

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

WINRHO[®] SDF

Rh_o(D) Immunoglobulin (Human) for Injection Single-Dose Vials:

600 international units (120 mcg)
1,500 international units (300 mcg)
2,500 international units (500 mcg)
5,000 international units (1,000 mcg)
15,000 international units (3,000 mcg)

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

Passive Immunizing Agent

Saol Therapeutics Research Limited

Dublin, Ireland

Distributor (in Canada):

Emergent BioSolutions Canada Inc.

Winnipeg, MB, R3T 5Y3

Submission Control #: 211513

Date of Approval: April 24, 2020

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE	4
CONTRAINDICATIONS	5
WARNINGS AND PRECAUTIONS	6
ADVERSE REACTIONS.....	12
DRUG INTERACTIONS	17
DOSAGE AND ADMINISTRATION	17
OVERDOSAGE	20
ACTION AND CLINICAL PHARMACOLOGY	21
STORAGE AND STABILITY	23
SPECIAL HANDLING INSTRUCTIONS	23
DOSAGE FORMS, COMPOSITION AND PACKAGING	23
PART II: SCIENTIFIC INFORMATION	24
PHARMACEUTICAL INFORMATION.....	24
CLINICAL TRIALS	25
DETAILED PHARMACOLOGY	31
TOXICOLOGY	32
REFERENCES	32
PART III: PATIENT MEDICATION INFORMATION	35

WinRho[®] SDF

Rho (D) Immunoglobulin (Human) for Injection

PART I: HEALTH PROFESSIONAL INFORMATION SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients ^a
Intravenous or Intramuscular	Solution for Injection: 600 international units (120 mcg) 1,500 international units (300 mcg) 2,500 international units (500 mcg) 5,000 international units (1,000 mcg) 15,000 international units (3,000 mcg)	Maltose Polysorbate 80 Water for injection

^a WinRho SDF may contain trace amounts of tri-n-butyl phosphate and octoxynol.

DESCRIPTION

WinRho[®] SDF, Rho (D) Immunoglobulin (Human), is available as a sterile liquid gamma globulin (IgG) fraction of human plasma containing antibodies to the Rho (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 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 octoxynol) that effectively inactivates lipid-enveloped viruses.⁴ 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 virus (HBV) and hepatitis C virus (HCV). In addition, an anion exchange step contributes to the removal of small non-lipid enveloped viruses. 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 by comparison to the World Health Organization (WHO) second anti-D immunoglobulin international standard. A 1,500 International Unit * (300 mcg) vial contains sufficient anti-Rho (D) to effectively suppress the immunizing potential of approximately 17 mL of Rho (D) (D-positive) red blood cells (RBCs).

The liquid product formulation is stabilized with 10% maltose and 0.03% (w/w) polysorbate 80. WinRho SDF does not contain preservatives or mercury. WinRho SDF contains not more than 40 mcg/mL IgA.

*In the past, a full dose of Rho (D) Immunoglobulin (Human) has traditionally been referred to as a "300 mcg" dose. Potency and dosing recommendations are now expressed in international units by comparison to the WHO anti-D standard. The conversion of "mcg" to "international units" is 1 mcg

= 5 international units.

INDICATIONS AND CLINICAL USE

Pregnancy and Other Obstetric Conditions

WinRho SDF, Rho (D) Immunoglobulin (Human) is indicated for the prevention of Rh immunization in Rho (D) negative mothers not previously sensitized to the Rho (D) factor. WinRho SDF is recommended for prevention of Rh immunization of Rho (D) negative women at risk of developing Rh antibodies. Rho (D) Immunoglobulin (Human) prevents the development of Rh antibodies in the Rho (D) negative and previously not sensitized mother carrying a Rho (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 Rho (D) positive or unknown.

