Kam*Rh$_o$*-D I.V.

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

WARNING: INTRAVASCULAR HEMOLYSIS (IVH)

Intravascular hemolysis (IVH) leading to death has been reported in patients treated for immune thrombocytopenic purpura (ITP) with Rh_0D immune Globulins.

IVH can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress syndrome (ARDS).

Serious complications including severe anemia, acute renal insufficiency, renal failure and disseminated intravascular coagulation (DIC) have also been reported.

Closely monitor patients treated with **Kam*Rh$_o$*-D I.V.** for ITP in a health care setting for at least eight hours after administration. Perform a dipstick urinalysis at baseline, 2 hours, 4 hours after administration and prior to the end of the monitoring period. Alert patients and monitor the signs and symptoms of IVH, including back pain, shaking chills, fever, and discolored urine or hematuria. Absence of these signs and/or symptoms of IVH within eight hours do not indicate IVH cannot occur subsequently. If signs and/or symptoms of IVH are present or suspected after **Kam*Rh$_o$*-D I.V.** administration, post-treatment laboratory tests should be performed, including plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect).

DESCRIPTION

Kam*Rh$_o$*-D I.V. is a sterile non-pyrogenic aqueous solution, containing 150 μg/mL (1500 IU/2 ml) of immune globulin anti-D. **Kam*Rh$_o$*-D I.V.** immune globulin is prepared from Human plasma by an ion - exchange column chromatography method, and it is manufactured from pooled Human venous plasma with a high content of anti-D antibodies. Each unit of plasma used in the manufacture of this product has been tested and found to be negative/non-reactive to Hepatitis B Surface Antigen (HBsAg), HIV-1 antigen, anti-HIV I-II and anti-HCV. In addition, the plasma has been tested by a NAT method and found to be negative for HAV, HIV, HBV and HCV and to contain < 10^4 I.U/mL Parvovirus B-19. The 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 such as Hepatitis B, Hepatitis C and HIV. In addition the process includes heat-treatment at 60°C for 10 hours, a process long known to inactivate non-enveloped viruses. Finally the purification process- itself has been found to be capable of reducing the concentration of non-enveloped type viruses by several logs.
The product is stabilized with 0.3 M Glycine and is preservative free.

Composition

Each vial of **Kam*Rh$_o$*-D I.V.** contains:
Rho (D) Immune Globulin 150 μg/mL (1500 IU/2 ml)
Glycine 2.25% W/V = 0.3 M

ACTIONS AND CLINICAL PHARMACOLOGY

Pharmacology

Kam*Rh$_o$*-D I.V. is a sterile non-pyrogenic purified gamma globulin (IgG) solution, manufactured from human plasma containing high titers of anti-Rh_o (D). **Kam*Rh$_o$*-D I.V.** is used to suppress the immune response of non-sensitized Rh_o (D) antigen-negative individuals following Rh_o (D) antigen-positive red blood cell exposure by fetomaternal hemorrhage during delivery of a Rh_o (D) antigen-positive infant, abortion (spontaneous or induced), amniocentesis, abdominal trauma or mismatched transfusion.

The mechanism of action is not completely understood. Rh_o (D) immune globulin, when administered within 72 hours of a full-term delivery of a Rh_o (D) antigen-positive infant by a Rh_o (D) antigen-negative mother, will reduce the incidence of Rh alloimmunization 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%. It has been found that when intravenous Rh immune globulin is given at a dose of 120 μg (600 IU), that antibody persists in the mother's circulation for about 6 weeks. Therefore, in order to assure persistence of antibody until the end of the pregnancy, a dose of 300 μg (1500 IU) is recommended for antenatal prophylaxis. Intravenous Rh immune globulin has also been found to raise the platelet count in Rh_o (D) positive patients with both acute and chronic idiopathic thrombocytopenic purpura (ITP). Adults, children and patients with ITP secondary to HIV infection have been shown to respond. Children respond better than adults. Between 79-90% of patients will have a good response to the drug usually starting within 3-5 days with a peak at 10 days to 2 weeks. Previously splenectomized patients may not respond. The mechanism of action is not fully understood, but may be related, at least in part, to induction of reticuloendothelial blockade by antibody-coated red blood cells, thereby permitting the patient's platelets to continue to circulate. The usual dose of **Kam*Rh$_o$*-D I.V.** for the treatment of ITP is 50 μg/kg body weight (250 IU/kg body weight). If the patient's hemoglobin level is less than 10 gm/100 ml, a lower dose should be given. Further treatment may be given, depending on the patient's platelet count, at doses between 25-60 μg/kg body weight (125 IU-300 IU/kg body weight).

