Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

WinRho SDF 1500 IU
(powder and solvent for solution for infusion and injection).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Human Anti-D Immunoglobulin

One vial of powder contains 1500 IU (300 micrograms) human Anti-D immunoglobulin.

IgG subclass distribution (Range is ± 1 Std. Dev.):

IgG_1: 52-71%
IgG_2: 21-39%
IgG_3: 7-10%
$IgG_{4:}$ 0.1-0.5%

The product contains ≤ 100 mg human plasma protein of which at least 96% is IgG.

Other Constituents:
IgA ≤ 80 µg/vial

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion and injection

- The powder is white to off white.
- The solvent is a clear or colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention of Rh_o (D) immunisation in Rh_o D-negative women:

- Pregnancy/delivery of a Rh_o (D) positive baby as summarised in the following table:

Mother	Child
D (Rhesus neg.)	D (Rhesus pos.)
D (Rhesus neg.)	D^u (D^u pos.)

Where doubts exist as to the Rh_o (D) antibody status of the mother, prophylactic measures should be taken in any event.

- Spontaneous/threatened abortion, artificial termination of pregnancy, ectopic pregnancy or removal of hydatidiform mole.

- Transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (APH) (including placenta praevia), amniocentesis, chorionic villous sampling, or obstetric manipulative procedures e.g. external cephalic version, or abdominal trauma.

Treatment of Rh_o (D) negative persons after incompatible transfusions of Rh_o(D) positive blood or other products containing red blood cells.

Treatment of Immune Thrombocytopenic Purpura (ITP)

WinRho SDF may also be used for the treatment of immune thrombocytopenic purpura (ITP) in Rh_o (D) positive non-splenectomised patients in clinical situations requiring an increase in platelet count, if medical intervention is considered necessary, to prevent excessive haemorrhage.

4.2 Posology and method of administration

4.2.1 Posology

4.2.1.1 Prevention of immunisation to Rh_o (D)

The dose of anti-D immunoglobulin is determined according to the level of exposure to Rh_o (D) positive red blood cells and has been established based on the knowledge that 0.5 mL of concentrated Rh_o (D) positive red blood cells or 1 mL of Rh_o (D) positive blood is neutralised by approximately 50 IU (10 μg) of anti-D immunoglobulin.

The following doses are recommended based on the clinical studies performed with WinRho SDF, however, consideration may be given to professional guidelines for the use of anti-D IgG in the individual EU member states.

Use in pregnancy, delivery and other interventions caused by pregnancy.

Antenatal prophylaxis	At 28 weeks gestation: -1500 IU (300 µg) by intramuscular or intravenous route A further dose of anti-D is necessary after delivery if the infant is rhesus positive.
Spontaneous/threatened abortion, artificial termination of pregnancy, ectopic pregnancy or removal of hydatidiform mole Transplacental haemorrhage (TPH) resulting from ante-natal haemorrhage (APH) (including placenta praevia), amniocentesis, chorionic villous sampling, or obstetric manipulative procedures e.g. external cephalic version, or abdominal trauma.	Prior to 12 weeks gestation: -600 IU (120 µg) intramuscularly or intravenously After 12 weeks gestation: -1500 IU (300 µg) intramuscularly or intravenously Administered as soon as possible (within 72 hours) after the event
Portpartum prophylaxis	As soon as possible (within 72 hours) after delivery -1500 IU (300 µg) by intramuscular route -600 IU (120 µg) by intravenous route
Foetomaternal haemorrhage of more than 4 mL of foetal blood	In addition to the postpartum prophylaxis (see above) 100 IU (20 µg) per mL of foetal blood given intramuscularly or intravenously,
Rh-positive platelet transfusion in Rh-negative females	600 IU (120 µg) by intravenous route
Rh-incompatible blood transfusion	per 2 mL of transfused blood or 1 mL of transfused RBC concentrate, at least 100 IU (20 µg) given intramuscularly or intravenously

The postpartum dose must still be given even when antepartum prophylaxis has been administered and even if residu activity from antenatal prophylaxis can be demonstrated in maternal serum.

If a large foetomaternal haemorrhage (> 4mL in 0.7-0.8% of women) is suspected, e.g. in the event of foetal/neonat anaemia or intrauterine foetal death, a suitable test (e.g. the Kleihauer-Betke test) is recommended in order to determi the proportion of foetal cells in the maternal circulation and thereby to assess the dose of WinRho SDF to b administered. Additional doses of anti-D should be administered accordingly (100 IU (20 µg) per 1 mL foetal blood).

