Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rhophylac 300 micrograms / 2 ml, solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 300 micrograms (1500 IU) human anti-D immunoglobulin*.
One ml contains 150 micrograms (750 IU) human anti-D immunoglobulin.

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.

Distribution of the IgG subclasses (approximate values):
IgG_1 84.1 %
IgG_2 7.6 %
IgG_3 8.1 %
IgG_4 1.0%

The content of immunoglobin A (IgA) is not more than 5 micrograms/ml.
*Produced from the plasma of human donors.

Excipient with known effect:
This medicine contains less than 1 mmol sodium (23 mg) per syringe, that is to say essentially "sodium-free".

Rhophylac contains no preservatives

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
The solution is clear or slightly opalescent and colourless or pale yellow.
Rhophylac has an osmolality of at least 240 mosmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of Rh(D) isoimmunisation in Rh(D) negative women

- Antepartum prophylaxis

- Planned antepartum prophylaxis
- Antepartum prophylaxis following complications of pregnancy including:
  Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole, intrauterine foetal death, transplacental haemorrhage resulting from antepartum haemorrhage, amniocentesis, chorionic biopsy, obstetric manipulative procedures e.g. external version, invasive interventions, cordocentesis, blunt abdominal trauma or foetal therapeutic intervention.

- Postpartum prophylaxis

- Delivery of a Rh(D) positive (D, D^{weak}, $D^{partial}$) baby

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

Treatment of Rh(D) negative adults, children and adolescents (0 – 18 years) after incompatible transfusions of Rh(D) positive blood or other products containing red blood cells e.g. platelet concentrate.

4.2 Posology and method of administration

Posology

The dose of anti-D immunoglobulin should be determined according to the level of exposure to Rh(D) positive red blood cells (RBCs) and based on the knowledge that 0.5 ml of packed Rh(D) positive RBCs or 1 ml of Rh(D) positive blood is neutralised by approximately 10 micrograms (50 IU) of anti-D immunoglobulin.

The following doses are recommended based on the clinical studies performed with Rhophylac. For specific study details see section 5.1.

Consideration should also be given to dose and dose schedules for human anti-D immunoglobulin for intramuscular and intravenous use recommended in other official guidance.

Prevention of Rh(D) isoimmunisation in Rh(D) negative women

- *Antepartum prophylaxis:* The recommended dose is a single dose of 300 micrograms (1500 IU) administered by intravenous or intramuscular injection.
    - Planned antepartum prophylaxis:A single dose of 300 micrograms at 28 - 30 weeks of pregnancy. If the need for antepartum prophylaxis is identified in the period beyond 30 weeks of pregnancy, Rhophylac should not be withheld but administered as soon as possible.
    - Antepartum prophylaxis following complications of pregnancy:A single dose of 300 micrograms should be administered as soon as possible and within 72 hours. If more than 72 hours have elapsed, the product should not be withheld but administered as soon as possible. If necessary, the dose may be repeated at 6 - 12 week intervals throughout the pregnancy.
- *Postpartum prophylaxis:* The recommended dose is a single dose of 300 micrograms (1500 IU), administered by intravenous or intramuscular injection. When administered intravenously, a minimum dose of 200 micrograms may be sufficient provided large foeto-maternal haemorrhage can be excluded.

For postpartum use, the product should be administered to the mother as soon as possible within 72 hours of delivery of a Rh(D) positive (D, D^{weak}, $D^{partial}$) infant. If more than 72 hours have elapsed, the product should not be withheld but administered as soon as possible.

The postpartum dose must still be given even when antepartum prophylaxis has been administered and even if residual activity from antepartum prophylaxis can be demonstrated in maternal serum.

If a large foeto-maternal haemorrhage (haemorrhage volume >4 ml of Rh(D) positive foetal blood) is suspected, e.g. in the event of foetal/neonatal anaemia or intrauterine foetal death, its extent should be determined by a suitable method, e.g. Kleihauer-Betke acid elution test to detect foetal haemoglobin (HbF) or flow cytometry which specifically identifies Rh(D) positive RBCs.

Additional doses of anti-D immunoglobulin should be administered accordingly (10 micrograms (50 IU) per 0.5 ml foetal RBCs or per 1ml Rh(D) positive foetal blood).

Incompatible transfusions of RBCs in Rh(D) negative patients
The recommended dose is 20 micrograms (100 IU) anti-D immunoglobulin per 2 ml of transfused Rh(D) positive blood or per 1 ml of Rh (D) positive RBC concentrate. The appropriate dose should be determined in consultation with a specialist in blood transfusion. Follow-up tests for Rh(D) positive RBCs should be done every 48 hours and further anti-D administered until all Rh(D) positive RBCs have cleared from the circulation.