INDICATIONS

Pregnancy/Other Obstetric Conditions

Kam*Rh$_o$*-D I.V. is indicated for the suppression of Rh immunization in non-sensitized Rh_o (D) negative women delivering an Rh_o positive baby, or when the baby's Rh type is unknown [1,2]. It is also indicated for 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. **Kam*Rh$_o$*-D I.V.** 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]. **Kam*Rh$_o$*-D I.V.** should be administered if there is any doubt about the mother's blood type.

Immune Thrombocytopenic Purpura (ITP):

Kam*Rh$_o$*-D I.V. is used in the treatment of non-splenectomized Rh_o (D) – positive adults with chronic ITP, children with chronic or acute ITP, and patients with thrombocytopenia secondary to HIV infection in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage.

CONTRAINDICATIONS

Individuals who are known to have an anaphylactic or severe systemic reaction to human globulin or other plasma proteins. Hypersensitivity to any of the components. **Kam*Rh$_o$*-D I.V.** contains trace amounts of IgA .

Do not use **Kam*Rh$_o$*-D I.V.** in patients who are IgA deficient with antibodies against IgA.
Do not use **Kam*Rh$_o$*-D I.V.** in patients with autoimmune hemolytic anemia.
Do not use **Kam*Rh$_o$*-D I.V.** in patients with pre-existing hemolysis or in patients at high risk for hemolysis.
Do not use **Kam*Rh$_o$*-D I.V.** in infants for the suppression of isoimmunization, Rh_0 (D)

WARNINGS

Intravascular Hemolysis (IVH)

Intravascular hemolysis (IVH) leading to death has been reported in patients treated for immune thrombocytopenic purpura (ITP) with Rh_0D immune Globulins.
IVH can lead to clinically compromising anemia and multi-system organ failure including acute respiratory distress symdrome (ARDS).
Serious complications including severe anemia, acute renal insufficiency, renal failure and disseminated intravascular coagulation (DIC) have also been reported.
Closely monitor patients treated with **Kam*Rh$_o$*-D I.V.** for ITP in a health care setting for at least eight hours after administration. Perform a dipstick urinalysis at baseline, 2 hours, 4 hours after administration and prior to the end of the monitoring period. Alert patients and monitor for signs and symptoms of IVH, including back pain, shaking chills, fever, and discolored urine or hematuria. Absence of these signs and/or symptoms of IVH within eight hours do not indicate IVH cannot occur subsequently. If signs and/or

symptoms of IVH are present or if IVH is suspected after **Kam*Rh$_o$*-D I.V.** administration, post-treatment laboratory tests should be performed including plasma hemoglobin.

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 infusion 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.

For patients judged to be at risk of developing thrombotic events, administer Rh_0 D immune Globulins at a minimum rate of infusion.

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.

Route of Administration
Kam*Rh$_o$*-D I.V. must be administered only intravenously. The solution must be withdrawn from the vial using the provided Filter Needle. See **Instructions for use and handling.**
For the suppression of Rh alloimmunization, administer to the mother. Do not administer to the infant.

Patients should be observed at least 20 minutes after administration.

If symptoms of an anaphylactic reaction or other allergic reactions occur, the injection should be discontinued immediately.

Transmissible Infectious Agents
Kam*Rho*-D I.V. is made of human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viruses (see **DESCRIPTION**). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All the infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kamada Ltd. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

General

Each plasma unit used in manufacturing **Kam*Rh$_o$*-D I.V.** has been tested in accordance with FDA regulations.

