KamRho-D I.M.

Rh_0 (D) Immune Globulin (Human) for intramuscular use only.

DESCRIPTION

KamRh$_0$-D I.M. is a sterile non-pyrogenic aqueous solution, containing 150 μg/ml of immune globulin anti-D. It is prepared from pooled Human venous plasma with a high content of anti-D antibodies. Each unit of plasma and each plasma pool used in the manufacture of this product has been tested and found to be non-reactive to Hepatitis B Surface Antigen (HBsAg), anti HIV I-II and anti-HCV. Kamada's manufacturing process includes a Solvent/Detergent step, that is, treatment with tri-(n-butyl) phosphate and Triton X-100, a step designed to increase the safety of the product by eliminating the risk of transmission of lipid enveloped viruses. In addition the process includes heat-treatment at 60°C for 10 hours, a process long-known to inactivate viruses. Finally the purification process itself has been found to be capable of reducing the concentration of a non-enveloped type virus by several logs.

The product is stabilized with 0.3 M Glycine and is preservative free.

Composition

Each vial of **KamRh$_0$-D I.M.** contains:

Rh_0 (D) Immune Globulin 150 μg/ml

Glycine 2.25% W/V = 0.3 M.

ACTIONS AND CLINICAL PHARMACOLOGY

Pharmacology

KamRh$_0$-D I.M. is a sterile non-pyrogenic purified gamma globulin (IgG) solution, manufactured from human plasma containing high titers of anti-Rh_0 (D). The manufacturing process includes a solvent/detergent treatment and heat - treatment at 60°C for 10 hours, steps that are effective in inactivating viruses such as hepatitis B, hepatitis C, HIV and others. These steps are designed to increase product safety by reducing the risk of virus transmission. **KamRh$_0$-D** immune globulin is prepared from human plasma by an ion-exchange column chromatography method.

KamRh$_0$-D I.M. is used to suppress the immune response of non-sensitized Rh_0 (D) antigen-negative individuals following Rh_0 (D) antigen-positive red blood cell exposure by fetomaternal hemorrhage during delivery of a Rh_0 (D) antigen-positive infant, abortion (spontaneous or induced), amniocentesis, abdominal trauma or mismatched transfusion.

The mechanism of action is not completely understood. Rh_0 (D) immune globulin, when administered within 72 hours of a full-term delivery of a Rh_0 (D) antigen-positive infant by a Rh_0 (D) antigen-negative mother, will reduce the incidence of Rh isoimmunization from between 12% and 13% to between 1% and 2%. The 1% to 2% treatment failures are due, for the most part, to isoimmunization during the last trimester of pregnancy. Thus, when treatment is given both antenatally at 28 weeks gestation and postpartum, the Rh immunization rate drops to approximately 0.1%.

INDICATIONS

Pregnancy/Other Obstetric Conditions:

Suppression of Rh immunization in non-sensitized Rh_0 (D) negative women delivering a Rh_0 positive baby, or when the baby's Rh type is unknown [1,2]. 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. **KamRh$_0$-D I.M.** should be given within 72 hours of the event. It may be given even after up to one month although efficacy may be somewhat reduced [3].

Transfusion

Suppression of Rh isoimmunization in Rh_0 (D) antigen-negative patients transfused with Rh_0 (D) antigen-positive RBCs or blood components containing Rh_0 (D) antigen-positive RBCs. Initiate treatment within 72 hours of exposure.

CONTRAINDICATIONS

Individuals known to have an anaphylactic or severe systemic reaction to human globulin or other plasma proteins. **KamRh$_0$-D I.M.** contains trace amounts of IgA (<2 μg per 1500 IU [300 μg]). Individuals who are deficient in IgA may have the potential for developing IgA antibodies and have anaphylactic reactions. Evaluate the potential benefit of treatment with Rh_0 (D) immune globulin against the potential for hypersensitivity reactions.

WARNINGS

Route of Administration

KamRh$_0$-D I.M. must be administered intramuscularly.

For the suppression of Rh isoimmunization in the mother. Do not administer to the infant.

Criteria for KamRh$_0$-D I.M. Administration to Prevent Alloimmunization

The criteria for an Rh-incompatible pregnancy requiring administration of Rh_0 (D) immune globulin at 28 weeks gestation and within 72 hours after delivery are: The mother is Rh_0 (D) antigen-negative; the mother is bearing a child whose father is either Rh_0 (D) antigen-positive or Rh_0 (D) unknown; the infant is either Rh_0 (D) antigen-positive or Rh_0 (D) unknown; the mother was not previously sensitized to the Rh_0 (D) antigen (and thus does not carry anti-Rh_0 (D) antibodies).

Pregnancy: Category C

It is not known whether Rh_0 (D) immune globulin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

Infants

KamRh$_0$-D I.M. is for the suppression of Rh Isoimmunization in the mother. Do not administer to the infant. (See **Warnings**).

Recommendations Regarding Thrombosis

- Care should be used when immune globulin products are given to individuals determined to be at increased risk of thrombosis.
- Patients at increased risk of thrombosis include those with acquired or hereditary hypercoagulable states, prolonged immobilization, in-dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output), and hyperviscosity (including cryoglobulins, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies).
- As noted in product labeling, patients at risk for thrombosis should receive immune globulin products at the slowest rate practicable, and these individuals should be monitored for thrombotic complications.
- Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

Recommendations Regarding Hemolysis

- Heightened awareness of the potential for hemolysis is recommended in individuals receiving immune globulin products, particularly those who are determined to be at increased risk.
- Patients at increased risk for hemolysis following treatment with immune globulins include those with non-O blood group types, those who have underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days.
- As noted in product labeling, patients receiving immune globulin products should be monitored for hemolysis, particularly those at increased risk.
- Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If these occur, appropriate laboratory testing should be obtained.

