

# Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human) WinRho<sup>®</sup> SDF

[win'rō s d f]

## DESCRIPTION

Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human) (Rh<sub>0</sub>(D) IGIV)—WinRho<sup>®</sup> SDF—is available as a sterile, lyophilized or liquid gamma globulin (IgG) fraction containing antibodies to the Rh<sub>0</sub>(D) antigen (D antigen). WinRho<sup>®</sup> SDF is prepared from human plasma by an anion-exchange column chromatography method.<sup>1-3</sup> The manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton<sup>®</sup> X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV.<sup>4</sup> WinRho<sup>®</sup> SDF is filtered using a Planova™ 20N Virus Filter which has been validated to be effective in the removal of some nonlipid enveloped viruses.<sup>5-6</sup> 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<sub>0</sub>(D) to effectively suppress the immunizing potential of approximately 17 mL of Rh<sub>0</sub>(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<sup>®</sup> SDF does not contain mercury. This product contains approximately 5 µg/mL IgA.

*\* In the past, a full dose of Rh<sub>0</sub>(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<sub>0</sub>(D) standard. The conversion of “µg” to “IU” is 1 µg = 5 IU.*

## CLINICAL PHARMACOLOGY

### Pharmacology

#### Treatment of Immune Thrombocytopenic Purpura (ITP)

WinRho<sup>®</sup> SDF, Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human), has been shown to increase platelet counts in non-splenectomized, Rh<sub>0</sub>(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<sub>0</sub>(D) (anti-D)-coated RBC complexes resulting in Fc receptor blockade, thus sparing antibody-coated platelets.<sup>7-8</sup>

#### Suppression of Rh Isoimmunization

WinRho<sup>®</sup> SDF is used to suppress the immune response of non-sensitized Rh<sub>0</sub>(D) negative individuals following exposure to Rh<sub>0</sub>(D) positive RBCs by fetomaternal hemorrhage during delivery of an Rh<sub>0</sub>(D) positive infant, abortion (spontaneous or induced), amniocentesis, abdominal trauma, or mismatched transfusion.<sup>9-11</sup> The mechanism of action is not completely understood.

WinRho<sup>®</sup> SDF when administered within 72 hours of a full-term delivery of an Rh<sub>0</sub>(D) positive infant by an Rh<sub>0</sub>(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%.<sup>12-15</sup>

When 600 IU (120 µg) of Rh<sub>0</sub>(D) IGIV is administered to pregnant women, passive anti-Rh<sub>0</sub>(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<sub>0</sub>(D) negative volunteers (nine males and one female), Rh<sub>0</sub>(D) positive red cells were completely cleared from the circulation within eight hours of intravenous administration of Rh<sub>0</sub>(D) IGIV. There was no indication of Rh isoimmunization of these subjects at six months after the clearance of the Rh<sub>0</sub>(D) positive red cells.

## Pharmacokinetics

### IM versus IV Administration (Lyophilized Powder)

In a clinical study involving Rh<sub>0</sub>(D) negative volunteers<sup>16</sup>, two subjects received 600 IU (120 µg) Rh<sub>0</sub>(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<sub>1/2</sub> for anti-Rh<sub>0</sub>(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<sup>17</sup>, 101 volunteers were administered the liquid or lyophilized formulation of WinRho<sup>®</sup> 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<sub>max</sub>) of anti-Rh<sub>0</sub>(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<sub>1/2</sub>) 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<sub>0</sub>(D) positive children with ITP of greater than six months duration were treated initially with 250 IU/kg (50 µg/kg) Rh<sub>0</sub>(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<sup>3</sup> 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<sup>3</sup> (range 43,300 to 456,000), and a mean duration of response of 36.5 days (range 6 to 84).<sup>18-19</sup>

### Childhood Acute ITP

A multicenter, randomized, controlled trial comparing Rh<sub>0</sub>(D) IGIV to high dose and low dose Immune Globulin Intravenous (Human) (IVIG) and prednisone was conducted in 146 non-splenectomized, Rh<sub>0</sub>(D) positive children with acute ITP and platelet counts less than 20,000/mm<sup>3</sup>. Of 38 patients receiving Rh<sub>0</sub>(D) IGIV (125 IU/kg (25 µg/kg) on days 1 and 2), 32 patients (84%) responded (platelet count ≥50,000/mm<sup>3</sup>) with a mean peak platelet count of 319,500/mm<sup>3</sup> (range 61,000 to 892,000), with no statistically significant differences compared to other treatment arms. The mean times to achieving ≥20,000/mm<sup>3</sup> or ≥50,000/mm<sup>3</sup> platelets for patients receiving Rh<sub>0</sub>(D) IGIV were 1.9 and 2.8 days, respectively. When comparing the different therapies for time to platelet count ≥20,000/mm<sup>3</sup> or ≥50,000/mm<sup>3</sup>, 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.<sup>20-21</sup>