WinRho SDF should be administered within 72 hours after delivery if the baby is Rho (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 Rho (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 Rho (D) negative female children and female adults in their child-bearing years transfused with Rho (D) positive RBCs or blood components with Rho (D) positive RBCs. Treatment should only then be carried out (without preceding exchange transfusion), if the transfused Rho (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-Rho (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 Rho (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 (greater than 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 SDF. 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 (less than 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 (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Prophylaxis of Rh Immunization

WinRho SDF should **not** be administered to patients:

- Who are Rho (D) positive
- Specifically, Rho (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 this drug or other human immune globulins
- Who are IgA deficient
- Who have antibodies to IgA or a history of IgA hypersensitivity
- 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 Rho (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 antiphospholipid antibody syndrome
- With a history of anaphylactic or other severe systemic reaction to this drug or other human

immune globulins

- Who are IgA deficient
- Who have antibodies to IgA or a history of IgA hypersensitivity
- 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 **Hemolysis** 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 (greater than 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 **Hypersensitivity** below)

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 and micrograms (mcg) 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 20N virus filter that effectively removes lipid-enveloped and non-enveloped viruses based on size and a solvent/detergent treatment step that effectively inactivates lipid-enveloped viruses by irreversibly destroying the lipid coat.⁴ 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 virus (HBV) and hepatitis C virus (HCV). 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 Saol Therapeutics Research Limited at 1-833-644-4216.

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 Rho (D) negative individuals who receive Rho (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^h test result. An individual with a positive D^h test result should be screened for a large fetomaternal hemorrhage and the WinRho SDF (Rho (D) Immunoglobulin (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: Hemolysis**). 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 Rho (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 **Hemolysis**).

Thromboembolic Events

Thrombosis may occur in patients receiving immune globulin treatment. Patients at risk may include those with a history of cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, history of arterial or venous thrombosis, estrogen use, indwelling central vascular catheters, and/or known or suspected hyperviscosity. Thrombosis may occur in the absence of known risk factors. 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).

Hemolysis

Although the mechanism of action of WinRho SDF in the treatment of ITP is not completely understood, it is postulated that anti-D binds to the Rho (D) RBC resulting in formation of antibody-coated RBC complexes. Immune-mediated clearance of the antibody-coated RBC complexes would spare the antibody-coated platelets because of the preferential destruction of antibody-coated RBC complexes by the macrophages located in the reticuloendothelial system.^{8,9,10} 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)¹¹ 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 less than 3.0 g/dL and occurs within 7-14 days after administration.¹² The decrease in hemoglobin levels in patients experiencing intravascular hemolysis is typically greater than or equal to 3.0 g/dL and usually occurs within 72 hours following WinRho SDF administration.^{11,13}

Potentially serious complications of intravascular hemolysis that have also been reported include clinically compromising anemia, acute renal insufficiency or disseminated intravascular coagulation (DIC) that have, in some cases, been fatal.¹³ The extent of risk of intravascular hemolysis and its complications is not known but is reported to be uncommon (greater than 0.1%), especially for DIC, which occurs in less than one in ten thousand cases.¹⁴ 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 predisposing conditions, renal and cardiovascular complications of IVH may occur more frequently. Patients of advanced age (age over 65) with co-morbid conditions, such as heart, lung, liver or kidney disease, 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, Rho (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: PATIENT MEDICATION 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 intravascular hemolysis is dependent on laboratory testing. (See [Monitoring and Laboratory Tests](#)).

If patients are to be transfused, Rho (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 international units/kg (25 to 40 mcg/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](#))

Acute Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, acute tubular necrosis, proximal tubular nephropathy, and death may occur in patients receiving immune globulin treatment, including WinRho SDF.^{15,16} 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 number of reports. **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.

Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine before the initial infusion of WinRho SDF and at appropriate intervals thereafter for those patients at risk of developing renal dysfunction/failure.

Transfusion-Related Acute Lung Injury (TRALI)

There have been rare reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV.¹⁷ 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-HLA and anti-neutrophil antibodies in both the product and patient serum.

Hypersensitivity

Allergic reactions have been reported following WinRho SDF administration (See [Adverse Drug Reaction Overview](#)). WinRho SDF should be administered in a setting where appropriate equipment, medication and personnel trained in the management of hypersensitivity, anaphylaxis and shock are available. 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 contains trace quantities of IgA (less than or equal to 40 mcg/mL). 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 mcg IgA/mL of blood product has elicited an anaphylactic reaction in IgA deficient individuals.¹⁸ 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 SDF. Clinical use of WinRho in the prophylaxis of Rh immunization in pregnant women has not resulted in any fetal harm.¹⁹ 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 (less than 16 years of age): WinRho has been administered safely to children less than 16 years of age. The safety profile of WinRho in children is similar to adults.

Geriatrics (greater than 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 international units/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 pyrroloquinoline quinone (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.

