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 1500 IU (300 micrograms) human anti-D immunoglobulin. One ml contains 750 IU (150 micrograms 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. The content of IgA is not more than 5 micrograms/ml.

For a 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) immunisation 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 (IUFD), transplacental haemorrhage (TPH) resulting from antepartum haemorrhage (APH), 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\text{weak}, D\text{partial}) baby

Treatment of Rh(D) negative persons 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 and based on the knowledge that 0.5 ml of packed Rh(D) positive red blood cells 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) immunisation 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 gestation.
  - Antepartum prophylaxis following complications of pregnancy:
    A single dose of 300 micrograms should be administered as soon as possible and within 72 hours and if necessary repeated at 6 - 12 week intervals throughout the pregnancy.

- **Postpartum prophylaxis:** For intravenous administration, 200 micrograms (1000 IU) is a sufficient dose. If administered intramuscularly, 200 micrograms (1000 IU) to 300 micrograms (1500 IU) is recommended
  
  For postpartum use, the product should be administered to the mother as soon as possible within 72 hours of delivery of an Rh(D) positive (D, Dweak, Dpartial) 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 (>4 ml (0.7% - 0.8% of women)) 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 HbF or flow cytometry which specifically identifies Rh(D) positive cells.

Additional doses of anti-D immunoglobulin should be administered accordingly (10 micrograms (50 IU) per 0.5 ml foetal red blood cells).

**Incompatible transfusions of red blood cells (RBCs)**

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 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 (15000 IU) 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. 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.

**Method of administration**
For intravenous use, 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 contra-indicated (bleeding disorders), Rhophylac should be administered intravenously.

**4.3 Contraindications**

Hypersensitivity to any of the components.
Hypersensitivity to human immunoglobulins.
The intramuscular route is contra-indicated in persons with severe thrombocytopenia or other disorders of haemostasis.

**4.4 Special warnings and precautions for use**

In the case of postpartum use, the product 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.

True allergic reactions are rare, but allergic-type responses to anti-D immunoglobulin may occur.

Rhophylac contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully to treat selected IgA-deficient individuals, individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of plasma-derived medicinal products containing IgA. The physician must therefore weigh the benefit of treatment with Rhophylac against the potential risks of hypersensitivity reactions.

Rarely, human anti-D immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with human immunoglobulin.

Suspicion of allergic or anaphylactic-type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

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.
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 HIV, HBV and HCV. They may be of limited value against non-enveloped viruses such as 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.

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. A, B, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Active immunisation with live virus vaccines (e.g. measles, mumps or rubella) should be postponed for 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 - 4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

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
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, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000), very rare (< 1/10,000).

<table>
<thead>
<tr>
<th>System Organ Class (SOC, MedDRA)</th>
<th>Adverse Reaction</th>
<th>Frequency of ADR (MedDRA Preferred Term (PT))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity, anaphylactic shock</td>
<td>rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td>rare</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting</td>
<td>rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin reaction, erythema, pruritus</td>
<td>uncommon</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>rare</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fever, malaise, chills</td>
<td>uncommon</td>
</tr>
<tr>
<td>System Organ Class (SOC, MedDRA)</td>
<td>Adverse Reaction</td>
<td>Frequency of ADR (MedDRA Preferred Term (PT))</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>--------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>At injection site: swelling, pain, erythema, induration, warmth, pruritus, rash</td>
<td>rare</td>
</tr>
</tbody>
</table>

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

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

4.9 Overdose

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.

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 red blood cells 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 red blood cells.

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

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 red blood cells resulted in an almost complete clearance of Rh(D) positive red blood cells within 24 hours.

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-D IgG had to be first absorbed from the injection site.
On an average, 70% of injected red cells were cleared 2 hours after intravenous administration of Rhophylac. After intramuscular administration, a similar degree of red cell clearance was measured after 12 hours.

Furthermore, the efficacy, safety and pharmacokinetics of Rhophylac are supported by the results of three clinical studies in patients. Rhophylac 200 micrograms (1000 IU) were administered postpartum in 139 per protocol patients. Rhophylac 300 micrograms (1500 IU) were administered antepartum as well as postpartum in 446 and 256 per protocol patients, respectively. None of the patients included in these studies developed antibodies against the Rh(D) antigen.

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

5.2 Pharmacokinetic properties

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 recipients’s circulation and reaches a maximum after a delay of 2 - 3 days.

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

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

5.3 Preclinical safety data

There are no preclinical data of relevance for anti-D immunoglobulin. Repeated dose testing and embryo-foetal toxicity studies have not been conducted and are impracticable due to induction of, and interference with antibodies. 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 product must 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. Keep the syringe (originally blistered) in the outer carton in order to protect from light.

6.5 Nature and contents of containers

2 ml solution in a pre-filled syringe (type 1 glass) with 1 injection needle in a pack size of 1.

6.6 Special precautions for disposal and other handling

Rhophylac should be brought to room or body temperature before use. Do not use solutions which are cloudy or have deposits. Use only once (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(S)

PA 800/6/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 2003 / 20 February 2006

10. DATE OF REVISION OF THE TEXT

28 July 2011