

PRODUCT MONOGRAPH

WINRHO[®] SDF

Rh_o(D) Immune Globulin (Human) for injection

Lyophilized: 600 IU (120 µg), 1500 IU (300 µg), 5000 IU (1000 µg)

Liquid: 600 IU (120 µg), 1500 IU (300 µg), 2500 IU (500 µg), 5000 IU (1000 µg), 15 000 IU (3000 µg)

World Health Organization (WHO) Anti-D Immune Globulin (Human) 2nd International Standard

Passive Immunizing Agent

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WinRho[®] SDF

Rh_o (D) Immune Globulin (Human) for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous or Intramuscular	Lyophilized / 600 IU (120 µg), 1500 IU (300 µg), 5000 IU (1000 µg)	For a complete listing see Dosage Forms, Composition and Packaging section.
	Liquid / 600 IU (120 µg), 1500 IU (300 µg), 2500 IU (500 µg), 5000 IU (1000 µg), 15 000 IU (3000 µg)	

DESCRIPTION

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human), is available as a sterile lyophilized or liquid gamma globulin (IgG) fraction of human plasma containing antibodies to the Rh_o (D) antigen (D antigen). WinRho[®] SDF is prepared from human plasma by using an anion-exchange column chromatography method^{1,2,3}.

WinRho[®] SDF is prepared from pools of human plasma that may contain the causative agents of hepatitis and other viral diseases. The manufacturing process includes both a Planova[®] 20N virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100[®]) that effectively inactivates lipid-enveloped viruses^{4,5,6}. These two processes are designed to increase product safety by reducing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B and hepatitis C. However, 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.

The product potency is expressed in International Units (IU) by comparison to the World Health Organization (WHO) second anti-D immune globulin international 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 final lyophilized product formulation is stabilized with 0.04M sodium chloride, 0.1M glycine and 0.01% (w/w) polysorbate 80. The accompanying sterile diluent contains 0.8% sodium chloride and 10mM sodium phosphate. The final liquid product formulation is stabilized with 10% maltose and 0.03% (w/w) polysorbate 80. There are no preservatives in either

formulation. WinRho[®] SDF does not contain mercury. WinRho[®] SDF contains not more than 40 µg/mL IgA when reconstituted as described below.

*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-D standard. The conversion of "µg" to "IU" is 1 µg = 5 IU.

INDICATIONS AND CLINICAL USE

Pregnancy and Other Obstetric Conditions

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human) is indicated for the prevention of Rh immunization in Rh_o (D) negative mothers not previously sensitized to the Rh_o (D) factor. WinRho[®] SDF is recommended for prevention of Rh immunization of Rh_o (D) negative women at risk of developing Rh antibodies. Rh_o (D) Immune Globulin (Human) prevents the development of Rh antibodies in the Rh_o (D) negative and previously not sensitized mother carrying a Rh_o (D) positive fetus, thus preventing the occurrence of hemolytic disease in the fetus or the newborn.

The administration of WinRho[®] SDF to women satisfying the above conditions should be done at about 28 weeks gestation when the child's father is either Rh_o (D) positive or unknown.

WinRho[®] SDF should be administered within 72 hours after delivery if the baby is Rh_o (D) positive or unknown.

WinRho[®] SDF administration is also recommended in these same women within 72 hours after spontaneous or induced abortion, amniocentesis, chorion villus sampling, ruptured tubal pregnancy, abdominal trauma or transplacental hemorrhage, unless the blood type of the fetus or father are confirmed to be Rh_o (D) negative. It should be administered as soon as possible in the case of maternal bleeding due to threatened abortion.

Transfusion

WinRho[®] SDF is recommended to prevent alloimmunization in Rh_o (D) negative female children and female adults in their child-bearing years transfused with Rh_o (D) positive RBCs or blood components with Rh_o (D) positive RBCs. Treatment should only then be carried out (without preceding exchange transfusion), if the transfused Rh_o (D) positive blood represents less than 20% of the total circulating red cells.

Immune Thrombocytopenic Purpura (ITP)

WinRho[®] SDF is recommended in the treatment of destructive thrombocytopenia of an immune etiology in situations where platelet counts must be increased to control bleeding. Clinical studies have shown that the peak platelet counts occur about seven days after IV anti-Rh_o (D) treatment. The effect is not curative but is transient; platelet counts are usually elevated from several days to several weeks. For individuals with chronic ITP, a maintenance dosage is recommended with the dosage schedule determined on an individual basis.

WinRho[®] SDF is recommended in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage for the treatment of non-splenectomized Rh_o (D) positive 1) children with chronic or acute ITP, 2) adults with chronic ITP, or 3) 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.

Geriatrics (> 65 years of age): Differences in response to treatment in those aged 65 or over as compared to younger subjects cannot be determined due to a limited number of study subjects aged 65 or over enrolled in clinical studies with WinRho,. Caution should be used when determining the dose for an elderly patient for the treatment of ITP and should take into account the increased frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy associated with advanced age. Doses starting at the low end of the dosing range should be considered when administering WinRho SDF to those aged 65 or older.

Pediatrics (< 16 years of age): WinRho[®] SDF has been evaluated in children for the treatment of chronic or acute ITP and in children with ITP secondary to HIV infection. The dosing recommendation in the treatment of children with ITP is the same as in adults^{7,8} (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Prophylaxis of Rh Immunization

WinRho[®] SDF should not be administered to patients:

- Who are Rh₀ (D) positive
- Specifically Rh₀ (D) negative women who are Rh immunized as evidenced by standard Rh antibody screening tests
- With a history of anaphylactic or other severe systemic reaction to human immune globulins
- Who are IgA deficient
- Who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

Treatment of ITP

WinRho[®] SDF should **not** be administered to patients:

- Who are Rh₀ (D) negative
- Who are splenectomised
- With ITP secondary to other conditions including Leukemia, lymphoma, or active viral infections with EBV or HCV.
- Who are elderly with underlying cardiac, renal or hepatic co-morbidities predisposing to complications of acute hemolytic reaction (AHR)
- With evidence of autoimmune hemolytic anemia (Evan's Syndrome), Systemic Lupus Erythematosus (SLE) or anti phospholipid antibody syndrome
- With a history of anaphylactic or other severe systemic reaction to human immune globulins
- Who are IgA deficient

- Who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

WinRho[®] SDF, prepared from pools of human plasma, may contain infectious agents such as viruses. (see **General** below)

Serious adverse events of intravascular hemolysis (IVH) and its complications have been reported following treatment with WinRho[®] SDF (See **Hematologic** below). A disproportionate number of IVH cases have been reported in patients with ITP secondary to hematological malignancies such as leukemia or lymphoma, or active viral infections with HCV and EBV. Some of these cases resulted in fatal outcome. Clinically compromising hemolytic anemia has the potential of precipitating acute respiratory distress syndrome (ARDS), and hemoglobinuria or hemoglobinemia may precipitate renal failure or DIC in susceptible patients. Patients of advanced age (> 65 years) with underlying cardiac, renal or hepatic co-morbidities are at increased risk of developing serious renal, hepatic or cardiovascular complications if they develop IVH. (See **WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics.**) Physicians are advised that if a patient has evidence of hemolysis (reticulocytosis greater than 3%) or is at high risk for hemolysis (positive DAT not attributed to previous immune globulin administration), alternate therapies must be used. Physicians should discuss the risks and benefits of WinRho[®] SDF and alert patients who are being treated for ITP, about the signs and/or symptoms.

Hypersensitivity reactions can occur in very rare cases of IgA deficiency or hypersensitivity to human globulin. (See **Sensitivity** below)

The liquid formulation of WinRho[®] SDF contains maltose. Maltose in IGIV products has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems. (See **Monitoring and Laboratory Tests** below)

General

Proper care should be taken when calculating the dose of WinRho[®] SDF to be administered. A confusion between International Units (IU) and Micrograms (μg) of product or between Pounds (lbs) and Kilograms (kg) for the patient's body weight could result in either an overdose that could lead to a severe hemolytic reaction (See **OVERDOSAGE** section) or a dose too low to be effective.

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. The manufacturing process includes both a Planova[®] 20N virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100[®]) that effectively inactivates lipid-enveloped viruses by

irreversibly destroying the lipid coat^{4,5,6}. These two processes are designed to increase product safety by reducing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B and hepatitis C. However, despite these measures, such products can still potentially transmit disease. The product may theoretically contain the Creutzfeldt-Jacob Disease (CJD) causing agent or Creutzfeldt-Jacob Disease variant (vCJD) agents. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to Aptevo BioTherapeutics at 1-844-859-6675.

Prophylaxis of Rh Immunization

Following administration of WinRho[®] SDF for prophylaxis of Rh immunization, patients should be kept under observation **for at least 20 minutes** for monitoring of potential adverse effects. This product should be administered under the supervision of a qualified health professional that is experienced in the use of passive immunizing agents and in the management of non-sensitized Rh_o (D) negative individuals who receive Rh_o (D) positive RBCs. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. An individual with a positive D^u test result should be screened for a large fetomaternal hemorrhage and the WinRho[®] SDF (Rh_o (D) Immune Globulin (Human)) dose adjusted accordingly.

Treatment of ITP

Following administration of WinRho[®] SDF (IV) for ITP treatment, patients should be kept under observation **for at least eight hours** for monitoring of potential adverse effects (See **WARNINGS AND PRECAUTIONS: Hematologic**). This product should be administered under the supervision of a qualified health professional that is experienced in the use of passive immunizing agents and patients diagnosed with ITP. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

WinRho[®] SDF must be administered via the intravenous route for the treatment of ITP as its efficacy has not been established by the intramuscular or subcutaneous routes.

WinRho[®] SDF should not be administered to Rh_o (D) negative or splenectomized individuals as its efficacy in these patients has not been demonstrated.

