PRODUCT MONOGRAPH

HYPERRHO™ S/D FULL DOSE

Rh_o(D) Immune Globulin [Human]

Bayer Standard

Solvent / Detergent Treated

Solution for Injection

Single use vials and pre-filled syringes

Passive Immunizing Agent

Manufactured by:

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Distributed and imported by:
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THERAPEUTIC CLASSIFICATION

Passive Immunizing Agent

ACTION AND CLINICAL PHARMACOLOGY

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is used to prevent isoimmunization in the Rh_o(D) negative individual exposed to Rh_o(D) positive blood as a result of a fetomaternal hemorrhage occurring during a delivery of an Rh_o(D) positive infant, abortion (either spontaneous or induced), or following amniocentesis or abdominal trauma. Similarly, immunization resulting in the production of anti-Rh_o(D) following transfusion of Rh positive red cells to an Rh_o(D) negative recipient may be prevented by administering Rh_o(D) Immune Globulin [Human].[1,2]

Rh hemolytic disease of the newborn is the result of the active immunization of an Rh_o(D) negative mother by Rh_o(D) positive red cells entering the maternal circulation during a previous delivery, abortion, amniocentesis, abdominal trauma, or as a result of red cell transfusion.[3,4] HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) acts by suppressing the immune response of Rh_o(D) negative individuals to Rh_o(D) positive red blood cells. The mechanism of action of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is not fully understood.

The administration of Rh_o(D) Immune Globulin [Human] within 72 hours of a full-term delivery of an Rh_o(D) positive infant by an Rh_o(D) negative mother reduces the incidence of Rh isoimmunization from 12%–13% to 1%–2%. [5]

The 1%–2% treatment failures are probably due to isoimmunization occurring during the latter part of pregnancy or following delivery.[6] Bowman and Pollock [7] have reported that the incidence of isoimmunization can be further reduced from approximately 1.6% to less than 0.1% by administering Rh_o(D) Immune Globulin [Human] in two doses, one antenatal at 28 weeks' gestation and another following delivery.

In a clinical study in eight healthy human adults receiving another hyperimmune immune globulin product treated with solvent/detergent, Rabies Immune Globulin [Human], prepared by the same manufacturing process, detectable passive antibody titers were observed in the serum of all subjects by 24 hours post injection and persisted through the 21 day study period. These results suggest that passive immunization with immune globulin products is not compromised by the solvent/detergent treatment.

INDICATIONS AND CLINICAL USE

Pregnancy - Post Partum Use

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is recommended for the prevention of Rh hemolytic disease of the newborn by its administration to Rh_o(D) negative mother within 72 hours after birth of an Rh_o(D) positive infant,[8] providing the following criteria are met:

1. The mother must be Rh_o(D) negative and must not already be sensitized to the Rh_o(D) factor.
2. Her child must be Rh_o(D) positive, and should have a negative direct antiglobulin test (see PRECAUTIONS).

Pregnancy - Ante Partum Use

If HYPERRHO™ S/D FULL DOSE is administered antepartum, it is essential that the mother receive another dose of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) after delivery of an Rh_o(D) positive infant. If the father can be determined to be Rh_o (D) negative, HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) need not be given. (See DOSAGE AND ADMINISTRATION, Pregnancy and Other Conditions).

Pregnancy - Other Obstetric Conditions

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be administered within 72 hours to all nonimmunized Rh_o(D) negative women who have undergone spontaneous or induced abortion, following ruptured tubal pregnancy, amniocentesis or abdominal trauma unless the blood group of the fetus or the father is known to be Rh_o(D) negative. [3,4] If the fetal blood group cannot be determined, one must assume that it is Rh_o(D) positive,[9] and HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be administered to the mother.

Transfusion

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) may be used to prevent isoimmunization in Rh_o(D) negative individuals who have been transfused with Rh_o(D) positive red blood cells or blood components containing red blood cells.[1, 10]

CONTRAINDICATIONS

None known.

WARNINGS

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is made from human plasma. 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. 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. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Bayer Inc. at 1-800-622-2937 ext 5425.

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer Rh_o(D) Immune Globulin [Human] to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

DO NOT ADMINISTER USING INTRAVENOUS INJECTION. INJECT ONLY INTRAMUSCULARLY.

DO NOT ADMINISTER TO NEONATES.

PRECAUTIONS

General

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. If there is any doubt about the mother's Rh type, she should be given Rh_o(D) Immune Globulin [Human]. A screening test to detect fetal red blood cells may be helpful in such cases.

If more than 15 mL of D-positive fetal red blood cells are present in the mother's circulation, more than a single dose of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is required. Failure to recognize this may result in the administration of an inadequate dose.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic reactions.

Drug Interactions

Other antibodies in the Rh_o(D) Immune Globulin [Human] preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Rh_o(D) Immune Globulin [Human] administration.

