

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rhesonativ 625 IU/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin.

1 ml contains:

Human anti-D immunoglobulin 625 IU (125 micrograms)

Human protein content: 165 mg

there of immunoglobulin G, at least 95%

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

One ampoule of 1 ml contains 625 IU (125 micrograms) of human anti-D immunoglobulin.

One ampoule of 2 ml contains 1250 IU (250 micrograms) of human anti-D immunoglobulin.

The potency is determined using the European Pharmacopoeia assay. The equivalence in International Units of the International Reference Preparation is stated by the World Health Organization.

Distribution of the IgG subclasses (approx. values):

IgG1 70.5%

IgG2 26.0%

IgG3 2.8%

IgG4 0,8%

The maximum IgA content is 82.5 micrograms/ml.

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The colour of the solution can vary from colourless to pale-yellow up to light brown.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of Rh(D) immunisation in Rh(D) negative childbearing age women.

- **Antenatal prophylaxis**

- Planned antenatal prophylaxis
- Antenatal prophylaxis following complications of pregnancy including Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole, intrauterine fetal death (IUFD), transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (APH), amniocentesis, chorionic biopsy, obstetric manipulative procedures, e.g. external version, invasive interventions, cordocentesis, blunt abdominal trauma or fetal therapeutic intervention.

- **Postnatal prophylaxis**

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

Treatment of Rh(D) negative childbearing age women 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 Rhesonativ.

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

- *Antenatal prophylaxis.* According to general recommendations, currently administered doses range from 50 – 330 micrograms or 250 - 1650 IU.

- Planned antenatal prophylaxi:

A single dose (e.g. 250 micrograms or 1250 IU) at 28 - 30 weeks of gestation or two doses at 28 and 34 weeks.

- Antenatal prophylaxis following complications of pregnancy:

A single dose (e.g. 125 micrograms or 625 IU before the 12th week of pregnancy) (e.g. 250 micrograms or 1250 IU after the 12th week of pregnancy) should be administered as soon as possible and within 72 hours and if necessary repeated at 6 – 12 week intervals throughout the pregnancy.

After amniocentesis and chorionic biopsy a single dose (e.g. 250 micrograms or 1250 IU) should be administered.

- *Postnatal prophylaxis.* According to general recommendations, currently administered doses range from 100 – 300 micrograms or 500 – 1500 IU. For specific study details see section 5.1. If the lower dose (100 micrograms or 500 IU) is administered then testing of the amount of fetal maternal haemorrhage should be performed.

Standard dose: 1250 IU (250 micrograms).

For postnatal use, the product should be administered to the mother as soon as possible within 72 hours of delivery of an Rh 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 postnatal dose must still be given even when antenatal prophylaxis has been administered and even if residual activity from antenatal prophylaxis can be demonstrated in maternal serum.

If a large feto-maternal haemorrhage (> 4 ml (0.7%-0.8% of women)) is suspected, e.g. in the event of fetal/neonatal anaemia or intrauterine fetal death, its extent should be determined by a suitable method e.g. Kleihauer-Betke acid elution test to detect fetal HbF or flow cytometry which specifically identifies Rh D positive cells. Additional doses of anti-D immunoglobulin should be administered accordingly (10 micrograms or 50 IU) per 0.5 ml fetal red blood cells.

Incompatible transfusions of red blood cells (RBCs)

The recommended dose is 20 micrograms (100 IU) anti-D immunoglobulin per 2ml of transfused Rh (D) positive blood or per 1 ml of RBC concentrate. It is recommended the consultation with a specialist in transfusion medicine in order to evaluate the feasibility of a red cell exchange procedure to reduce the load of D positive red cells in circulation and to define dose of anti-D immunoglobulin required to suppress immunisation. Follow-up tests for D positive red cells should be undertaken every 48 hours and further anti-D given until there are no detectable D positive red cells in circulation. In any case, due to possible risk of haemolysis it is suggested to not exceed a maximum dose of 3000 micrograms (15000 IU).

The use of an alternative intravenous product is recommended as it will achieve adequate plasma levels immediately. If no intravenous product is available, the very large volume should be administered intramuscularly over a period of several days (see section 4.4).

Paediatric population

The safety and efficacy in children has not yet been established.

Overweight patients

In case of overweight/obese patients the use of an intravenous anti-D product should be considered (see section 4.4).

Method of administration

Intramuscular use.

If large total doses (>2 ml for children or >5 ml for adults) are required, it is advisable to administer them in divided doses at different injection sites.

If intramuscular administration is contraindicated (bleeding disorders), an alternative intravenous product should be used. The injection can be administered subcutaneously if no intravenous product is available. Careful manual pressure with a compress should be applied to the site after injection.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1. Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

4.4 Special warnings and precautions for use

Ensure that Rhesonativ is not administered into a blood vessel, because of the risk of shock. Injections have to be given intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

In the case of postnatal 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.

Patients should be observed for at least 20 minutes after administration and for at least 1 hour after an accidental intravenous injection.

Hypersensitivity

True hypersensitivity reactions are rare but allergic type 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.

Rhesonativ contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully in 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 Rhesonativ 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.

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.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Although thromboembolic events have not been observed for Rhesonativ, patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity) especially when higher doses of Rhesonativ are prescribed.

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

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, for example the antiglobulin test (Coombs' test) particularly in Rh(D) positive neonates whose mothers have received antenatal prophylaxis.

Overweight/obese patients

In overweight/obese patients, due to the possible lack of efficacy in case of intramuscular administration, an intravenous anti-D product is recommended.

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), and for the non-enveloped virus hepatitis A virus (HAV).

The measures taken may be of limited value against non-enveloped viruses such as 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 Rhesonativ 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.