A maximum dose of 3000 micrograms (15,000 IU) is sufficient even if more than 300 ml of Rh(D) positive blood or 150 ml of Rh(D) positive erythrocyte concentrate was transfused. Due to possible risk of haemolysis, however, it is suggested to not exceed the dose of 3000 micrograms (15000 IU).

Intravenous use is recommended as it will achieve adequate plasma levels immediately.
If given by intramuscular injection the large volume should be administered over a period of several days.

The dose recommendations for prevention of Rh(D) isoimmunisation are summarised in the following table:

Indication	**Timing of Administration**	**Dose**
Antepartum prophylaxis:		
Planned antepartum prophylaxis	At 28 to 30 weeks of pregnancy	300 micrograms (1500 IU) as a single dose
Antepartum prophylaxis following complications of pregnancy	Within 72 h of complication	300 micrograms (1500 IU) as a single dose[‡]
Postpartum prophylaxis:	Within 72 h of birth	300 micrograms (1500 IU) as a single dose[‡]
Large foeto-maternal haemorrhage (>4ml)		300micrograms (1500 IU) as a single dose ***plus*****:** 10 micrograms (50 IU) per 0.5ml Rh(D) positive foetal RBCs or, 10 micrograms (50 IU) per 1ml Rh(D) positive foetal blood
Incompatible transfusions	Within 72 h of exposure	10 micrograms (50 IU) per 0.5ml transfused Rh(D) positive RBCs concentrate or, 10 micrograms (50 IU) per 1ml transfused Rh(D) positive blood

[‡]The Rhophylac dose may need to be increased if the patient is exposed to >15 ml of Rh(D) positive foetal RBCs. In this case, follow the dosing guidelines for large foeto-maternal haemorrhage.

Paediatric population
As the posology in case of incompatible transfusion depends on the volume of Rh(D) positive blood or RBC concentrate transfused, the recommended dose in children and adolescents (0-18 years) is not considered to be different to that of adults. However, the appropriate dose should be determined in consultation with a specialist in blood transfusion.

Use in the elderly
As the posology in case incompatible transfusion depends on the volume of Rh(D)-positive blood or Rh(D) positive RBC concentrate transfused, the recommended dose in elderly patients (≥ 65 years of age) is not considered to be different to that of adults. The appropriate dose should be determined in consultation with a specialist in blood transfusion.

Method of administration

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

For intravenous or intramuscular use, to be administered by slow injection.
If a large volume (>2 ml for children or >5 ml for adults) is required and intramuscular injection is chosen, it is recommended to administer this in divided doses at different sites.

If intramuscular administration is contraindicated (bleeding disorders), Rhophylac should be administered intravenously.

Obesity
In patients with a body mass index (BMI) ≥30 intravenous administration should be considered (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of Rhophylac listed in section 6.1.

Hypersensitivity to human immunoglobulins.

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

4.4 Special warnings and precautions for use

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

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

Hypersensitivity
Allergic reactions to anti-D immunoglobulin may occur even in patients who have tolerated previous administrations. 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 micrograms/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 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 an increased risk of lack of efficacy. Therefore, in patients with a BMI ≥30, intravenous administration should be considered.

Excipients
Rhophylac contains less than 1 mmol sodium (23 mg) per syringe, that is to say essentially "sodium-free".

Information on safety with respect to transmissible agents
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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). They may be of limited value against non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that 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.

4.5 Interaction with other medicinal products and other forms of interactions

Live attenuated virus vaccines
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.

Interference with serological testing
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.

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

4.6 Fertility, pregnancy and lactation

Fertility
No animal fertility studies have been conducted with Rhophylac. Nevertheless, clinical experience with human anti-D immunoglobulin suggests that no harmful effects on fertility are to be expected.

Pregnancy
This medicinal product is intended for use in pregnancy.

No study drug-related adverse events were reported in children delivered of 432 women who received antepartum administration of Rhophylac 300 micrograms.

Breastfeeding
This medicinal product can be used during breastfeeding.
Immunoglobulins are excreted in human milk. No study drug-related adverse events were reported in children delivered of 256 women who received postpartum administration of Rhophylac 300 micrograms, nor in children delivered of 139 women who received postpartum administration of Rhophylac 200 micrograms.

4.7 Effects on ability to drive and use machines

Rhophylac has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most serious adverse reactions observed during the treatment are hypersensitivity or allergic reactions which may in rare cases progress to a sudden fall in blood pressure and anaphylactic shock even when the patient has shown no hypersensitivity to previous administration. When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness may be observed at the injection site.

Tabulated list of adverse reactions
The following adverse reactions have been reported from 592 patients in clinical studies and from post-marketing experience. The summary table presented below is 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 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000).

