a clinical study comparing the pharmacokinetics of intravenous versus intramuscular administration, 14 Rh(D)-negative pregnant women received a single 1500 IU (300 µg) dose of Rhophylac® at week 28 of gestation.

Following intravenous administration, peak serum levels of Rh(D) immunoglobulin 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 titers were detected in all women up to at least 9 weeks following administration of Rhophylac®.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

CLINICAL TRIALS

In two clinical studies, 446 Rh(D)-negative pregnant women received a 1500 IU (300 µg) 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 µg) dose within 72 hours of birth.

- Study 1 – Eight of the women who participated in the pharmacokinetic study gave birth to an Rh(D)-positive baby and received the postpartum dose of 1500 IU (300 µg) of Rhophylac®. Antibody tests performed 6 to 8 months later were negative for all women. This suggests that no Rh(D) sensitisation occurred.
- Study 2 – In an open-label, single-arm clinical study at 22 centres in the US and United Kingdom, 432 pregnant women received the antepartum dose of 1500 IU (300 µg) of Rhophylac® either as an intravenous or intramuscular injection (two randomised groups of 216 women each). Subjects received an additional 1500 IU (300 µg) dose if an obstetric complication occurred between the routine antepartum dose and birth or if extensive foeto-maternal haemorrhage was measured after birth. Of the 270 women who gave birth to an Rh(D)-positive baby, 248 women were evaluated for Rh(D) sensitisation 6 to 11.5 months postpartum. None of these women developed antibodies against the Rh(D) antigen.

INDICATIONS

Rhophylac® is indicated for:

- Prevention of Rh sensitisation in Rh(D)-negative females at or below child-bearing age and
- Treatment of Rh(D)-negative persons after incompatible transfusions of Rh(D)-positive blood or other products containing red blood cells.

CONTRAINDICATIONS

Hypersensitivity to any of the components.

Hypersensitivity to human immunoglobulins.

The intramuscular route is contraindicated in persons with severe thrombocytopenia or other disorders of haemostasis.

PRECAUTIONS

In the case of postpartum use, anti-D immunoglobulin is intended for maternal administration. It should not be given to the newborn infant.

The product is neither intended for use in Rh(D)-positive individuals, nor for individuals already immunised to Rh(D) antigen.

Hypersensitivity

Allergic responses to anti-D immunoglobulin may occur even in patients who have tolerated previous administration. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. In case of shock, the current medical standards for treatment of shock should be observed. If symptoms of allergic or anaphylactic type reactions occur, immediate discontinuation of the administration is required.

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 successfully to treat selected IgA deficient patients, individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with Rhophylac® against the potential risks of hypersensitivity reactions.

Haemolytic reactions

Patients in receipt of an incompatible transfusion who receive very large doses of anti-D immunoglobulin should be monitored clinically and by biological parameters because of the risk of haemolytic reaction.

Obesity

There have been reports that the intramuscular administration of Rhophylac® in patients with a body mass index (BMI) ≥30 is associated with a risk of lack of efficacy. Therefore, in patients with a BMI ≥30 intravenous administration should be considered.

Pathogen safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

It is strongly recommended that every time Rhophylac® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Genotoxicity, carcinogenicity and effects on fertility

No genotoxicity, carcinogenicity and fertility studies have been performed with Rhophylac® anti-D immunoglobulin.

Use in pregnancy

This medicine is used in pregnancy. No drug-related adverse events were reported for the children delivered of 432 patients who received ante-partum administration of Rhophylac®.

No embryofoetal toxicity studies with Rhophylac® have been performed in pregnant animals.

Use in lactation

This medicine is used in nursing mothers. Immunoglobulins are excreted in breast milk. No undesirable effects are expected on nursing infants.

Paediatric use

The safety and effectiveness of Rhophylac® have not been investigated in paediatric subjects.

Use in the elderly

The safety and effectiveness of Rhophylac® have not been investigated in subjects 65 years of age and older.

Effect on laboratory tests

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient’s blood may result in misleading positive results in serological testing.

When performing red blood cell antibody screening take blood prior to the administration of Rhophylac®.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, C, D may interfere with some serological tests for red cell antibodies e.g. the antiglobulin test (Coombs' test), particularly in Rh(D)-positive neonates whose mothers have received antepartum prophylaxis.

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

Summary of the safety profile

When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness can be observed at the injection site.

Tabulated list of adverse reactions

The adverse reactions in **Table 1** have been reported from 592 patients in clinical studies and from post-marketing experience. The summary table is presented according to the MedDRA system organ classification (SOC and preferred term level).

Frequency has been evaluated using the following criteria: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000), Very rare (<1/10,000).