Serious adverse events of IVH have been reported following treatment of ITP patients with WinRho[®] SDF. (See **WARNINGS AND PRECAUTIONS** box and **Hematologic**)

Cardiovascular

Rare thrombotic events have been reported in association with immune globulin intravenous (Human) (IGIV)^{9,10,11}. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Although the risk of thrombotic adverse events following WinRho[®] SDF is extremely low, care

should be taken in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

There is also clinical evidence of an association between intravenous immunoglobulin product administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses, which in the case of WinRho[®] SDF, may be related to hemolysis in at risk patients. Caution should be exercised in prescribing WinRho[®] SDF in obese patients and in patients with pre-existing risk factors for thrombotic events (such as age over 65, hypertension, diabetes mellitus and a history of vascular disease including ischemic disorders or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, or severely hypovolemic patients).

Hematologic

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 Rh_o (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^{12,13,14}. 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.

Among patients treated for ITP, there have been post marketing reports of signs and symptoms consistent with intravascular hemolysis (IVH)¹⁵ that included back pain, shaking chills, fever and discoloured urine occurring, in most cases, within four hours of administration. The expected maximum decrease in hemoglobin levels (extravascular hemolysis) following WinRho[®] SDF is usually < 3.0 g/dL and occurs within 7-14 days after administration^{7,8,16-18,19}. The decrease in hemoglobin levels in patients experiencing intravascular hemolysis is typically ≥ 3.0 g/dL and usually occurs within 72 hours following WinRho[®] SDF administration^{15,20}. 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 fatal²⁰. The extent of risk of intravascular hemolysis and its complications is not known but is reported to be uncommon (> 0.1%), especially for DIC, which occurs in less than one in ten thousand cases²¹. In the rare cases reported following anti-D administration, there was no discernible contribution of gender, concomitantly administered blood/blood products, or previous treatment with WinRho[®] SDF to the development of intravascular hemolysis and its complications. (See POST MARKET ADVERSE REACTIONS) A disproportionate number of IVH cases have been reported in patients with ITP secondary to hematological malignancies such as leukemia or lymphoma, as well as active viral infections with HCV and EBV. Some of these cases resulted in fatal outcome.

Clinically compromising hemolytic anemia has the potential of precipitating acute respiratory distress syndrome (ARDS), and IVH may precipitate renal failure or DIC in susceptible patients. In patients with pre-disposing conditions, renal and cardiovascular complications of IVH may occur more frequently. Patients of advanced age (age over 65) with co-morbid conditions may be at an increased risk of developing sequelae from acute hemolytic reactions. (See **Special Populations: Geriatrics** .) Physicians are advised that if a patient has evidence of hemolysis

(reticulocytosis greater than 3%) or is at high risk for hemolysis (positive DAT not attributed to previous immune globulin administration), alternate therapies must be used.

Following administration of WinRho[®] SDF, Rh_o (D) positive ITP patients should be monitored for signs and/or symptoms of intravascular hemolysis and its complications, which include:

- Hemoglobinuria or Hemoglobinemia
- Pallor
- Hypotension
- Tachycardia
- Oliguria or anuria
- Edema
- Increased bruising and prolongation of bleeding time and clotting time which may be difficult to detect in the ITP population

For those patients eligible to receive WinRho[®] SDF for the treatment of ITP, physicians should discuss the risks and benefits of WinRho[®] SDF and alert the patients about the signs and symptoms associated with serious adverse events reported through post-marketing surveillance (see **PART III: CONSUMER INFORMATION**).

Closely monitor patients treated with WinRho[®] SDF for ITP in a healthcare setting for at least eight hours after administration. A dipstick urinalysis to monitor for hematuria and hemoglobinuria is to be performed at baseline and then after administration at 2 hours, 4 hours 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[®] SDF administration, post treatment laboratory tests should be performed including plasma hemoglobin, haptoglobin, LDH, and plasma bilirubin (direct and indirect).

Prior to discharge, patients should be instructed to self-monitor for these signs and symptoms of IVH over at least 72 hours, especially for discoloration of urine, and **advised to seek medical attention immediately in the event that signs/symptoms of IVH occur following WinRho[®] SDF administration.**

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

The diagnosis of a serious complication of an intravascular hemolysis is dependent on laboratory testing. (See **Monitoring and Laboratory Tests**).

If patients are to be transfused, Rh_o (D) negative red blood cells (PRBCs) should be used so as not to exacerbate ongoing IVH. 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) body weight should be given to minimize the risk of increasing the severity of anemia in the patient. In patients with a hemoglobin level that is less than 8 g/dL, alternative therapies should be used due to the risk of

increasing the severity of the anemia. (See **DOSAGE AND ADMINISTRATION**, Treatment of ITP)

Renal

IGIV products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, proximal tubular nephropathy, and death^{22,23}. Although these reports of renal dysfunction and acute renal failure have been associated with the use of many licensed IGIV products, those that contained sucrose as a stabilizer and were administered at daily doses of 400 mg of sucrose (or greater) have accounted for a disproportionate share of the total number²⁴. **WinRho[®] SDF does not contain sucrose** as a stabilizer.

Renal failure after intravenous WinRho[®] SDF administration may be related to hemoglobinuria (indicating IVH) in patients with pre-existing risk factors such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, sepsis, concomitant nephrotoxic medicinal products or age over 65.

Respiratory

There have been rare reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV²⁵. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support. The possibility of the rare occurrence of TRALI after WinRho[®] SDF administration cannot be ruled out. Care should be taken in patients with pre-existing respiratory conditions.

WinRho[®] SDF recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

Sensitivity

Allergic reactions have been reported following WinRho[®] administration (See **Adverse Drug Reaction Overview**). In the event of an allergic or anaphylactoid reaction to WinRho[®] SDF, a subcutaneous injection of epinephrine hydrochloride should be instituted followed by intravenous administration of hydrocortisone if necessary.

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human) contains trace quantities of IgA. Although WinRho[®] SDF has been used successfully to treat selected IgA deficient individuals, the physician must weigh the potential benefit of treatment with WinRho[®] SDF against the potential for hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA; Burks et al. (1986) have reported that as little as 15 µg IgA/mL of blood product has elicited an anaphylactic reaction in IgA deficient individuals²⁶. Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive WinRho[®] SDF or any other Immune Globulin (Human).

Patients should be informed of the early signs of hypersensitivity reaction including hives, generalized urticaria, chest tightness, wheezing, hypotension, and anaphylaxis.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with WinRho[®]. Clinical use of WinRho[®] in the prophylaxis of Rh immunization in pregnant women has not resulted in any fetal harm²⁷. WinRho[®] SDF is not indicated for the treatment of ITP in pregnancy. WinRho[®] SDF should be given to a pregnant woman with ITP only if clearly needed based on a risk: benefit assessment.

Nursing Women: It is unknown if WinRho[®] SDF is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

Pediatrics (< 16 years of age): WinRho[®] has been administered safely to children <16 years of age. The safety profile of WinRho[®] in children is similar to adults.

Geriatrics (> 65 years of age): Reported clinical experience suggests that patients of advanced age (age over 65) with co-morbid conditions such as cardio-respiratory decompensation, hepatic failure or renal insufficiency/failure may be at an increased risk of developing sequelae if an acute haemolytic reactions such as IVH occurs. Patients receiving doses in excess of 300 IU/kg of WinRho[®] SDF may also be at an increased risk of developing increased hemolysis. Most of the rare cases with fatal outcomes associated with IVH and its complications have occurred in patients of advanced age (age over 65) with co-morbid conditions.

In general, caution should be used when determining the dose for an elderly patient for the treatment of ITP. Dose selection should take into account the increased frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy associated with advanced age. Doses starting at the low end of the dosing range should be considered when administering WinRho SDF to those aged 65 or older.

Monitoring and Laboratory Tests

The liquid formulation of WinRho[®] SDF contains maltose. Maltose in IGIV 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.

In addition to anti-D antibody, WinRho[®] SDF contains trace amounts of anti-C, E, A, and B. These antibodies may be detected by laboratory screening tests.

The presence of passively administered anti-Rh₀ (D) can lead to positive direct antiglobulin and indirect antiglobulin (Coombs') test. Interpretation of direct and indirect antiglobulin tests must be made in the context of the patient's underlying clinical condition and supporting laboratory data.

Prophylaxis of Rh Immunization

The presence of passively administered Rh antibody in maternal or fetal blood can lead to a positive direct antiglobulin (Coombs') test.

Treatment of 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 and microscopic urinalysis, 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).

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 and DIC, leading in some cases to death. (See **WARNINGS AND PRECAUTIONS**).

Adverse Drug Reaction Overview

In addition to the adverse reactions described above, the following have been reported infrequently in clinical trials and/or post marketing experience, in patients treated for ITP and/or the prevention of Rh immunization, and are thought to be temporally associated with WinRho[®] use: asthenia, abdominal or back pain, hypotension, pallor, diarrhea, increased LDH, arthralgia, myalgia, dizziness, nausea, vomiting, hypertension, hyperkinesia, somnolence, vasodilation, pruritus, rash and sweating.

As is the case with all drugs of this nature, there is a remote chance of an allergic or anaphylactoid reaction with WinRho[®] SDF in individuals with hypersensitivity to blood products. An immediate reaction (anaphylaxis) is characterized by collapse, rapid pulse, shallow respiration, pallor, cyanosis, edema or generalized urticaria.

Prophylaxis of Rh Immunization

Reactions to Rh₀ (D) Immune Globulin (Human) are rare in Rh₀ (D) negative individuals. Discomfort and light swelling at the site of injection and slight elevation in temperature have been reported in a small number of cases.

Treatment of ITP

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human), is administered to Rh₀ (D) positive patients with ITP. Therefore, side effects related to the destruction of Rh₀ (D) positive red blood cells, most notably decreased hemoglobin, can be expected.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Prophylaxis of Rh Immunization

The safety of WinRho[®] was evaluated in clinical trials (n= 2062) in pregnant Rh_o (D)-negative women whose baby's father's Rh_o (D) serotype was either positive or unknown²⁸⁻³⁰. Only 1 adverse reaction was reported during the clinical studies. The adverse reaction was an anaphylactic type reaction due to a considerably large dose administered within a short time period (12 x 600 IU).

