

Rh_o(D) Immune Globulin Intravenous (Human)

WinRho[®] SDF

[win5 r h s d f]

DESCRIPTION

Rh_o(D) Immune Globulin Intravenous (Human) (Rh_o(D) IGIV) - WinRho[®] SDF - is available as a sterile, lyophilized or liquid gamma globulin (IgG) fraction containing antibodies to the Rh_o(D) antigen (D antigen). WinRho[®] SDF is prepared from human plasma by an anion-exchange column chromatography method.¹⁻³ The manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton[®] X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV.⁴ WinRho[®] SDF is filtered using a Planova[™] 35 nm Virus Filter which has been validated to be effective in the removal of some nonlipid enveloped viruses.⁵⁻⁶ These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and nonenveloped viruses, respectively.

The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard. A 1,500 International Unit [IU]* (300 µg) vial contains sufficient anti-Rh_o(D) to effectively suppress the immunizing potential of approximately 17 mL of Rh_o(D) (D-positive) red blood cells (RBCs).

The lyophilized powder is stabilized with 0.1 M glycine, 0.04M sodium chloride, and 0.01% polysorbate 80, while the liquid formulation is stabilized with 10% maltose and 0.03% polysorbate 80. There are no preservatives in either formulation. WinRho[®] SDF does not contain mercury. This product contains approximately 5 µg/mL IgA.

* In the past, a full dose of Rh_o(D) Immune Globulin (Human) has traditionally been referred to as a “300 µg” dose. Potency and dosing recommendations are now expressed in IU by comparison to the WHO anti-Rh_o(D) standard. The conversion of “µg” to “IU” is 1 µg = 5 IU.

CLINICAL PHARMACOLOGY

Pharmacology

Treatment of Immune Thrombocytopenic Purpura (ITP)

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), has been shown to increase platelet counts in non-splenectomized, Rh_o(D) positive patients with ITP. Platelet counts usually rise within one to two days and peak within seven to 14 days after initiation of therapy. The duration of response is variable; however, the average duration is approximately 30 days. The mechanism of action is not completely understood, but is thought to be due to the formation of anti-Rh_o(D) (anti-D)-coated RBC complexes resulting in Fc receptor blockade, thus sparing antibody-coated platelets.⁷⁻⁸

Suppression of Rh Isoimmunization

WinRho[®] SDF is used to suppress the immune response of non-sensitized Rh_o(D) negative individuals following exposure to Rh_o(D) positive RBCs by fetomaternal hemorrhage during delivery of an Rh_o(D) positive infant, abortion (spontaneous or induced), amniocentesis, abdominal trauma, or mismatched transfusion.⁹⁻¹¹ The mechanism of action is not completely understood.

WinRho[®] SDF when administered within 72 hours of a full-term delivery of an Rh_o(D) positive infant by an Rh_o(D) negative mother, will reduce the incidence of Rh isoimmunization from 12-13% to 1 - 2%. The 1 - 2% is, for the most part, due to isoimmunization during the last trimester of pregnancy. When treatment is given both antenatally at 28 weeks gestation and postpartum, the Rh immunization rate drops to about 0.1%.¹²⁻¹⁵

When 600 IU (120 µg) of Rh_o(D) IGIV is administered to pregnant women, passive anti-Rh_o(D) antibodies are not detectable in the circulation for more than six weeks and therefore a dose of 1,500 IU (300 µg) should be used for antenatal administration.

In a clinical study with Rh_o(D) negative volunteers (nine males and one female), Rh_o(D) positive red cells were completely cleared from the circulation within eight hours of intravenous administration of Rh_o(D) IGIV. There was no indication of Rh isoimmunization of these subjects at six months after the clearance of the Rh_o(D) positive red cells.