Use following a Rh-incompatible blood transfusion (Rh-positive cells into Rh-negative recipients).

Following a Rh-incompatible blood transfusion (whole blood or other products containing red blood cells), the recommended dose is 100 IU (20 µg) anti-D IgG per 2 mL of transfused Rh_o (D) positive blood or per 1 mL of RBC concentrate. The IV route is recommended. If given by intramuscular administration, the total quantity should be administered over several days in divided doses.

In Rh-negative female children or females of child-bearing age, following the transfusion of Rh-positive platelets, 600 IU is sufficient to cover up to 10 standard doses of platelets given over a 28 day period. The intravenous route is recommended.

4.2.1.2 Treatment of Immune Thrombocytopenic Purpura (ITP)

For the treatment of Immune Thrombocytopenic purpura. WinRho SDF should be used on the advice of a physician with experience in haematology.

WinRho SDF **must be given by intravenous injection** for the treatment of ITP.

Initial Dosing: After confirming that the patient is Rh_0 (D) positive, an initial dose of 250 IU/kg (50 µg/kg), given as a single injection, is recommended for the treatment of ITP. The initial dose may be administered in two divided doses given on separate days, if desired. If the patient has a haemoglobin level that is less than 10 g/dL, a reduced dose of 125 to 200 IU/kg (25 to 40 µg/kg) should be given to minimize the risk of increasing the severity of anaemia in the patient. All patients should be monitored to determine clinical response by assessing the platelet count, red cell count, haemoglobin and reticulocyte counts.

Subsequent Dosing: If subsequent therapy is required to elevate platelet counts, an intravenous dose of 125 to 300 IU/kg (25 to 60 µg/kg) is recommended. The frequency of dosing and dose used in maintenance therapy should be determined by the patient's clinical response by assessing the platelet count, red cell count, haemoglobin and reticulocyte counts.

The ITP dosage recommendations are summarised in the following table:

Indication	**Recommended Dose**	**Frequency of Injections**
Immune Thrombocytopenic Purpura	***Initial Dosing:*** 250 IU/kg (50 µg/kg) If the patient has a haemoglobin level that is <10 g/dL, a reduced dose of 125 to 200 IU/kg (25 to 40 µg/kg) should be given to minimize the risk of increasing the severity of anaemia in the patient. ***Subsequent Dosing (if required):*** 125 to 300 IU/kg (25 to 60 µg/kg)	The initial dose may be administered in two divided doses given on separate days, if desired. The frequency of dosing and dose used in maintenance therapy should be determined by the patient's clinical response by assessing the platelet count, red cell count, haemoglobin and reticulocyte counts.

4.2.2 Method of Administration: Directions for Use by Healthcare Professionals

In cases of severe thrombocytopenia or other coagulation disorders where intramuscular injections are contraindicated, WinRho SDF should be administered by the intravenous route.

For the treatment of ITP, WinRho SDF must be administered by the intravenous route only.

Intravenous Injection: Aseptically administer the product intravenously in a suitable vein with a rate of injection of 1500 IU (300 µg)/ 5 to 15 seconds.

Intramuscular Injection: The preferred injection site is 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 the injection site. If large total doses (> 5 mL) are required and the intramuscular route is chosen, it is advisable to administer them in divided doses at different sites.

Instructions for preparation are presented *in section 6.6.*

4.3 Contraindications

WinRho SDF should not be used in patients who have known hypersensitivity to plasma products or to any of the excipients contained in WinRho SDF.

4.4 Special warnings and precautions for use

General

Following the administration of WinRho SDF (IV or IM), patients should be kept under observation for at least 20 minutes.

If symptoms of an anaphylactic reaction or other allergic reactions occur, the injection should be discontinued immediately.

True hypersensitivity reactions are rare, but allergic responses to anti-D immunoglobulin may occur. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, chest tightness, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. In case of shock, the standard medical treatment for shock should be implemented.

WinRho SDF contains trace quantities of IgA. Although WinRho SDF has been used successfully to treat IgA deficient individuals, such individuals have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must weigh the potential benefit of treatment with WinRho SDF against the potential for hypersensitivity reactions.