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-Rho (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 SDF 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 Rho (D) Immunoglobulin (Human) are rare in Rho (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, Rho (D) Immunoglobulin (Human), is administered to Rho (D) positive patients with ITP. Therefore, side effects related to the destruction of Rho (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 Rho (D)-negative women whose baby's father's Rho (D) serotype was either positive or unknown. 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 international units).

In a clinical study with 5 healthy Rho (D) negative males, Rho (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 international units (120 mcg) 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 $7.88 \times 10^9/L$ (p less than 0.01) and monocytes from 0.38 to $0.64 \times 10^9/L$ (p less than 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-Rho (D) mediated clearance of Rho (D) positive fetal red cells as it was not observed at much higher dosages

of WinRho SD when no Rho (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. 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; less than 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 greater than or equal to 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 (less than 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 greater than or equal to 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 international units /kg IV) N=38
	No. of Patients (%)			
All Body System	21 (60%)	14 (41%)	15 (39%)	10 (26%)
Body as a Whole	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%)
Digestive System	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%)
Nervous System	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
Respiratory System	0	2 (6%)	1(3%)	2 (5%)
Skin & Appendages	1 (3%)	0	2 (5%)	0
Acne	0	0	2 (5%)	0

Due to the proposed mechanism of action (i.e. Fc blockade, platelet sparing via anti-RBC antibodies), it is anticipated that administration of WinRho SDF to Rho (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 Rho (D)-positive subjects, the decrease in hemoglobin levels following WinRho SDF administration appeared to be dose-dependent. ¹²

In 4 clinical trials of patients treated with the recommended initial intravenous dose of 250

international units/kg (50 mcg/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 international units/kg (25 to 40 mcg/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 adverse events have been reported (spontaneous reporting) during the post-marketing use of WinRho SDF (Table 3). Since these events have been reported voluntarily from a population of uncertain size, the indication and causal relationship is not always known and the exact frequency rates cannot be precisely calculated; however, they have been rarely or very rarely reported.¹⁴

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 (less than 10 g/dL), concomitantly administered PRBCs, or WinRho SDF dose in excess of 300 international units/kg. In patients with predisposing conditions and advanced age (greater than 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.

Table 3: Reported Post-Marketing Adverse Drug Reactions

Blood and Lymphatic	Intravascular haemolysis
	Disseminated intravascular coagulation
	Haemoglobinemia
Cardiac*	Cardiac failure
	Myocardial infarction
	Tachycardia
Gastrointestinal	Nausea
General	Chest pain
	Fatigue
	Edema
	Pain
Hepatobiliary	Jaundice
Immune System	Anaphylactic reaction/shock
	Hypersensitivity
	Injection site reaction including induration, pruritis and/or swelling
Musculoskeletal	Myalgia
	Muscle spasm
	Pain in extremities
Renal	Renal failure
	Anuria
	Chromaturia
	Haematuria
	Haemoglobinuria
Respiratory	Acute respiratory distress syndrome
	Dyspnea
	Transfusion related acute lung injury
Skin	Hyperhidrosis
	Pruritus
	Rash

* 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
<ul style="list-style-type: none"> • 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 varicella ²⁰⁻²² (See [Drug-Drug Interactions, Table 4](#)). 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 SDF 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 4: Established or Potential Drug-Drug Interactions

Rho (D) Immunoglobulin (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: 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) and has historically had another (micrograms, mcg; 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, kilogram (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 5 provides
 Saol Page 18 of 44

dosing guidelines based on the condition being treated.

Table 5: Obstetric Indications and Recommended Dose

Indication	Timing of Administration	Dose (Administer IM or IV)
<i>Pregnancy:</i>		
Routine antepartum prophylaxis	At Week 28-30 of gestation*	1500 international units (300 mcg)
Postpartum prophylaxis (required only if the newborn is Rh ₀ (D)-positive or unknown)	Within 72 hours of birth of Rh (D) positive baby**	600 international units (120 mcg)
<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	1500 international units (300 mcg) 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 international units (300 mcg)

mcg, 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, Rh₀ (D) Immunoglobulin (Human) should be administered for treatment of incompatible blood transfusions or massive fetal hemorrhage as outlined in Table 6.

