Product Information

Rh(D) Immunoglobulin-VF

Australia

NAME OF THE MEDICINE

Human Anti-D Rh_o Immunoglobulin, solution for intramuscular injection.

DESCRIPTION

Rh(D) Immunoglobulin-VF is a sterile, preservative-free solution containing human plasma proteins and 22.5 mg/mL glycine. The solution has a pH of 6.6. At least 98% of the protein is immunoglobulins (mainly IgG), with an anti-D (Rh_o) antibody content of 625 IU per vial/ ≥30 mg/mL human plasma proteins or 250 IU per vial/ ≥10 mg/mL human plasma proteins.

Rh(D) Immunoglobulin-VF is manufactured from plasma donated by Australia's voluntary and non-remunerated donors who have been immunised to the Rh antigen 'D'. Donations are selected on the basis that they contain high levels of antibodies to the Rh antigen 'D'. Immunoglobulins for intramuscular injection, prepared by this process from plasma screened by current methods, have not been implicated in the transmission of viral infectious diseases including human immunodeficiency virus (HIV). Studies using plasma spiked with HIV have shown that the Cohn cold-ethanol fractionation process produces a very large reduction in virus titre with undetectable levels in the immunoglobulin fraction. Epidemiological studies have not recognised any cluster of AIDS patients or HIV seroconversion in immunoglobulin recipients. The manufacturing process for Rh(D) Immunoglobulin-VF contains specific steps to reduce the possibility of viral transmission including pasteurisation for viral inactivation and nanofiltration for virus removal.

PHARMACOLOGY

Rh(D) Immunoglobulin-VF contains high levels of antibodies (mainly IgG) directed against the D antigen of Rh-positive red cells. Rh(D) Immunoglobulin-VF acts by suppressing the immune response in Rh negative individuals to Rh(D) positive red cells. Such exposure follows the passage of cells from the foetal to the maternal circulation or the accidental transfusion of Rh(D) positive red cells to an Rh(D) negative individual.

Clinical studies indicate that the administration of anti-D immunoglobulin to an Rh(D) negative mother within 72 hours of the birth of an Rh(D) positive infant reduces the incidence of Rh isoimmunisation from 12–13% to 1–2%. A small number (1.5–1.8%) of

Rh negative mothers are immunised by their Rh positive foetuses despite administration of anti-D immunoglobulin postpartum. Studies have shown that this number can be reduced to less than 1.0% by administering two doses of anti-D immunoglobulin, the first at 28 weeks gestation and the second following delivery.

CLINICAL TRIALS

A comparative clinical trial was conducted to investigate the effect of pasteurisation on the *in vivo* behaviour of intramuscular immunoglobulins using Hepatitis B Immunoglobulin (pasteurised and unpasteurised) as the representative of this group of products.
Fifty-eight (58) healthy subjects (28 males and 30 females) each received an intramuscular injection of pasteurised (viral inactivated) or unpasteurised Hepatitis B Immunoglobulin. No significant clinical differences were observed.

Twenty-eight (28) subjects received the viral inactivated product. Maximal serum concentration of IgG was reached after 8.0±5.5 days (mean±s.d.), and the estimated half life of IgG was 27.2±6.6 days (mean±s.d.). These values are consistent with ranges observed with other intramuscular immunoglobulin products.

A clinical trial with Rh(D) Immunoglobulin-VF has not been conducted.

INDICATIONS

Rh(D) Immunoglobulin-VF is indicated for the prevention of Rh sensitisation in Rh(D) negative females at or below child bearing age.

CONTRAINDICATIONS

Rh(D) Immunoglobulin-VF should not be given to:

1. An Rh(D) positive or D^u positive individual.
2. An Rh(D) negative and D^u negative individual previously sensitised to the Rh(D) antigen.
   Note: Although there is no benefit in administering Rh(D) Immunoglobulin-VF to a woman who is already sensitised to the Rh factor, there is no more risk than when it is given to a woman who is not sensitised.
3. Individuals with isolated Immunoglobulin A (IgA) deficiency, unless they have been tested and shown not to have circulating anti-IgA antibodies.

4. Individuals who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

PRECAUTIONS

Rh(D) Immunoglobulin-VF MUST NOT be administered intravenously because of the potential for anaphylactic reactions. Injections must be made intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

Rh(D) Immunoglobulin-VF should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations. In the case of shock, treatment should follow the guidelines of shock therapy.