In a clinical study with 5 healthy Rh_o (D) negative males, Rh_o (D) positive fetal red cells were administered to volunteers by IV infusion and then 1 to 2 days later the fetal red cells were cleared by IV administration of 600 IU (120 µg) WinRho[®] SD. At 6 to 8 hours after administration of WinRho[®] SD to these subjects, there was an elevation in mean levels of granulocytes from 4.25 to 7.88 x 10⁹/L (p < 0.01) and monocytes from 0.38 to 0.64 x 10⁹/L (p < 0.02). Levels of phagocytic leucocytes returned to pretreatment levels by 24 hours after WinRho[®] SD treatment. This effect of WinRho[®] SD is believed to result from the anti-Rh_o (D) mediated clearance of Rh_o (D) positive fetal red cells as it was not observed at much higher dosages of WinRho[®] SD when no Rh_o (D) positive red cells were present in the circulation.

Treatment of ITP

The safety of WinRho[®] was evaluated in clinical trials (n=161) in children and adults with acute and chronic ITP and adults and children with ITP secondary to HIV^{7,8,16-18}. Overall 417 adverse events were reported by 91 patients (57%). The most common adverse events were headache (14% of the patients), fever (11% of the patients), and asthenia (11% of the patients). A total of 117 adverse drug reactions were reported by 46 patients (29%). Headache, chills, and fever were the most common related adverse events (Table 1). With respect to safety profile per administration, 60 of 848 (7%) of infusions in the clinical trials 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 immunoglobulin infusion.

Table 1 Adverse Drug Reactions in Patients with ITP Treated with WinRho, with an Incidence ≥ 5%

Body System	Adverse Event	All Studies	Children	Adults
		# of Patients (%)		
All Body Systems	Overall	46 (29)	19 (26)	27 (31)
Body as a Whole	Overall	40 (25)	19 (26)	21 (24)
	Asthenia	6 (4)	2 (3)	4 (5)
	Chills	13 (8)	4 (5)	9 (10)
	Fever	9 (6)	5 (7)	4 (5)
	Headache	18 (11)	8 (11)	10 (12)
	Infection	4 (3)	4 (5)	0 (0)
Nervous System	Overall	9 (6)	4 (5)	5 (6)
	Dizziness	6 (4)	2 (3)	4 (5)

Less common adverse drug reactions (< 5%) include:

Body as a whole: abdominal pain, asthenia, back pain, infection, malaise, pain;

Cardiovascular system: hypertension, palpitation;

Digestive system: anorexia, diarrhea, gastroenteritis, gastrointestinal disorder, glossitis, ulcerative stomatitis, vomiting;

Hematic and Lymphatic system: anemia, hypochromic anemia;

Metabolic and nutritional system: weight gain;

Musculoskeletal system: arthralgia;

Nervous system: anxiety, dizziness, hypertonia, hypesthesia, somnolence, tremor;

Respiratory system: asthma, dyspnea, pharyngitis, rhinitis;

Skin and appendages: urticaria.

The safety of WinRho[®] was compared to high dose IGIV (2.0 g/kg), low dose IGIV (0.8 g/kg), and prednisone in children with acute ITP. The most common related adverse events in the WinRho[®] group were chills, fever, and headache (Table 2), similar to the related adverse events reported in all ITP studies (Table 1). The most common related adverse events after high dose and low dose IGIV administrations were headache and vomiting and after prednisone administration was increased appetite.

Table 2 Adverse Drug Reactions with an Incidence ≥ 5% in Children with Acute ITP

Body System Preferred Term	High Dose IGIV (2.0 g/kg) N=35	Low Dose IGIV (0.8 g/kg) N=34	Prednisone (4.0 mg/kg/day) N=39	WinRho (250 IU /kg IV) N=38
	No. of Patients (%)			
All Body System	21 (60%)	14 (41%)	15 (39%)	10 (26%)
<u>Body as a Whole</u>	19 (54%)	10 (29%)	5 (13%)	10 (26%)
Abdominal Pain	0	3 (9%)	3 (8%)	2 (5%)
Chills	5 (14%)	1 (3%)	0	3 (8%)
Fever	9 (26%)	3 (9%)	1 (3%)	3 (8%)
Headache	12 (34%)	8 (24%)	2 (5%)	3 (8%)
<u>Digestive System</u>	10 (29%)	5 (15%)	9 (23%)	3 (8%)
Anorexia	0	0	0	2 (5%)
Diarrhea	0	0	2 (5%)	1 (3%)
Dyspepsia	0	0	2 (5%)	0
Increased Appetite	0	0	5 (13%)	0
Vomiting	10 (30%)	5 (15%)	3 (8%)	1 (3%)

Body System Preferred Term	High Dose IGIV (2.0 g/kg) N=35	Low Dose IGIV (0.8 g/kg) N=34	Prednisone (4.0 mg/kg/day) N=39	WinRho (250 IU /kg IV) N=38
	No. of Patients (%)			
<u>Nervous System</u>	4 (11%)	1 (3%)	6 (15%)	0
Emotional Liability	0	0	3 (8%)	0
Nervousness	0	0	2 (5%)	0
Tremor	2 (6%)	0	1 (3%)	0
<u>Respiratory System</u>	0	2 (6%)	1(3%)	2 (5%)
<u>Skin & Appendages</u>	1 (3%)	0	2 (5%)	0
Acne	0	0	2 (5%)	0

Due to the proposed mechanism of action (i.e. F_c blockade, platelet sparing via anti-RBC antibodies), it is anticipated that administration of WinRho[®] SDF to Rh_o (D)-positive patients will produce some degree of extravascular hemolysis. The mean decrease in hemoglobin within 7 days after WinRho[®] SDF administration was 1.2 g/dL in all ITP studies. In a clinical study in normal healthy Rh_o (D)-positive subjects, the decrease in hemoglobin levels following WinRho[®] SDF administration appeared to be dose-dependent¹⁹.

In 4 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 of 137 patients (3.7%) had a maximum decrease in hemoglobin of greater than 4 g/dL (range 4.2 to 6.1 g/dL). In most cases, the RBC destruction is believed to occur in the spleen. However, signs and symptoms consistent with IVH, including back pain, shaking chills, and/or hemoglobinuria, have been reported, occurring within minutes and up to a few days after WinRho[®] SDF administration.

Post-Market Adverse Drug Reactions

In addition to the adverse events experienced by subjects during clinical trials, the following additional adverse events have been reported (spontaneous reporting) during the post-marketing use of WinRho[®] SDF. Since these events have been reported voluntarily from a population of uncertain size, the exact frequency rates cannot be precisely calculated; however, they have been rarely or very rarely reported²¹.

Evaluation and interpretation of the post-marketing events is confounded by underlying diagnosis, concomitant medications, pre-existing conditions and inherent limitations of passive surveillance. Due to the complexity of the clinical reports and the minimal amount of pre- and post-WinRho SDF data provided, causation has not been described for the cases below.

In the post-marketing surveillance of WinRho SDF from March 1993 to March 2010 a total of 187 serious cases of suspected and confirmed cases of IVH were reported. Of the 187 serious

cases, 54 cases were considered definite IVH (with evidences of hemoglobinuria and/or hemoglobinemia), 60 were probable IVH and 56 were possible IVH. The remaining reported cases were either unlikely IVH (n=11) or there was no additional clinical information available (n=6). Of the 54 serious Definite IVH cases reported, 23 were associated with acute onset or exacerbation of renal insufficiency, 11 cases with DIC, 13 cases with cardiovascular events, and 6 cases with respiratory distress syndrome. Seventeen (17) of the 54 serious IVH cases reported had fatal outcome. Approximately 76% of the patients with fatal outcomes were over 65 years of age and in 16 out of those 17 fatal cases (94%), the patients had history of serious underlying co-morbid diseases that are considered to have either induced or exacerbated pathological conditions leading to fatal outcomes.

The etiology of IVH following WinRho® SDF administration is unknown. Risk factors associated with this adverse event include: active viral infections (including EBV or HCV), hematological malignancies (including non-Hodgkin’s lymphoma, Hodgkin’s disease or Chronic Lymphocytic Leukemia), autoimmune disorders (SLE, antiphospholipid syndrome, and autoimmune hemolytic anemia), pre-treatment renal insufficiency, pre-treatment low haemoglobin levels (< 10g/dL), concomitantly administered PRBCs, or WinRho® SDF dose in excess of 300 IU/kg. In patients with predisposing conditions and advanced age (> 65 years old) IVH occurrence, complication of IVH and the severity of its complications, including occurrence of death, are substantially higher than in patients less than 65 years of age.

The listing of adverse drug reactions in all patients treated for Prophylaxis of Rh immunization and ITP is given below in Table 3 and Table 4, respectively.

Table 3 Post-marketing adverse drug reactions in patients treated for Prophylaxis of Rh Immunization

<u>General disorders and administration site condition</u>	Injection site reaction *
<u>Immune disorders</u>	Hypersensitivity
	Anaphylactic reaction
<u>Skin and subcutaneous tissue disorders</u>	Pruritus
	Rash

* Includes induration, pruritus or swelling at injection site.

