

(English translation of official Dutch version)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RheDQuin 375 IU solution for injection
RheDQuin 1000 IU solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin prepared from plasma of human donors.

The product contains 100 - 180 grams of protein per litre. The protein fraction consists of at least 90% immunoglobulin G (IgG). The maximal IgA content is 6 g/l.

RheDQuin is supplied in quantities of 1000 IU (at least 400 IU human anti-D immunoglobulin per ml) and 375 IU (at least 150 IU human anti-D immunoglobulin per ml).

For the complete listing of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection for intramuscular administration.

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
 - Delivery of a Rh(D) positive (D, D^{weak}, D^{partial}) baby or of a baby of which the rhesus (D)-factor is unknown.

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. Also after organ or tissue transplant, in particular of a kidney or of bone tissue, from a rhesus (D) positive donor.

4.2 Posology and method of administration

Posology

The anti-D immunoglobulin dose should be determined based upon the exposure to Rh(D) positive
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erythrocytes and in the knowledge that 0.5 ml Rh(D) positive erythrocyte concentrate or 1.0 ml Rh(D) positive blood is neutralized by approximately 50 IE anti-D immunoglobulin.

Posology

a) 1000 IU RheDQuin is administered in the following situations to rhesus (D) negative women:

1. after the birth of a rhesus (D) positive child.

N.B.: In the event of substantial foetomaternal haemorrhaging more than 20 ml, the standard dose of 1000 IU must be **supplemented** with 50 IU of Anti-Rhesus (D) Immunoglobuline for each millilitre of foetal blood lost in excess of 20 ml.

2. after external version of a breech presentation;

3. after amniocentesis from the 26th week of pregnancy;

4. after spontaneous or provoked abortion from the 20th week;

5. as antenatal prophylaxis during the 30th week;

6. in puncture of the umbilical cord.

b) 375 IU RheDQuin is administered in the following situations to rhesus (D) negative women:

1. after abortion before the 20th week;

2. after amniocentesis before the 26th week of pregnancy;

3. after termination of an extra-uterine pregnancy;

4. in hydatid mole;

5. in chorionic villus biopsy.

c) in the following indications or if a large foetomaternal haemorrhage is suspected the dose should be derived from the amount of foetal blood in the maternal circulation:

1. after massive transplacental haemorrhage (blow to the abdomen causing trauma);

2. caesarean section, multiple pregnancy, foetal death, manual removal of the placenta, after the birth of an anaemic baby, at fundus expression.

To c): The amount of foetal blood in the maternal circulation is estimated with the Kleistenhauer test or another appropriate test such as the flow cytometric detection of rhesus D positive erythrocytes. The dose of RheDQuin is 50 IU per ml of foetal blood or 100 IU per ml of foetal erythrocytes.

To a), b) and c):

1. 1000 IU of RheDQuin should always be administered after the birth of a rhesus (D) positive child, i.e. even if RheDQuin has already been administered during the pregnancy after an incident or intervention.

2. RheDQuin is only indicated in rhesus (D) negative women who have not yet developed rhesus (D) antibodies.

d)

1. after incompatible blood transfusion with rhesus (D) positive blood the recommended dose is 100 IU per ml of erythrocytes transfused. The dose should be discussed with a physician specialized in blood transfusion.

Control on the presence of rhesus (D) positive erythrocytes should take place every 48 hours and further anti-D immunoglobulin should be administered until this control becomes negative.

In case over 300 ml incompatible rhesus (D) positive erythrocytes concentrate has been transfused, a maximum dose of 15000 IE is sufficient.

The use of an alternative intravenous product is recommended as it will reach the plasma immediately. If no intravenous product is available, it is recommended to spread the administration of a large volume over a period of several days.

2. after administration of rhesus (D) positive thrombocytes to a rhesus (D)-negative person.

Dose: 375 IU RheDQuin

e) after transplantation of a rhesus (D)-positive kidney or rhesus (D)-positive bone tissue in a rhesus (D)-negative person 375 IU RheDQuin must be administered.

Administration should be carried out as soon as possible, but no more than 48 hours after the birth, incident or intervention takes place. If RheDQuin is administered later, it is doubtful whether the treatment will still lead to the desired result. Nevertheless, administration of the product up to 14 days after the birth or operation is still advisable. Administration is not worthwhile after this time.

Method of administration

RheDQuin should be administered slowly as a deep intramuscular injection.

It is recommended that the product be warmed to body temperature before administration.