Pharmacokinetics

IM versus IV Administration (Lyophilized Powder)

In a clinical study involving Rh_o(D) negative volunteers¹⁶, two subjects received 600 IU (120 µg) Rh_o(D) IGIV by intravenous (IV) administration and two subjects received this dose by intramuscular (IM) administration. Peak levels (36 to 48 ng/mL) were reached within two hours of IV administration and peak levels (18 to 19 ng/mL) were reached at five to 10 days after IM administration. Although no statistical comparisons were made, the calculated areas under the

curve were comparable for both routes of administration. The $t_{1/2}$ for anti-Rh_o(D) was about 24 days following IV administration and about 30 days following IM administration.

Lyophilized Powder versus Liquid Formulation

In two comparative pharmacokinetics studies¹⁷, 101 volunteers were administered the liquid or lyophilized formulation of WinRho[®] SDF intravenously (N=41) or intramuscularly (N=60). The formulations were bioequivalent following IV administration based on area under the curve to 84 days and had comparable pharmacokinetics following IM administration. The average peak concentrations (C_{max}) of anti-Rh_o(D) for both formulations were comparable following IV or IM administration and occurred within 30 minutes or 2-4 days of administration, respectively. Both formulations also had similar elimination half-lives ($t_{1/2}$) following IV or IM administration.

Clinical Studies

Treatment of ITP

Efficacy was documented in four subgroups of patients with ITP:

Childhood Chronic ITP

In an open-label, single arm, multicenter study, 24 non-splenectomized, Rh_o(D) positive children with ITP of greater than six months duration were treated initially with 250 IU/kg (50 µg/kg) Rh_o(D) Immune Globulin Intravenous (Human) (125 IU/kg (25 µg/kg) on days 1 and 2, with subsequent doses ranging from 125 to 275 IU/kg (25 to 55 µg/kg)). Response was defined as a platelet increase to at least 50,000/mm³ and a doubling of the baseline. Nineteen of 24 patients responded for an overall response rate of 79%, an overall mean peak platelet count of 229,400/mm³ (range 43,300 to 456,000), and a mean duration of response of 36.5 days (range 6 to 84).¹⁸⁻¹⁹

Childhood Acute ITP

A multicenter, randomized, controlled trial comparing Rh_o(D) IGIV to high dose and low dose Immune Globulin Intravenous (Human) (IVIG) and prednisone was conducted in 146 non-splenectomized, Rh_o(D) positive children with acute ITP and platelet counts less than 20,000/mm³. Of 38 patients receiving Rh_o(D) IGIV (125 IU/kg (25 µg/kg) on days 1 and 2), 32 patients (84%) responded (platelet count \geq 50,000/mm³) with a mean peak platelet count of 319,500/mm³ (range 61,000 to 892,000), with no statistically significant differences compared to other treatment arms. The mean times to achieving \geq 20,000/mm³ or \geq 50,000/mm³ platelets for patients receiving Rh_o(D) IGIV were 1.9 and 2.8 days, respectively. When comparing the different therapies for time to platelet count \geq 20,000/mm³ or \geq 50,000/mm³, no statistically significant differences among treatment groups were detected, with a range of 1.3 to 1.9 days and 2.0 to 3.2 days, for IVIG and prednisone respectively.²⁰⁻²¹

Adult Chronic ITP

Twenty-four non-splenectomized, Rh_o(D) positive adults with ITP of greater than six months duration and platelet counts <30,000/mm³ or requiring therapy were enrolled in a single-arm, open-label trial and treated with 100 to 375 IU/kg (20 to 75 µg/kg) Rh_o(D) IGIV (mean dose 231 IU/kg (46.2 µg/kg)). Twenty-one of 24 patients responded (increase ≥20,000/mm³) during the first two courses of therapy for an overall response rate of 88% with a mean peak platelet count of 92,300/mm³ (range 8,000 to 229,000).²²⁻²³