### Adult Chronic ITP

Twenty-four non-splenectomized, Rh<sub>0</sub>(D) positive adults with ITP of greater than six months duration and platelet counts <30,000/mm<sup>3</sup> 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<sub>0</sub>(D) IGIV (mean dose 231 IU/kg (46.2 µg/kg)). Twenty-one of 24 patients responded (increase ≥20,000/mm<sup>3</sup>) during the first two courses of therapy for an overall response rate of 88% with a mean peak platelet count of 92,300/mm<sup>3</sup> (range 8,000 to 229,000).<sup>22-23</sup>

### ITP Secondary to HIV Infection

Eleven children and 52 adults, who were non-splenectomized and Rh<sub>0</sub>(D) positive, with all Walter Reed classes of HIV infection and ITP, with initial platelet counts of ≤30,000/mm<sup>3</sup> or requiring therapy, were treated with 100 to 375 IU/kg (20 to 75 µg/kg) Rh<sub>0</sub>(D) IGIV in an open label trial. Rh<sub>0</sub>(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<sup>3</sup>) 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<sup>3</sup> (range -2,000 to 565,000), and the mean peak platelet count was 81,700/mm<sup>3</sup> (range 16,000 to 593,000).<sup>23-25</sup>

### Suppression of Rh Isoimmunization

The pivotal study<sup>26</sup> supporting this indication was conducted in 1,186 nonsensitized, Rh<sub>0</sub>(D) negative pregnant women in cases in which the blood types of the fathers were Rh<sub>0</sub>(D) positive or unknown. Rh<sub>0</sub>(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<sub>0</sub>(D) positive. Of 1,186 women who received antenatal Rh<sub>0</sub>(D) IGIV, 806 were given Rh<sub>0</sub>(D) IGIV postnatally following the delivery of an Rh<sub>0</sub>(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<sub>0</sub>(D) IGIV).

## INDICATIONS AND USAGE

### Treatment of ITP

WinRho<sup>®</sup> 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<sub>0</sub>(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<sup>®</sup> 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<sub>0</sub>(D) negative.

### Suppression of Rh Isoimmunization

#### **Pregnancy and Other Obstetric Conditions**

WinRho<sup>®</sup> SDF may be administered by either intramuscular injection or intravenously. WinRho<sup>®</sup> SDF is indicated for the suppression of Rh isoimmunization in non-sensitized, Rh<sub>0</sub>(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<sub>0</sub>(D) negative. In the case of maternal bleeding due to threatened abortion, WinRho<sup>®</sup> SDF should be administered as soon as possible. Suppression of Rh isoimmunization reduces the likelihood of hemolytic disease in an Rh<sub>0</sub>(D) positive fetus in present and future pregnancies. WinRho<sup>®</sup> SDF should not be administered to infants born to Rh incompatible mothers.

The criteria for an Rh-incompatible pregnancy requiring administration of WinRho<sup>®</sup> SDF at 28 weeks gestation and within 72 hours after delivery in an Rh<sub>0</sub>(D) negative mother are:

- the mother is carrying a child whose father is either Rh<sub>0</sub>(D) positive or Rh<sub>0</sub>(D) unknown,
- the baby is either Rh<sub>0</sub>(D) positive or Rh<sub>0</sub>(D) unknown, and
- the mother must not be previously sensitized to the Rh<sub>0</sub>(D) factor.

#### **Transfusion**

WinRho<sup>®</sup> SDF, Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human), is recommended for the suppression of Rh isoimmunization in Rh<sub>0</sub>(D) negative female children and female adults in their childbearing years transfused with Rh<sub>0</sub>(D) positive RBCs or blood components containing Rh<sub>0</sub>(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<sub>0</sub>(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<sub>0</sub>(D) positive RBCs.

WinRho<sup>®</sup> SDF, Rh<sub>0</sub>(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<sub>0</sub>(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<sub>0</sub>(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<sup>®</sup> SDF, Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human), or any other Immune Globulin (Human). WinRho<sup>®</sup> 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<sup>®</sup> SDF must be weighed against the potential for hypersensitivity reactions.