Table 6: Transfusion Indication and Recommended Dose

Route of Administration	WinRho SDF Dose	
	If exposed to Rh ₀ (D) Positive Whole Blood	If exposed to Rh ₀ (D) Positive Red Blood Cells
Intravenous	45 international units (9 mcg)/mL blood	90 international units (18 mcg)/mL of red blood cells
Intramuscular	60 international units (12 mcg)/mL blood	120 international units (24 mcg)/mL of red blood cells

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

Administer 6,000 international units (1,200 mcg) 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 international units/kg (60 mcg/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, Rho (D) Immunoglobulin (Human), must be given by intravenous administration for the treatment of ITP. An intravenous dose of 125 to 300 international units/kg (25 to 60 mcg/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 international units/kg (60 mcg/kg) has not been evaluated and is not recommended.

Initial Dosing

After confirming that the patient is Rho (D) positive, an initial dose of 250 international units/kg (50 mcg/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 international units/kg (25 to 40 mcg/kg) should be given to minimize the risk of increasing the severity of anemia in the patient (See **WARNINGS AND PRECAUTIONS**). 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 international units/kg (25 to 60 mcg/kg) body weight of WinRho SDF, Rho (D) Immunoglobulin (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

Parenteral products such as WinRho SDF, Rh_o (D) Immunoglobulin (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 international units (300 mcg)/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.

The following table describes the target fill volumes for each of the dosage sizes for WinRho SDF.

Table 7: WinRho SDF Dosage Size and Target Fill Volumes

Vial Size	Target Fill Volume*
600 international units (120 mcg)	0.5 mL
1,500 international units (300 mcg)	1.3 mL
2,500 international units (500 mcg)	2.2 mL
5,000 international units (1,000 mcg)	4.4 mL
15,000 international units (3,000 mcg)	13.0 mL

*Extractable volumes are confirmed using a 21 gauge needle as per USP General Chapters <1> Injections.

Note: The entire contents of the vial should be removed to obtain the labelled dosage of WinRho SDF, Rh_o (D) Immunoglobulin (Human) for injection. 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 mcg and international units (1mcg = 5 international units), 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 mcg and international units, a

patient with significant comorbidities 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, Rho (D) Immunoglobulin (Human), is used to suppress the immune response of non-sensitized Rho (D)-negative individuals who receive Rho (D)-positive RBCs either by fetomaternal hemorrhage during delivery of an Rho (D) positive infant, abortion (either spontaneous or induced), following amniocentesis, abdominal trauma or mismatched transfusion^{19, 24, 25}. Administration of anti-Rho (D) antibody to the Rho (D)-negative mother prevents an immune response with subsequent anti- Rho (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 Rho (D)-positive infant by an Rho (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%.^{19,26,27}

Treatment of ITP

In a clinical study of WinRho therapy of children with chronic ITP (duration of ITP greater than 6 months), administration of anti-Rho (D) increased platelet counts from 36 plus or minus 14 x 10⁹/L to 263 plus or minus 138 x 10⁹/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 Rho (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-Rho (D) (anti-D) to the Rho (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 system.⁸⁻¹⁰

Pharmacodynamics

Two pharmacodynamic studies (WR-002 and 5696-2) measuring the clearance of Rho (D)- positive RBCs from the bloodstream after injection of WinRho and WinRho SD have been conducted. These 15 Rho (D)-negative subjects received fetal Rho (D)-positive erythrocytes followed by WinRho, given either IM (n = 10) or IV (n = 5). Clearance of Rho (D)-positive RBCs was complete

within 24 hours. Six months later 5 subjects were re-challenged with Rho (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 Rho (D)- negative females exposed to Rho (D)-positive blood.

Pharmacokinetics

Pharmacokinetics of IV and IM administrations of WinRho SDF were evaluated (WS-031). 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). In WS-029 the pharmacokinetic parameters of IV administration of the two 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 route. When 600 international units (120 mcg) of product was administered to non-pregnant volunteers, the peak levels of passive anti- Rho (D) antibody were about 20 ng/mL and 40 ng/mL when the product was administered by IM and IV routes, respectively.

Distribution: When only 600 international units (120 mcg) of drug is administered to pregnant women, passive anti-Rho (D) antibodies are not detectable in the circulation for more than six weeks and therefore a dose of 1,500 international units (300 mcg) 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 spaces²⁸. Based on AUC comparisons from pharmacokinetic studies of WinRho SDF and other hyperimmune products, IM administration is expected to be nearly 100% bioavailable.²⁹

Metabolism: Immune globulins and immune complexes are metabolized in the reticuloendothelial system.²⁸

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.

