

COMPANY CORE SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rhesonativ 1250 IU, powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin ≥ 1250 IU/vial (≥ 250 μg /vial)

Human protein content 0.2 g/vial

thereof immunoglobulin G at least 95%

1 ml of the reconstituted solution contains 625 IU (125 μg) human anti-D immunoglobulin.

The content of IgA does not exceed 0.05% of the total protein content.

Rhesonativ is produced from human plasma, collected in Sweden, Finland, and at FDA-approved donation centers in USA.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection

The powder is white or slightly yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Rh immunization in Rh-negative or Rh-partial women

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

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

4.2 Posology and method of administration

Posology

1. In connection with pregnancy, child birth and gynecological interventions:

- after interruption of pregnancy, ectopic pregnancy, or hydatidiform mole:
 - before the 12th week of pregnancy: 625 IU (125 µg)
 - after the 12th week of pregnancy: 1250 IU (250 µg)
- for other indications 1250 IU (250 µg)

For postnatal use, Rhesonativ should be administered as soon as possible within 72 hours of delivery. If a large foeto-maternal hemorrhage is suspected, its extent should be determined by a suitable method and additional doses of anti-D should be administered as indicated.

Rhesonativ should be administered in connection with abortion, amniocentesis, establishment of ectopic pregnancy, or as soon as there is any reason to suspect foeto-maternal hemorrhage. In connection with abortion, induced by intra- or extra-amniotic instillation, the prophylaxis should be given within 48 hours also if the foetus has not been delivered.

2. Following a transfusion of Rh-incompatible blood:

Per 15 ml of transfused red blood cells, 1250 IU (250 µg) Rhesonativ should be administered as soon as possible within 72 hours. If required, a specialist in transfusion medicine should be consulted.

Method of administration

For intramuscular use

In case of hemorrhagic disorders where intramuscular injections are contraindicated, Rhesonativ may be administered subcutaneously. Careful manual pressure with a compress should be applied to the site after injection.

If large total doses (>5 ml) are required, it is advisable to administer them in divided doses at different sites.

4.3 Contraindications

Hypersensitivity to any of the components

4.4 Special warnings and special precautions for use

Do not inject this product intravenously (risk of shock).

In the case of postpartum use, the product is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh-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.

True hypersensitivity reactions are rare but allergic type responses to Rhesonativ may occur. 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. In case of shock, the current medical standards for shock treatment should be observed.

Viral safety

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV. Additional screening of each unit of plasma with respect to alanine aminotransferase (ALT).
- testing of plasma pools for HCV genomic material
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, HBV, HAV and parvovirus B19.

The main viral inactivation procedure is based on chemical treatment with a solvent/detergent (S/D) combination consisting of tri-(n-butyl)-phosphate (TNBP) and polysorbate 80, which specifically and completely inactivates lipid-enveloped viruses, such as HIV and hepatitis B and C viruses. In addition, removal of fraction III by a specific step in the modified Cohn ethanol fractionation process has been shown to remove significant amounts of both lipid enveloped and non-enveloped viruses. The hepatitis A and parvovirus B19 antibody content makes an important contribution to the viral safety.

In the interest of patients, it is recommended that, whenever possible, every time that Rhesonativ is administered, the name and batch number of the product is registered.

4.5 Interaction with other medicinal products and other forms of interaction

Active immunization with live virus vaccines (e.g. measles, mumps or rubella) 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.

The results of blood typing and antibody testing including the Coombs or antiglobulin test are significantly affected by the administration of anti-D immunoglobulin.

4.6 Use during pregnancy and lactation

This medicinal product is used in pregnancy.

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

Local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.

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|----------------------------|---|
| Uncommon (1/100-1/1000) | General: Transient fever (38-40°C), malaise, headache, chills Skin: Local pain and tenderness at the injection site |
| Rare (<1/1000) | General: Allergic or anaphylactic type reactions, including dyspnoea, shock, hypotension and tachycardia Skin: Cutaneous reactions Gastrointestinal: Nausea, vomiting |

For information on viral safety see 4.4.

4.9 Overdose

No data are available on overdosage. Patients with incompatible transfusion, who receive a high dose of anti-D immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of hemolytic reaction.

In other Rh-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: J06B B01.

Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rh) antigen of human erythrocytes.

5.2 Pharmacokinetic properties

Measurable levels of antibodies are obtained approximately 20 minutes after intramuscular injection. Peak serum levels are usually achieved 2 to 3 days later.

The half-life in the circulation of individuals with normal IgG levels is 3 to 4 weeks.

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

5.3 Preclinical safety data

Immunoglobulins are normal substances in the body. Toxicity studies after single doses to animals are not relevant as higher doses result in overload. Toxicity studies after repeated doses and embryotoxicity and foetotoxicity studies cannot be performed due to induction by and interference with antibodies. The effect of Rhesonativ on the immune system of neonates has not been studied.

As clinical experience gives no reason to suspect any tumorigenic or mutagenic effects of immunoglobulins, experimental studies are not considered necessary, particularly not in heterologous species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Solvent: Sterilized water for injections

6.2 Incompatibilities

Rhesonativ must not be mixed with other medicinal products.

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at 2°C-8°C. Storage at room temperature (not above 25°C) for 1 month does not affect the stability of the product.

Reconstituted Rhesonativ should not be kept above 25°C and should be used within 12 hours.

6.5 Nature and content of container

Powder:

Type I glass vial, 8 ml, stoppered with a bromobutyl rubber stopper (Ph.Eur.).

Solvent:

Type I glass ampoule, 2 ml.

6.6 Instructions for use and handling, and disposal

To dissolve the powder, the water for injections should be injected down the side of the vial to avoid the formation of foam. The vial is swirled slowly until the powder is dissolved (5-10 minutes). Shaking or handling in any way causing the solution to foam will delay dissolution. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

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

7 MARKETING AUTHORIZATION HOLDER

Local or

Octapharma AB
SE-112 75 Stockholm
Sweden

8 NUMBER(S) IN THE COUNTRY REGISTER OF MEDICINAL PRODUCTS

Local

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Local

10 DATE OF REVISION OF THE TEXT

2002-11-06