ITP Secondary to HIV Infection

Eleven children and 52 adults, who were non-splenectomized and Rh_o(D) positive, with all Walter Reed classes of HIV infection and ITP, with initial platelet counts of ≤30,000/mm³ or requiring therapy, were treated with 100 to 375 IU/kg (20 to 75 µg/kg) Rh_o(D) IGIV in an open label trial. Rh_o(D) IGIV was administered for an average of 7.3 courses (range 1 to 57) over a mean period of 407 days (range 6 to 1,952). Fifty-seven of 63 patients responded (increase ≥ 20,000/mm³) during the first six courses of therapy for an overall response rate of 90%. The overall mean change in platelet count for six courses was 60,900/mm³ (range -2,000 to 565,000), and the mean peak platelet count was 81,700/mm³ (range 16,000 to 593,000).²³⁻²⁵

Suppression of Rh Isoimmunization

The pivotal study²⁶ supporting this indication was conducted in 1,186 non-sensitized, Rh_o(D) negative pregnant women in cases in which the blood types of the fathers were Rh_o(D) positive or unknown. Rh_o(D) IGIV was administered according to one of three regimens: 1) 93 women received 600 IU (120 µg) at 28 weeks; 2) 131 women received 1200 IU (240 µg) each at 28 and 34 weeks; 3) 962 women received 1200 IU (240 µg) at 28 weeks. All women received a postnatal administration of 600 IU (120 µg) if the newborn was found to be Rh_o(D) positive. Of 1,186 women who received antenatal Rh_o(D) IGIV, 806 were given Rh_o(D) IGIV postnatally following the delivery of an Rh_o(D) positive infant, of which 325 women underwent testing at six months after delivery for evidence of Rh isoimmunization. Of these 325 women, 23 would have been expected to display signs of Rh isoimmunization; however, none was observed (p <0.001 in a Chi-square test of significance of difference between observed and expected isoimmunization in the absence of Rh_o(D) IGIV).

INDICATIONS AND USAGE

Treatment of ITP

WinRho[®] SDF must be administered via the intravenous route when used in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage in the treatment of non-splenectomized, Rh_o(D) positive:

- children with chronic or acute ITP,

- adults with chronic ITP, or
- children and adults with ITP secondary to HIV infection

The safety and efficacy of WinRho[®] have not been evaluated in clinical trials for patients with non-ITP causes of thrombocytopenia or in previously splenectomized patients or in patients who are Rh_o(D) negative.

Suppression of Rh Isoimmunization

Pregnancy and Other Obstetric Conditions

WinRho[®] SDF may be administered by either intramuscular injection or intravenously. WinRho[®] SDF is indicated for the suppression of Rh isoimmunization in non-sensitized, Rh_o(D) negative (D-negative) women within 72 hours after spontaneous or induced abortions, amniocentesis, chorionic villus sampling, ruptured tubal pregnancy, abdominal trauma or transplacental hemorrhage or in the normal course of pregnancy unless the blood type of the fetus or father is known to be Rh_o(D) negative. In the case of maternal bleeding due to threatened abortion, WinRho[®] SDF should be administered as soon as possible. Suppression of Rh isoimmunization reduces the likelihood of hemolytic disease in an Rh_o(D) positive fetus in present and future pregnancies. WinRho[®] SDF should not be administered to infants born to Rh incompatible mothers.

The criteria for an Rh-incompatible pregnancy requiring administration of WinRho[®] SDF at 28 weeks gestation and within 72 hours after delivery in an Rh_o(D) negative mother are:

- the mother is carrying a child whose father is either Rh_o(D) positive or Rh_o(D) unknown,
- the baby is either Rh_o(D) positive or Rh_o(D) unknown, and
- the mother must not be previously sensitized to the Rh_o(D) factor.

Transfusion

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), is recommended for the suppression of Rh isoimmunization in Rh_o(D) negative female children and female adults in their childbearing years transfused with Rh_o(D) positive RBCs or blood components containing Rh_o(D) positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh_o(D) positive blood represents less than 20% of the total circulating red cells. A 1,500 IU (300 µg) dose will suppress the immunizing potential of approximately 17 mL of Rh_o(D) positive RBCs.