Table 4 Post-marketing adverse drug reaction in patients treated for ITP

MedDRA System Organ Class	MedDRA Preferred Term
Blood and lymphatic system disorders	Intravascular haemolysis
	Disseminated intravascular coagulation
	Haemolysis
	Haemolytic anaemia
	Haemoglobinemia
Cardiac disorders*	Cardiac arrest
	Cardiac failure
	Myocardial infarction
	Tachycardia
Gastrointestinal disorders	Nausea

MedDRA System Organ Class	MedDRA Preferred Term
General disorders and administration site conditions	Chest pain
	Fatigue
	Oedema
Hepatobiliary disorders	Jaundice
Immune Disorders	Hypersensitivity
	Anaphylactic reaction
Investigations	Decreased Haemoglobin
	Blood lactate dehydrogenase increased
Musculoskeletal and connective tissue disorders	Myalgia
	Muscle spasm
	Pain in extremities
Renal and urinary disorders	Renal failure
	Renal impairment
	Anuria
	Chromaturia
	Haemoglobinuria
Respiratory, thoracic, and mediastinal disorders	Haematuria
	Acute respiratory distress syndrome
Skin and subcutaneous tissue disorders	Transfusion related acute lung injury
	Hyperhidrosis
Vascular disorders	Pruritus
	Hypotension
	Pallor
	Vasodilation

* Most of the cases reporting cardiac events in association with the WinRho SDF administration presented other co-morbid conditions that might precipitate or exacerbate the cardiac events.

DRUG INTERACTIONS

Serious Drug Interactions

- Live attenuated virus vaccines: immune globulin administration may impair the efficacy of live attenuated virus vaccines for a period of 3 months or more. (see **Overview** below)

Overview

Immune globulin administration may impair the efficacy of live attenuated vaccines such as measles, rubella, mumps and varicella³¹⁻³³ **Drug-Drug Interactions** (Table 5). Vaccination with live virus vaccines should be deferred until approximately three months after administration of WinRho[®] SDF. Patients who have received WinRho[®] SDF shortly after live virus vaccination, should be revaccinated 3 months after the administration of the immune globulin.

Administration of WinRho[®], Rh_o (D) Immune Globulin (Human) concomitantly with other drugs has not been evaluated. It is recommended that WinRho[®] SDF be administered separately from other drugs (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions

Table 5 Established or Potential Drug-Drug Interactions

Rho (D) Immune Globulin (Human)	Ref	Effect	Clinical comment
Live attenuated virus vaccines (e.g. measles, rubella, mumps, varicella)	T	Immune globulin may impair efficacy	If WinRho [®] SDF is given less than 14 days after vaccination, revaccination should be considered.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

After administration of WinRho[®] SDF, a transitory increase of passively transferred antibodies in the patient’s blood may result in misleading positive results in serological testing (e.g. Coombs’ test).

DOSAGE AND ADMINISTRATION

As WinRho[®] SDF has one principle unit of measure (international units, IU) and has historically had another (micrograms, µg; See [DESCRIPTION](#)), physicians and pharmacists must use the appropriate unit of measure to determine the amount of WinRho[®] SDF administered, as per recommendations below. As ITP treatment is weight-based, the correct unit for dose determination (kg) must be used to determine total WinRho[®] SDF dose. Misuse of either the WinRho[®] SDF dosing unit or patient weight determination in pounds will result in overdose or underdose situations.

Recommended Dose and Dosage Adjustment

Prophylaxis of Rh Immunization

Pregnancy and Other Obstetric Conditions

WinRho[®] SDF should be administered by intravenous or intramuscular injection.

Table 6 provides dosing guidelines based on the condition being treated.

Table 6 Obstetric Indications and Recommended Dose

Indication		Dose (Administer IM or IV)
<i>Pregnancy:</i>		
Routine antepartum prophylaxis	At Week 28-30 of gestation*	1,500 IU (300 µg)
Postpartum prophylaxis (required only if the newborn is Rh _o (D)-positive)	Within 72 hours of birth of Rh (D) positive baby**	600 IU (120 µg)
<i>Obstetric Conditions:</i>		
Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage)	Within 72 hours of complication	1,500 IU (300 µg) ³⁴
Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) [†] or obstetric manipulative procedures (e.g., external version, abdominal trauma)	Within 72 hours of procedure	1500 IU (300 µg)

IU, international units; µg, micrograms

*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.

†For amniocentesis and chorionic villus sampling repeat every 12 weeks during pregnancy

Transfusion

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human) should be administered for treatment of incompatible blood transfusions or massive fetal hemorrhage as outlined in the table below:

Table 7 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 of red blood cells
Intramuscular	60 IU (12 µg)/mL Blood	120 IU (24 µg)/mL of red blood 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.

Patients receiving an incompatible transfusion and those with ITP, who receive doses of anti-D immunoglobulin exceeding 300 IU/kg (60µg/kg), are at an increased risk of developing chills, fever and headache as well as a larger hemoglobin decrease and IVH.

Treatment of 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 **MUST** be used (see **WARNINGS AND PRECAUTIONS**).

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human), must be given by intravenous administration for the treatment of ITP. An intravenous dose of 125 to 300 IU/kg (25 to 60µg/kg) body weight is recommended for individuals with ITP. **Since WinRho[®] SDF is administered on a weight-based regimen per kilogram (kg), patient weight determination must be taken in kilograms (kg) as inappropriate use of pounds (lbs) will result in significant overdosing of WinRho[®] SDF.**

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

Initial Dosing

After confirming that the patient is Rh_o (D) positive, an initial dose of 250 IU/kg (50µg/kg) body weight is recommended for the treatment of ITP. If the patient has a hemoglobin level between 8-10 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 (See **WARNINGS AND PRECAUTIONS, Hematologic**). The initial dose may be administered in two divided doses given on separate days, if desired. In patients with a hemoglobin level less than 8 g/dL, alternative treatments should be used due to the risk of increasing the severity of the anemia.

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, Rh_o (D) Immune Globulin (Human), is recommended. The frequency and dose used should be administered based on the patient's clinical response by assessing platelet counts, red cell counts, hemoglobin, and reticulocyte levels.

Administration

WinRho[®] SDF, Lyophilized Formulation, should be reconstituted only with the accompanying vial of **Sterile Diluent**. If reconstituted product is not used immediately, then it should be stored at room temperature for no longer than four hours. It should not be administered concurrently with other products. There is no reconstitution required for the Liquid Formulation of WinRho[®] SDF.

Parenteral products such as WinRho[®] SDF, Rh_o (D) Immune Globulin (Human) should be inspected for particulate matter and discoloration prior to administration.

Bring the product to room temperature prior to dosing.

Aseptically administer the product intravenously in a suitable vein with a rate of injection of 1,500 IU (300 µg)/5 to 15 seconds. If dilution of WinRho SDF is preferred prior to intravenous administration, use normal saline as diluent. Do not use Dextrose (5%) in water (D5W). No other diluents have been tested.

Intramuscular injections are made 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. Discard any unused portion.

Lyophilized Formulation

Reconstitution:

WinRho[®] SDF should be reconstituted only with the accompanying vial of sterile diluent. Use aseptic technique throughout.

1. Reconstitute shortly before use.
2. Remove caps from the diluent and product vials.
3. Wipe exposed central portion of the rubber stopper with suitable disinfectant.
4. Withdraw diluent using a suitable syringe and needle. Use 1.25 to 2.5 mL of **sterile diluent** for intravenous injection or 1.25 mL for intramuscular injection for 600 IU (120 µg) and 1,500 IU (300 µg). Use 8.5 mL of **sterile diluent** for intravenous and intramuscular injection for 5,000 IU (1,000 µg) (see Table 8). Discard any unused diluent.
5. Inject diluent slowly at an angle so that the liquid is directed onto the inside glass wall of the vial containing the freeze-dried pellet.
6. Wet pellet by gently tilting and inverting the vial. **Do not shake.** Avoid frothing. Gently swirl upright vial until dissolved (less than ten minutes).

Table 8 Reconstitution of WinRho[®] SDF

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
Intravenous Injection			
600 IU (120 µg)	2.5 mL	2.4 mL	240 IU (48 µg)/mL
1,500 IU (300 µg)	2.5 mL	2.4 mL	600 IU (120 µg)/mL
5,000 IU (1,000 µg)	8.5 mL	8.2 mL	588 IU (118 µg)/mL
Intramuscular Injection			
600 IU (120 µg)	1.25 mL	1.2 mL	480 IU (96 µg)/mL
1,500 IU (300 µg)	1.25 mL	1.2 mL	1,200 IU (240 µg)/mL
5,000 IU (1,000 µg)	8.5 mL	8.2 mL*	588 IU (118 µg)/mL

* To be administered into several sites

Liquid Formulation

The following table describes the target fill volumes for each of the dosage sizes for the liquid presentation of WinRho[®] SDF.

Table 9 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 labelled dosage of WinRho[®] SDF, Rh₀ (D) Immune Globulin Intravenous (Human). If partial vials are required for dosage calculation, then calculation should be based on the target fill volume. For ease in withdrawing the contents of the vial, draw back the plunger of a sterile syringe (with the needle and needle cover in place) to admit air into the syringe. Depress the plunger of the syringe to inject air into the vial. Invert vial and aspirate content of vial into syringe.

OVERDOSAGE

Treatment of ITP and Prophylaxis of Rh Immunization

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 fetomaternal hemorrhage. Adverse events reported in ITP patients have included chills, fever, headache and larger hemoglobin decreases while no hemolytic reactions were reported in prophylaxis of Rh immunization 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Prophylaxis of Rh Immunization

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human), is used to suppress the immune response of non-sensitized Rh₀ (D)-negative individuals who receive Rh₀ (D)-positive RBCs either by fetomaternal hemorrhage during delivery of an Rh₀ (D) positive infant, abortion (either spontaneous or induced), following amniocentesis, abdominal trauma or mismatched transfusion^{27,35,36}. Administration of anti-Rh₀ (D) antibody to the Rh₀ (D)-negative mother

prevents an immune response with subsequent anti- Rh₀ (D) antibody formation. The exact mechanism of action has yet to be determined.

WinRho[®] SDF, when administered within 72 hours of a full-term delivery of an Rh₀ (D)-positive infant by an Rh₀ (D)-negative mother, will reduce the incidence of Rh alloimmunization from 12 – 13% to 1 – 2%. The 1 – 2% is, for the most part, due to alloimmunization 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%^{27,37,38}.

