RHO-D KAMADA

Summary of Product Characteristics |

1. NAME OF THE MEDICINAL PRODUCT

Rho-D Kamada

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Anti-D immunoglobulins 150 micrograms/ml, solution for injection:

1%-6% Human protein content of which at least 95% is IgG.

Each 2 ml vial contains 1500 IU* human anti-D immunoglobulin.

Each 1.7 ml vial contains approximately 1275 IU* human anti-D immunoglobulin.

Each 1 ml vial contains approximately 750 IU* human anti-D immunoglobulin.

Each 0.85 ml vial contains approximately 637.5 IU* human anti-D immunoglobulin.

One ml contains at least 750 IU human anti-D immunoglobulin.

*100 micrograms of human anti-D immunoglobulin correspond to 500 international units (IU).

The potency is determined using in house method which is based on 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…….54-68%

IgG2……23-41%

IgG3…….5-8%

IgG4…….0.1-0.4%

The IgA content is not more than 100 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 solution is clear to slightly opalescent, and colorless to pale yellow. May contain some protein particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Pregnancy/Other Obstetric Conditions:

Suppression of Rh immunization in non-sensitized Rho (D) negative women delivering a Rho positive baby, or when the baby's Rh type is unknown.

Suppression of Rh immunization after spontaneous or induced abortions, threatened abortion associated with maternal bleeding, amniocentesis, chorionic villus sampling, ruptured tubal pregnancy, and significant abdominal trauma.

Transfusion

Suppression of Rh isoimmunization in Rho (D) antigen-negative patients transfused with Rho (D) antigen-positive RBCs or blood components containing Rho (D) antigen-positive RBCs.

4.2. Posology and method of administration

Posology

Rho-D Kamada must be administered intramuscularly only.

Pregnancy

A 1,500 IU (300 micrograms) dose of Rho-D Kamada should be administered at 28 weeks gestation. If Rho-D Kamada is administered early in the pregnancy, it is recommended that Rho-D Kamada be administered at 12-week intervals in order to maintain an adequate level of passively acquired anti- Rh. A 600 IU (120 micrograms) dose should be administered as soon as possible after delivery of a confirmed Rho (D) positive baby and normally no later than 72 hours after delivery. In the event that the Rh status of the baby is not known at 72 hours, Rho-D Kamada should be administered to the mother at 72 hours after delivery. If more than 72 hours have elapsed, Rho-D Kamada should not be withheld, but administered as soon as possible up to 28 days after delivery.

Other Obstetric Conditions

A 600 IU (120 micrograms) dose of Rho-D Kamada should be administered immediately after abortion, amniocentesis (after 34 weeks gestation) or any other manipulation late in pregnancy (after 34 weeks gestation) associated with increased risk of Rh isoimmunization. Administration should take place within 72 hours after the event.

A 1,500 IU (300 micrograms) dose of Rho-D Kamada should be administered immediately after amniocentesis before 34 weeks gestation or after chorionic villus sampling. This dose should be repeated every 12 weeks while the woman is pregnant. In case of threatened abortion, Rho-D Kamada should be administered as soon as possible.

Transfusion

Rho-D Kamada should be administered within 72 hours after exposure to treatment of incompatible blood transfusions or massive fetal hemorrhage as outlined in the table below:

Route of Administration	Dose and Frequency	Rho-D Kamada Dosage	
		Rh+ Blood	Rh + Red Cells
Intramuscular	6,000 IU (1,200 micrograms) every 12 hours until total dose administered	60 IU (12 micrograms)/ml blood	120 IU (24 micrograms)/ml cells

Injection

Parenteral products such as Rho-D Kamada should be inspected for foreign particulate matter and coloration prior to administration.

Method of Administration

Intramuscular administration.

Administer into the deltoid muscle of the upper arm or the anterolateral aspects of the upper thigh. Due to the risk of sciatic nerve injury, the gluteal region should not be used as a routine injection site. If the gluteal region is used, use only the upper, outer quadrant.