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), is not indicated for use as immunoglobulin replacement therapy for immune globulin deficiency syndromes. It should not be used for the treatment of ITP in Rh_o(D) negative or splenectomized individuals; efficacy in these patients has not been demonstrated.

CONTRAINDICATIONS

Treatment of ITP and Suppression of Rh Isoimmunization

When used for the suppression of Rh isoimmunization, Rh_o(D) should not be administered to the infant.

Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), or any other Immune Globulin (Human).

WinRho[®] SDF contains trace amounts of IgA (approximately 5 µg/mL).

Individuals who are deficient in IgA may have the potential for developing IgA antibodies and have anaphylactic reactions.

The potential benefit of treatment with WinRho[®] SDF must be weighed against the potential for hypersensitivity reactions.

WARNINGS

Physicians should discuss the risks and benefits of WinRho[®] SDF and alert the patients who are being treated for ITP, about the signs and symptoms associated with the following rare serious adverse events reported through postmarketing surveillance:

Among patients treated for ITP, there have been rare postmarketing reports of signs and symptoms consistent with intravascular hemolysis²⁷ that included back pain, shaking chills, fever and discolored urine occurring, in most cases, within four hours of administration. Potentially serious complications of intravascular hemolysis that have also been reported include clinically compromising anemia, acute renal insufficiency or disseminated intravascular coagulation (DIC) that have, in some cases, been fatal²⁸. The extent of risk of intravascular hemolysis and its complications is not known but is reported to be rare, especially for DIC, which is very rare²⁹. In the rare cases reported following anti-D administration, there was no discernible contribution of age, gender, pretreatment renal function, pretreatment hemoglobin, concomitantly administered blood/blood products, co-morbid conditions or previous treatment with WinRho[®] SDF to the development of intravascular hemolysis and its complications. (See ADVERSE REACTIONS: Postmarketing.).

The liquid formulation of WinRho[®] SDF contains maltose. Maltose in IVIG products has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems (for example, by systems based on glucose dehydrogenase pyrroloquinolinequinone

(GDH-PQQ) or glucose-dye-oxidoreductase methods). Due to the potential for falsely elevated glucose readings, only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving maltose-containing parenteral products, including WinRho[®] SDF Liquid.

The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose-containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

WinRho[®] SDF Rh₀(D) Immune Globulin Intravenous (Human), is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. 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 virus infections, and by inactivating and/or removing certain viruses. The WinRho[®] SDF manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton[®] X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV. WinRho[®] SDF is filtered using a Planova[™] 35 nm Virus Filter that is effective in reducing the level of some non-lipid enveloped viruses such as hepatitis A. These two processes are designed to increase product safety by reducing the risk of transmission of lipid enveloped and non-lipid enveloped viruses, respectively. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to the distributor, Baxter Healthcare Corporation (1-800-423-2090). The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

General

Intravenous immune globulin (human) products have been reported to produce renal dysfunction in patients that are predisposed to acute renal failure or those that have renal insufficiency. In such patients, it has been recommended that intravenous immune globulin (human) products be administered at a minimum practical concentration and infusion rate. While renal dysfunction has been reported with various intravenous immune globulin intravenous (human) products³⁰⁻³², the vast majority of these reports have involved products that utilize sucrose as a stabilizer. **WinRho[®]**

SDF does not contain sucrose as a stabilizer. Regardless, it is recommended that renal function be assessed prior to IV administration of WinRho[®] SDF and at appropriate intervals following administration, especially for patients at risk of developing acute renal failure. If renal dysfunction occurs, clinical judgment should be used to determine whether the infusion rate of WinRho[®] SDF should be decreased or the product should be discontinued.

