Rh_o(D) Immune Globulin Intravenous (Human)

WinRho® SDF

WARNING: INTRAVASCULAR HEMOLYSIS (IVH)

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

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 WinRho® SDF 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 WinRho®administration, post-treatment laboratory tests should be performed, including plasma hemoglobin, , haptoglobin, LDH, and plasma bilirubin (direct and indirect).

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] 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.[2] WinRho® SDF is filtered using a Planova™ 20N virus filter which has been validated to be effective in the removal of some non-lipid enveloped viruses.[3] These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses, respectively.

The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard. A 1,500 Unit (International Unit [IU])* (300 microgram

[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 micrograms/mL IgA.

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

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.[4,5]

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.[6]. 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%.[7,8]

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 volunteers, 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 $t_{½}$ 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 studies[9], 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 ($t_{½}$) 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/mm^3 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/mm^3 (range 43,300 to 456,000), and a mean duration of response of 36.5 days (range 6 to 84).[10]

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/mm^3. 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/mm^3) with a mean peak platelet count of 319,500/mm^3 (range 61,000 to 892,000), with no statistically significant differences compared to other treatment arms. The mean times to achieving $\geq$ 20,000/mm^3 or $\geq$ 50,000/mm^3 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/mm^3 or $\geq$ 50,000/mm^3, 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.[11,12]

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/mm^3 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/mm^3) during the first two courses of therapy for an overall response rate of 88% with a mean peak platelet count of 92,300/mm^3 (range 8,000 to 229,000).[13-15]

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/mm^3 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/mm^3) 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/mm^3 (range -2,000 to 565,000), and the mean peak platelet count was 81,700/mm^3 (range 16,000 to 593,000).[13-16]

Suppression of Rh Isoimmunization

A pivotal study 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® SDF 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

- **Do not use WinRho SDF in patients with known anaphylactic or severe hypersensitivity responses to human immune globulin products**
- **Do not use WinRho® SDF in patients with autoimmune hemolytic anemia**
- **Do not used WinRho® SDF in patients with pre-existing hemolysis or in patients at high risk for hemolysis**
- **Do not use WinRho® SDF in patients who are IgA deficient with antibodies against IgA**
- **Do not use WinRho SDF in infants for the suppression of isoimmunization, Rh_o (D)**

WARNINGS

INTRAVASCULAR HEMOLYSIS (IVH)

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

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 WinRho® SDF 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 theses 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 WinRho administration, post-treatment laboratory tests should be performed including plasma hemoglobin.

False high blood glucose levels

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.

Transmissible Infectious Agents

WinRho® SDF is made from 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 virus infections, and by inactivating and/or removing certain 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 infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, at 1-800-423-2090. The Physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

General

Hypersensitivity

Severe hypersensitivity reactions may occur [see CONTRAINDICATIONS]. In case of hypersensitivity discontinue WinRho® SDF infusion immediately and institute appropriate treatment. Medications such as epinephirine should be available for immediate treatment of acute hypersensitivity reactions.

WinRho SDF contains approximately 5 micrograms/mL IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. WinRho SDF is contraindicated in patients with antibodies agains IgA and a history of hypersensitivity reaction [See CONTRAINDICATIONS]

Treatment of ITP

Renal Failure

Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death[17]. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs. WinRho® SDF does not contain sucrose.

For patients at risk of renal dysfunction or failure, administer WinRho® SDF at the minimum infusion rate practicable.

Thrombotic Events

Thrombotic events may occur following treatment with WinRho® SDF and other IGIV products[18, 19]. Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be a risk of developing thrombotic events, administer WinRho® SDF at the minimum rate of infusion practicable.

Hemolysis

Although the mechanism of action of WinRho®SDF in the treatment of ITP is not completely understood, it is postulated that anti-D binds to the Rho(D) RBC resulting in formation of antibody-coated RBC complexes. Immune-mediated 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[4, 5, 20]. The side effect of this action 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 WinRho®SDF.

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 DOSAGE AND ADMINISTRATION, Treatment of ITP].

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 (see PRECAUTIONS: Laboratory tests). Previous uneventful administration of WinRho® SDF does not preclude the possibility of an occurrence of IVH and its complications following any subsequent administration of WinRho® SDF. 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).

Patients should be **instructed to immediately report** symptoms of back pain, shaking, 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, Rh_o(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 Rh_o(D) positive donors are transfused.

Transfusion-related Acute Lung Injury

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment[21]. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. 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 [see PRECAUTIONS: Laboratory Tests].

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

Information for Patients

ITP

Instruct patients being treated with WinRho® SDF 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 WinRho® SDF administration.

ITP and Suppression of Rh Isoimmunization

Inform patients of the early signs of hypersensitivity reactions to WinRho® SDF including hives, generalized urticaria, chest tightness, wheezing, hypotension, and anaphylaxis and advise them to notify their physician if they experience these symptoms.

Laboratory Tests

ITP

For all ITP patients, blood type, blood count, reticulocyte count, DAT and dipstick urinalysis are recommended before deciding to treat patients with WinRho® SDF. In patients with evidence of hemolysis or patients at risk of hemolysis, other treatments should be used (see WARNINGS).

Patients administered WinRho SDF are closely monitored for at least 8 hours post administration and a dipstick urinalysis is performed at baseline, 2 hours, 4 hours after administration and prior to the end of the monitoring period.

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).

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at an increased risk of developing acute renal failure [see PRECAUTIONS]. Assess renal function in these at-risk patients, including measurement of BUN and serum creatinine, before the initial infusion of WinRho® SDF and at appropriate intervals thereafter.

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [see PRECAUTIONS].

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)[22] 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 also 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.