Individuals known to have had an anaphylactic or severe systemic reaction to human immunoglobulin should not receive WinRho SDF or any other immunoglobulin.

Prevention of Immunisation to Rh_o (D)

In the case of postpartum use, the product is intended for maternal administration. It should not be given to the new-born infant.

In the indication of the prevention of immunisation to Rh_o (D), the product is not intended for use in Rh_o (D) positive individuals.

Treatment of Immune Thrombocytopenic Purpura (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 Rh_o (D) negative or splenectomised individuals, as its efficacy in these patients has not been demonstrated.

Following administration of WinRho SDF to Rh_0 (D) positive ITP patients, patients should be monitored and alerted to signs and/or symptoms of intravascular haemolysis (IVH) and its potential complications. Signs and symptoms consistent with IVH include back pain, shaking chills, discoloration of the urine (chromaturia), haemoglobinemia, haemoglobinuria, pallor, hypotension, tachycardia, oliguria or anuria, oedema, dyspnoea, increased bruising and prolongation of bleeding time or clotting time. These signs and symptoms have been reported to occur within minutes up to a few days after WinRho SDF administration. Potential clinically compromising complications include acute onset or exacerbations of anaemia and renal insufficiency, or disseminated intravascular coagulation (DIC). Further, very rarely, IVH complications have resulted in death. IVH and its potential complications were identified from spontaneous post marketing reports. The nature of spontaneous reports prevents accurate frequency calculation, however, these events are generally considered to be rare or very rare.

If patients are to be transfused, Rh_0 (D) negative red blood cells (RBCs) should be used so as not to exacerbate ongoing IVH. Platelet concentrates may contain up to 5.0 mL of RBCs, thus caution should likewise be exercised if platelets from Rh_0 (D) positive donors are transfused.

If the patient has a lower than normal haemoglobin level (less than 10 g/dL), a reduced dose of 125 to 200 IU/kg (25 to 40 µg/kg) should be given to minimize the risk of increasing the severity of anaemia. WinRho SDF must be used with extreme caution in patients with a haemoglobin level less than 8 g/dL due to the risk of increasing the severity of the anaemia. *(See section 4.2)*

ITP patients should be carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human immunoglobulin, patients switched from an alternative product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect.

Viral Safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations, and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV.

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A or parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time WinRho SDF is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of product.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Live virus vaccines

Active immunisation with live virus vaccines (eg. measles, rubella, mumps and varicella) should be postponed until 3 months after the last administration of anti-D immunoglobulin, as the efficacy of the live virus vaccine may be impaired for a period of at least 6 weeks and up to 3 months.
If anti-D immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

Interference with serological testing

After injection of immunoglobulin passive transmission of antibodies to erythrocyte antigens (e.g. A, B, C or D) may result in misleading positive results of serological tests. The results of blood typing and antibody testing, including the Coombs' or antiglobulin test, are significantly affected by the administration of anti-D immunoglobulin for at least 3 months post-infusion. There is an increased incidence of positive Coombs' test in neonates whose mothers have received antenatal prophylaxis.

4.6 Pregnancy and lactation

This medicinal product is used routinely in pregnancy and the immediate puerperium in doses recommended for prevention of immunisation to Rh_o (D).

The safety of WinRho SDF doses recommended for ITP treatment in pregnant patients has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of the pregnancy, or on the foetus and the neonate are to be expected.

4.7 Effects on ability to drive and use machines

No studies exist on the effects of WinRho SDF on the ability to drive and use machines. WinRho SDF may cause dizziness and somnolence *(see section 4.8)* which may impair the patient's reaction. Patients must therefore be warned that these effects may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

General

The most frequently observed adverse reactions for all indications are: headaches, chills, fevers, malaise, asthenia, pallor, diarrhea, nausea, vomiting, arthralgia, myalgia, dizziness, abdominal or back pain, hypotension, hypertension, somnolence, pruritus, rash and sweating.

There have also been reports of allergic or anaphylactic type reactions, including dyspnoea and shock, even when the patient has shown no hypersensitivity to previous administration.

For information on viral safety *see section 4.4.*

Prevention of Immunisation to Rho (D)/Treatment of Rh Incompatible Blood Transfusions

In the case of intramuscular administration, local pain and tenderness at the injection site may occur occasionally. This may be avoided by dividing up large doses among various injection sites.