Treatment of ITP

In a clinical study of WinRho[®] therapy of children with chronic ITP (duration of ITP > 6 months), administration of anti-Rh₀ (D) increased platelet counts from $36 \pm 14 \times 10^9/L$ to $263 \pm 138 \times 10^9/L$; peak platelet levels were recorded at about one week after WinRho[®] therapy; the effect of WinRho[®] on platelet levels lasted a median of 29 days from the start of therapy. Comparable results were obtained in a clinical study of both adult and children with ITP of varying etiologies including ITP secondary to HIV infection. However, larger increases in platelet levels were seen in children than in adults.

WinRho[®] SDF is used to increase platelet counts in non-splenectomized Rh₀ (D) positive patients with ITP and to alleviate clinical signs of bleeding in this patient population. The mechanism of action is not completely understood, but is thought to be due to binding of anti-Rh₀ (D) (anti-D) to the Rh₀ (D) RBC resulting in production of anti-D coated RBC complexes. This results in Fc receptor blockade, thus sparing antibody-coated platelets because of the preferential destruction of antibody-coated RBC complexes by the macrophages located in the reticuloendothelial system¹²⁻¹⁴.

Pharmacodynamics

Two pharmacodynamic studies (WR-002 and 5696-2) measuring the clearance of Rh₀ (D)-positive RBCs from the bloodstream after injection of WinRho[®] and WinRho[®] SD have been conducted^{30,39}. These 15 Rh₀ (D)-negative subjects received fetal Rh₀ (D)-positive erythrocytes followed by WinRho[®], given either IM (n = 10) or IV (n = 5). Clearance of Rh₀ (D)-positive RBCs was complete within 24 hours. Six months later 5 subjects were re-challenged with Rh₀ (D)-positive RBCs and none of them had evidence of a secondary immune response after having received a second administration of WinRho[®]. Up to 102 days after the second injection, no demonstrable anti-D antibodies were present in the sera of any of the subjects. These pharmacodynamic results are consistent with the prophylaxis of Rh alloimmunization in Rh₀ (D)-negative females exposed to Rh₀ (D)-positive blood.

Pharmacokinetics

Pharmacokinetics of IV and IM administrations of WinRho[®] SDF were evaluated (WS-031)⁴⁰. The area under the curve (AUC_{0-t}) was similar after administration of IV and IM WinRho[®] SDF which suggests IM administration is nearly 100% bioavailable. Peak levels (C_{max}) following IV administration was higher than the IM administration. The half-life (t_{1/2}) after IM administration was longer than the IV administration.

The pharmacokinetics of the lyophilized and the liquid formulations of WinRho[®] SDF were compared in 2 clinical studies (WS-029 and WS-038)^{41,42}. In WS-029 the pharmacokinetic parameters of IV administration of the 2 formulations were evaluated. The measured mean of

AUC_{0-t} and the C_{max} were similar after IV administrations of lyophilized and liquid WinRho[®] SDF. However, the 90% Confidence interval fell outside the predefined range of 80 to 125 % for the ratio of AUC_{0-t} after correction for actual product potency. The t_{1/2} after IV administration of the 2 formulations was similar. The pharmacokinetics of the IM administrations of lyophilized and the liquid formulations of WinRho[®] SDF were also compared (WS-038). The AUC_{0-t} and the C_{max} appeared to be comparable after IM administrations of the 2 formulations, but a number of subjects were excluded in order to show comparability. Data from this trial was insufficient to demonstrate bioequivalence, based on the predefined criteria. The t_{1/2} was the same after IM administration of the lyophilized and liquid WinRho[®] SDF (26 days).

Absorption: Following WinRho[®] administration by an IV route, peak levels are achieved within two hours, while the mean time to peak is 4 to 12 days when the drug is administered by an IM route⁴³. When 600 IU (120 µg) of product was administered to non-pregnant volunteers, the peak levels of passive anti- Rh₀ (D) antibody were about 20 ng/mL and 40ng/mL when the product was administered by IV and IM routes, respectively⁴³.

Distribution: When only 600 IU (120 µg) of drug is administered to pregnant women, passive anti-Rh₀ (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.

The bioavailability following IV administration of WinRho[®] SDF is expected to be immediate and complete, with passive antibodies quickly distributed between plasma and extravascular spaces⁴⁴. Based on AUC comparisons from pharmacokinetic studies of WinRho[®] SDF and other hyperimmune products, IM administration is expected to be nearly 100% bioavailable^{40,45}.

Metabolism: Immune globulins and immune complexes are metabolized in the reticuloendothelial system⁴⁴.

Excretion: Based on numerous pharmacokinetic studies, in normal healthy individuals, WinRho[®] has typically an elimination half-life of 18 to 24 or 24 to 30 days following IV or IM administration, respectively. The half-life is expected to vary from patient to patient^{40-42,46}.

Duration of Effect

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human), has been shown to increase platelets in ITP patients^{7,17,29,47-49}. 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.

STORAGE AND STABILITY

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human) is stable at 2-8°C until the expiry date indicated on the label. Store WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human) at 2-8°C. **Do not freeze. Do not use after expiration date.**

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature immediately prior to use. Following reconstitution of lyophilized WinRho[®] SDF, the product should be clear or slightly opalescent.

Do not use solutions that appear cloudy or contain deposits.

DOSAGE FORMS, COMPOSITION AND PACKAGING

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human) is available in the dosage forms outlined below:

Lyophilized

Product Contents

A carton box containing approximately **600 IU (120 µg)** of anti-Rh_o (D), supplied freeze-dried in a 3 mL type 1 glass tubing vial fitted with a 13 mm lyophilization stopper of rubber formulation and a 13 mm flip-off seal, one single dose vial of **sterile diluent**, non-pyrogenic for reconstitution of WinRho[®] SDF and a package insert.

A carton box containing approximately **1,500 IU (300 µg)** of anti-Rh_o (D), supplied freeze-dried in a 3 mL type 1 glass tubing vial fitted with a 13 mm lyophilization stopper of rubber formulation and a 13 mm flip-off seal, one single dose vial of **sterile diluent**, non-pyrogenic for reconstitution of WinRho[®] SDF and a package insert.

A carton box containing approximately **5,000 IU (1,000 µg)** of anti-Rh_o (D), supplied freeze-dried in a 6 mL type 1 glass tubing vial fitted with a 20 mm lyophilization stopper of rubber formulation and a 20 mm flip-off seal, one single dose vial of **sterile diluent**, non-pyrogenic for reconstitution of WinRho[®] SDF and a package insert.

Liquid

Product Contents

A carton box containing a **0.5 mL** single dose vial of **600 IU (120 µg)** of anti-Rh_o (D) in a 3 mL type 1 glass tubing vial fitted with a 13 mm stopper of rubber formulation and a 13 mm flip-off seal and a package insert.

A carton box containing a **1.3 mL** single dose vial of **1,500 IU (300 µg)** of anti-Rh_o (D) in a 3 mL type 1 glass tubing vial fitted with a 13 mm stopper of rubber formulation and a 13 mm flip-off seal and a package insert.

A carton box containing a **2.2 mL** single dose vial of **2,500 IU (500 µg)** of anti-Rh_o (D) in a 3 mL type 1 glass tubing vial fitted with a 13 mm stopper of rubber formulation and a 13 mm flip-off seal and a package insert.

A carton box containing a **4.4 mL** single dose vial of **5,000 IU (1,000 µg)** of anti-Rh_o (D) in a 6 mL type 1 glass tubing vial fitted with a 20 mm stopper of rubber formulation and a 20 mm flip-off seal and a package insert.

A carton box containing a **13.0 mL** single dose vial of **15,000 IU (3,000 µg)** of anti-Rh_o (D) in a 20 mL type 1 glass tubing vial fitted with a 20 mm stopper of rubber formulation and a 20 mm flip-off seal and a package insert.

Composition

WinRho[®] SDF, Rh_o (D) Immune Globulin (Human) for injection, is available as a sterile lyophilized or liquid gamma globulin (IgG) fraction of human plasma containing antibodies to the Rh_o (D) antigen (D antigen).

Lyophilized

The final product formulation includes the addition of sodium chloride to yield 0.04 M, glycine to yield 0.1 M and polysorbate 80 to yield 0.01% (w/w). The accompanying sterile diluent contains 0.8 % sodium chloride and 10 mM sodium phosphate.

Liquid

The final liquid product formulation is stabilized with 10% maltose and 0.03% (w/w) polysorbate 80.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Rh ₀ (D) Immune Globulin (Human)
Chemical name:	Rh ₀ (D) Immune Globulin (Human)
Molecular formula and molecular mass:	Glycoprotein of approximately 160 kDa
Structural formula:	Gamma Immune Globulin (IgG)
Physicochemical properties:	IgG is a monomeric protein with a sedimentation coefficient of 7S and a molecular weight ranging from 146 to 170 kDa. Carbohydrate content of IgG is approximately 2-3%.

Product Characteristics

WinRho[®] SDF, Rh₀ (D) Immune Globulin (Human), is available as a sterile lyophilized or liquid gamma globulin (IgG) fraction of human plasma containing antibodies to the Rh₀ (D) antigen (D antigen). WinRho[®] SDF is prepared from human plasma by using an anion-exchange column chromatography method.

Viral Inactivation

The manufacturing steps are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, using tri-n-butyl phosphate and Triton X-100[®] (Triton[®] is a trademark of Rohm and Haas Company) is effective in inactivating known enveloped viruses such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Immunodeficiency virus (HIV). Virus filtration using a Planova[®] 20N Virus Filter (Planova[®] is a trademark of Asahi Kasei Kogyo Kabushiki Kaisha Corporation) is effective in reducing some known enveloped and non-enveloped model viruses. In addition, the anion exchange chromatographic step has been shown to contribute to the removal of the non-lipid enveloped viruses HAV (hepatitis A virus) and MMV (murine minute virus), which is a model for parvovirus B19.

The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in (Table 10).

