(English translation of official Dutch version)

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Human anti-D immunoglobulin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- Do you get any side effects that are mentioned in section 4? Or, do you get a side effect that is not mentioned in this package leaflet? Talk to your doctor, pharmacist or nurse.

What is in this leaflet:

1. What is this product used for?
2. What you need to know before you use this product
3. How to use this product?
4. Possible side effects
5. How to store this product?
6. Contents of the pack and other information

1. WHAT IS THIS PRODUCT USED FOR?

RheDQuin is a solution for injection which contains the protein “human anti-rhesus (D) immunoglobulin" (human rhesus (D)-antibody). Immunoglobulins are antibodies and normal constituents of human blood and they protect you against infections. This involves an immunoglobulin G (= IgG) antibody that is active against the rhesus (D)-factor. The maximum IgA content is 6 g/l.

RheDQuin is given in certain circumstances to rhesus (D)-negative women in order to prevent the women from producing antibodies against the so-called “rhesus (D) factor”. The rhesus (D)-factor is a normal occurring characteristic of the red blood cells. If you have this characteristic, you are rhesus (D)-positive. If you do not have this characteristic, you are rhesus (D)-negative. The rhesus (D)-factor plays an important role in blood transfusions, organ transplants and in pregnancy.

You are rhesus (D)-negative and pregnant with a rhesus (D)-positive baby:

There is a small risk that some of the baby’s blood enters the mother’s bloodstream during pregnancy. The risk is largest at childbirth. When blood from a rhesus (D)-positive baby enters the bloodstream of a rhesus (D)-negative mother, the mother may produce antibodies against the rhesus (D)-factor. The rhesus (D)-antibodies are mostly formed after childbirth. Therefore, the risk that problems will occur with the first child is very small. The rhesus (D)-antibodies may, in a subsequent pregnancy, reach the blood of the (unborn) baby through the umbilical cord and break down the red blood cells, thus causing the baby to take ill (a so-called “rhesus-baby”).

Preventing you from having a rhesus-baby:

Your rhesus (D)-factor will be determined around the 12th week of pregnancy. If in week 12 you appear to be rhesus (D)-negative, then your blood will be investigated in week 27 for rhesus (D)-antibodies, and the rhesus (D)-factor of your unborn baby will be determined. If you have not produced rhesus (D)-antibodies, and your unborn baby is rhesus (D)-positive, then you will receive an injection with RheDQuin within one week. The injection greatly reduces the risk that you will produce antibodies against the baby’s rhesus (D)-factor.
If your child is rhesus (D)-positive, you will receive another injection with RheDQuin within 48 hours after childbirth. In this case, your body will not produce antibodies, because the baby’s rhesus (D)-positive red blood cells that enter the mother’s blood are immediately destroyed. This is important for a possible following pregnancy with a rhesus (D)-positive child.

You will also receive (extra) RheDQuin in a number of special obstetric situations.

You are rhesus (D)-negative and you have had a transfusion with rhesus (D)-positive blood or rhesus (D)-positive blood platelets:
Or
You are rhesus (D)-negative and you have had a kidney or bone tissue transplant from a rhesus (D)-positive donor:

If you are rhesus (D)-negative and you have had a blood transfusion with rhesus (D)-positive blood or with rhesus (D)-positive blood platelets (blood substances that play a role in coagulation), it is necessary to administer RheDQuin to you. This is to prevent you from producing antibodies against the rhesus (D)-factor. In case of future pregnancy with a rhesus (D)-positive baby, these rhesus (D)-antibodies may reach the blood of the (unborn) baby through the umbilical cord and break down the baby's red blood cells. This will cause the baby to take ill (a so-called "rhesus-baby"). The administration of RheDQuin prevents you from having a rhesus-baby in the future. This is also appropriate whenever you have had a transplant of a rhesus (D)-positive kidney or rhesus (D)-positive bone tissue.

Consult your obstetrician, physician or pharmacist for further detailed information.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE THIS PRODUCT

Do not use this product:

If you are allergic (hypersensitive) to immunoglobulins or any of the other ingredients of RheDQuin. You can find these ingredients in section 6.

In case of an allergic reaction the administration of RheDQuin should be discontinued immediately.

The product is not suitable for intravenous administration (administration into a vein).

Warnings and precautions

For side effects you can consult section 4 of this package leaflet.

Thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins.
Contact you doctor immediately if you experience symptoms like shortness of breath, chest pain, pain and swelling of a limb, weakness or numbness on one side of your body after administration of RheDQuin.

Other medicines and RheDQuin

Do not mix RheDQuin with other medicinal products.

Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines.