Laboratory Test

The intrapartum administration of Rho-D Kamada may result in a positive direct antiglobulin test in the baby after delivery. In rare cases, this may also put into question the true status of the infant's Rh blood type. Appropriate laboratory tests should be performed to resolve such problems. The presence of administered Rho-D Kamada in the maternal circulation may cause a positive indirect antiglobulin test. If there is uncertainty about mother's Rh group or immune status, Rho-D Kamada should be administered to the mother.

The occurrence of a large fetomaternal hemorrhage late in pregnancy or at delivery may cause spurious mixed field agglutination reactions in a Rho (D) negative mother, and may result in her being mistyped as Rho (D) positive or Du. Such instances may indicate the need for a larger than normal dose of Rho-D Kamada.

4.3. Contraindications

The product is not intended for use in Rh(D) positive individuals.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

Hypersensitivity to human immunoglobulins especially in patients with antibodies against IgA.

4.4. Special warnings and precautions for use

Ensure that Rho-D Kamada is not administered into a blood vessel, because of the risk of shock.

In the case of post-natal use, the product is intended for maternal administration. It should not be given to the new-born infant.

Hypersensitivity

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

Rho-D Kamada 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 Rho-D Kamada 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 Rho-D Kamada, patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with pre-existing 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 immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity), especially when higher doses of Rho-D Kamada 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). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A and 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 Rho-D Kamada 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 virus vaccines

Active immunization 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.

No interaction studies have been performed.

4.6. Fertility, pregnancy and lactation

Pregnancy

This medicinal product is intended for use in pregnancy.

Breast-feeding

This medicinal product can be used during breast-feeding.

Immunoglobulins are excreted in human milk and may contribute to protecting the neonate from pathogens which have a mucosal port of entry.

Fertility

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

4.7. Effects on ability to drive and use machines

Rho-D Kamada has no influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary 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 administration sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash. The following adverse reactions have been reported from post-marketing experience.

Tabulated list of adverse reactions

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1,1000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Adverse reaction**	**Frequency**
Immune system disorders	Hypersensitivity, anaphylactic shock	Not known
Nervous system disorders	Headache	Not known
Cardiac disorders	Tachycardia	Not known
Vascular disorders	Hypotension	Not known
Gastrointestinal disorders	Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Skin reaction, erythema, pruritus	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, back pain	Not known

MedDRA System Organ Class	Adverse reaction	Frequency
General disorders and administration site conditions	Pyrexia, malaise, chills At the injection site: swelling, pain, erythema, induration, warmth, pruritus, rash	Not known

For safety information with respect to transmissible agents, see section 4.4.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov. Additionally, you should also report to Kamada LTD to email address: pharmacovigilance@kamada.com

4.9. Overdose

Consequences of an overdose are not known.

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.

It can also contain antibodies to other Rh antigens e.g. anti-Rh C antibodies.

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 foetus 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 foetal 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.

5.2. Pharmacokinetic properties

Absorption and Distribution

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.

Biotransformation and Elimination

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

5.3. Preclinical safety data

Anti-D immunoglobulin is a preparation of human plasma proteins, so safety testing in animals is not particularly relevant to the safety of use in man. Acute toxicity studies in rat and mouse showed species specific reactions, which bear no relevance to administration in humans.

Repeated dose safety testing is impracticable due to the induction of and interference with antibodies to human protein. Clinical experience provides no sign of tumourigenic and mutagenic effects.

No formal studies were performed with Rho-D Kamada.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycine

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

The expiry date of the product is indicated on the packaging materials.

Once a vial has been opened, the solution should be used immediately.

6.4. Special precautions for storage

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

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

6.5. Nature and contents of container

0.85 ml, or 1 ml, or 1.7 ml, or 2 ml of solution in a single use vial (Type I glass), with a rubber stopper and a flip-off seal.

Rho-D Kamada vials are for single use only.

Not all fill volumes may be marketed.

Pack sizes

Pack size of 1 vial.

6.6. Special precautions for disposal and other handling

The product should be brought to room or body temperature before use. Do not use solutions that are cloudy or have deposits.

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

7. MANUFACTURER AND MARKETING AUTHORIZATION HOLDER

Kamada Ltd.

Kibbutz Beit Kama

M.P Negev 8532500

Israel

8. MARKETING AUTHORIZATION NUMBER(S)

108-73-28991

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