Duration of Effect

WinRho SDF, Rho (D) Immunoglobulin (Human), has been shown to increase platelets in ITP patients.^{30,32} 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, Rho (D) Immunoglobulin (Human) is stable at 2-8°C until the expiry date indicated on the label. Store WinRho SDF, Rho (D) Immunoglobulin (Human) at 2-8°C. **Do not freeze. Do not use after expiration date. Protect from light.**

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature immediately prior to use. WinRho SDF contains no preservatives. Discard any unused portion.

Do not use solutions that appear cloudy or contain deposits.

DOSAGE FORMS, COMPOSITION AND PACKAGING

WinRho SDF, Rho (D) Immunoglobulin (Human) is available in the dosage forms outlined below:

Product Contents

A carton box containing a **0.5 mL** single dose vial of **600 international units (120 mcg)** of anti-Rho (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 **1500 international units (300 mcg)** of anti-Rho (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 **2500 international units (500 mcg)** of anti-Rho (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 **5000 international units (1,000 mcg)** of anti-Rho (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 international units (3,000 mcg)** of anti-Rho (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

Saol

WinRho SDF, Rho (D) Immunoglobulin (Human) for injection, is available as a sterile liquid gamma globulin (IgG) fraction of human plasma containing antibodies to the Rho (D) antigen (D antigen). The 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 _o (D) Immunoglobulin (Human)
Chemical name:	Rh _o (D) Immunoglobulin (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, Rh_o (D) Immunoglobulin (Human), is available as a sterile 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.

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 octoxynol) 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 20N Virus Filter 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 8.

Table 8: Viral Validation of Model Viruses in Laboratory Studies

	Enveloped			Non-Enveloped			
Genome	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 (Partitioning)	Not Evaluated			2.3	NE	3.4	NE
20 N Filtration (Size Exclusion)	greater than or equal to 4.7	greater than or equal to 3.5	greater than or equal to 5.6 ^a	NE	4.8	NE	4.1
Solvent/Detergent	greater than or equal to 4.7	greater than or equal to 7.3	greater than or equal to 5.5	Not Evaluated			
Total Reduction (log ₁₀)	greater than 9.4	greater than or equal to 10.8	greater than or equal to 11.1	2.3	4.8	3.4	4.1

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

^aThe 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 greater than or equal to 5.6 reduction is considered applicable.

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-003 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 1,186 Rh_o(D)-negative pregnant women were administered WinRho in study WR-003. 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 9: 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 plus or minus SD (Range)	Gender
WR-003	Phase 3, open label, single arm study in pregnant Rh _o (D)-negative women	1) 600 international units (IV) at 28 weeks + 600 international units (IV) postpartum	93	n/a	All female
		2) 600 international units (IV) at 28 & 34 weeks + 600 international units (IV) postpartum	131		
		3) 1,200 international units (IV) at 28 weeks + 600 international units (IV) postpartum	962		
PM-010	Phase 4, open-label study in pregnant Rh _o (D)-negative women	Individual antenatal infusions of 600-1,500 international units (IV or IM), 600 international units (IV) postpartum	226	28.1 plus or minus 5.7 Years (15-41)	All female

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n = number)	Mean Age plus or minus SD (Range)	Gender
PM-011	Phase 4, open-label study in pregnant Rh _o (D)-negative women	1 x 600 international units (IV)	648	29.8 plus or minus 5.4 Years (15-45)	All female

Study Results

In all 3 studies the primary efficacy endpoint was the rate of Rh immunization of the pregnant Rh_o (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 10).