Treatment of ITP

Following administration of WinRho[®] SDF, patients should be monitored for signs and/or symptoms of intravascular hemolysis and its complications including clinically compromising anemia, acute renal insufficiency, and DIC. Patients experiencing intravascular hemolysis may present with back pain, shaking chills, fever and will most consistently present with hemoglobinuria (see PRECAUTIONS: Information for Patients). Significant anemia may present with pallor, hypotension, or tachycardia while acute renal insufficiency may present with oliguria or anuria, edema and dyspnea. Patients with intravascular hemolysis 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 intravascular hemolysis is dependent on laboratory testing (see PRECAUTIONS: Laboratory tests for Adverse Events). Previous uneventful administration of WinRho[®] SDF does not preclude the possibility of an occurrence of intravascular hemolysis and its complications following any subsequent administration of WinRho[®] SDF. ITP patients presenting with signs and/or symptoms of intravascular hemolysis 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).

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

If ITP patients are to be transfused, Rh₀(D) negative red blood cells (PRBCs) should be used so as not to exacerbate ongoing hemolysis. Platelet products may contain up to 5.0 mL of RBCs, thus caution should likewise be exercised if platelets from Rh₀(D) positive donors are transfused.

If the patient has a lower than normal hemoglobin level (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. WinRho[®] SDF, Rh₀(D) Immune Globulin Intravenous

(Human), must be used with extreme caution in patients with a hemoglobin level that is less than 8 g/dL due to the risk of increasing the severity of the anemia. (See DOSAGE AND ADMINISTRATION, Treatment of ITP).

Information for Patients

ITP

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, and/or shortness of breath to their physicians.

Laboratory Tests

ITP

ITP patients presenting with signs and/or symptoms of intravascular hemolysis 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).

Suppression of Rh Isoimmunization

WinRho[®] SDF should not be administered to Rh_o(D) negative individuals who are Rh immunized as evidenced by an indirect antiglobulin (Coombs') test revealing the presence of anti-Rh_o(D) (anti-D) antibody.

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 WinRho[®] SDF adjusted accordingly. The presence of passively administered anti-Rh_o(D) in maternal or fetal blood can lead to a positive direct antiglobulin (Coombs') test. If there is an uncertainty about the father's Rh group or immune status, WinRho[®] SDF should be administered to the mother.

Drug Interactions

Treatment of ITP and Suppression of Rh Isoimmunization

Administration of WinRho[®] SDF concomitantly with other drugs has not been evaluated. Other antibodies contained in WinRho[®] SDF may interfere with the response to live virus vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after WinRho[®] SDF administration.

Drug/Laboratory Test Interactions

WinRho[®] SDF contains trace amounts of anti-A, anti-B, anti-C, anti-E and other blood group antibodies (for example, anti-Duffy, anti-Kidd (anti-JK^a) antibodies)³³ that may be detectable in direct and indirect antiglobulin (Coombs') tests obtained following WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), 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.

Pregnancy Category C

Treatment of ITP and Suppression of Rh Isoimmunization

Animal reproduction studies have not been conducted with WinRho[®] SDF. It is not known whether WinRho[®] SDF can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. WinRho[®] SDF should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

The most serious adverse reactions have been observed in patients receiving WinRho for treatment of ITP. These include: intravascular hemolysis, clinically compromising anemia, acute renal insufficiency, DIC, and death. (See WARNINGS.)

The most common adverse reactions observed for **all** indications are: headaches, chills, fevers, asthenia, pallor, diarrhea, nausea, vomiting, arthralgia, myalgia, dizziness, hyperkinesia, abdominal or back pain, hypotension, hypertension, increased LDH, somnolence, vasodilation, pruritus, rash and sweating.

The following sections describe the adverse events observed during clinical studies for each of the labelled indications. Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a specific drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice.

Treatment of ITP

In clinical trials of subjects (n=161) with childhood acute ITP, adults and children with chronic ITP, and adults and children with ITP secondary to HIV, 60/848 (7%) of infusions were associated with at least one adverse event that was considered to be related to the study medication. The most common adverse events were headache (19 infusions; 2%), chills (14 infusions; <2%), and fever (nine infusions; 1%). All are expected adverse events associated with infusions of immunoglobulins.