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

If intramuscular administration is contra-indicated (bleeding disorders), the injection can be administered subcutaneously **if no intravenous product is available (see section “4.4 Special warnings and special precautions for use”)**.

4.3 Contra-indications

Hypersensitivity to **the product or** any of the components.

Hypersensitivity to human immunoglobulins.

For more information related to hypersensitivity, see section 4.4.

4.4 Special warnings and special precautions for use

The product is not suitable for intravenous administration.

The product is neither intended for use in Rh(D) positive women nor for women already immunised to Rh(D) antigen.

Ensure that RheDQuin is not administered into a blood vessel, because of the risk of shock.

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

Subcutaneous administration of the product can be considered for patients with severe thrombocytopenia or haemorrhagic diathesis. It should be noted that no tests have been carried out to ascertain whether the action of the product in preventing immunisation against the rhesus (D) antigen is guaranteed by this route of administration.

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.

The patient must be kept under observation for at least 20 minutes after administration.

Patients in receipt of incompatible Rh(D) positive erythrocyte transfusion, who receive very large doses of anti-D immunoglobulin are at risk of haemolytic reaction. Therefore, there should be accurate clinical monitoring, haemolysis parameters should be determined (urine control for chromaturia (discoloration of the urine) and haemoglobinuria; reticulocyte count in the blood; serum monitoring of haptoglobin, bilirubin, LDH, haemoglobin) and renal function should be monitored.

RheDQuin should be administered to the mother after childbirth, not to the child. If this nevertheless happens rhesus (D)-positive erythrocytes of the child will be sensitised by the administered RheDQuin, by which haemolysis may appear.

Foetal maternal transfusion and immunisation may occur after spontaneous abortion. However, when no instrumentation (curettage) takes place, this risk before week 10 of pregnancy is so small that in this case no RheDQuin needs to be administered to the rhesus (D)-negative woman. With instrumentation, and after week 10 RheDQuin does need to be administered.

Administration of RheDQuin in week 30 influences laboratory diagnostics in regard to rhesus (D) serology. The antibody screening at the mother becomes positive and the child's antiglobin test becomes positive, while there is no degradation of red blood cells. This is just a temporary phenomenon. Administration of the product in week 30 therefore should take place after blood has been taken for the screening of rhesus (D) antibodies.

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 RheDQuin, patients should be sufficiently hydrated before use of immunoglobulins. 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 RheDQuin 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.

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 hepatitis A virus. 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. It is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that RheDQuin 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 Interaction with other medicinal products and other forms of interaction

Live attenuated 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. In case administration is nevertheless essential, revaccination should be performed three months after the administration of RheDQuin.

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, Rh(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 anti-D prophylaxis.

4.6 Pregnancy and lactation

This medicinal product is intended for use in pregnancy.

4.7 Effects on ability to drive and use machines

There are no indications that immunoglobulins may impair the ability to drive or use machines.

4.8 Undesirable effects

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	Frequency
Immune system disorders	Hypersensitivity reactions, anaphylactic reactions including shock*	Rare
Nervous system disorders	Headache	Rare
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous tissue disorders	Skin reaction, erythema, pruritus	Rare
Musculoskeletal and connective tissue	Arthralgia	Rare

After intramuscular administration the immunoglobulin administered to the patient is gradually released from the intramuscular depot into the circulation. The maximum level is achieved after two to three 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

Immunoglobulins are normal constituents of the human body. Animal experiments about the toxicity of a single administration are not relevant, since over dosage occurs at higher doses. Research about toxicity following repeated administration, and about toxicity for the embryo or fetus is not feasible due to induction of, and disturbance by, antibodies. No research has been carried out regarding the effects of the product on the immune system of neonates.

Given that clinical trials have not shown any evidence of a carcinogenic or mutagenic effect of immunoglobulins, experimental research, especially in heterological species, is considered unnecessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, water for injections.

6.2 Incompatibilities

Given the lack of investigation on incompatibilities, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

The product should be used immediately after piercing the vial.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

375 IU and 1000 IU in colourless, glass vials (glass type I) fitted with a bromobutyl rubber stopper and sealed with an aluminium cap.

6.6 Instructions for disposal and other instructions

It is recommended that the product is brought to body temperature before administration.

During the storage period a slight cloudiness or formation of a small amount of deposits might occur. This is no impediment for clinical use.

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

7. MARKETING AUTHORISATION HOLDER

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the Netherlands

8. MARKETING AUTHORISATION NUMBER

RVG 16928 (375 IU)
RVG 16929 (1000 IU).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 1997

10. DATE OF REVISION OF THE TEXT

02 September 2016