## WARNINGS

**Physicians should discuss the risks and benefits of WinRho<sup>®</sup> 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 hemolysis<sup>27</sup> 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 fatal<sup>28</sup>. 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 rare<sup>29</sup>. 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<sup>®</sup> SDF to the development of intravascular hemolysis and its complications. (See ADVERSE REACTIONS: Postmarketing.)**

**The liquid formulation of WinRho<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> SDF Rh<sub>0</sub>(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<sup>®</sup> SDF manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton<sup>®</sup> X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV. WinRho<sup>®</sup> SDF is filtered using a Planova<sup>™</sup> 20N 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 (human) products<sup>30-32</sup>, the vast majority of these reports have involved products that utilize sucrose as a stabilizer. **WinRho<sup>®</sup> SDF does not contain sucrose as a stabilizer.** Regardless, it is recommended that renal function be assessed prior to IV administration of WinRho<sup>®</sup> 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<sup>®</sup> SDF should be decreased or the product should be discontinued.

### Treatment of ITP

Following administration of WinRho<sup>®</sup> 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). 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, Rh<sub>0</sub>(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<sub>0</sub>(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, Rh<sub>0</sub>(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<sub>0</sub>(D) negative individuals who are Rh immunized as evidenced by an indirect antiglobulin (Coombs') test revealing the presence of anti-Rh<sub>0</sub>(D) (anti-D) antibody.

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D<sup>u</sup> 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<sub>0</sub>(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<sup>a</sup>) antibodies)<sup>33</sup> that may be detectable in direct and indirect antiglobulin (Coombs') tests obtained following WinRho® SDF, Rh<sub>0</sub>(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® SDF 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<sub>0</sub>(D) Immune Globulin Intravenous (Human), is administered to Rh<sub>0</sub>(D) positive patients with ITP. Therefore, side effects related to the destruction of Rh<sub>0</sub>(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<sub>0</sub>(D) Immune Globulin Intravenous (Human) are infrequent in Rh<sub>0</sub>(D) negative individuals. In the clinical trial<sup>26</sup> of 1,186 Rh<sub>0</sub>(D) negative pregnant women, no adverse events were attributed to Rh<sub>0</sub>(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<sub>0</sub>(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<sub>0</sub>(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<sub>0</sub>(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<sub>0</sub>(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:

- 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

### 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<sub>0</sub>(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)
Pregnancy:	
• 28 weeks gestation	1,500 IU (300 µg)
• Postpartum (if newborn Rh positive)	600 IU (120 µg)
Obstetric Conditions:	
• 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 <sub>0</sub> (D) Positive Whole Blood:	If exposed to Rh <sub>0</sub> (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<sub>0</sub>(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 <sub>0</sub> (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 <sub>0</sub> (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 <sub>0</sub> (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 <sub>0</sub> (D) IGIV and a package insert
0944-2967-03	A box containing a single dose vial of 1,500 IU (300 µg) anti-Rh <sub>0</sub> (D) IGIV and a package insert
0944-2967-07	A box containing a single dose vial of 2,500 IU (500 µg) anti-Rh <sub>0</sub> (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 <sub>0</sub> (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 <sub>0</sub> (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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**Date of Revision: April 2006**

Part No. 35015800

# Rh<sub>0</sub>(D) Immune Globulin Intravenous (Human) WinRho<sup>®</sup> SDF

## INFORMATION FOR PATIENTS BEING TREATED FOR ITP

You should read this leaflet carefully each time before you are scheduled to receive a treatment for your Immune Thrombocytopenic Purpura (ITP) with WinRho<sup>®</sup> SDF. This leaflet is a summary of the important information you need to know about your medicine, and does not take the place of talking with your doctor and does not contain all of the information available about WinRho<sup>®</sup> SDF. If you have any questions after reading this leaflet, make sure you ask your doctor or nurse.

### 1. WHAT IS WinRho<sup>®</sup> SDF? Pronounced, “Win Row S D F”

WinRho<sup>®</sup> SDF is a medicine that belongs to the group of medicines called immune therapy and is used to treat people with the bleeding disorder called ITP. ITP is a bleeding disorder caused by an abnormally low number of platelets. Platelets are found in the bloodstream and are needed for your blood to clot properly. When blood does not clot properly, there is a tendency to bruise and bleed easily.

WinRho<sup>®</sup> SDF is also used as a form of protection against the development of antibodies in a person with Rh-negative blood who is given Rh-positive blood, and in pregnancy to prevent an Rh-negative mother's immune system from destroying an Rh-positive baby's red blood cells.

### 2. HOW DOES WinRho<sup>®</sup> SDF WORK?

WinRho<sup>®</sup> SDF is a medicine that contains antibodies. Antibodies are made by your body's immune system and help your body fight infections caused by bacteria and viruses and defend your body against other foreign substances. When your immune system is working properly, the antibodies made by your body coat the bacteria, viruses or foreign substances, which are then removed by an organ in your abdomen called the spleen. But, sometimes, these antibodies can also attack the healthy cells in your body, which is what happens when you have ITP. In ITP, the body mistakenly produces antibodies against its own platelets. These antibodies coat your platelets, and the spleen removes them so the number of platelets in your blood stream decreases.