PRECAUTIONS

General

Plasma used in manufacturing **KamRh$_0$-D I.M.** has been extensively tested in accordance with the Pharmacopoeal and FDA regulations. The process includes Solvent/Detergent treatment to inactivate lipid enveloped viruses and heat treatment at 60°C for 10 hours, a well established technique for inactivating viral pathogens. However, the possibility of transmission of infectious disease cannot be excluded. As with all preparations administered by the I.M. route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

KamRh$_0$-D I.M. should not be administered to Rh_0 (D) negative individuals who are Rh immunized as evidenced by standard manual Rh antibody screening tests.

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. Such an individual should be assessed for a large fetomaternal hemorrhage and the dose of **KamRh$_o$-D I.M.** adjusted accordingly.

KamRh$_o$-D I.M. should be administered if there is any doubt about the mother's blood type.

Drug Interactions

It is recommended that **KamRh$_o$-D I.M.** be administered independently of other drugs.

Other antibodies in the **KamRh$_o$-D I.M.** preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within three months after **KamRh$_o$-D I.M.** administration.

ADMINISTRATION AND DOSAGE

KamRh$_o$-D I.M. must be administered intramuscularly only.

Pregnancy

A 1,500 IU (300 μg) dose of **KamRh$_o$-D I.M.** should be administered at 28 weeks gestation. If **KamRh$_o$-D I.M.** is administered early in the pregnancy, it is recommended that **KamRh$_o$-D I.M.** be administered at 12-week intervals in order to maintain an adequate level of passively acquired anti-Rh. A 600 IU (120 μg) dose should be administered as soon as possible after delivery of a confirmed Rh$_o$ (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, **KamRh$_o$-D I.M.** should be administered to the mother at 72 hours after delivery. If more than 72 hours have elapsed, **KamRh$_o$-D I.M.** should not be withheld, but administered as soon as possible up to 28 days after delivery.

Other Obstetric Conditions

A 600 IU (120 μg) dose of **KamRh$_o$-D I.M.** 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 μg) dose of **KamRh$_o$-D I.M.** 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, **KamRh$_o$-D I.M.** should be administered as soon as possible.

Transfusion

KamRh$_o$-D I.M. 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	**KamRh$_o$-D I.M.** Dosage	
		Rh+ Blood	Rh+ Red Cells
Intramuscular	6,000 IU (1,200 μg) every 12 hours until total dose administered	60 IU (12 μg)/ml blood	120 IU (24 μg)/ml cells

Injection

Parenteral products such as **KamRh$_o$-D I.M.** should be inspected for foreign particulate matter and coloration prior to 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 **KamRh$_o$-D I.M.** 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 **KamRh$_o$-D I.M.** in the maternal circulation may cause a positive indirect antiglobulin test. If there is uncertainty about mother's Rh group or immune status, **KamRh$_o$-D I.M.** 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 Rh$_o$ (D) negative mother, and may result in her being mistyped as Rh$_o$ (D) positive or D^u. Such instances may indicate the need for a larger than normal dose of **KamRh$_o$-D I.M.**

ADVERSE REACTIONS

Rh Isoimmunization Suppression

Adverse reactions to Rh$_o$ (D) immune globulin are infrequent in Rh$_o$ (D) antigen-negative individuals. Discomfort and swelling at the site of injection and slight elevation in temperature might occur in a small number of cases. As is the case with all drugs of this nature, there is a remote chance of an anaphylactic reaction in individuals with hypersensitivity to blood products. In the event of an immediate reaction (anaphylaxis) characterized by collapse, rapid pulse, shallow respiration, pallor, cyanosis, edema or generalized urticaria, subcutaneous injection of epinephrine hydrochloride 0.3 ml 1:1000 aqueous solution should be immediately instituted, followed by intravenous administration of hydrocortisone, 50 to 100 mg, if necessary.

Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh$_o$ (D) Immune Globulin (Human), following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

OVERDOSAGE

Symptoms and Treatment of Overdosage

A Rh$_o$ (D) positive individual treated with large doses of **KamRh$_o$-D I.M.** may develop a mild anemia. However this condition is normally compensated for by elevated red cell production. In most cases, medical intervention other than discontinuation of **KamRh$_o$-D I.M.** treatment would not be required.

STORAGE

Store at 2°-8°C. Do not freeze.

Do not use after expiration date.

Discard any unused portion.

PRESENTATION

Vials of 1 or 2 ml of Rh$_o$ (D) Immune Globulin containing 150 μg/ml, for I.M. use.

CAUTION

This product may not be dispensed without a doctor's prescription.

REFERENCES

(1) Pollack W., Gorman J.G., Freda V.J., et al. Results of Clinical Trials of RhoGAM in Women. *Transfusion* 8:151, 1968.

(2) Freda V.J., Gorman J.G., Pollack W. et al. Prevention of Rh Isoimmunization. Progress Report of the Clinical Trials in Mothers. *JAMA* 199:390, 1967.

(3) Samson D., Mollison P.L. Effect on Primary Rh Immunization of Delayed Administration of anti-Rh. *Immunology* 28:349, 1975.

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Kamada Ltd.

Beit Kama

ISRAEL

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