Table 10: 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 less than 0.001
PM-010	Rh isoimmunization of mother at delivery	Chi-square test between observed (0/226) and expected* (4/226) isoimmunization / p less than 0.05
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. ^{19,33,34}

Treatment of ITP

The efficacy and safety of WinRho in the treatment of ITP was evaluated in 4 clinical studies (Table 11). 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 11: 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 international units/kg	38	6.8 plus or minus 4.5 years (0.7-15)	15M:23F
		IGIV at 2.0 g/kg	35	6.1 plus or minus 3.8 years (1-15)	22M:13F
		IGIV at 0.8 g/kg	34	5.9 plus or minus 4.4 years (1-16)	17M:17F
		Prednisone at 4.0 mg/kg/day for 7days	39	6.3 plus or minus 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 international units /kg and additional doses if clinically required	25	10.6 plus or minus 4.6 (years (2-18)	8M:17F
BITP-1	Phase 3, open-label, single arm study in children and adults with ITP secondary to HIV	WinRho/WinRho SD at 50-375 international units /kg	65	30.7 plus or minus 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 international units /kg	26	44.3 plus or minus 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 international units /kg	7	51.7 plus or minus 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 $20 \times 10^9/L$. Of 38 patients receiving Rh₀ (D) IGIV (125 international units /kg [25 mcg/kg] on days 1 and 2), 32 patients (84%) responded (platelet count greater than or equal to $50 \times 10^9/L$) with a mean peak platelet count of $319.5 \times 10^9/L$ (range $61 \times 10^9/L$ to $892 \times 10^9/L$), with no statistically significant differences compared to other treatment arms. The mean times to achieving greater than or equal to $20 \times 10^9/L$ or greater than or equal to $50 \times 10^9/L$ 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 greater than or equal to $20 \times 10^9/L$ or greater than or equal to $50 \times 10^9/L$, 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 12: 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 greater than or equal to $50 \times 10^9/L$ (days)	2.8	2.6	2.0	3.2
Time to reach platelet count greater than or equal to $20 \times 10^9/L$ (days)	1.9	1.6	1.3	1.9

Childhood Chronic ITP (CITP)

In an open-label, single arm, multicenter study, 25 non-splenectomized, Rh₀ (D) positive children with ITP of greater than six-months duration were treated initially with 250 international units /kg (50 mcg/kg) Rh₀ (D) Immune Globulin (Human) (125 international units /kg [25 mcg/kg] on days 1 and 2), with subsequent doses ranging from 125 to 275 international units/kg (25 to 55 μ g/kg). Response was defined as a platelet increase to at least $50 \times 10^9/L$ 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 $229.4 \times 10^9/L$ (range $43.3 \times 10^9/L$ to $456 \times 10^9/L$), and a mean duration of response of 36.5 days (range 6 to 84).

Table 13: 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 ($\times 10^9/L$)	241.1	225.6
Maximum change in platelet count from baseline ($\times 10^9/L$)	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 less than or equal to $30 \times 10^9/L$ or requiring therapy, were treated with 50 to 375 international units/kg (10 to 75 mcg/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 greater than or equal to $20 \times 10^9/L$) 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 $60.9 \times 10^9/L$ (range $-2 \times 10^9/L$ to $565 \times 10^9/L$), and the mean peak platelet count was $81.7 \times 10^9/L$ (range $16 \times 10^9/L$ to $593 \times 10^9/L$).

Table 14: 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 ($\times 10^9/L$)	87.3	81.7
Maximum change in platelet count from baseline ($\times 10^9/L$)	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 less than $30 \times 10^9/L$ or requiring therapy were enrolled in a single-arm, open-label trial and treated with 50 to 375 international units/kg (20 to 75 mcg/kg) Rh_o (D) IGIV (mean dose 231 international units /kg [46.2 mcg/kg]). In the per protocol analysis, 21 of 24 patients responded (increase greater than or equal to $20 \times 10^9/L$) 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 15: 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, Rh_o (D) positive adults with ITP of less than six months duration and platelet counts less than $30 \times 10^9/L$ or requiring therapy were enrolled in a single-arm, open-label trial and treated with 50 to 375 international units/kg (20 to 75 mcg/kg) Rh_o (D) IGIV (mean dose 187 international units /kg [37.3 mcg/kg]). In the per protocol analysis, 5 of 6 patients responded (increase greater than or equal to $20 \times 10^9/L$) 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), 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-Rho (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 16: Pharmacokinetic Parameters for Liquid and Lyophilized WinRho SDF in Healthy Volunteers (IV Administration)

WinRho SDF IV - Liquid vs Lyophilized				
From measured data				
Arithmetic Mean (+SD)				
Parameter	Liquid Formulation	Lyophilized Formulation	% Ratio of Geometric Means	Confidence Interval
$AUC_{0-\infty}$ (ng*day/mL)	24,163 (15,514)	24,993 (13,674)		
AUC_0 (ng*day/mL)	17,890 (7,334)	18,096 (7,154)	100.17	81.85-122.60
C_{MAX} (ng/mL)	1,473 (142)	1,494 (268)	99.89	92.08-108.38
T_{MAX} (days)	0.011 (0.014)	0.029 (0.073)		
$t_{1/2}$ (days)	44 (28)	48 (31)		

Table 17: 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)	67,113 (11,582)	60,248 (14,115)	109.8	100.0-120.5
AUC _{0-t} (ng*h/mL)	95,638 (27,812)	77,235 (30,539)		
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 _{1/2} (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.