Table 1: List of adverse reactions

MedDRA System Organ Class	Adverse Reactions MedDRA Preferred Term	Adverse Reactions Frequency Category
Immune system disorders	Hypersensitivity, anaphylactic shock	Rare
Nervous system disorders	Headache	Uncommon
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous tissue disorders	Skin reaction, erythema, pruritus	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Rare
General disorders and administration site conditions	Fever, malaise, chills	Uncommon
	At injection site: swelling, pain, erythema, induration, warmth, pruritus, rash	Rare

There have been spontaneous reports of severe intravascular haemolysis when anti-D has been administered intravenously to Rh(D)-positive ITP patients. Haemolysis resulting in death has been reported. The exact frequency of this adverse event is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

DOSAGE AND ADMINISTRATION

Dosage

It is recommended that prescribed doses of Rhophylac® should be expressed as International Units written in full.

Prevention of Rh(D) sensitisation in Rh(D)-negative women

Table 2 provides dosing guidelines for the prevention of Rh(D) sensitisation in Rh(D)-negative women.

Table 2: Dosing guidelines

Indication	Timing of administration	Dose
Antepartum prophylaxis	At week 28–30 of gestation	1500 International Units (300 µg)
Postpartum prophylaxis (required only if the newborn is Rh(D) positive)	Within 72 hours of delivery	1500 International Units (300 µg)*
Prophylaxis following complications of pregnancy (abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental haemorrhage resulting from antepartum haemorrhage)	Within 72 hours of complication	1500 International Units (300 µg)*
Invasive procedures during pregnancy (amniocentesis, chorionic biopsy or obstetric manipulative procedures such as external version or abdominal trauma)	Within 72 hours of procedures	1500 International Units (300 µg)*
Large foeto-maternal haemorrhage (>15 mL)	Within 72 hours of complication	1500 International Units (300 µg) *plus* 100 International Units (20 µg) per mL foetal red blood cells in excess of 15 mL

* A 1500 IU (300 µg) dose will suppress the immunising potential of <15 mL of Rh(D)-positive red blood cells. If a large foeto-maternal haemorrhage (greater than 4 mL) is suspected, e.g. in the event of foetal anaemia or intrauterine foetal death, its extent should be determined by a suitable method (e.g. Kleihauer-Betke test) and additional doses of anti-D should be administered as indicated for large foeto-maternal haemorrhage.

Incompatible transfusions

The recommended dose is 100 IU (20 µg) anti-D immunoglobulin per 2 mL of transfused Rh(D)-positive blood or per 1 mL of erythrocyte concentrate. The intravenous route of administration is recommended. If given by intramuscular administration the large doses should be applied over a period of several days. A maximum dose of 15,000 IU (3000 µg) is

sufficient in the case of larger incompatible transfusions independent of whether the transfusion volume is greater than 300 mL of Rh(D)-positive blood.

Treatment with an anti-D immunoglobulin can usually be given without a preceding exchange transfusion when the transfused Rh(D)-positive blood represents less than 20% of the total circulating red blood cells. If the volume exceeds 20%, an exchange transfusion should be considered prior to administering Rhophylac®.

Administration

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

Rhophylac® can be administered by intravenous or intramuscular injection. In case of haemorrhagic disorders where intramuscular injections are contraindicated, Rhophylac® should be administered intravenously. If large doses (more than 5 mL) are required and intramuscular injection is chosen, it is advisable to administer them in divided doses at different sites.

Overweight patients

In patients with a body mass index (BMI) ≥30 intravenous administration should be considered (see **PRECAUTIONS**).

Rhophylac® is for single use only and should be brought to room or body temperature before use. The solution should be clear or slightly opalescent. Do not use if solution is cloudy or has deposits.

Rhophylac® does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening and any unused product or waste material must be disposed of appropriately.

OVERDOSAGE

No data is available on overdosage.

PRESENTATION AND STORAGE CONDITIONS

Rhophylac® solution for injection is available as a single-use pre-filled 2 mL syringe containing 1500 IU (300 µg) of anti-D immunoglobulin.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Do not use after the expiry date shown on the label.

MANUFACTURED BY

Rhophylac® is manufactured by:

CSL Behring AG, Switzerland
A company of the CSL Group

NAME AND ADDRESS OF SPONSOR AND DISTRIBUTOR

CSL Behring (Australia) Pty Ltd
ABN 48 160 734 761
189–209 Camp Road
Broadmeadows VIC 3047
Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 December 2009

DATE OF MOST RECENT AMENDMENT

3 February 2016

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For Medical/Technical Enquiries

TOLL FREE: 1800 642 865

For Customer Service Enquiries

TOLL FREE: 1800 063 892

customerservice@cslbehring.com.au

www.cslbehring.com.au