Table 10 Viral validation of model viruses in laboratory studies

Genome	Enveloped			Non-Enveloped			
	RNA		DNA	RNA		DNA	
Virus	HIV-1	BVDV	PRV	HAV	EMC	MMV	PPV
Family	Retro	Flavi	Herpes	Picorna		Parvo	
Size (nm)	80-100	50-70	120-200	25-30	30	20-25	18-24
Anion-Exchange Chromatography	Not Evaluated			2.3	NE	3.4	NE

(Partitioning)							
20 N Filtration (Size Exclusion)	≥ 4.7	≥ 3.5	≥ 5.6 ^a	NE	4.4	NE	3.5 ^b
Solvent/Detergent	> 4.7	≥ 7.1	≥ 5.4	Not Evaluated			
Total Reduction (log₁₀)	≥ 9.4	≥ 10.6	≥ 11.0	2.3	4.4	3.4	3.5

Abbreviations:

HIV-1: human immunodeficiency virus-1; relevant virus for human immunodeficiency virus-1 and model for HIV-2

BVDV: bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)

PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes

HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general

EMC: encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general

MMV: murine minute virus; model for human B19 parvovirus and for small non-enveloped viruses in general

PPV: porcine parvovirus; model for human B19 parvovirus and for small non-enveloped viruses in general

NE.: not evaluated

^a The PRV was retained by the 0.1µ pre-filter during the virus validation. Since manufacturing employs a 0.1µm pre-filter before the 20N filter, the claim of □ ≥5.6 reduction is considered applicable.

^b One of the five PPV runs for the 20N filter yielded a 1.25 log clearance over the 0.1 µm pre-filter. Since production employs a 0.1 µm pre-filter before the 20N filter, the 1.25 logs were added to the 2.2 log clearance obtained over the 20N filter, and the value of 3.5 was used for determination of the mean reduction factor.

CLINICAL TRIALS

Prophylaxis of Rh Immunization

The efficacy and safety of WinRho[®] in prophylaxis of Rh immunization was evaluated in 3 clinical trials. Study WR-003⁵⁰ was a phase 3 study that evaluated the efficacy and safety of WinRho[®] in pregnant Rh_o (D)-negative women whose husband’s Rh_o (D) serotype was either positive or unknown. The study PM-010 was a phase 4 retrospective survey of the results of pregnancies treated with WinRho[®] SDF to prevent Rh immunization. Based on a prospective protocol, a case report form was designed to transfer information out of an existing medical database of women who had received WinRho[®] SDF in order to assess efficacy and safety of the product in antenatal prophylaxis of Rh immunization. Study PM-011 was a phase 4 post-marketing surveillance of efficacy and safety of WinRho[®] SD in the prophylaxis of Rh immunization following the introduction of WinRho[®] SD in Ireland.

Study demographics and trial design

A total of 1186 Rh_o (D)-negative pregnant women were administered WinRho[®] in study WR-003⁵⁰. In addition, WinRho[®] was administered to the mother postpartum if the Rh_o (D) serotype of the infant was positive. In study PM-010, 226 Rh_o (D)-negative pregnant women were treated antenatally and postpartum with WinRho[®] SDF. One patient had a spontaneous abortion and the Rh_o (D) blood type of the fetus was unknown. All analyses were done on the intent-to-treat population which included 226 subjects. In study PM-011, a total of 650 Rh_o (D)-negative women were administered WinRho[®] SD antenatally or postpartum.

Table 11 Summary of patient demographics for clinical trials in prophylaxis of Rh immunization studies

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender
WR-003	Phase 3, open label, single arm study in pregnant Rh _o (D)-negative women	1) 600 IU (IV) at 28 weeks + 600 IU (IV) postpartum	93	n/a	All female
		2) 600 IU (IV) at 28 & 34 weeks + 600 IU (IV) postpartum	131		
		3) 1200 IU (IV) at 28 weeks + 600 IU (IV) postpartum	962		
PM-010	Phase 4, open-label study in pregnant Rh _o (D)-negative women	Individual antenatal infusions of 600-1500 IU (IV or IM), 600 IU (IV) postpartum	226	28.1 ± 5.7 Years (15-41)	All female
PM-011	Phase 4, open-label study in pregnant Rh _o (D)-negative women	1 x 600 IU (IV)	648	29.8 ± 5.4 Years (15-45)	All female
		2 x 600 IU (IV)	1		
		12 x 600 IU (IV)	1		

Study results

In all 3 studies the primary efficacy endpoint was the rate of Rh immunization of the pregnant Rho (D)-negative mother by her Rh_o (D)-positive baby at delivery (studies WR-003 and PM-010), 6 months post-delivery (studies WR-003 and PM-011), and 12 months post-delivery (study PM-011). These results demonstrated the effectiveness of WinRho[®] in preventing Rh immunization.

Table 12 Results of studies WR-003, PM-010, and PM-011 in prophylaxis of Rh immunization

Study #	Primary Endpoints	Results Statistical Test/P value
WR-003	Rh isoimmunization of mother at delivery and at 6 months post-delivery	Chi-square test between observed (0/806) and expected* (15/806) isoimmunization / p<0.001
PM-010	Rh isoimmunization of mother at delivery	Chi-square test between observed (0/226) and expected* (4/226) isoimmunization / p<0.05

Study #	Primary Endpoints	Results Statistical Test/P value
PM-011	Rh isoimmunization of mother at 6 and/or 12 months post-delivery	None of the mothers were Rh immunized at 6 months and/or 12 months follow-up

* Based on historical data. ^{27,51,52}

Treatment of ITP

The efficacy and safety of WinRho[®] in the treatment of ITP was evaluated in 4 clinical studies. Study AITP was a phase 3 study in children with acute ITP. In AITP, the efficacy and the safety of WinRho[®] was compared to standard therapies for treatment of acute ITP in children: 1- high dose IGIV, 2- low dose IGIV, and 3-prednisone. Study CITP was a phase 3 study that evaluated the efficacy and safety of WinRho[®] in children with chronic ITP. Study BITP-1 was a phase 3 study that evaluated the efficacy and safety of WinRho[®]/WinRho[®] SD in adults and children with ITP secondary to HIV infection. Study BITP-2 was a phase 3 study that evaluated the efficacy and safety of WinRho[®]/WinRho[®] SD in adults with chronic ITP. Study BITP-3 was a phase 3 study that evaluated the efficacy and safety of WinRho[®]/WinRho[®] SD in adults with acute ITP.

Table 13 Summary of patient demographics for clinical trials in ITP studies

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender
AITP	Phase 3, open label, randomized, parallel arm study in children with acute ITP	WinRho at 250 IU/kg	38	6.8 ± 4.5 years (0.7-15)	15M:23F
		IGIV at 2.0 g/kg	35	6.1 ± 3.8 years (1-15)	22M:13F
		IGIV at 0.8 g/kg	34	5.9 ± 4.4 years (1-16)	17M:17F
		Prednisone at 4.0 mg/kg/day for 7days	39	6.3 ± 4.6 years (0.9-16)	25M:14F
CITP	Phase 3, open label, single arm study in children with chronic ITP	WinRho/WinRho SD at 250 IU/kg and additional doses if clinically required	25	10.6 ± 4.6 (years (2-18))	8M:17F

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender
BITP-1	Phase 3, open-label, single arm study in children and adults with ITP secondary to HIV	WinRho/WinRho SD at 50-375 IU/kg	65	30.7 ±14.0 years) (0.5-58)	60M:5F
BITP-2	Phase 3, open-label, single arm study in adults with chronic ITP	WinRho/WinRho SD at 50-375 IU/kg	26	44.3 ± 20.7 years (18-80)	13M:13F
BITP-3	Phase 3, open-label, single arm study in adults with acute ITP	WinRho/WinRho SD at 50-375 IU/kg	7	51.7 ± 22.5 years (19-84)	3M:4F

Study results

Childhood Acute ITP (AITP)

A multicenter, randomized, controlled trial comparing Rh₀ (D) IGIV to high dose and low dose Immune Globulin (Human) and prednisone was conducted in 146 non-splenectomized, Rh₀ (D) positive children with acute ITP and platelet counts less than 20 x 10⁹/L. Of 38 patients receiving Rh₀ (D) IGIV (125 IU/kg [25 µg/kg] on days 1 and 2), 32 patients (84%) responded (platelet count ≥ 50 x 10⁹/L) with a mean peak platelet count of 319.5 x 10⁹/L (range 61 x 10⁹/L to 892 x 10⁹/L), with no statistically significant differences compared to other treatment arms. The mean times to achieving ≥ 20 x 10⁹/L or ≥ 50 x 10⁹/L platelets for patients receiving Rh₀ (D) IGIV were 1.9 and 2.8 days, respectively. When comparing the different therapies for time to platelet count ≥ 20 x 10⁹/L or ≥ 50 x 10⁹/L, 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, respectively.

Table 14 Results of study AITP in treatment of acute ITP in children

Primary Endpoints	WinRho	High Dose IGIV	Low Dose IGIV	Prednisone
Time to reach platelet count ≥ 50 x 10 ⁹ /L (days)	2.8	2.6	2.0	3.2
Time to reach platelet count ≥ 20 x 10 ⁹ /L (days)	1.9	1.6	1.3	1.9

Childhood Chronic ITP (CITP)

In an open-label, single arm, multicenter study, 25 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 (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 x 10⁹/L and a doubling of the baseline. In the per protocol analysis, 19 of 24 patients responded for an overall response rate of 79%, an overall mean peak platelet count of 229.4 x 10⁹/L (range 43.3 x 10⁹/L to 456 x 10⁹/L), and a mean duration of response of 36.5 days (range 6 to 84).

