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

Human Anti-D immunoglobulin

Each 2 ml solution in pre-filled syringe contains:
Human anti-D immunoglobulin 1500 IU (300 micrograms)
Corresponding to a concentration of 750 IU (150 micrograms) per ml

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 micrograms/ml IgA.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Pregnancy/delivery of a Rh(D)-positive baby
- Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole
- Transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (AMH), amniocentesis, chorionic biopsy or obstetric manipulative procedures e.g. external version, or abdominal trauma.

Treatment of Rh(D)-negative persons after incompatible transfusions of Rh(D)-positive blood or other products containing red blood cells

4.2 Posology and method of administration

Posology
The following dose schedules are recommended based on the clinical studies performed with Rhophylac, however consideration must be given to professional guidelines for the use of anti-D IgG in the individual EU member states.

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 at 28 - 30 weeks of gestation.

• 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. Rhophylac should be administered as soon as possible within 72 hours of delivery. The post partum dose must be given even when antepartum prophylaxis has been administered. If a large foeto-maternal haemorrhage (greater than 4 ml (0.7% - 0.8% of women)) 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 (20 micrograms/100IU for each 1 ml of foetal red blood cells).

• Prophylaxis following complications of pregnancy:
- Interventions and incidents occurring up to 12 weeks gestation: 200 micrograms (1000 IU) should be administered by intravenous or intramuscular injection as soon as possible and not later than 72 hours after the at-risk event.

- Interventions and incidents occurring after 12 weeks of gestation: at least 200 micrograms (1000 IU) should be administered by intravenous or intramuscular injection as soon as possible and not later than 72 hours after the at-risk event.

- Chorionic villus sampling: 200 micrograms (1000 IU) should be administered by intravenous or intramuscular injection as soon as possible and not later than 72 hours after the at-risk event.

Incompatible transfusions:
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 erythrocyte concentrate. The intravenous administration is recommended. If given by intramuscular administration the large doses should be applied over a period of several days. A maximum dose of 3000 micrograms 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.

Method of administration
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 (>5 ml) are required and intramuscular injection is chosen, it is advisable to administer them in divided doses at different sites.

4.3 Contraindications

Hypersensitivity to any of the components.

The intramuscular injection 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 newborn infant.

The product is not intended for use in Rh(D)-positive individuals.

Patients should be observed for at least 20 minutes after administration. If symptoms of allergic or anaphylactic type reactions occur, immediate discontinuation of the administration is required.

Allergic responses to anti-D immunoglobulin may occur. 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. If necessary, the current medical standards for shock treatment should be observed.

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.

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 HIV, HBV and HCV.
They may be of limited value against non-enveloped viruses such as HAV or parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatits 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 Interactions with other medicinal products and other forms of interactions

Interactions of Rhophylac with other treatments have not been investigated. The information given in this section is derived from the literature and current guidelines.

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- 4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing for red blood cell antibodies e.g. Coomb’s test in the neonate.

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

4.6 Pregnancy and lactation

This medicinal product is used in pregnancy.

No study drug-related adverse events were reported for the children delivered of 432 patients who received antepartum administration of Rhophylac.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

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

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

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

4.9 Overdose

No data are available on overdosage. 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. In other Rh(D)-negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Rhophylac contains specific IgG antibodies against the Rh(D) antigen of human erythrocytes. 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 women 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 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) was administered postpartum in 139 per protocol patients. Rhophylac 300 micrograms (1500 IU) was 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

Measurable levels of antibodies are obtained approximately 4 hours after intramuscular injection. Peak serum levels are usually achieved 5 days later.

Measurable levels of antibodies are obtained immediately after intravenous injection. The mean half-life in the circulation of pregnant women with normal IgG levels was 17 days. 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

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.
Store out of the reach and sight of children.

6.5 Nature and contents of containers

Glass syringe (type I glass) pre-filled with 2 ml solution for injection (1500 IU anti-D IgG).
Pack size: 1 blister pack contains 1 pre-filled syringe and 1 injection needle.

6.6 Instructions for use and handling and disposal

Rhophylac should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent. 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)

PL 15036/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 June 2006

10. DATE OF REVISION OF THE TEXT

21 September 2007