The safety of WinRho SDF was evaluated in clinical trials (n=2062) in pregnant Rh_0 (D)-negative whose baby's father's Rh_0 (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 IU).

Immune Thrombocytopenia Purpura (ITP)

The safety of WinRho SDF was evaluated in 5 clinical studies (n=161) in children and adults with acute and chronic ITP and adults and children with ITP secondary to HIV. A total of 117 adverse drug reactions were reported by 46 patients (29%). 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 study medication.

The ADRs from five ITP clinical studies are summarized and categorized according to the MedDRA system organ class in Table 1. Frequency has been evaluated using the following criteria: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1 000, <1/100), rare (>1/10 000, <1/1 000), very rare (<1/10 000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Drug related adverse reactions (ADRs) in ITP clinical studies with WinRho SDF

MedDRA System Organ Class	**MedDRA Preferred Term**	**ADR Frequency Category***
Infection and infestations	Infection†	Common
Blood & lymphatic system disorders	Anaemia, Hypochromic Anaemia	Common
Metabolism and nutrition disorders	Anorexia	Common
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Headache	Very Common
	Dizziness	Common
	Hypertonia, Hypoaesthesia, Tremor, Somnolence	Uncommon
Cardiac disorders	Palpitation	Uncommon
Vascular disorders	Hypertension	Uncommon
Respiratory, thoracic and mediastinal disorders	Asthma	Common
	Dyspnoea, Pharyngitis, Rhinitis	Uncommon
Gastrointestinal disorders	Abdominal Pain	Common
	Gastroenteritis, Gastrointestinal disorder, Diarrhoea, Vomiting, Glossitis, Mouth ulceration	Uncommon
Skin and subcutaneous tissue disorders	Urticaria	Uncommon
Musculoskeletal, connective tissue and bone disorders	Arthralgia	Common
	Back pain	Uncommon
General disorders and administration site conditions	Pyrexia, Pain, Asthenia, Chills	Common
	Malaise	Uncommon
Investigations	Weight Increased	Uncommon

* n= 161; Very Common = >15 subjects experienced this ADR, Common = between 15 and 2 subjects experienced this ADR, Uncommon = 1 subject experienced this ADR

† There maybe a temporal and not a causal association between administration of WinRho and these infections. In addition, these infections were not blood-born such as HIV, HBV, HCV, HAV and parvovirus B19 infections.

Post-Marketing Experience

The following events have been reported under spontaneous post-marketing surveillance and occur primarily in patients treated for ITP. Frequency of event reporting can not be established under a spontaneous reporting system. However, these events are generally considered to be rare or very rare.

Blood and lymphatic system disorders: Intravascular haemolysis *(see section 4.4),* Disseminated intravascular coagulation, Haemolysis, Haemolytic anaemia, Jaundice, Heamoglobinemia.

Immune system disorders: Hypersensitivity, Anaphylactic reaction

Cardiac disorders: Tachycardia

Vascular disorders: Hypotension, Pallor, Vasodilation

Respiratory, thoracic, and mediastinal disorders: Acute respiratory distress syndrome (ARDS), Transfusion related acute lung injury (TRALI)

Gastrointestinal disorders: Nausea

Skin and subcutaneous tissue disorders: Hyperhidrosis, Pruritus

Musculoskeletal and connective disuse disorders: Myalgia, Muscle spasm, Pain in extremities

Renal and urinary disorders: Renal failure, Renal impairment *(see section 4.4),* Anuria, Chromaturia, Haemoglobinuria, Haematuria

General disorders and administration site conditions: Chest pain**,** Fatigue, Oedema

Investigations: Decreased Haemoglobin, Blood lactate dehydrogenase increased

The signs and symptoms of intravascular haemolysis and its complications include back pain, shaking chills, discoloration of the urine (chromaturia or haematuria), haemoglobinemia, haemoglobinuria, pallor, hypotension, tachycardia, oliguria or anuria, oedema, dyspnoea, increased bruising and prolongation of bleeding time or clotting time. IVH may also result in clinically compromising anaemia, renal insufficiency or renal failure, which may require dialysis, or disseminated intravascular coagulation *(see section 4.4)* and may be fatal.