The process includes Solvent/Detergent and heat treatment to inactivate non-enveloped viruses. In addition, the purification process itself has been shown to reduce non-enveloped viruses by several logs. However, the possibility of transmission of infectious disease cannot be excluded. As with all preparations administered by the I.V. route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders. **Kam*Rh$_o$*-D** (Human) should not be administered to Rh$_o$ (D) negative individuals who are Rh immunized as evidenced by standard 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 **Kam*Rh$_o$*-D I.V.** adjusted accordingly.

Hypersensitivity

Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. **Kam*Rh$_o$*-D I.V.** is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (see **CONTRAINDICATIONS).**

True hypersensitivity reactions are rare, but allergic responses to anti-D immunoglobulin may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, chest tightness, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. In case of shock, the standard medical treatment for shock should be implemented.

Renal failure

In general**,** acute renal failure (ARF) is reported to be associated with the administration of Intravenous Immunoglobulin (IGIV) products. **Kam*Rh$_o$*-D I.V.** does not contain sucrose or any other sugar as a stabilizer. Nevertheless, it is recommended that renal function be assessed prior to and following IV administration of **Kam*Rh$_o$*-D I.V.,** especially in patient at risk of developing ARF. In these patients, the IVIG product should be administrated at the minimum practical dosage and rate of infusion.

It is recommended that, whenever possible, each time **Kam*Rh$_o$*-D I.V.** is administrated, the name and batch number of the product is recorded in the patient file.

Criteria for Kam*Rh$_o$*-D I.V. Administration to Prevent Alloimmunization

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

For Treatment of ITP:

For the treatment of ITP do not administer to Rh$_o$ (D) antigen-negative individuals. Its efficacy in splenectomized patients has not been clearly demonstrated.

Post marketing surveillance of different Rh$_0$ (D) immune globulin intravenous (Anti-D IGIV) products indicates some rare but serious adverse events associated with the use of Anti-D IGIV for treatment of ITP (See **ADVERSE REACTIONS**). Physicians should discuss the risks and benefits of **Kam*Rh$_o$*-D I.V.** and alert patients who are being treated for ITP, about the signs and symptoms associated with these rare serious adverse events

Following administration of **Kam*Rh$_o$*-D I.V.**, Rh$_o$(D) positive ITP patients should be monitored for signs and/or symptoms of acute hemoglobinemia or hemoglobinuria or IVH and its complications, compromising anemia, and renal insufficiency as well as signs and symptoms of disseminated intravascular coagulation (DIC), which include:

- hemoglobinuria
- pallor
- hypotension
- tachycardia

- oliguria or anuria
- edema
- chest pain
- dyspnea
- increased bruising and prolongation of bleeding time and clotting time which may be difficult to detect in the ITP population.

The diagnosis of a serious complication of an acute hemoglobinemia or hemoglobinuria is dependent on laboratory testing.

Previous, uneventful administration of anti-D IGIV provides no assurance that a subsequent administration will be uneventful [4]

Patients being treated for ITP should be instructed to immediately report symptoms of back pain, shaking chills, fever, discolored urine, decreased urine output, sudden weight gain, fluid retention/edema, chest pain and/or shortness of breath, to their physicians.

If transfusion is indicated, Rh_o(D) negative packed red blood cells (PRBC) should be used so as not to exacerbate ongoing acute hemoglobinemia or hemoglobinuria. Platelet products may contain up to 5.0 mL of red blood cells; thus caution should likewise be exercised if platelets from Rh_o (D) positive donors are transfused.

If the patient's hemoglobin level is lower than 10 g/dL, a reduced dose should be administered (See **ADMINISTRATION and DOSAGE**). In patients with hemoglobin levels that are less than 8 g/dL, alternative treatments should be sought due to the risk of increasing the severity of anemia.

ITP patients should be carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human immunoglobulin, patients switched from an alternative product or when there has been a long interval since the previous infusion. Patients should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect.