Geriatric Use

Clinical studies of WinRho® SDF 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 WinRho® SDF 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 WinRho® SDF for treatment of ITP. These include: intravascular hemolysis (IVH), 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. All adverse reactions listed occurred in ≤2% of WinRho® doses administered in clinical trials.

The following sections describe the adverse drug reactions 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 WinRho® infusions had at least one adverse reaction, with no adverse drug reactions reported in more than 2% of infusions. The most common adverse reactions were headache (19 infusions; 2%), chills (14 infusions; <2%), and fever (nine infusions; 1%), which are expected adverse drug reactions following intravenous administration of human immune globulins.

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 rare in Rh_o(D) negative individuals (<0.1%)[23]. In the clinical trial of 1,186 Rh_o(D) negative pregnant women, no adverse reactions were reported to Rh_o(D) IGIV.

Post-marketing

ITP

The following post-marketing adverse reactions are reported voluntarily from a population of uncertain size; hence, it is not possible to estimate their frequency. These adverse reactions are classified by system organ class.

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

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

Blood and lymphatic system disorders: Intravascular hemolysis, Disseminated intravascular coagulation, Hemoglobinemia
Cardiac disorders: Cardiac arrest, Cardiac failure, Myocardial infarction, Tachycardia
Gastrointestinal disorders: Nausea
General disorders and administration site conditions: Chest pain, Fatigue, Edema
Hepatobiliary disorders: Jaundice
Immune system disorders: Anaphylactic reaction, Hypersensitivity
Musculoskeletal and connective tissue disorders: Myalgia, Muscle spasm, Pain in extremities
Renal and urinary disorders: Renal failure, Renal impairment, Anuria, Chromaturia, Hemoglobinuria, Hematuria
Respiratory, thoracic, and mediastinal disorders: Acute respiratory distress syndrome, Transfusion related acute lung injury
Skin and subcutaneous tissue disorders: Hyperhidrosis

Suppression of Rh Isoimmunization

The following post-marketing adverse reactions are reported voluntarily from a population of uncertain size; hence, it is not possible to estimate their frequency. These adverse reactions are classified by system organ class.

General disorders and administration site conditions: Injection site reactions (includes induration, pruitus or swelling at injection site)
Immune system disorders: Hypersensitivity, Anaphylactic reaction
Skin and subcutaneous tissue disorders: Pruritus, Rash

Healthcare professionals should report serious adverse reactions following the administration 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

In post marketing spontaneous reporting, there has been a limited number of medication error reports related to dosage calculations in which higher doses than that recommended for WinRho® SDF were administered. These calculation errors arose due to confusion between µg and IU (1 µg = 5 IU), confusion between kilograms and pounds and miscalculation of required dosage following a large feto-maternal hemorrhage. Adverse reactions reported in ITP patients have included chills, fever, headache and larger hemoglobin decreases while no hemolytic reactions were reported in suppression of Rh isoimmunization patients. In one ITP case report that involved an overdose due to confusion between µg and IU, a patient with significant co-morbidities developed IVH and had a fatal outcome. In the event of overdose patients should be monitored closely for signs and symptoms of hemolysis and the treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

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.

Preparation and Handling

Reconstitution of Lyophilized Powder

Aseptically reconstitute the product shortly before use with the supplied Sterile Diluent as described in Table 1 below. Discard unused portion of diluent. Inject the diluent slowly onto the inside wall of the vial and gently swirl until dissolved. **Do not shake.**

Table 1: Reconstitution of WinRho® SDF

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

* Administer in divided doses at several sites.

Liquid WinRho® SDF

There is no reconstitution required. Table 2 describes the target fill volumes for each of the dosage sizes for the liquid presentation of WinRho® SDF.

Table 2: Liquid WinRho® SDF Dosage size and target fill volumes

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.

Treatment of ITP

Intravenous use only.

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.

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 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 of dosing and the 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 a 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, alternative treatments should be used.

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

- weight in lbs./2.2083 = weight in kg
- weight in kg X selected IU (µg) dosing level = dosage
- dosage / vial size = number of vials needed

Safety and efficacy of WinRho® SDF in the treatment of ITP at doses exceeding 300 IU/kg (60µg/kg) has not been established.

Suppression of Rh Isoimmunization

Intravenous or intramuscular use.

For 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.

For 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.

Pregnancy and other Obstetric Indications

Table 3 provides dosing guidelines based on the condition being treated.

Table 3: Obstetric Indications and Recommended Dose

Indication	**Timing of Administration**	**Dose (Administer IM or IV)**
Rh-incompatible Pregnancy:		
Routine antepartum prophylaxis	28 weeks gestation*	1,500 IU (300 µg)
Postpartum (if newborn Rh positive)	Within 72 hours of birth**	600 IU (120 µg)
Obstetric Conditions:		
Threatened abortion at any time	Immediately	1,500 IU (300 µg)
Amniocentesis and chorionic villus sampling before 34 weeks gestation	Immediately after procedure†	1,500 IU (300 µg)
Abortion, amniocentesis, or any other manipulation after 34 weeks gestation	Within 72 hours	600 IU (120 µg)

* 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 adequate levels of passively acquired anti-Rh.

** 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.

†Repeat every 12 weeks during pregnancy

Transfusion

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

Table 4: 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-Rh_o(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-Rh_o(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-Rh_o(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-Rh_o(D) IGIV and a package insert
0944-2967-03	A box containing a single dose vial of 1,500 IU (300 µg) anti-Rh_o(D) IGIV and a package insert

0944-2967-07	A box containing a single dose vial of 2,500 IU (500 µg) anti-Rh_o(D) IGIV and a package insert
0944-2967-05	A box containing a single dose vial of 5,000 IU (1,000 µg) anti-Rh_o(D) IGIV and a package insert
0944-2967-09	A box containing a single dose vial of 15,000 IU (3,000 µg) anti-Rh_o(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.

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