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), is administered to Rh_o(D) positive patients with ITP. Therefore, side effects related to the destruction of Rh_o(D) positive red blood cells, most notably a decreased hemoglobin, can be expected. In four clinical trials of patients treated with the recommended initial intravenous dose of 250 IU/kg (50 µg/kg), the mean maximum decrease in hemoglobin was 1.70 g/dL (range: +0.40 to -6.1 g/dL). At a reduced dose, ranging from 125 to 200 IU/kg (25 to 40 µg/kg), the mean maximum decrease in hemoglobin was 0.81 g/dL (range +0.65 to -1.9 g/dL). Only 5/137 (3.7%) of patients had a maximum decrease in hemoglobin of greater than 4 g/dL (range -4.2 to -6.1 g/dL).

The mean maximum decrease in hemoglobin in patients who were not transfused with PRBCs was 3.7 g/dL (range: 0.0-7.6 g/dL). Transfusions for treatment-associated anemia were administered within hours to days of the onset of IVH and consisted of between 1-6 units of PRBCs. Acute renal insufficiency was noted within 2 to 48 hours of the onset of IVH. The mean maximum increase in serum creatinine was 3.5 mg/dL (range: 0.8-10.3 mg/dL) and occurred within 2-9 days. The renal insufficiency in all surviving patients resolved with medical management, including dialysis, within 4-23 days.

Suppression of Rh Isoimmunization

Adverse reactions to Rh_o(D) Immune Globulin Intravenous (Human) are infrequent in Rh_o(D) negative individuals. In the clinical trial²⁶ of 1,186 Rh_o(D) negative pregnant women, no adverse events were attributed to Rh_o(D) IGIV.

Postmarketing

ITP

The following postmarketing adverse events are reported voluntarily from a population of uncertain size; hence, it is not possible to estimate their frequency.

The following additional adverse reactions were reported following the use of WinRho[®] SDF for treatment of patients with ITP: intravascular hemolysis, clinically compromising anemia, acute renal insufficiency and DIC, leading in some cases to death. (See WARNINGS.)

Evaluation and interpretation of these postmarketing events is confounded by underlying diagnosis, concomitant medications, pre-existing conditions and inherent limitations of passive surveillance.

Suppression of Rh Isoimmunization

Discomfort and slight swelling at the site of injection and slight elevation in temperature have been reported in a small number of cases. As is the case with all plasma derivatives, there is a remote chance of an idiosyncratic or anaphylactic reaction with WinRho[®] SDF in individuals with a hypersensitivity to blood products.-

Healthcare professionals should report serious adverse events possibly associated with the use of WinRho[®] SDF to Baxter Healthcare Corporation at 1-800-423-2090 or FDA's MedWatch reporting system by phone (1-800-FDA-1088).

OVERDOSAGE

Treatment of ITP and Suppression of Rh Isoimmunization

There are no reports of known overdoses in patients being treated for Rh isoimmunization or ITP.

DOSAGE AND ADMINISTRATION

Treatment of ITP

WinRho[®] SDF **must be administered intravenously.**

Suppression of Rh Isoimmunization

WinRho[®] SDF Rh_o(D) Immune Globulin Intravenous (Human) **may be administered either intramuscularly or intravenously.**

Reconstitution of Lyophilized Powder

Intravenous Administration

Aseptically reconstitute the product shortly before use with 2.5 mL of – Sterile Diluent for 600 IU (120 µg) and 1,500 IU (300 µg) and 8.5 mL of Sterile Diluent for 5,000 IU (1,000 µg) (see the next table). Discard unused portion of diluent. Inject the diluent slowly onto the inside wall of the vial and gently swirl until dissolved. **Do not shake.**