Thrombotic Events
Thrombotic events may occur following treatment with Rh_0D immune Globulins (see **Warnings**). For patients judged to be a risk of developing thrombotic events, administer Rh_0D immune Globulins **at a minimum rate of infusion.**

Hemolysis
Although the mechanism of action of Rh_0 D immune Globulins in the treatment of ITP is not completely understood, it is postulated that anti-D binds to the Rh_0(D) RBC resulting in formation of antibody-coated RBC complexes. Immune-medicated clearance of the antibody-coated RBC complexes would spare the antibody-coated platelets because of the preferential destruction of antibody-coated RBC complexes by the macrophages located in the reticuloendothelial system. The side effects of this reaction is a decrease in hemoglobin levels (extravascular hemolysis). The pooled data from ITP clinical studies demonstrated a maximum decrease from baseline in hemoglobin levels of 1.2 g/dL within 7 days after administration of Rh_0D immune Globulins.

If the patient has lower than normal hemoglobin levels (less than 10 g/dL), a reduced dose of 125 to 200 IU/Kg (25 to 40 µg/kg) should be given to minimize the risk of increasing the severity of anemia in the patient. Alternative treatments should be used in patients with hemoglobin levels that are less than 8 g/dL due to the risk of increasing the severity of the anemia. (see **ADMINISTRATION and DOSAGE)**

Transfusion-related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema may occur in patients following IGIV treatment. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilator support.

Drug Interactions
Administration of **Kam*Rh*$_o$-D I.V.**, concomitantly with other drugs has not been evaluated. Therefore, it is recommended that **Kam*Rh*$_o$-D I.V.** be administered independently of other drugs.

Other antibodies in the **Kam*Rh*$_o$-D I.V.** 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 **Kam*Rh*$_o$-D I.V.** administration.

Drug/Laboratory Test Interactions
Passively acquired anti-A, anti-B, anti-C, and anti-E blood group antibodies may be detectable in direct and indirect antiglobulin (Coombs) tests obtained following **Kam*Rh*$_o$-D I.V.** administration. Interpretation of direct and indirect antiglobulin tests must be made in the context of the patient's underlying clinical condition and supporting laboratory data.
Significant anemia may present with pallor, hypotension, or tachycardia while acute renal insufficiency may present with oliguria or anuria, edema and dyspnea. Patients with IVH who develop DIC may exhibit signs and symptoms of increased bruising and prolongation of bleeding time and clotting time which may be difficult to detect in the ITP population. Consequently the diagnosis of this serious complication of IVH is dependent on laboratory testing. Previous uneventful administration of **Kam*Rh*$_o$-D I.V.** does not preclude the possibility of an occurrence of IVH and its complications following any subsequent administration of **Kam*Rh*$_o$-D I.V.**. ITP patients presenting with signs and/or symptoms of IVH and its complications after anti-D administration should have confirmatory laboratory testing that may include, but is not limited to, CBC (i.e. hemoglobin, platelet counts), haptoglobin, plasma hemoglobin, urine dipstick, assessment of renal function (i.e. BUN, serum creatinine), liver function (i.e. LDH, direct and indirect bilirubin) and DIC specific tests such as D-dimer or Fibrin Degradation Products (FDP) or Fibrin Split Products (FSP).

Pregnancy: Category C
It is not known whether Rh_o (D) immune globulin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **Kam*Rh*$_o$-D I.V.** should be given to a pregnant woman only if clearly needed.

Geriatric Use
Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience suggests that patients of advanced age (age over 65) with co-morbid conditions such as active infection (including HCV), hematological malignancies (including non-Hodgkin's lymphoma, Hodgkin's disease or Chronic Lymphocytic Leukemia), autoimmune disorders (SLE, antiphosholipid syndrome, and autoimmune hemolytic anemia) may be at an increased risk of developing acute haemolytic reactions such as IVH. Patients receiving doses in excess of 300 IU/kg of **Kam*Rh*$_o$-D I.V.** may also be at an increased risk of developing increased hemolysis. Fatal outcomes associated with IVH and its complications have occurred most frequently in patients of advanced age (age over 65) with co-morbid conditions.
In general, caution should be used in dose selection for an elderly patient, with consideration given to starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most serious adverse reactions have been observed in patients receiving **Kam*Rh*$_o$-D I.V.** for treatment of ITP. These include: intravascular hemolysis (IVH), clinically compromising anemia, acute renal insufficiency, DIC, and death. [See **WARNINGS**.]