Drug/Laboratory Interactions

Babies born of women given Rh_o(D) Immune Globulin [Human] antepartum may have a weakly positive direct antiglobulin test at birth.

Passively acquired anti-Rh_o(D) may be detected in maternal serum if antibody screening tests are performed subsequent to antepartum or postpartum administration of Rh_o(D) Immune Globulin [Human].

Pregnancy

Animal reproduction studies have not been conducted with HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]). It is also not known whether Rh_o(D) Immune Globulin [Human] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Reactions to Rh_o(D) Immune Globulin [Human] are infrequent in Rh_o(D) negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation.

While sensitization to repeated injections of human immune globulin is extremely rare, it has occurred. Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_o(D) Immune Globulin [Human] following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

DOSAGE AND ADMINISTRATION

DO NOT ADMINISTER USING INTRAVENOUS INJECTION. INJECT ONLY INTRAMUSCULARLY.

DO NOT ADMINISTER TO NEONATES.

Dosage

Pregnancy and Other Obstetric Conditions

1. For postpartum prophylaxis, administer one vial or syringe of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) (300 µg*), preferably within 72 hours of delivery. Although a lesser degree of protection is afforded if Rh antibody is administered beyond the 72-hour period, HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) may still be given.[3, 11] Full-term deliveries can vary in their dosage requirements depending on the magnitude of the fetomaternal hemorrhage. One 300 µg* vial or syringe of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) provides sufficient antibody to prevent Rh sensitization if the volume of red blood cells that has entered the circulation is 15 mL or less.[9, 12, 13] In instances where a large (greater than 30 mL of whole blood or 15 mL red blood cells) fetomaternal hemorrhage is suspected, a fetal red cell count by an approved laboratory technique (e.g., modified Kleihauer-Betke acid elution stain technique) should be performed to determine the dosage of immune globulin required.[4,14] The red blood cell volume of the calculated fetomaternal hemorrhage is divided by 15 mL to obtain the number of vials or syringes of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) for administration.[4, 10, 12] If more than 15 mL of red cells is suspected or if the dose calculation results in a fraction, administer the next higher whole number of vials or syringes (e.g., if 1.4, give 2 vials or 2 syringes).

2. For antenatal prophylaxis, one 300 µg* vial or syringe of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is administered at approximately 28 weeks' gestation. This **must** be followed by another 300 µg* dose, preferably within 72 hours following delivery, if the infant is Rh positive.

3. Following threatened abortion at any stage of gestation with continuation of pregnancy, it is recommended that 300 µg* of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) be given. If more than 15 mL of red cells is suspected due to fetomaternal hemorrhage, the same dose modification in No. 1 above applies.

4. Following miscarriage, abortion, or termination of ectopic pregnancy at or beyond 13 weeks' gestation, it is recommended that 300 µg* of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) be given. If more than 15 mL of red cells is suspected due to fetomaternal hemorrhage, the same dose modification in No. 1 above applies. If pregnancy is terminated prior to 13 weeks' gestation, where licensed, a single dose of BAYRHO-D™ MINI-DOSE (approximately 50 µg*) may be used instead of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]).

5. Following amniocentesis at either 15 to 18 weeks' gestation or during the third trimester, or following abdominal trauma in the second or third trimester, it is recommended that 300 µg* of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) be administered. If there is a fetomaternal

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hemorrhage in excess of 15 mL of red cells, the same dose modification in No. 1 applies.

If abdominal trauma, amniocentesis, or other adverse event requires the administration of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) at 13 to 18 weeks' gestation, another 300 μg* dose should be given at 26 to 28 weeks. To maintain protection throughout pregnancy, the level of passively acquired anti-Rh_o(D) should not be allowed to fall below the level required to prevent an immune response to Rh positive red cells. The half-life of IgG is 23 to 26 days. In any case, a dose of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be given within 72 hours after delivery if the baby is Rh positive. If delivery occurs within 3 weeks after the last dose, the postpartum dose may be withheld unless there is a fetomaternal hemorrhage in excess of 15 mL of red blood cells.[15]

Transfusion

In the case of a transfusion of Rh_o(D) positive red cells to an Rh_o(D) negative recipient, the volume of Rh positive whole blood administered is multiplied by the hematocrit of the donor unit giving the volume of red blood cells transfused. The volume of red blood cells is divided by 15 mL which provides the number of vials or syringes of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) to be administered.

If the dose calculated results in a fraction, the next higher whole number of vials or syringes should be administered (e.g., if 1.4, give 2 vials or 2 syringes). HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) should be administered within 72 hours after an incompatible transfusion, but preferably as soon as possible.

