

Rh₀(D) Immune Globulin Intravenous (Human) WinRho SDF® [win' rō s d f]

DESCRIPTION

Rh₀(D) Immune Globulin Intravenous (Human) (Rh₀(D)IGIV)–WinRho SDF®–is a sterile, freeze-dried gamma globulin (IgG) fraction containing antibodies to the Rh₀(D) antigen (D antigen). WinRho SDF® is prepared from human plasma by an anion-exchange column chromatography method.¹⁻³ The manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton® X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV.⁴ WinRho SDF® is filtered using a Planova™ 35 nm Virus Filter which has been validated to be effective in the removal of some nonlipid enveloped viruses.⁵⁻⁶ These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and nonenveloped viruses, respectively.

The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard. A 300 µg (1,500 International Unit [IU] *) vial contains sufficient anti-Rh₀(D) to effectively suppress the immunizing

potential of approximately 17 mL of Rh₀(D) (D-positive) red blood cells (RBCs). This product contains approximately 5 µg/mL IgA.

The product is stabilized with 0.1 M glycine, 0.04 M sodium chloride, and 0.01% polysorbate 80. It contains no preservative.

Treatment of ITP

For use in the treatment of immune thrombocytopenic purpura (ITP), WinRho SDF® **must be administered intravenously**.

Suppression of Rh Isoimmunization

For use in the suppression of Rh isoimmunization, WinRho SDF® may be administered either intramuscularly or intravenously.

* In the past, a full dose of Rh₀(D) Immune Globulin (Human) has traditionally been referred to as a "300 µg" dose. Potency and dosing recommendations are now expressed in IU by comparison to the WHO anti-Rh₀(D) standard. The conversion of "µg" to "IU" is 1 µg = 5 IU.

CLINICAL PHARMACOLOGY

Treatment of ITP

WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), has been shown to increase platelet counts in non-splenectomized, Rh₀(D) positive patients with ITP. Platelet counts usually rise within one to two days and peak within seven to 14 days after initiation of therapy. The duration of response is variable; however, the average duration is approximately 30 days. The mechanism of action is not completely understood, but is thought to be due to the formation of anti-Rh₀(D) (anti-D)-coated RBC complexes resulting in Fc receptor blockade, thus sparing antibody-coated platelets.⁷⁻⁸

Suppression of Rh Isoimmunization

WinRho SDF® is used to suppress the immune response of non-sensitized Rh₀(D) negative individuals following exposure to Rh₀(D) positive RBCs by fetomaternal hemorrhage during delivery of an Rh₀(D) positive infant, abortion (spontaneous or induced), amniocentesis, abdominal trauma, or mismatched transfusion.⁹⁻¹¹ The mechanism of action is not completely understood.

WinRho SDF®, when administered within 72 hours

of a full-term delivery of an Rh₀(D) positive infant by an Rh₀(D) negative mother, will reduce the incidence of Rh isoimmunization from 12 - 13% to 1 - 2%. The 1 - 2% is, for the most part, due to isoimmunization during the last trimester of pregnancy. When treatment is given both antenatally at 28 weeks gestation and postpartum, the Rh immunization rate drops to about 0.1%.¹²⁻¹⁵

When 120 µg (600 IU) of Rh₀(D) IGIV is administered to pregnant women, passive anti-Rh₀(D) antibodies are not detectable in the circulation for more than six weeks and therefore a dose of 300 µg (1,500 IU) should be used for antenatal administration.

In a clinical study with Rh₀(D) negative volunteers (nine males and one female), Rh₀(D) positive red cells were completely cleared from the circulation within eight hours of intravenous administration of Rh₀(D) IGIV. There was no indication of Rh isoimmunization of these subjects at six months after the clearance of the Rh₀(D) positive red cells.

Pharmacokinetics - IM versus IV Administration

In a clinical study involving Rh₀(D) negative volunteers, two subjects received 120 µg (600 IU) Rh₀(D) IGIV by intravenous (IV) administration and two subjects received this dose by intramuscular (IM) administration. Peak levels (36 to 48 ng/mL) were reached within two hours of IV administration and peak levels (18 to 19 ng/mL) were reached at five to 10 days after IM administration. The calculated areas under the curve were the same for both routes of administration. The t_{1/2} for anti-Rh₀(D) was about 24 days following IV administration and about 30 days following IM administration.

INDICATIONS AND CLINICAL USE

Treatment of ITP

WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), is recommended for the treatment of non-splenectomized, Rh₀(D) positive

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

in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage. The safe-

ty and efficacy of WinRho have not been evaluated in clinical trials for patients with non-ITP causes of thrombocytopenia or in previously splenectomized patients.