Intravascular hemolysis (IVH) leading to death has been reported in patients treated for immune thrombocytopenic purpura (ITP) with Rh_0D immune Globulins.

Occasionally fever, malaise, headache, cutaneous reaction and chills occur. In rare cases: nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reaction, including dyspnea and shock, are reported, even when the patient has shown no hypersensitivity to previous administration.

Rh Alloimmunization 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 the 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.

ITP
Side effects related to the destruction of Rh_o (D) antigen-positive red cells, such as decreased hemoglobin, can be expected. The most common adverse events are: headache, chills and fever. Such symptoms are commonly associated with infusions of immunoglobulins.
Among patients treated for ITP with anti-D IGIV, there have been rare postmarketing reports of signs and symptoms consistent with acute hemoglobinemia or hemoglobinuria [5] that included back pain, shaking chills, fever and discolored urine occurring, in most cases, within four hours of administration. Potentially serious complications of acute hemoglobinemia or hemoglobinuria that have also been reported include clinically compromising anemia, acute renal insufficiency or disseminated intravascular coagulation (DIC) that have, in some cases, been fatal. One case of acute respiratory distress syndrome (ARDS) was reported [4]. For further information please refer to the literature referenced below [4,5].
Instruct patients being treated with **Kam*Rh$_o$*-D I.V.** for ITP to immediately report symptoms of intravascular hemolysis including back pain, shaking chills, fever, discolored urine, decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath to their physicians.
Prior to discharge, instruct patients to continue self-monitor for the signs and symptoms of IVH over 72 hours, especially for discoloration of urine, and to seek medical attention immediately in the event that signs/symptoms of IVH occur following **Kam*Rh$_o$*-D I.V.** administration.
If signs and/or symptoms of IVH and its complications are present after anti-D administration, appropriate confirmatory laboratory testing should be done that may include, but is not limited to, CBC (i.e. hemoglobin, platelet counts), haptoglobin, plasma hemoglobin, urine dipstick, assessment of renal function (i.e. BUN, serum creatinine), liver function (i.e. LDH, direct and indirect bilirubin) and DIC specific tests such as D-dimer or Fibrin Degradation Products (FDP) or Fibrin Split Products (FSP).

ITP and suppression of RH Isoimmunization
Inform patient of the early signs of hypersensitivity reactions to **Kam*Rh$_o$*-D I.V.**, including hives, generalized urticaria, chest tightness, wheezing, hypotension and anaphylaxis and advise them to notify their physician if they experience these symptoms.

The most common adverse reactions observed for all indications are: Headaches, chills, fever, asthenia, pallor, diarrhea, nausea, vomiting, myalgia, dizziness, hyperkinesia , abdominal or back pain, hypotension, hypertension, increased LDH, somnolence, vasodilatation, pruritus, rash and sweating. All adverse reactions listed occurred in≤2% of Rh_0D immune Globulins doses administered in clinical trials.

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
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
Additionally, you should also report to Kamada LTD to email address: pharmacovigilance@kamada.com

ADMINISTRATION and DOSAGE

Kam*Rh$_o$*-D I.V. must be administered only intravenously.

Pregnancy
A 300 μg (1500 IU) dose of **Kam*Rh$_o$*-D I.V.** should be administered at 28 weeks gestation. If **Kam*Rh$_o$*-D I.V.** is administered early in the pregnancy, it is recommended that **Kam*Rh$_o$*-D I.V.** be administered at

12-week intervals in order to maintain an adequate level of passively acquired anti-Rh immunity. A 120 μg (600 IU) 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, **Kam*Rh*$_o$-D I.V.** should be administered to the mother within 72 hours after delivery. If more than 72 hours have elapsed, **Kam*Rh*$_o$-D I.V.** should not be withheld, but administered as soon as possible up to 28 days after delivery.

Other Obstetric Conditions

A 120 μg (600 IU) dose of **Kam*Rh*$_o$-D I.V.** 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 alloimmunization. Administration should take place within 72 hours after the event. A 300 μg (1500 IU) dose of **Kam*Rh*$_o$-D I.V.** 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, **Kam*Rh*$_o$-D I.V.** should be administered as soon as possible.