Intramuscular Administration

Aseptically reconstitute the product shortly before use with 1.25 mL of Sterile Diluent for 600 IU (120 µg) and 1,500 IU (300 µg) and 8.5 mL of Sterile Diluent for 5,000 IU (1,000 µg) (see the next table). Discard unused portion of diluent. Inject the diluent slowly onto the inside wall of the vial and gently swirl until dissolved. **Do not shake.**

Reconstitution of WinRho[®] SDF

| Vial Size | Volume of Diluent to be added to Vial |
|-------------------------|--|
| Intravenous Injection | - |
| 600 IU (120 µg) | 2.5 mL |
| 1,500 IU (300 µg) | 2.5 mL |
| 5,000 IU (1,000 µg) | 8.5 mL |
| Intramuscular Injection | - |
| 600 IU (120 µg) | 1.25 mL |
| 1,500 IU (300 µg) | 1.25 mL |
| 5,000 IU (1,000 µg) | 8.5 mL* |

* To be administered into several sites.

Liquid

There is no reconstitution required. The following table describes the target fill volumes for each of the dosage sizes for the liquid presentation of WinRho[®] SDF.

| Vial Size | Target Fill Volume |
|----------------------|--------------------|
| 600 IU (120 µg) | 0.5 mL |
| 1,500 IU (300 µg) | 1.3 mL |
| 2,500 IU (500 µg) | 2.2 mL |
| 5,000 IU (1,000 µg) | 4.4 mL |
| 15,000 IU (3,000 µg) | 13.0 mL |

Note: The entire contents of the vial should be removed to obtain the labeled dosage of WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human). If partial vials are required for dosage calculation, the entire contents of the vial should be withdrawn to ensure accurate calculation of the dosage requirement.

Injection

Parenteral products such as WinRho[®] SDF should be inspected for particulate matter and discoloration prior to administration. Use the product within 12 hours of reconstitution. Discard any unused portion.

Intravenous Administration

The entire dose of WinRho[®] SDF may be injected into a suitable vein as rapidly as over three to five minutes. WinRho[®] SDF should be administered separately from other drugs.

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.

Treatment of ITP

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), **must be given by intravenous administration** for the treatment of ITP.

Initial Dosing: After confirming that the patient is Rh_o(D) positive, an initial dose of 250 IU/kg (50 µg/kg) body weight, given as a single injection, is recommended for the treatment of ITP. The initial dose may be administered in two divided doses given on separate days, if desired. If the patient has a hemoglobin level that is 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. All patients should be monitored to determine clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels (see PRECAUTIONS, Treatment of ITP).

Subsequent Dosing: If subsequent therapy is required to elevate platelet counts, an intravenous dose of 125 to 300 IU/kg (25 to 60 µg/kg) body weight of WinRho[®] SDF is recommended. The frequency and dose used in maintenance therapy should be determined by the patient's clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels.

If patient responded to initial dose with a satisfactory increase in platelets:

Maintenance Therapy:

Dosing (125-300 IU/kg (25-60 µg/kg)) individualized based on platelet and Hgb levels.

If patient did not respond to initial dose, administer a subsequent dose based on Hgb:

If Hgb between 8-10 g/dL, redose between 125-200 IU/kg (25-40 µg/kg).

If Hgb > 10 g/dL, redose between 250-300 IU/kg (50-60 µg/kg).

If Hgb < 8 g/dL, use with caution.

The following equations are provided to determine the dosage and number of vials needed for the treatment of ITP:

- $\text{weight in lbs.} / 2.2083 = \text{weight in kg}$
- $\text{weight in kg} \times \text{selected IU } (\mu\text{g}) \text{ dosing level} = \text{dosage}$
- $\text{dosage} / \text{vial size} = \text{number of vials needed}$

Suppression of Rh Isoimmunization

WinRho[®] SDF may be given by intravenous or intramuscular administration for the suppression of Rh isoimmunization.

Pregnancy

The same dosage, as described below, is to be administered by either the intramuscular or intravenous routes.