System Organ Class (SOC, MedDRA)	**Adverse Reaction** (MedDRA Preferred Term (PT)	**Frequency of ADR**
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	Pyrexia, 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 patients with primary immune thrombocytopenia (ITP). Haemolysis resulting in death has been reported. The exact frequency of this adverse event is not known.

For safety information with respect to transmissible agents, see section 4.4.

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 via:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517; website: www.hpra.ie; Email: medsafety@hpra.ie

4.9 Overdose

No data are available on overdosage. Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: Anti-D (Rh) immunoglobulin. ATC Code: J06BB01.

Mechanism of action

Rhophylac contains specific antibodies (IgG) against the Rh(D) antigen of human erythrocytes. It can also contain antibodies to other Rh antigens, e.g. anti-Rh C antibodies.

During pregnancy, and especially at the time of childbirth, foetal RBCs may enter the maternal circulation. When the woman is Rh(D) negative and the foetus Rh(D) positive, the woman may become immunised to the Rh(D) antigen and produce anti-Rh(D) antibodies which cross the placenta and may cause haemolytic disease of the new-born.
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 soon enough after exposure to Rh(D) positive foetal RBCs.

The mechanism by which anti-D immunoglobulin suppresses immunisation to Rh(D) positive RBCs is not known. Suppression may be related to the clearance of the RBCs 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 effects

Prevention of Rh(D) isoimmunisation
In Rh(D) negative healthy male volunteers, both the intravenous and intramuscular administration of 200 micrograms (1000 IU) of Rhophylac at 48 hours after injection of 5 ml of Rh(D) positive RBCs resulted in an almost complete clearance of Rh(D) positive RBCs within 24 hours.

While the intravenous administration of Rhophylac caused an instant onset of Rh(D) positive RBC disappearance, the onset of elimination of Rh(D) positive RBCs following intramuscular administration was delayed as anti-D IgG had to be first absorbed from the injection site.

On an average, 70% of injected Rh(D) positive RBCs were cleared 2 hours after intravenous administration of Rhophylac.

After intramuscular administration, a similar degree of Rh(D) positive RBC clearance was measured after 12 hours.

Furthermore, the efficacy, safety and pharmacokinetics of Rhophylac are supported by the results of three clinical studies in pregnant women.

In one clinical study, Rhophylac 200 micrograms(1000 IU) was administered postpartum in 139 per protocol subjects.

In the other two clinical studies, Rhophylac 300 micrograms (1500 IU) was administered antepartum in 408 per protocol subjects and in addition postpartum in 256 subjects who gave birth to a Rh(D) positive baby.

None of the pregnant women included in these studies developed antibodies against the Rh(D) antigen.

In the clinical studies with Rhophylac 300, 207 per protocol subjects were given the antepartum dose of Rhophylac 300 intravenously and 201 per protocol subjects were given it intramuscularly. In more than 99 % of cases, the method of post- and antepartum administration was the same.

Clinical studies with Rhophylac at doses below 200 micrograms (1000 IU) have not been conducted.

Paediatric population

The safety and efficacy of Rhophylac have not been established in clinical studies in paediatric subjects after incompatible transfusion of Rh(D) positive blood or other products containing Rh(D) positive RBCs.

5.2 Pharmacokinetic properties

Absorption and Distribution
The bioavailability of human anti-D immunoglobulin for intravenous use is complete and immediate. IgG is quickly distributed between plasma and extravascular fluid.

Human anti-D immunoglobulin for intramuscular administration is slowly absorbed into the recipient’s circulation and reaches a maximum after a delay of 2 to 3 days.

Elimination
Human anti-D immunoglobulin has a half-life of about 3 to 4 weeks. This half-life may vary individually from patient to patient.

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

5.3 Preclinical safety data

Due to induction of and interference with antibodies, there are limitedpreclinical data of relevance for anti-D immunoglobulin.

Repeated dose testing and embryo-foetal toxicity studies have not been conducted and are impracticable to conduct.

The potential for mutagenic effects of immunoglobulins have not been studied.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Glycine
Sodium chloride
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal productmust not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (+2°C to +8°C). Do not freeze.

The product must not be used after the expiry date (EXP) printed on the outer carton.

Keep the syringe originally blistered in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml solution in a pre-filled syringe (type 1 glass) with 1 injection needle in a pack size of 1 or in a multi-pack consisting of 5 single packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Rhophylac should be brought to room temperature (25°C) before use.

Rhophylac should be inspected visually for particulate matter and discolouration prior to administration.

Do not use solutions which are cloudy or have deposits.

Rhophylac is for single use only (one syringe – one patient).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0800/006/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 17 October 2003

Date of last renewal: 20 February 2006

10 DATE OF REVISION OF THE TEXT

November 2019