Vaccination
Tell your doctor if you have been vaccinated in the past 3 to 4 weeks, or will shortly be vaccinated (within 3 months after administration of RheDQuin). RheDQuin might impair the efficacy of vaccines, such as measles, rubella (German measles), mumps and varicella (chicken pox). After using RheDQuin an interval of at least three months should elapse before vaccination with any of these vaccines.

Effects on blood tests

The use of RheDQuin may influence the results of certain blood tests.

RhedQuin with food, drink and alcohol?

No effects of food, drink and alcohol on the use of RhedQuin are known.

Pregnancy and breast-feeding

This medicinal product is intended for use in pregnancy.

Driving and using machines

No effects on the ability to drive or operate machinery have been observed.

Special warnings and precautions for use

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These measures include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of RheDQuin the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Excipients

The product contains the following excipients: glycine and water for injections.

3. HOW TO USE THIS PRODUCT?

Administration

RheDQuin should be performed by a physician or obstetrician to the mother. RheDQuin must be injected deep into the muscle (intramuscular). The injection will generally be given in the upper arm or buttock. 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 injections sites.

The administration of RheDQuin must be carried out as soon as possible, within 48 hours after childbirth, the incident or the intervention. Efficacy cannot be guaranteed if the product is administered at a later point in time. Nevertheless, administration of the product up to 14 days after the birth or intervention is still advisable. Administration is not worthwhile after this time.

The product may not be too cold when it is administered. It is recommended to bring the product to body temperature before administration.

The product can be administered underneath the skin (subcutaneous) in patients with a seriously lowered number of blood platelets (blood substances that play a role in coagulation) or with an special tendency towards spontaneous, sometimes long lasting, haemorrhages. The effectiveness of the product cannot be guaranteed in this case. If rhesus (D)-positive blood platelets (blood substances that play a role in coagulation) are administered, the physician may administer the RheDQuin underneath the skin (subcutaneous). This is because these patients have an elevated tendency towards haemorrhage.

RheDQuin must be administered to the mother, not to the child, after childbirth. If RheDQuin is nonetheless administered to the child, the product can break down the child's rhesus (D)-positive red blood cells.
After you have had a miscarriage, blood from the unborn child can find its way into your blood and you may form antibodies against the rhesus (D)-factor. This risk is small with a miscarriage before the 10th week of pregnancy, where no curettage has taken place. In that case, no RheDQuin needs to be administered to you.
If you had a miscarriage after week 10 and curettage has taken place, then you will receive RheDQuin.
The administration of RheDQuin in week 30 can influence the result of the rhesus (D)-antibody test in blood. Therefore, the administration of RheDQuin in week 30 will occur, after blood has been taken from you in order to see if your body itself has produced antibodies against the rhesus (D)-factor.

Dosage
The dosage is determined by a physician or obstetrician. The appropriate dose in case of a transfusion is determined by your physician based on blood results.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions are rare. In case of a very severe hypersensitivity reaction (anaphylactic shock), administration must be discontinued immediately and standard medical treatment for the reaction must be given.

The following side effects are possible: pain/sensitivity, swelling, redness, induration, local heat, itching and rash at the site of injection.
Rare side effects are: fever, nausea, vomiting, fall in blood pressure, increased heart rate (tachycardia), malaise, chills, hypersensitivity reactions, headache, arthralgia, skin reaction and itching and redness of the skin.

The risk of transfer of pathogens through the use of a blood product is exceptionally small.

Reporting side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE THIS PRODUCT?

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the container in the outer carton in order to protect from light.

Keep this medicine out of the sight and reach of children.

Do not use RheDQuin after the expiry date which is stated on the carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist what to do with medicines you no longer use. It will then be destroyed in a responsible way and will not end up in the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What RheDQuin contains

- The active substance is human anti-rhesus(D) immunoglobulin
- The other ingredients in this medicine are glycine and water for injections

What RheDQuin looks like and contents of the pack

RheDQuin is a clear solution. The colour of the solution can vary from colourless or light yellow to light brown.

The commercial package of RheDQuin consists of a box containing:
- A vial RheDQuin of 375 IU or 1000 IU.

The product is supplied as solution for injection for intramuscular use (for injection into the muscles).

Marketing authorisation holder and manufacturer

Sanquin Plasma Products B.V., Plesmanlaan 125, 1066 CX Amsterdam, the Nederlands, tel. 020 - 512 3355

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

This leaflet was last approved in September 2016.

The following information is intended for healthcare professionals only:

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).

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.

Posology

The anti-D immunoglobulin dose should be determined based upon the exposure to Rh(D) positive 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").**

Contra-indications

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

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 reaction 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.

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

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 antiglobinetest 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.

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.

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.

List of excipients

Glycine, water for injections.

Incompatibilities

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

Shelf life

2 years.
The product should be used immediately after piercing the vial.

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.

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.

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.