A 1,500 IU (300 μg) dose of WinRho[®] SDF should be administered at 28 weeks gestation. If WinRho[®] SDF is administered early in the pregnancy, it is recommended that WinRho[®] SDF 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, WinRho[®] SDF should be administered to the mother at 72 hours after delivery. If more than 72 hours have elapsed, WinRho[®] SDF should not be withheld, but administered as soon as possible up to 28 days after delivery.

Other Obstetric Conditions

The same dosage, as described below, is to be administered by either the intramuscular or intravenous routes.

A 600 IU (120 μg) dose of WinRho[®] SDF 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 WinRho[®] SDF 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 the case of threatened abortion, WinRho[®] SDF should be administered as soon as possible.

Obstetric Indications and Recommended Dose

| Indication | Dose (Administer IM or IV) |
|---|----------------------------|
| <i>Pregnancy:</i> | |
| • 28 weeks gestation | 1,500 IU (300 µg) |
| • Postpartum (if newborn Rh positive) | 600 IU (120 µg) |
| <i>Obstetric Conditions:</i> | |
| • Threatened abortion at any time | 1,500 IU (300 µg) |
| • Amniocentesis and chorionic villus sampling before 34 weeks gestation | 1,500 IU (300 µg) |
| • Abortion, amniocentesis, or any other manipulation after 34 weeks gestation | 600 IU (120 µg) |

Transfusion

WinRho[®] SDF should be administered within 72 hours after exposure for treatment of incompatible blood transfusions or massive fetal hemorrhage.

Transfusion Indication and Recommended Dose

| Route of Administration | WinRho [®] SDF Dose | |
|-------------------------|---|---|
| | If exposed to Rh _o (D) Positive Whole Blood: | If exposed to Rh _o (D) Positive Red Blood Cells: |
| Intravenous | 45 IU (9 µg)/mL blood | 90 IU (18 µg)/mL cells |
| Intramuscular | 60 IU (12 µg)/mL blood | 120 IU (24 µg)/mL cells |

Administer 3,000 IU (600 µg) every 8 hours via the intravenous route, until the total dose, calculated from the above table, is administered.

Administer 6,000 IU (1,200 µg) every 12 hours via the intramuscular route, until the total dose, calculated from the above table, is administered.

HOW SUPPLIED

WinRho[®] SDF, Rh_o(D) Immune Globulin Intravenous (Human), is available in packages containing:

Lyophilized Powder

| NDC Number | Contents |
|--------------|---|
| 0944-2950-02 | A box containing a single dose vial of 600 IU (120 µg) anti-Rho(D) IGIV, a single dose vial of Sterile Diluent, and a package insert |
| 0944-2950-04 | A box containing a single dose vial of 1,500 IU (300 µg) anti-Rho(D) IGIV, a single dose vial of Sterile Diluent, and a package insert |
| 0944-2950-06 | A box containing a single dose vial of 5,000 IU (1000 µg) anti-Rho(D) IGIV, a single dose vial of Sterile Diluent, and a package insert |

Liquid

| NDC Number | Contents |
|--------------|---|
| 0944-2967-01 | A box containing a single dose vial of 600 IU (120 µg) anti-Rho(D) IGIV and a package insert |
| 0944-2967-03 | A box containing a single dose vial of 1,500 IU (300 µg) anti-Rho(D) IGIV and a package insert |
| 0944-2967-07 | A box containing a single dose vial of 2,500 IU (500 µg) anti-Rho(D) IGIV and a package insert |
| 0944-2967-05 | A box containing a single dose vial of 5,000 IU (1,000 µg) anti-Rho(D) IGIV and a package insert |
| 0944-2967-09 | A box containing a single dose vial of 15,000 IU (3,000 µg) anti-Rho(D) IGIV and a package insert |

STORAGE

Store at 2 to 8°C (36 to 46°F). Do not freeze. Do not use after expiration date.

If the reconstituted product is not used immediately, store it at room temperature for no longer than 12 hours. Do not freeze the reconstituted product. Discard the product if not administered within 12 hours.

Rx Only

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