Table 15 Results of study CITP in treatment of chronic ITP in children

Primary Endpoints	First Course	Overall
Proportion of responding patients	92%	92%
Mean Peak platelet count (x 10 ⁹ /L)	241.1	225.6
Maximum change in platelet count from baseline (x 10 ⁹ /L)	206.6	192.6

ITP Secondary to HIV Infection (BITP-1)

Eleven (11) children and 52 adults who were non-splenectomized, Rh_o (D) positive with all Walter Reed classes of HIV infection and ITP, with initial platelet counts of ≤ 30 x 10⁹/L or requiring therapy, were treated with 50 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 (57) of 63 patients responded (increase ≥ 20 x 10⁹/L) 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 60.9 x 10⁹/L (range -2 x 10⁹/L to 565 x 10⁹/L), and the mean peak platelet count was 81.7 x 10⁹/L (range 16 x 10⁹/L to 593 x 10⁹/L).

Table 16 Results of study BITP-1 in treatment of ITP secondary to HIV infection in children and adults

Primary Endpoints	First Course	Overall
Proportion of responding patients	75%	90%
Mean Peak platelet count (x 10 ⁹ /L)	87.3	81.7
Maximum change in platelet count from baseline (x 10 ⁹ /L)	66.6	60.9

Adult Chronic ITP (BITP-2)

Twenty-six (26) non-splenectomized, Rh_o (D) positive adults with ITP of greater than six months duration and platelet counts < 30 x 10⁹/L or requiring therapy were enrolled in a single-arm,

open-label trial and treated with 50 to 375 IU/kg (20 to 75 µg/kg) Rh₀ (D) IGIV (mean dose 231 IU/kg [46.2 µg/kg]). In the per protocol analysis, 21 of 24 patients responded (increase $\geq 20 \times 10^9/L$) during the first two courses of therapy for an overall response rate of 88% with a mean peak platelet count of $92.3 \times 10^9/L$ (range 8.0 to $229 \times 10^9/L$).

Table 17 Results of study BITP-2 in treatment of chronic ITP in adults

Primary Endpoints	First Course	Overall
Proportion of responding patients	83%	88%
Mean Peak platelet count ($\times 10^9/L$)	92.6	92.3
Maximum change in platelet count from baseline ($\times 10^9/L$)	66.7	65.6

Adult Acute ITP (BITP-3)

Seven (7) non-splenectomized, Rh₀ (D) positive adults with ITP of less than six months duration and platelet counts $< 30 \times 10^9/L$ or requiring therapy were enrolled in a single-arm, open-label trial and treated with 50 to 375 IU/kg (20 to 75 µg/kg) Rh₀ (D) IGIV (mean dose 187 IU/kg [37.3 µg/kg]). In the per protocol analysis, 5 of 6 patients responded (increase $\geq 20 \times 10^9/L$) during the only course of therapy for a response rate of 83% with a mean peak platelet count of $106.8 \times 10^9/L$ (range 18.0 to $240 \times 10^9/L$).

Comparative Bioavailability Studies

In two comparative pharmacokinetics studies, 101 volunteers were administered the liquid or lyophilized formulation of WinRho[®] SDF IV (N=41) or IM (N=60). In WS-029 the pharmacokinetic parameters of IV administration of the 2 formulations were evaluated. The measured mean of AUC_{0-t} and the C_{max} were similar after IV administrations of lyophilized and liquid WinRho[®] SDF. However, the 90% Confidence interval fell outside the predefined range of 80 to 125% for the ratio of AUC_{0-t} after correction for actual product potency. The AUC_{0-t} and the C_{max} appeared to be comparable after IM administrations of the 2 formulations (study WS-038)⁴², but a number of subjects were excluded in order to show comparability. Data from this trial was insufficient to demonstrate bioequivalence, based on the predefined criteria. The average peak concentrations (C_{max}) of anti-Rh₀ (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.

Table 18 Pharmacokinetic Parameters for Liquid and Lyophilized WinRho SDF in Healthy Volunteers (IV Administration)

<p>WinRho[®] SDF IV</p> <p>Liquid vs Lyophilized</p> <p>From measured data</p> <p>Arithmetic Mean (+SD)</p>
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Parameter	Liquid Formulation	Lyophilized Formulation	% Ratio of Geometric Means	Confidence Interval
AUC _{0-∞} (ng*day/mL)	24163 (15514)	24993 (13674)		
AUC _{0-t} (ng*day/mL)	17890 (7334)	18096 (7154)	100.17	81.85-122.60
C _{MAX} (ng/mL)	1473 (142)	1494 (268)	99.89	92.08-108.38
T _{MAX} (days)	0.011 (0.014)	0.029 (0.073)		
t _½ (days)	44 (28)	48 (31)		

Table 19 Pharmacokinetic Parameters for Liquid and Lyophilized WinRho SDF in Healthy Volunteers (IM Administration)

WinRho[®] SDF IM				
Liquid vs Lyophilized				
From measured data¹				
Arithmetic Mean (+SD)				
Parameter	Liquid Formulation	Lyophilized Formulation	% Ratio of Geometric Means	Confidence Interval
AUC ₀₋₂₈ (ng*h/mL)	67113 (11582)	60248 (14115)	109.8	100.0-120.5
AUC _{0-t} (ng*h/mL)	95638 (27812)	77235 (30539)		
C _{MAX} (ng/mL)	151 (30.6)	132 (38.6)	112.5	99.9-126.7
T _{MAX} (days)	3.2 (1.0)	3.8 (1.9)		
t _½ (days)	25.5 (10.2)	25.7 (9.0)		

¹ The presented values were obtained after exclusion of 5 of 60 subjects in the trial.

DETAILED PHARMACOLOGY

Pharmacokinetics

Six pharmacokinetic studies (WR-001, 5696-1, WS-019, WS-029, WS-031, and WS-038) were conducted with different generations of the lyophilized formulation WinRho[®] SDF. Study WR-001 compared the pharmacokinetics of IM versus IV using first generation product, WinRho[®]. In study 5696-1 the pharmacokinetics of WinRho[®] were compared to the second generation product, WinRho[®] SD. In study WS-019 pharmacokinetics of the early development formulation of WinRho[®] SD (without polysorbate 80) were compared to the commercial formulation of WinRho[®] SD (with polysorbate 80). In study WS-031 pharmacokinetics of different doses and routes of administration of the third generation product, WinRho[®] SDF, were compared. From the pharmacokinetic studies it was shown that the 3 generations of the product, WinRho[®], WinRho[®] SD, and WinRho[®] SDF, have similar pharmacokinetic parameters and that modifications to the manufacturing and formulation of the product over the years did not affect its pharmacokinetic profile^{40-43,46,53}.

In 2 clinical studies (WS-029 and WS-031) the pharmacokinetics of the lyophilized and the liquid formulations of WinRho[®] SDF were compared. Please refer to the **CLINICAL TRIALS, Comparative Bioavailability Studies** section for additional information.

Pharmacodynamics

A clinical study (WR-002) was conducted with 10 Rh_o (D)-negative volunteers³⁰. All subjects were administered an IV infusion of Rh_o (D)-positive fetal red cells. Two days after injection of the red cells, five subjects were given an IM injection of 600 IU (120 µg) WinRho[®] and five subjects were given an IV injection of 600 IU (120 µg) WinRho[®]. Fetal red cells were cleared from the circulation of the subjects within eight hours of IV administration of the drug or within 24 hours of IM administration of the drug. None of the subjects had evidence of Rh alloimmunization either by screening for anti-Rh_o (D) (two stage papain, indirect Coombs, saline and low ionic Autoanalyzer techniques) or by challenge of the subjects with Rh_o (D) fetal cells six months after first clearance of the red cells with WinRho[®] (Table 20).

Another clinical study (5696-2) was conducted with five Rh_o (D)-negative volunteers; the same study design was used for clearance of Rh_o (D)-positive red cells after IV administration of 600 IU (120 µg)³⁹. All fetal red cells were cleared from the circulation of the volunteers within eight hours of administration of WinRho SD[®] (Table 20). None of the subjects had evidence of Rh alloimmunization by screening for anti- Rh_o (D) antibodies at three and six months after WinRho[®] SD administration (Table 20).

Table 20 Comparison of Rho (D)-positive RBC Clearance

Time (hr) after Administration of Drug	WinRho [®] SD Treated Subjects 5696-2		WinRho [®] Treated Subjects WR-002	
	Fetal RBC	% Fetal RBC	Fetal RBC	% Fetal RBC
Pre-treatment	481 ± 106	100%	342 ± 27	100%

Time (hr) after Administration of Drug	WinRho [®] SD Treated Subjects 5696-2		WinRho [®] Treated Subjects WR-002	
	Fetal RBC	% Fetal RBC	Fetal RBC	% Fetal RBC
1	390 ± 106	82% ± 19%	236 ± 53	70% ± 18%
3	38 ± 35	7% ± 7%	55 ± 11	16% ± 2%
8	0	0	0	0
24	0	0	0	0

TOXICOLOGY

An IV acute toxicity study was conducted in mice using WinRho[®], Rh_o (D) Immune globulin (Human). An LD50 was not determined, as the maximal dose used did not kill any experimental animals. A lower limit of 18,750 IU (3,750 µg) anti-Rh_o (D)/kg body weight was established as the LD50 for this drug. Neither observation nor necropsy of the experimental animals revealed any acute toxicity related to the study drug.

In a clinical study with healthy Rh_o (D)-negative male volunteers, WinRho[®] SD, Rh_o (D) Immune Globulin (Human), has been administered IV at a dose of 250 IU/kg (50 µg/kg) of body weight. In that study, there were no signs of toxicity which could be attributed to WinRho[®] SD. There was a moderate elevation of serum LDH levels ($p < 0.03$).

WinRho[®] has undergone clinical testing in Rh_o (D)-positive individuals with Immune Thrombocytopenic Purpura. In these studies, subjects received multiple intravenous injections from 1,500 IU (300 µg) anti-Rh_o (D) (total) to 375 IU (75 µg) anti- Rh_o (D)/kg body weight. In these studies the only associated signs of toxicity, which were identified, were mild compensated hemolysis.