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 volunteers. 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 international units (120 mcg) WinRho and five subjects were given an IV injection of 600 international units (120 mcg) 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 18).

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 international units (120 mcg). All fetal red cells were cleared from the circulation of the volunteers within eight hours of administration of WinRho SD. 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 18).

Table 18: 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 plus or minus 106	100%	342 plus or minus 27	100%
1	390 plus or minus 106	82% plus or minus 19%	236 plus or minus 53	70% plus or minus 18%
3	38 plus or minus 35	7% plus or minus 7%	55 plus or minus 11	16% plus or minus 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 international units (3,750 mcg) 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 international units /kg (50 mcg/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 less than 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 international units (300 mcg) anti-Rh_o (D) (total) to 375 international units (75 mcg) anti- Rh_o (D)/kg body weight. In these studies, the only associated signs of toxicity which were identified were mild compensated hemolysis.

REFERENCES

1. Bowman JM, Chown B, Pollock J. Low protein Rh immune globulin purity - stability activity and prophylactic value. *Vox Sang* 1973; 24:301-316.
2. Bowman JM, Friesen AD, Pollock JM, Taylor WE. WinRho: Rh immune globulin prepared by ion exchange for intravenous use. *Can Med Assoc J* 1980; 123:1121-1127.
3. Friesen AD, Bowman JM, Price HW. Column ion exchange preparation and characteristics of an Rh immune globulin (WinRho) for intravenous use. *J Appl Biochem* 1981; 3:164-175.
4. Horowitz B. Investigations into the application of tri(n-butyl)phosphate/detergent mixtures to blood derivatives. *Curr Stud Hematol Blood Transfus* 1989; (56):83-96.
5. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994; 44(2):223-226.
6. Wolberg AS, Kon RH, Monroe DM, Hoffman M. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am J Hematol* 2000; 65(1):30-34.
7. Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; 2(8500):217-218.
8. Ballow, M. Mechanism of action of intravenous immunoglobulin therapy and potential use in autoimmune connective tissue diseases. *Cancer* 1991;68: 1430-1436.
9. Knicker WT. Immunosuppressive agents, (-globulin, immunomodulation, immunization, and apheresis. *J Aller Clin Immunol* 1989; 84:1104-1106.
10. Lazarus AH, Crow AR. Mechanism of action of IVIG and anti-D in ITP. *Transfus Apheresis Sci* 2003; 28(3):249-255.
11. Gaines AR. Acute onset hemoglobinemia and/or hemobloginuria and sequelae following Rho(D) immune globulin intravenous administration in immune thrombocytopenic purpura patients. *Blood* 2000; 95 (8):2523-2529.
12. Zunich K, Harkonen W, Hafkin B, Titus D, Garer D, Woloski M. A dose ranging evaluation of the effect of a single administration of Rh (D) immune globulin intravenous in healthy volunteer. *Blood* 1994; 84 (Suppl):664a.
13. Gaines AR. Disseminated intravascular coagulation associated with acute hemoglobinemia and/or hemoglobinuria following Rho(D) immune globulin intravenous administration for immune thrombocytopenic Purpura. *Blood* 2005; 106(5):1532-7.
14. CIOMS. Current challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva 2001. Page 122.
15. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *Am Soc Nephrol*. 1997 Nov;8(11):1788-94.
16. Perazella MA, Cayco AV. Acute renal failure and intravenous immune globulin: sucrose nephropathy in disguise? *Am J Ther* 1998; 5(6):399-403.
17. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after