WinRho<sup>®</sup> SDF is thought to protect the platelets of Rh-positive people by coating their red blood cells, causing the red blood cells to be removed by the spleen instead of the platelets. As a result, there is an increased number of platelets in your blood and fewer symptoms of ITP. But, because your red blood cells are being removed, you could become severely anemic (See WHAT IS THE MOST IMPORTANT INFORMATION I NEED TO KNOW ABOUT TREATMENT WITH WinRho<sup>®</sup> SDF FOR ITP?)

### 3. WHAT IS THE MOST IMPORTANT INFORMATION I NEED TO KNOW ABOUT TREATMENT WITH WinRho<sup>®</sup> SDF FOR ITP?

A small decrease in the amount of red blood cells is expected after treatment with WinRho<sup>®</sup> SDF. However, a small number of patients have experienced a potentially life threatening reaction in which a large number of red blood cells are destroyed while in the blood stream. In the patients that experienced this reaction, most had symptoms within 4 hours of receiving WinRho<sup>®</sup> SDF.

If you experience any of the following symptoms after receiving WinRho<sup>®</sup> SDF, you should **call your doctor immediately**:

- shaking chills, fever or back pain,
- discolored or darkened urine,
- decreased urine production,
- swelling,
- shortness of breath.

If you have been told that you have an IgA deficiency, you have a greater risk of having an allergic reaction to WinRho<sup>®</sup> SDF. While there is only a rare chance that you may experience a sudden, severe allergic reaction after receiving WinRho<sup>®</sup> SDF, you should be aware of the early symptoms of an allergic reaction. These are:

- hives,
- rash,
- chest tightness,
- wheezing,
- shortness of breath,
- feeling light-headed or dizzy when you stand (this could mean a drop in blood pressure).

If you experience any of these symptoms, **call your doctor immediately**.

WinRho<sup>®</sup> SDF is prepared from donated human plasma. When products of this type are administered, the possibility of passing on infection from the donors can not be totally ruled out. This also applies to viruses or infections that are not yet known. A number of measures are taken to reduce the risk of passing on infection/viruses by WinRho<sup>®</sup> SDF including careful selection of blood and plasma donors to make sure those at risk of carrying infections/viruses can not donate, and the testing of each donation and the pools of plasma for signs of viruses such as AIDS virus HIV, hepatitis B virus and hepatitis C virus. The manufacturing process for WinRho<sup>®</sup> SDF also includes a number of steps that remove or inactivate viruses such as a solvent/detergent step and a special filter for removing viruses.

#### **4. WHAT ARE THE MOST COMMON SIDE EFFECTS OF WinRho® SDF?**

Like all medicines, WinRho® SDF can have side effects.

The most common side effects of WinRho® SDF are muscle pain or tenderness at the injection site, chills, skin reactions (rash and itching), fever and headache.

#### **5. WHO SHOULD NOT USE WinRho® SDF**

If you have had a severe allergic reaction such as swelling of the airway, difficulty breathing, or feeling light-headed or dizzy when you stand (drop in blood pressure), after receiving WinRho® SDF or other human immune globulins you should tell your doctor before you are given WinRho® SDF. Your doctor may choose another treatment for you.

If you know your blood type and you are Rh-negative, or if you are Rh-positive and have had your spleen surgically removed, you should not be given WinRho® SDF.

#### **6. CAN I GET WinRho® SDF IF I AM TAKING OTHER MEDICINES?**

Tell your doctor or healthcare provider that will be giving you the injection of WinRho® SDF if you are taking or have recently taken other prescription or over the counter medicines, and any supplements.

You should tell your doctor if you have recently been vaccinated or are planning to be vaccinated. WinRho® SDF may interfere with the response to certain vaccines (e.g. measles, rubella, mumps, and chicken pox) and it may be necessary to delay vaccination.

WinRho® SDF can interfere with certain blood tests. If you have a blood test after your WinRho® SDF injection, tell the person taking your blood or your doctor that you have received WinRho® SDF.

#### **7. HOW CAN I ACCESS BAXTER'S PATIENT RESOURCES?**

You can contact Baxter to receive more product information.

Product information Hotline:  
1-800-4WINRHO (1-800-494-6746)

Product Website: [www.winrho.com](http://www.winrho.com)

You can call Baxter at 1-800-423-2090 to receive more information on patient assistance programs available to you.

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