4.9 Overdose

No data are available on overdosage. Patients in receipt of an incompatible transfusion and those with immune thrombocytopenic purpura (ITP), who receive very large doses of anti-D immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of haemolytic reaction.

In other Rh_o (D) negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: immune sera and immunoglobulins: Anti- D (Rho) immunoglobulin. ATC Code: J06BB01.

Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rho) antigen of human erythrocytes. WinRho SDF can also contain antibodies to other Rh antigens e.g. anti-Rh C antibodies, which may be detected by sensitive serological tests.

The effect of WinRho SDF is based on the neutralisation of the potentially antigenic Rho (D) positive erythrocytes for a Rho (D) negative person.

During pregnancy, and especially at the time of childbirth, foetal red blood cells may enter the maternal circulation. When the woman is Rho (D)-negative and the foetus Rho (D)-positive, the women may become immunised to the Rho (D) antigen and produce anti-Rho (D) antibodies which cross the placenta and may cause haemolytic disease of the newborn. Passive immunisation with anti-D immunoglobulin prevents Rho (D) immunisation in more than 99% of cases provided that a sufficient dose of anti-D immunoglobulin is administered soon enough after exposure to Rho (D)-positive foetal red blood cells.

The mechanism by which anti-D immunoglobulin suppresses immunisation to Rho (D)-positive red cells is not known. Suppression may be related to the clearance of the red cells from the circulation before they reach immunocompetent sites or, it may be due to more complex mechanisms involving recognition of foreign antigen and antigen presentation by the appropriate cells at the appropriate sites in the presence or absence of antibody.

Suppression of Rh Isoimmunisation
The pivotal study supporting this indication was conducted in 1,186 non-sensitized, Rho (D) negative pregnant women in cases in which the blood types of the fathers were either Rho (D) positive or unknown. Rho (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 postnatal intravenous administration of 120 μg (600 IU) if the newborn was found to be Rho (D) positive. Of 1,186 women who received antenatal Rho (D) IGIV, 806 were given Rho (D) IGIV postnatally following the delivery of an Rho (D) positive infant, of which 325 women underwent testing at six months after delivery for evidence of Rh isoimmunisation. Of these 325 women, 23 would have been expected to display signs of Rh isoimmunisation; however, none was observed ($p<0.001$ in a Chi-square test of significance of difference between observed and expected isoimmunisation in the absence of Rho (D) IGIV.

In clinical studies involving Rho (D) negative persons, transfused Rho (D) positive erythrocytes were completely cleared from the circulation within 8 hours following the intravenous administration of Rho (D) immunoglobulin.

Childhood Chronic ITP

In an open-label, single arm, multicenter study, 24 non-splenectomised, Rho (D) positive children with ITP of greater than six months duration were treated initially with 250 IU/kg (50 μg/kg) Rho (D) Immune Globulin (Human) (125 IU/kg [25 μg/kg] on days 1 and 2, with subsequent doses ranging from 125 to 275 IU/kg (25 to 55 μg/kg). Response was defined as a platelet increase to at least 50,000/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).

Childhood Acute ITP

A multicenter, randomised, controlled trial comparing Rho (D) IGIV to high dose and low dose Immune Globulin (Human) and prednisone was conducted in 146 non-splenectomised, Rho (D) positive children with acute ITP and platelet counts less than 20,000/mm3.
Of 38 patients receiving Rho (D) IGIV (125 IU/kg [25 μg/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 Rho (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.

Adult Chronic ITP

Twenty-four non-splenectomised, Rho (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 50 to 375 IU/kg (10 to 75 μg/kg) Rho (D) IGIV (mean initial dose 231 IU/kg [46.2 μg/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). The median duration of maintaining platelet counts greater than 15 000/mm3 above baseline levels was 34 days.

ITP Secondary to HIV Infection

Eleven children and 52 adults who were non-splenectomised, Rho (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 50 to 375 IU/kg (10 to 75 μg/kg) Rho (D) IGIV in an open-label trial. Rho (D) IGIV was administered for an average of 7.3 courses (range 1 to 57) over a mean period of 407 days (range 6 to 1,952). Fifty-seven of 63 patients responded (increase ≥ 20,000/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). The median duration of maintaining platelet counts greater than 15 000/mm3 above baseline platelet levels was 32 days.