- the infusion of IVIG. *Transfusion*. 2001; 41(2):264-8.
18. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N Eng J Med* 1986; 314:560-564.
 19. Bowman JM. The prevention of Rh immunization. *Transfus Med Rev* 1988; 2(3):129-150.
 20. Miura M, Katada Y, Ishihara J. Time interval of measles vaccination in patients with Kawasaki disease treated with additional intravenous immune globulin. *Eur J Pediatr* 2004; 163(1):25-29.
 21. Ruderman JW, Barka N, Peter JB, Stiehm ER. Antibody response to MMR vaccination in children who received IVIG as neonates. *Am J Dis Child* 1991; 145(4):425-426.
 22. Zaia JA, Levin MJ, Preblud SR, Leszczynski J, Wright GG, Ellis RJ, et al. Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. *J Infect Dis* 1983 Apr;147(4):737-43.
 23. Fung KFK, Eason E. Prevention of Rh Alloimmunization. *J Obstet Gynaecol Can* 2003; 25(9):765-773.
 24. Bowman JM, Chown B. Prevention of Rh immunization after massive Rh-positive transfusion. *Can. Med Assoc J* 1968; 99:385-388.
 25. Chown B, Bowman JM, Pollock J, Lowen B, Pettett A. The effect of anti-D IgG on D-positive recipients. *Can Med Assoc J* 1970; 102:1161-1164.
 26. Bowman JM, Pollock JM. Failures of intravenous Rh immune globulin prophylaxis: An analysis of the reasons for such failures. *Trans Med Rev* 1987; 1:101-112.
 27. Bowman JM, Pollock JM. Antenatal prophylaxis of Rh isoimmunization 28 weeks-gestation service program. *Can Med Assoc J* 1978; 118:627-633.
 28. Committee for medicinal products for human use. Core SPC for human normal immunoglobulin for intravenous administration (IVIg). European Medicines Agency. 2004.
 29. Finlayson JS, Tankersley DL. Availability of intramuscular immunoglobulin. *Lancet* 1984; 2(8397):296-297.
 30. Andrew M, Blanchette VS, Adams M, Ali K, Barnard D, Chan KW, et al. A multicenter study of the treatment of childhood chronic idiopathic thrombocytopenic purpura with anti- D. *J Pediatr* 1992; 120:522-7.
 31. Blanchette V, Imbach P, Andrew M, Adams M, McMillan J, Wang E, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. *Lancet* 1994; 344:703-7.
 32. Bussel JB, Graziano JN, Kimberly RP, Pahwa S, Aledort LM. Intravenous anti-D treatment of immune thrombocytopenic purpura: Analysis of efficacy, toxicity, and mechanism of effect. *Blood* 1991; 77:1884-93.
 33. Bowman JM, Chown B, Lewis M, Pollock JM. Rh isoimmunization during pregnancy: antenatal prophylaxis. *Can Med Assoc J* 1978; 118:623-7.
 34. Bowman JM. Suppression of Rh immunization. *Obstet & Gynec* 1978; 52:385-393.

PART III: PATIENT MEDICATION INFORMATION

WinRho® SDF

Rho (D) Immunoglobulin (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 patients. 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.

Injections may also be given in connection with abortion, miscarriage or amniocentesis or because of 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:

Rho (D) Immunoglobulin (Human)

What the important nonmedicinal ingredients are:

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:

Liquid: 600 international units (120 mcg), 1,500 international units (300 mcg), 2,500 international units (500 mcg), 5,000 international units (1,000 mcg), 15,000 international units (3,000 mcg)

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 international units (300 mcg) of WinRho SDF is given at 28 weeks of pregnancy. A 600 international units (120 mcg) dose of WinRho SDF is given after delivery of an Rh-positive baby.

A 1,500 international units (300 mcg) 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 international units (300 mcg) 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 international units/mL and 120 international units/mL (9 mcg/mL and 24 mcg/mL).

Treatment of ITP

WinRho SDF is given at an initial dose of 250 international units/kg (50 mcg/kg). If you need additional therapy to increase your platelet counts, then a dose of 125 to 300 international units/kg (25 to 60 mcg/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,
- yellow color to skin or eyes,
- 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	✓		
Uncommon	Allergic reaction		✓	✓
	Back pain, discoloured urine, darkened urine, decreased urine output, yellow color to skin or eyes, 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.

Protect from light.

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 Saol Therapeutics Research Limited at 1-833-644-4216.

This leaflet was prepared by Saol Therapeutics Research Limited.

WinRho[®] SDF is a registered trademark of Saol.

Last revised: April 24, 2020