Administration

DO NOT INJECT INTRAVENOUSLY. DO NOT ADMINISTER TO NEONATES. HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is administered **intramuscularly**, preferably in the anterolateral aspects of the upper thigh and the deltoid muscle of the upper arm. The gluteal region should not be used routinely as an injection site because of the risk of injury to the sciatic nerve. If the gluteal region is used, the central region MUST be avoided; only the upper, outer quadrant should be used.[17]

A. Single Vial or Syringe Dose

   INJECT ENTIRE CONTENTS OF THE VIAL OR SYRINGE INTO THE SELECTED MUSCLE.

B. Multiple Vial or Syringe Dose

   1. Calculate the number of vials or syringes of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) to be given (see Dosage section).

   2. The total volume of HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human])can be given in divided doses at different sites at one time or the total dose may be divided and injected at intervals, provided the total dosage is given within 72 hours of the fetomaternal hemorrhage or transfusion.

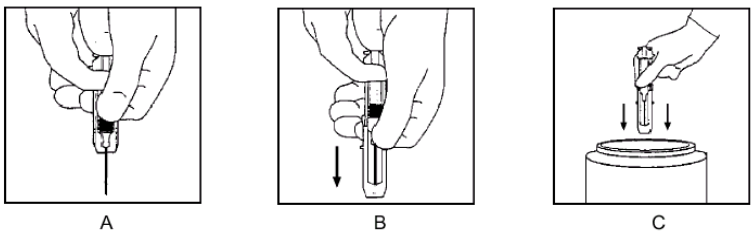
      USING STERILE TECHNIQUE, INJECT THE ENTIRE CONTENTS OF EACH CALCULATED NUMBER OF VIALS OR SYRINGES INTO THE SELECTED MUSCLE OF THE PATIENT.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HYPERRHO™ S/D FULL DOSE is supplied with a syringe and an attached UltraSafe® Needle Guard for protection and convenience. Please follow instructions below for proper use of syringe and UltraSafe® Needle Guard.

Directions for Syringe Usage

1. Remove the pre-filled syringe from the package. Lift syringe by barrel, **not** by plunger.
2. Twist the plunger rod clockwise until the threads are seated.
3. With the rubber needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the rubber stopper and the glass syringe barrel.
4. Remove the needle shield and expel air bubbles.
5. Proceed with hypodermic needle puncture.
6. Aspirate prior to injection to confirm that the needle is not in a vein or artery.
7. Inject the medication.
8. Keeping hands behind the needle, grasp the guard with the free hand and slide forward toward needle until it is completely covered and guard clicks into place. If audible click is not heard, guard may not be completely activated. (See diagram A and B)
9. Place entire pre-filled glass syringe with guard activated into an approved sharps container for proper disposal. (see diagram C)



A B C

PHARMACEUTICAL INFORMATION

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) treated with solvent/detergent is a sterile solution of immune globulin containing antibodies to Rh_o(D) for intramuscular administration; it contains no preservative.

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is prepared by cold ethanol fractionation from human plasma. The immune globulin is isolated from solubilized Cohn fraction II. The fraction II solution is adjusted to a final concentration of 0.3% tri-n-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration and finally ultrafiltration and diafiltration. HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is formulated as a 15–18% protein solution at a pH of 6.4–7.2 in 0.21–0.32 M glycine. The pH is adjusted using sodium carbonate. HYPERRHO™ S/D FULL DOSE is then incubated in the final container for 21–28 days at 20–27°C. The potency is equal to or greater than that of the U.S. Food and Drug Administration Reference Rho(D) Immune Globulin. Each single dose vial or syringe contains sufficient anti-Rh_o(D) (approximately 300 µg*) to effectively suppress the immunizing potential of 15 mL of Rh_o(D) positive red blood cells. [9, 12, 13]

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) has been validated in laboratory studies. Human Immunodeficiency Virus, Type 1 (HIV-1), was chosen as the relevant virus for blood

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products; Bovine Viral Diarrhea Virus (BVDV) was chosen to model Hepatitis C virus; Pseudorabies virus (PRV) was chosen to model Hepatitis B virus and the Herpes viruses; and Reo virus type 3 (Reo) was chosen to model non-enveloped viruses and for its resistance to physical and chemical inactivation. Significant removal of model enveloped and non-enveloped viruses is seen in the Fraction II + IIIW to Effluent III step and significant removal of PRV and Reovirus is seen in the Effluent III to Filtrate III step. Significant inactivation of enveloped viruses is achieved at the time of treatment of the solubilized Cohn Fraction II solvent/detergent.

STORAGE

Store at 2–8°C (36–46°F). Do not freeze.

AVAILABILITY OF DOSAGE FORMS

HYPERRHO™ S/D FULL DOSE (Rh_o(D) Immune Globulin [Human]) is available in single use vials and single-use pre-filled syringes with an attached UltraSafe® Needle Guard.

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

No warranty, express or implied, including any warranty of merchantability or fitness is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labeling, including the package insert for this product, except by printed notice from the Company's headquarters. The prescriber and user of this product must accept the terms hereof.

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