Suppression of Rh Isoimmunization

Pregnancy and Other Obstetric Conditions

WinRho SDF® is recommended for the suppression of Rh isoimmunization in non-sensitized, Rh₀(D) negative (D-negative) women within 72 hours after spontaneous or induced abortions, amniocentesis, chorionic villus sampling, ruptured tubal pregnancy, abdominal trauma or transplacental hemorrhage or in the normal course of pregnancy unless the blood type of the fetus or father is known to be Rh₀(D) negative. In the case of maternal bleeding due to threatened abortion, WinRho SDF® should be administered as soon as possible. Suppression of Rh isoimmunization reduces the likelihood of hemolytic disease in an Rh₀(D) positive fetus in present and future pregnancies.

The criteria for an Rh-incompatible pregnancy requiring administration of WinRho SDF® at 28 weeks gestation and within 72 hours after delivery are:

- the mother must be Rh₀(D) negative,
- the mother is carrying a child whose father

- is either Rh₀(D) positive or Rh₀(D) unknown,
- the baby is either Rh₀(D) positive or Rh₀(D) unknown, and
- the mother must not be previously sensitized to the Rh₀(D) factor.

Transfusion

WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), is recommended for the suppression of Rh isoimmunization in Rh₀(D) negative female children and female adults in their childbearing years transfused with Rh₀(D) positive RBCs or blood components containing Rh₀(D) positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh₀(D) positive blood represents less than 20% of the total circulating red cells. A 300 µg (1,500 IU) dose will suppress the immunizing potential of approximately 17 mL of Rh₀(D) positive RBCs.

CLINICAL TRIALS

Treatment of ITP

Efficacy was documented in four subgroups of patients with ITP:

Childhood Chronic ITP

In an open-label, single arm, multicenter study,

24 non-splenectomized, Rh₀(D) positive children with ITP of greater than six months duration were treated initially with 50 µg/kg (250 IU/kg) Rh₀(D) Immune Globulin Intravenous (Human) (25 µg/kg (125 IU/kg) on days 1 and 2, with subsequent doses ranging from 25 to 55 µg/kg (125 to 275 IU/kg)). Response was defined as a platelet increase to at least 50,000/mm³ and a doubling of the baseline. Nineteen of 24 patients responded for an overall response rate of 79%, an overall mean peak platelet count of 229,400/mm³ (range 43,300 to 456,000), and a mean duration of response of 36.5 days (range 6 to 84).¹⁶⁻¹⁷

Childhood Acute ITP

A multicenter, randomized, controlled trial comparing Rh₀(D) IGIV to high dose and low dose Immune Globulin Intravenous (Human) and prednisone was conducted in 146 non-splenectomized, Rh₀(D) positive children with acute ITP and platelet counts less than 20,000/mm³. Of 38 patients receiving Rh₀(D) IGIV (25 µg/kg (125 IU/kg) on days 1 and 2), 32 patients (84%) responded (platelet count ≥ 50,000/mm³) with a mean peak platelet count of 319,500/mm³ (range 61,000 to 892,000), with no statistically significant differences compared to other treatment arms. The mean times to achieving ≥ 20,000/mm³ or ≥ 50,000/mm³ platelets for patients receiving

Rh₀(D) IGIV were 1.9 and 2.8 days, respectively. When comparing the different therapies for time to platelet count ≥ 20,000/mm³ or ≥ 50,000/mm³, no statistically significant differences among treatment groups were detected, with a range of 1.3 to 1.9 days and 2.0 to 3.2 days, respectively.¹⁸⁻¹⁹

Adult Chronic ITP

Twenty-four non-splenectomized, Rh₀(D) positive adults with ITP of greater than six months duration and platelet counts < 30,000/mm³ or requiring therapy were enrolled in a single-arm, open-label trial and treated with 20 to 75 µg/kg (100 to 375 IU/kg) Rh₀(D) IGIV (mean dose 46.2 µg/kg (231 IU/kg)). Twenty-one of 24 patients responded (increase ≥ 20,000/mm³) during the first two courses of therapy for an overall response rate of 88% with a mean peak platelet count of 92,300/mm³ (range 8,000 to 229,000).²⁰⁻²¹

ITP Secondary to HIV Infection

Eleven children and 52 adults, who were non-splenectomized and Rh₀(D) positive, with all Walter Reed classes of HIV infection and ITP, with initial platelet counts of ≤ 30,000/mm³ or requiring therapy, were treated with 20 to 75 µg/kg (100 to 375 IU/kg) Rh₀(D) IGIV in an open label trial. Rh₀(D) IGIV was administered for an aver-

age of 7.3 courses (range 1 to 57) over a mean period of 407 days (range 6 to 1,952). Fifty-seven of 63 patients responded (increase ≥ 20,000/mm³) during the first six courses of therapy for an overall response rate of 90%. The overall mean change in platelet count for six courses was 60,900/mm³ (range -2,000 to 565,000), and the mean peak platelet count was 81,700/mm³ (range 16,000 to 593,000).²¹⁻²³

