

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS (INSTRUCTIONS FOR USE)

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 µg)
Human protein content	165 mg
thereof 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 µg) of human anti-D immunoglobulin.

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

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 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**
 - Pregnancy/delivery of a Rh(D) positive (D, D^{weak}, D^{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 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. For specific study details see Section 5.1.
 - **Planned antenatal prophylaxis:**

A single dose (e.g. 250 µg 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 µg or 625 IU before the 12th week of pregnancy) (e.g. 250 µg 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. 250µg or 1250 IU) should be administered.
- **Postpartum 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 µg).

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 post partum dose must still be given even when antepartum 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. 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 red blood cells.

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

Paediatric population

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

Method of administration**For intramuscular use.**

If a large volume (>2 ml for children or >5 ml for adults) is required, it is recommended to administer this in divided doses at different sites.

If intramuscular administration is contra-indicated (bleeding disorders), 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.

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 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.

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

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.

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of

immunoglobulins. Thromboembolic events have not been observed for Rhesonativ which may be due to the low doses commonly used. Caution should be exercised in patients with preexisting risk factors for thrombotic events (such as advanced age, 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.

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 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 blood components containing IgA. The physician must therefore weigh the benefit of treatment with Rhesonativ against the potential risks of hypersensitivity 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.

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, and for the non-enveloped 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.

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 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

Pregnancy

This medicinal product is intended for use in pregnancy.

Fertility

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

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 by more than 450 women who received standard doses of Rhesonativ in the postpartum period.

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.

For safety with respect to transmissible agents, see 4.4.

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

MedDRA Standard System Organ Class	Undesirable effects
Blood and lymphatic system disorders	Haemolytic reaction
Immune system disorders	Anaphylactic shock, anaphylactic/anaphylactoid reaction, hypersensitivity
Nervous system disorders	Headache
Cardiac disorders	Tachycardia
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Wheezing

MedDRA Standard System Organ Class	Undesirable effects
Gastrointestinal disorders	Vomiting, nausea
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching, pruritus, urticaria
Musculoskeletal and connective tissue disorders	Arthralgia
General disorders and administration site conditions	Pyrexia, chest discomfort, malaise, chills, injection site reaction (i.e. swelling, pain, erythema, induration, warmth, pruritus, rash)

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.

4.9 Overdose

Consequences of an overdose are not known. 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.

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.

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

During pregnancy, and especially at the time of childbirth, fetal 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 ANP*, n=103	negative/positive	0.3% 0%	6-8 months 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 Transfusion of 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 µg 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 µg 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 µg 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 µg 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 µg in 8 and 250 µg 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 µg in these women was in line with what could be expected from the literature (see section 5.2).

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.

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). Do not freeze. Keep the ampoule in the outer carton in order to protect from light. Within its shelf-life, the product may be stored below 25 °C for up to 1 months, without being refrigerated again during this period, and must be discarded if not used after this.

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 AG
Seidenstrasse 2
CH-8853 Lachen
Switzerland

8 MANUFACTURER

OCTAPHARMA AB
SE- 1275 Stockholm
Sweden

9 DATE OF REVISION OF THE TEXT

07/2015

SUMMARY OF PRODUCT CHARACTERISTICS (INSTRUCTIONS FOR USE)

1 NAME OF THE MEDICINAL PRODUCT

Rhesonativ 750 IU/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin.

1 ml contains:

Human anti-D immunoglobulin	750 IU (150 µg)
Human protein content	165 mg
thereof immunoglobulin G, at least	95%

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

One ampoule of 2 ml contains 1500 IU (300 µg) of human anti-D immunoglobulin.

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 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**
 - Pregnancy/delivery of a Rh(D) positive (D, D^{weak}, D^{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 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. For specific study details see Section 5.1.
 - Planned antenatal prophylaxis:

A single dose (e.g. 300 µg or 1500 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. 150 µg or 750 IU before the 12th week of pregnancy) (e.g. 300 µg or 1500 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. 300µg or 1500 IU) should be administered.
- **Postpartum 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: 1500 IU (300 µg).

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

If a large fetomaternal 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. 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 red blood cells.

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

Paediatric population

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

Method of administration**For intramuscular use.**

If a large volume (>2 ml for children or >5 ml for adults) is required, it is recommended to administer this in divided doses at different sites.

If intramuscular administration is contra-indicated (bleeding disorders), 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.

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 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.

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

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.

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 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 blood components containing IgA. The physician must therefore weigh the benefit of treatment with Rhesonativ against the potential risks of hypersensitivity 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.

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, and for the non-enveloped 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.

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 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

Pregnancy

This medicinal product is intended for use in pregnancy.

Fertility

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

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 by more than 450 women who received standard doses of Rhesonativ in the postpartum period.

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.

For safety with respect to transmissible agents, see 4.4.

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

MedDRA Standard System Organ Class	Undesirable effects
Immune system disorders	Anaphylactic shock, anaphylactic/anaphylactoid reaction, hypersensitivity
Nervous system disorders	Headache
Cardiac disorders	Tachycardia
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Wheezing
Gastrointestinal disorders	Vomiting, nausea
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching, pruritus, urticaria
Musculoskeletal and connective tissue disorders	Arthralgia

MedDRA Standard System Organ Class	Undesirable effects
General disorders and administration site conditions	Pyrexia, chest discomfort, malaise, chills, injection site reaction (i.e. swelling, pain, erythema, induration, warmth, pruritus, rash)
Injury, poisoning and procedural complications	Haemolytic reactions

4.9 Overdose

Consequences of an overdose are not known. 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.

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.

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

During pregnancy, and especially at the time of childbirth, fetal 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
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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 Transfusion of 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 µg 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 µg 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 µg 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 µg 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 µg in 8 and 250 µg 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 µg in these women was in line with what could be expected from the literature (see section 5.2).

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.

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). Do not freeze. Keep the ampoule in the outer carton in order to protect from light. Within its shelf-life, the product may be stored below 25 °C for up to 1 month, without being refrigerated again during this period, and must be discarded if not used after this.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack sizes: 1x2 ml and 5x2 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

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8 MANUFACTURER

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9 DATE OF REVISION OF THE TEXT

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