WinRho SDF should not be used in previously splenectomised patients. WinRho SDF has been shown to increase platelet counts in non-splenectomised, Rho (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 the anti-Rho (D) –coated RBC complexes resulting in Fc receptor blockade, thus sparing antibody-coated platelets.

WinRho SDF 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 a decreased haemoglobin, can be expected. In four clinical trials of patients treated with the recommended initial intravenous dose of 250 IU/kg (50 μg/kg), the mean maximum decrease in haemoglobin was 1.70 g/dL (range +0.40 to -6.1 g/dL). At a reduced dose, ranging from 125 to 200 IU/kg (25 to 40 μg/kg) the mean maximum decrease in haemoglobin was 0.81 g/dL (range +0.65 to -1.9 g/dL). Only 5/137 (3.7%) of patients had a maximum decrease in haemoglobin of greater than 4 g/dL (range 4.2 to 6.1 g/dL).

The mean maximum decrease in haemoglobin in patients who were not transfused with concentrated RBCs was 3.7 g/dL (range 0.1-7 g/dL). Transfusions for treatment associated anaemia were administered within hours to days of the onset of IVH and consisted of between 1-6 units of RBCs. Acute renal insufficiency was noted within 2 to 48 hours of the onset of IVH.
The mean maximum increase in serum creatinine was 2.9 mg/dL (range 0.1-10.3 mg/dL) and occurred within 2-9 days. The renal insufficiency in all surviving patients resolved with medical management, including dialysis, within 4-23 days.

The etiology of IVH following WinRho SDF administration is unknown. No known risk factors associated with this adverse event have yet been identified among those examined, which included age, gender, pre-treatment renal function, pre-treatment haemoglobin, concomitantly administered concentrated RBCs or WinRho SDF dose.

5.2 Pharmacokinetic properties

Administration by the intravenous route results in immediate bioavailability with peak serum levels being achieved within two hours. Following intramuscular administration, measurable antibodies are first detected in1-3 hours, while the mean time to apparent peak serum level is 5-10 days. The half-life in the circulation of individuals with normal IgG levels is 3-4 weeks.

IgG and IgG-complexes are broken down in cells in the reticulo-endothelial system.

5.3 Preclinical safety data

Pre-clinical data and literature reveal no special hazard for humans with respect to acute toxicity and safety pharmacology, genotoxicity, carcinogenic potential and toxicity to reproduction. The active ingredient is human immune globulin, thus repeated dose toxicity and developmental toxicity studies are not relevant due to immunological nature of the active ingredient when given to animals. Preclinical effects are expected only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sodium chloride
Glycine
polysorbate 80

Solvent
Sodium chloride
Sodium phosphate monobasic monohydrate
Sodium phosphate dibasic dodecahydrate
Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

Shelf life of WinRho SDF as packaged for sale: 3 years

Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 12 hours at 25^{o}C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8^{o}C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Storage Conditions: +2°C to +8°C

- Store in a refrigerator
- Do not freeze
- Keep the vials in the outer carton in order to protect from light

For storage conditions of the reconstituted medicinal product, *see section 6.3.*

6.5 Nature and contents of container

Pack containing 1500 IU (300 µg)
Powder: Vial (Type 1 glass), bromobutyl rubber stopper, aluminum seal
Solvent: Vial (Type 1 glass) bromobutyl rubber stopper, aluminum seal

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

WinRho SDF must only be reconstituted using the accompanying sterile diluent. Use aseptic technique throughout.

To reconstitute the powder:

1. Remove the protective cap from the bottle containing the powder and the bottle containing the solvent.
2. Wipe exposed central portion of the rubber stoppers on both bottles with suitable disinfectant.
3. Withdraw the solvent using a suitable syringe and needle. See table below for solvent volumes required for reconstitution. Discard any unused portion of solvent.

Vial Size	Volume of Solvent Required	
	Intravenous Injection	Intramuscular Injection
1500 IU	2.5 mL	1.25 mL

4. Slowly inject the solvent into the bottle containing the powder.
5. Dissolve the powder by gently tilting and inverting the bottle. Do not shake it and avoid creating any foam. The powder dissolves fully in less than 10 minutes.

The reconstituted solution should be brought to room temperature or body temperature before use.

The reconstituted solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. The reconstituted preparation should be inspected visually for particulate matter and discoloration prior to administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 March 2005

10 DATE OF REVISION OF THE TEXT

July 2008