Important information about some of the ingredients of Rhesonativ

This medicine contains less than 1 mmol sodium (23 mg) per 1 mL (625 IU), that is to say essentially 'sodium-free'.

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 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

Pregnancy

This medicinal product is intended for use in pregnancy.

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 more than 450 women who received postpartum administration of Rhesonativ.

Fertility

No animal fertility studies have been conducted with Rhesonativ. Clinical experience with human anti-D immunoglobulin suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effectsSummary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at injection sites: swelling, soreness, redness, induration, local heat, itching, bruising, local pain, tenderness and rash, some of these reactions can be prevented by dividing larger doses over several injection sites.

For safety with respect to transmissible agents, see 4.4.

There are no robust data on the frequency of adverse reactions from clinical trials. The following adverse reactions have been reported:

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Haemolytic reaction	not known
Immune system disorders	Anaphylactic shock, anaphylactic/anaphylactoid reaction, hypersensitivity	not known
Nervous system disorders	Headache	not known
Cardiac disorders	Tachycardia	not known
Vascular disorders	Hypotension	not known
Respiratory, thoracic and mediastinal disorders	Wheezing	not known
Gastrointestinal disorders	Vomiting, nausea	not known
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching, pruritus, urticaria	not known

Musculoskeletal and connective tissue disorders	Arthralgia	not known
General disorders and administration site conditions	Pyrexia, chest discomfort, malaise, chills, At the injection site: swelling, pain, erythema, induration, warmth, pruritus, rash, itching	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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Consequences of an overdose are not known. Patients in receipt of incompatible transfusion, who receive very large doses 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, immunoglobulins, specific immunoglobulins:
- anti-D (Rh) immunoglobulin,

ATC code: J06BB01

Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rh) 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 fetus 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 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 soon enough after exposure to Rh(D)-positive fetal 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.

Studies in Patients with Postpartum Prophylaxis (Study 1-6) and in Patients with Antenatal Prophylaxis (Study 7)

Clinical trials with Rhesonativ were initiated with the aim to evaluate the efficacy and safety of the product. The following table provides an overview on the most important findings in terms of efficacy:

Study ID	Indication, No. of Subjects	Rh Status Mother / Child	Incidence of Anti-D Antibodies	Time of Follow-up
1	PPP, n=1,937	negative/positive	0.4%	6 months
2	PPP, n=2,117 PPP, n=723	negative/positive subsequent positive child	0.1% 0.7%	4-6 months; at next pregnancy or delivery
3	PPP, n=917	negative/positive	0.3%	6 months
4	PPP, n=665	negative/positive	0.2%	6 months
5	PPP, n=608	negative/positive	0.3%	6-8 months

	ANP*, n=103		0%	8 months
6	PPP, n=475	negative/positive	0%	n.r.
7	ANP* & PPP, n=529	negative/positive	0.4%	8 months

PPP: postpartum prophylaxis; ANP: antenatal prophylaxis; n.r.: not reported

* 6-8 weeks before expected date of delivery.

From these studies it can be reasonably concluded that treatment with Rhesonativ provides effective anti-D prophylaxis.

Study in Rh-incompatible blood components

Study 8 assessed the efficacy of Rhesonativ in 21 Rh-negative volunteers who were injected with Rh-positive, ABO-compatible fetal red cells in amounts corresponding to 10 mL cord blood (1 case), 25 mL (10 cases) and 50 mL (10 cases). Two to 3 days later 260 micrograms of Rhesonativ were given intramuscularly. Six months (in 1 case 9 months) after the start of the experiment no serologic evidence for Rh-immunization was found in any individual. Six months to 2.5 years later, 8 subjects of the 25 mL group and all 10 subjects of the 50 mL group received 5 mL Rh-positive, ABO-compatible cord blood. After 2 to 3 days, 260 respectively 333 micrograms Rhesonativ were injected. After another 6 months (in 1 case after 8 months) no Rh-antibodies were detected in any subject.

From these experimental findings it was concluded that Rh-prophylaxis is achieved with 10 micrograms of anti-D immunoglobulin per mL of fetal blood. It was concluded that, as far as Rh-immunization due to fetomaternal haemorrhage at the end of the pregnancy is concerned, a dose of 260 micrograms Rhesonativ prevents serologically detectable Rh-immunisation in at least 998 Rh-negative mothers out of a thousand.

Pharmacokinetic Study with Rhesonativ

The basic pharmacokinetics and turnover of Rhesonativ were investigated in fifteen Rh- negative pregnant women who were given Rhesonativ intramuscularly at 28 weeks' gestation. The doses were 125 micrograms in 8 and 250 micrograms in 7 of the women. In addition three non-pregnant Rh- negative women were given the smaller dose.

The biological half life of anti-D IgG after an intramuscular injection of 125 microgram in these women was in line with what could be expected from the literature (see section 5.2).

5.2 Pharmacokinetic properties

Human anti-D immunoglobulin for intramuscular administration is slowly absorbed into the recipient'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 nonclinical safety data for human anti-D immunoglobulin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium chloride
Sodium acetate
Polysorbate 80
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

30 months.

The content of an opened ampoule should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2° C - 8°C). Keep the ampoule in the outer carton in order to protect from light. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml and 2 ml of solution in an ampoule (type I glass).

Pack sizes: 1x1 ml, 1x2 ml and 10x2 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.

The colour can vary from colourless to pale-yellow up to light-brown. Do not use solutions that are cloudy or have deposits.

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

7 MARKETING AUTHORISATION HOLDER

Octapharma (IP) SPRL
Allée de la Recherche 65
1070 Anderlecht
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2219/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st January 2012

10 DATE OF REVISION OF THE TEXT

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