Idiopathic Thrombocytopenic Purpura (ITP):

To raise the platelet count in appropriately selected patients with ITP, an initial dose of 50 μg/kg (250 IU/kg) body weight of **Kam*Rh*$_o$-D I.V.** should be administered. If the patient's hemoglobin level is < 10 g/dL, the dose should be reduced to 25-40 μg/kg (125-200 IU/kg) body weight. Additional doses of between 25-60 μg/kg body weight may be administered depending on the patient's clinical response. Treatment should be monitored by measuring the patient's hemoglobin level, reticulocyte count, and platelet count. Patients who develop anemia after treatment may require lower doses, or discontinuation of the drug depending on the severity of the anemia.

In patients with hemoglobin levels that are less than 8g/dL, alternative treatments should be sought due to the risk of increasing the severity of anemia.

Injection

Parenteral products such as **Kam*Rh*$_o$-D I.V**. should be inspected for foreign particulate and discoloration prior to administration. The color may vary from colorless to pale yellow. Do not use solutions that are cloudy.

Intravenous Administration

The recommended dose may be injected into a suitable vein at a rate of 2 ml per 60 seconds. **Kam*Rh*$_o$-D I.V.** should be administered separately from other drugs.

In patients at risk for acute renal failure or thromboembolic adverse reactions, intravenous immunoglobulin products should be administered at the minimum infusion-rate practicable.

Laboratory Tests

The intrapartum administration of **Kam*Rh*$_o$-D I.V.** 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 **Kam*Rh*$_o$-D I.V.** in the maternal circulation may cause a positive indirect antiglobulin test. If there is uncertainty about mother's Rh group or immune status, **Kam*Rh*$_o$-D I.V.** should be administered to the mother. The occurrence of a large feto-maternal hemorrhage late in pregnancy or at delivery may cause spurious mixed field agglutination reactions in an 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 **Kam*Rh*$_o$-D.**

ITP patients presenting with signs and/or symptoms of acute hemoglobinemia or hemoglobinuria and its complications after anti-D IGIV administration should have confirmatory laboratory testing that may include, but are not limited to, CBC (i.e. hemoglobin, platelet counts), haptoglobin, plasma hemoglobin, PT and PTT, urine dipstick, assessment of renal function (i.e. BUN, serum creatinine), liver function (i.e. LDH, direct and indirect bilirubin) and DIC specific tests such as D-dimer or Fibrin Degradation Products (FDP) or Fibrin Split Products (FSP).

OVERDOSAGE

Symptoms and Treatment of Overdosage

An Rh_o (D) positive individual treated with large doses of **Kam*Rh$_o$*-D I.V.** 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 **Kam*Rh$_o$*-D I.V.** treatment would not be required.

Instructions for use and handling

1. Follow the prescribing information for calculating the required dose of **Kam*Rh$_o$*-D I.V.** (see **ADMINISTRATION AND DOSAGE**)
2. Remove the plastic cap from the vial.
3. Swab the exposed stopper surface with Ethanol 70% solution.
4. Attach the sterile 5μm filter needle, provided in the box to a sterile plastic syringe of appropriate volume, and remove the plastic cover guard from the filter needle. With filter needle attached to the syringe insert the needle through the stopper into the vial and withdraw **Kam*Rh$_o$*-D I.V.** solution into the syringe.
5. It is recommended that the required dose will be withdrawn into one syringe. The contents of each vial should be withdrawn using a new filter needle by repeating the process (steps 2 to 4) for each vial of **Kam*Rh$_o$*-D I.V.** Discard each filter needle after use to a puncture resistant container.
6. To administer **Kam*Rh$_o$*-D I.V.** replace the filter needle with an appropriate injection needle and follow the procedure for I.V administration.

STORAGE

Store at 2°-8°C. Do not freeze.
Do not use after expiration date.
Discard any unused portion.

PRESENTATION

Vials of 1 ,2 or 10 ml of Rh_o (D) Immune Globulin containing 150 μg/ml (1500 IU/2ml), for I.V. use.
5 μm Filter Needle.

CAUTION

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

REFERENCES

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