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PART III: CONSUMER INFORMATION

WinRho[®] SDF

Rh₀ (D) Immune Globulin (Human) for injection

This leaflet is part III of a three-part "Product Monograph" published when WinRho[®] SDF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about WinRho[®] SDF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Protection (prophylaxis) against the development of harmful antibodies in Rh-negative women exposed to Rh-positive blood. This exposure can occur in an Rh-negative woman:
 - o Upon receipt of an Rh-positive blood transfusion
 - o During pregnancy or after delivery if the baby is Rh-positive or the Rh status is unknown.
- Treatment of Immune Thrombocytopenic Purpura (ITP)
 - o In children with chronic or acute ITP
 - o In adults with chronic ITP
 - o In children and adults with ITP secondary to HIV infection

What it does:

Protection (prophylaxis) against the development of harmful antibodies in Rh-negative women exposed to Rh-positive blood.

Pregnant women often have different blood groups from their babies. This is normal and usually not a problem. However, in some cases, these blood groups differ in an important way, which is the presence or absence of a particular protein on the outside of the red blood cell. If you have this protein, you are "Rh positive". If you do not have this protein, you are "Rh negative".

Sometimes during pregnancy and delivery, a small amount of the baby's blood can cross the placenta and enter the mother's blood stream. This can also happen in events such as a miscarriage, abdominal injury, abortion and amniocentesis. If this transfer of blood occurs from an Rh positive fetus to an Rh negative mother, the mother's immune system will see the baby's blood as "foreign" and will produce antibodies which destroy the baby's blood cells. In the first pregnancy, most of these antibodies will remain in the mother's circulation and the baby is usually not significantly affected. During subsequent pregnancies, however, a problem may occur if the new baby is Rh positive and if there is another transfer of blood across the placenta. The mother's immune system has a good memory. It can rapidly produce the same antibodies again, and they can re-cross the placenta in large numbers and start to destroy the new baby's own blood before birth, causing a number of serious complications.

WinRho[®] SDF is an injection of antibodies administered with every pregnancy, when the mother is known to be Rh-negative. It works in your bloodstream to destroy any circulating blood cells from your baby before your immune system has a chance to make its own antibodies. Your baby is not affected by this injection.

WinRho[®] SDF Product Monograph

Injections may also be given in connection with abortion, miscarriage or amniocentesis or because of mismatched blood transfusion. As a result of the WinRho[®] SDF injection, your immune system never makes its own antibodies to your baby's Rh positive red blood cells, so you and your baby are protected.

Treatment of ITP

ITP is a bleeding disorder caused by an abnormally low level of platelets. Platelets are found in the bloodstream and are needed for blood to clot properly. When blood does not clot properly, there is a tendency to bruise and bleed easily. ITP is a disorder of the immune system. Usually, the body will manufacture antibodies which coat disease-causing organisms, aiding their removal by the spleen. This process helps the immune system fight infection in the body. In ITP, the body mistakenly produces antibodies against its own platelets. When these antibodies coat the platelets, it results in their rapid and premature destruction by the spleen. ITP can affect adults or children; it can occur without warning and for no apparent reason, or it can occur as a result of a primary illness or infection. There is no evidence to suggest that ITP is inherited or related to personal habits or diet. It cannot be passed to other people like the common cold.

WinRho[®] SDF contains a concentration of antibodies which specifically bind to Rh positive red blood cells. When administered to an Rh positive patient, it is thought that WinRho[®] SDF coats the Rh positive red cells, causing their destruction by the spleen, thereby preventing the destruction of platelets. This results in increased levels of circulating platelets and an alleviation of the symptoms of ITP.

When it should not be used:

- WinRho[®] SDF must not be used if you are hypersensitive (allergic) to human immunoglobulin or to any other ingredients of WinRho[®] SDF.
- WinRho[®] SDF should not be used for Rh prevention if you are Rh-positive or if you are Rh-negative but have been previously Rh immunized.
- WinRho[®] SDF should not be used to treat ITP if you are Rh-negative, or if you have had your spleen surgically removed.
- WinRho[®] SDF should not be used to treat ITP if you have Leukemia, lymphoma or active viral infections such as Hepatitis C or Epstein Barr Virus (EBV).
- WinRho[®] SDF should not be used to treat ITP if you have a condition that causes red blood cell destruction (i.e. haemolytic anemia).
- WinRho SDF should not be used to treat ITP if you are elderly with conditions that could increase the risk of developing acute haemolytic reactions (AHR) or its complications.
- WinRho[®] SDF should not be used to treat patients who are IgA deficient.

What the medicinal ingredient is:

Rh₀ (D) Immune Globulin (Human)

What the important nonmedicinal ingredients are:

Lyophilized (Freeze-dried) Formulation

Human plasma protein
Sodium Chloride
Glycine
Polysorbate 80

Liquid Formulation

Human plasma protein
Maltose
Polysorbate 80

WinRho[®] SDF may contain trace amounts of tri-n-butyl phosphate and Triton X-100.

What dosage forms it comes in:

Lyophilized: 600 IU (120 µg), 1500 IU (300 µg),
5000 IU (1000 µg)

Liquid: 600 IU (120 µg), 1500 IU (300 µg),
2500 IU (500 µg), 5000 IU (1000 µg),
15 000 IU (3000 µg)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- WinRho[®] SDF is made from human plasma, which may contain the causative agents of viral disease. The risk of getting a disease from this product has been reduced by screening plasma donors, testing for the presence of certain viruses and by utilizing manufacturing steps that inactivate and remove certain viruses. However, there is still a possibility that plasma products could transmit disease
- In rare cases WinRho[®] SDF may cause intravascular hemolysis (breakdown of red blood cells in the blood vessel) or its complications. Before using WinRho[®] SDF, discuss the risks and the benefits with your doctor.
- The liquid formulation of WinRho[®] SDF contains maltose. Maltose in similar products has been shown to give falsely high blood glucose levels in certain types of blood glucose testing systems.
- Allergic or anaphylactic reactions are rare. These reactions can occur in patients with a history of allergies to blood products or in patients lacking the IgA blood protein.

BEFORE you use WinRho[®] SDF talk to your doctor or pharmacist if:

- You have experienced allergic reactions to blood products in the past
- You have a known IgA deficiency
- You have recently received any vaccinations
- You are allergic to WinRho[®] SDF or any of its ingredients or components of the container
- You are taking any other medications including over the counter medications and herbal products.

- You are over 65 years of age and have other co-existing medical conditions such as those related to your heart, lungs, liver or kidneys.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with WinRho[®] SDF have not been established.

Immune globulins like WinRho[®] SDF may reduce the effectiveness of certain live virus vaccines such as measles, rubella (i.e. German measles), mumps and varicella (i.e. chickenpox). Talk to your doctor if you have been recently vaccinated.

PROPER USE OF THIS MEDICATION

Usual dose:

Protection against the development of harmful antibodies in Rh-negative women exposed to Rh-positive blood

Pregnancy and other obstetric conditions:

A dose of 1,500 IU (300 µg) of WinRho[®] SDF is given at 28 weeks of pregnancy. A 600 IU (120 µg) dose of WinRho[®] SDF is given after delivery of an Rh-positive baby.

A 1500 IU (1300 µg) dose of WinRho[®] SDF is given within 72 hours of obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage).

A dose of 1,500 IU (300 µg) of WinRho[®] SDF is given within 72 hours of invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or obstetric manipulative procedures (e.g., external version, abdominal trauma). In case of threatened abortion, WinRho[®] SDF is given as soon as possible.

Transfusion

If you are exposed to Rh-positive blood or red blood cells, WinRho[®] SDF will be administered by your doctor to prevent development of harmful antibodies. The usual dose of WinRho[®] SDF is between 45 IU/mL and 120 IU/mL (9 µg/mL and 24 µg/mL).

Treatment of ITP

WinRho[®] SDF is given at an initial dose of 250 IU/kg (50 µg/kg). If you need additional therapy to increase your platelet counts, then a dose of 125 to 300 IU/kg (25 to 60 µg/kg) is given.

Overdose:

In the treatment of ITP patients, WinRho[®] SDF overdoses have been reported to result in more chills, fever and headaches in patients as well as greater decreases in red blood cell measures (i.e. hemolysis with urine discoloration). One of these cases resulted in death. Patients should discuss with their physician the WinRho[®] SDF dose they are receiving and report the side effects to the physician without delay.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

GENERAL

If you have been told that you have an IgA deficiency, you have a greater risk of having an allergic reaction to WinRho[®] SDF. While there is only a rare chance that you may experience a

sudden, severe allergic reaction after receiving WinRho[®] SDF, you should be aware of the 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.**

Protection against the development of harmful antibodies in Rh-negative women exposed to Rh-positive blood

Reactions to WinRho[®] SDF are rare in Rh-negative individuals. Discomfort or slight swelling at the injection site and slight elevation in temperature have been reported in a small number of cases.

Treatment of ITP

Most WinRho[®] SDF patients do not experience any drug related adverse effects. Among the few who do, the most commonly reported effects include headache, chills and fever. Rare side effects such as vomiting, nausea, low blood pressure, an increase in your heartbeat, joint pain, anemia (decrease in red blood cells), intravascular hemolysis (destruction of red blood cells), back pain, shaking chills, hemoglobinuria (brownish discoloration of urine), and acute renal insufficiency (kidney failure) may also occur. If you experience any of the following symptoms after receiving WinRho[®] SDF, you should **call your doctor immediately:**

- back pain,
- discolored or darkened urine,
- decreased urine production,
- jaundice,
- swelling,
- shortness of breath.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Discomfort or swelling at injection site, elevation in temperature	✓		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Uncommon	Allergic reaction		✓	✓
	Back pain, discoloured urine, darkened urine, decreased urine output, jaundice, swelling, shortness of breath		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking WinRho[®] SDF, contact your doctor or pharmacist.

HOW TO STORE IT

Store WinRho[®] SDF under refrigeration.

Do not freeze.

Do not use after expiration date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reaction associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect[™] Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Aptevo BioTherapeutics at 1-844-859-6675.

This leaflet was prepared by Aptevo BioTherapeutics.

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