Suppression of Rh Isoimmunization

The pivotal study²⁴ supporting this indication was conducted in 1,186 non-sensitized, Rh₀(D) negative pregnant women in cases in which the blood types of the fathers were either Rh₀(D) positive or unknown. Rh₀(D) IGIV was administered according to one of three regimens: 1) 93 women received 120 µg (600 IU) at 28 weeks; 2) 131 women received 240 µg (1200 IU) each at 28 and 34 weeks; 3) 962 women received 240 µg (1200 IU) at 28 weeks. All women received a postnatal administration of 120 µg (600 IU) if the newborn was found to be Rh₀(D) positive. Of 1,186 women who received antenatal Rh₀(D) IGIV, 806 were given Rh₀(D) IGIV postnatally following the delivery of an Rh₀(D) positive infant, of which 325 women underwent testing at six months after delivery for evidence of Rh isoimmunization. Of these 325 women, 23 would have

been expected to display signs of Rh isoimmunization; however, none was observed (p < 0.001 in a Chi-square test of significance of difference between observed and expected isoimmunization in the absence of Rh₀(D) IGIV).

CONTRAINDICATIONS

Treatment of ITP and

Suppression of Rh Isoimmunization

Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), or any other Immune Globulin (Human). WinRho SDF® contains trace amounts of IgA (approximately 5 µg/mL). Individuals who are deficient in IgA may have the potential for developing IgA antibodies and have anaphylactic reactions. The physician must weigh the potential benefit of treatment with WinRho SDF® against the potential for hypersensitivity reactions.

WARNINGS

WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that such

products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. The WinRho SDF® manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton® X-100) that is effective in inactivating lipid enveloped viruses such as hepatitis B, hepatitis C, and HIV. WinRho SDF® is filtered using a Planova™ 35 nm Virus Filter that is effective in reducing the level of some non-lipid enveloped viruses such as hepatitis A. These two processes are designed to increase product safety by reducing the risk of transmission of lipid enveloped and non-lipid enveloped viruses, respectively. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported to the distributor, Nabi® Biopharmaceuticals at 1-800-4WINRHO (1-800-494-6746). The physician should discuss the risks and benefits of this product with the patient.

Treatment of ITP

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 Rh₀(D) negative or splenectomized individuals as its efficacy in these patients has not been demonstrated.

Suppression of Rh Isoimmunization

For the suppression of Rh isoimmunization in the mother, do not administer to the infant.

PRECAUTIONS

WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), should not be administered as immunoglobulin replacement therapy for immune globulin deficiency syndromes.

Treatment of ITP

Following administration of WinRho SDF®, Rh₀(D) positive ITP patients should be monitored for signs and/or symptoms of intravascular hemolysis (IVH), clinically compromising anemia, and renal insufficiency.

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

Rh₀(D) positive donors are transfused.

If the patient has a lower than normal hemoglobin level (less than 10 g/dL), a reduced dose of 25 to 40 µg/kg (125 to 200 IU/kg) should be given to minimize the risk of increasing the severity of anemia in the patient. WinRho SDF® must be used with extreme caution in patients with a hemoglobin level that is less than 8 g/dL due to the risk of increasing the severity of the anemia (See DOSAGE AND ADMINISTRATION, Treatment of ITP).

Suppression of Rh Isoimmunization

WinRho SDF® should not be administered to Rh₀(D) negative individuals who are Rh immunized as evidenced by an indirect antiglobulin (Coombs') test revealing the presence of anti-Rh₀(D) (anti-D) antibody.

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^a test result. Such an individual should be assessed for a large fetomaternal hemorrhage and the dose of WinRho SDF® adjusted accordingly. WinRho SDF® should be administered if there is any doubt about the mother's blood type.

Laboratory Tests

In addition to anti-D, WinRho SDF® contains trace amounts of anti-A, anti-B, anti-C and anti-E anti-

bodies.

Treatment of ITP

Passively acquired anti-A, anti-B, anti-C, and anti-E blood group antibodies may be detectable in direct and indirect antiglobulin (Coombs') tests obtained following WinRho SDF®, Rh₀(D) Immune Globulin Intravenous (Human), administration. Interpretation of direct and indirect antiglobulin tests must be made in the context of the patient's underlying clinical condition and supporting laboratory data.

Suppression of Rh Isoimmunization

The presence of passively administered anti-Rh₀(D) in maternal or fetal blood can lead to a positive direct antiglobulin (Coombs') test. If there is an uncertainty about the mother's Rh group or immune status, WinRho SDF® should be administered to the mother.

Drug Interactions

Treatment of ITP and

Suppression of Rh Isoimmunization

Administration of WinRho SDF® concomitantly with other drugs has not been evaluated. Other antibodies contained in WinRho SDF® may interfere with the response to live virus vaccines such as measles, mumps, polio or rubella. Therefore,

immunization with live vaccines should not be given within 3 months after WinRho SDF® administration.

Refer to Dosage and Administration section for information on drug compatibility.

Pregnancy Category C

Treatment of ITP and

Suppression of Rh Isoimmunization

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

ADVERSE REACTIONS

Treatment of ITP

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

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