Rh(D) Immunoglobulin-VF must not be given to the Rh(D) positive postpartum infant. Babies born of women given Rh(D) Immunoglobulin-VF antepartum may have a weakly positive Coombs test at birth.

There is some evidence that the intramuscular administration of Rh(D) Immunoglobulin-VF in patients with a body mass index (BMI) ≥30 is associated with an increased risk of lack of effect. Therefore in these patients, it is recommended that the clearance of foetal cells and the presence of Rh(D) antibody be confirmed post administration.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents, 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 infectious agents and by testing for the presence of certain viral markers.

In addition, virus removal and inactivation procedures are included in the manufacturing process. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped viruses, such as hepatitis A virus (HAV) and human parvovirus B19. Additionally, the product contains specific antibodies directed against human parvovirus B19.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Genotoxicity, carcinogenicity and impairment of fertility

No genotoxicity, carcinogenicity or reproductive toxicity studies have been conducted with Rh(D) Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL's plasma derived products.

Use in pregnancy and lactation

The safety of this medicinal product for use in human pregnancy or during lactation has not been established in controlled clinical trials. The use of anti-D immunoglobulin during the third trimester in doses as high as 1500 IU antibody has been reported to produce no evidence of haemolysis in the infant. The presence of passively administered Rh(D) Immunoglobulin-VF in the maternal blood sample can, however, affect the interpretation of laboratory tests to identify the patient as a candidate for Rh(D) Immunoglobulin-VF. Immunoglobulins are excreted in breast milk, however, it is not known whether this applies to passively administered Rh(D) Immunoglobulin-VF.

Paediatric use and use in the elderly

The use of this product in the paediatric and elderly populations has not been established in appropriate studies. To date, these populations are not over-represented in spontaneous reports of adverse events associated with the use of CSL's intramuscular immunoglobulin products.

Interactions with other medicines

Rh(D) Immunoglobulin-VF should not be mixed with other pharmaceutical products, except as indicated (see **DOSAGE AND ADMINISTRATION**).

Live attenuated virus vaccines: Passively acquired antibody can interfere with the response to live, attenuated virus vaccines. Therefore, administration of such vaccines, e.g. poliomyelitis or measles, should be deferred until approximately three months after passive immunisation. By the same token, immunoglobulins should not be administered for at least two weeks after such a vaccine has been given.

Passive transfer of antibodies and effect on laboratory tests

After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

The results of blood typing and antibody testing including the Coombs test, are significantly affected by the administration of anti-D immunoglobulin. **When performing red cell antibody screening, take blood prior to the administration of Rh(D) Immunoglobulin-VF.**

There is no evidence to date that parvovirus B19 can be transmitted by Rh(D) Immunoglobulin-VF, which is known to contain antibodies to the virus and the nanofiltration step of the manufacturing process has been shown to remove such viruses (or viruses of similar size).

ADVERSE EFFECTS

Local tenderness, erythema and stiffness may occur at the site of injection and may persist for several hours. This may occur after any intramuscular injection. In the clinical trial with Hepatitis B Immunoglobulin, the following general and local reactions were recorded in the 58 healthy subjects (total number of events, up to and including 7 days post injection; pasteurised/unpasteurised product): malaise (20/22 events), drowsiness (13/17 events), induration (10/4 events), sensation of fever (4/4 events), chills (3/3 events), sweating (3/1 events) and warmth/heat when touched (0/4 events). There was an overall higher reporting of local tolerance adverse events at the injection site for the unpasteurised product, such as pain (32/52 events), bruising (10/22 events), redness (2/8 events) and irritation (2/4 events).

Mild pyrexia, malaise, drowsiness and urticaria have been reported occasionally after injections of immunoglobulins. True allergic responses are rare. Skin lesions, headache, dizziness, nausea, generalised hypersensitivity reactions and convulsions have been reported on rare occasions.

DOSAGE AND ADMINISTRATION

Dosage

Sensitising events in pregnancy (unless the blood type of the foetus is confirmed to be Rh(D) negative)

The recommended dose of anti-D immunoglobulin is:

- 250 IU after sensitising events in the first trimester of pregnancy and
- 625 IU after sensitising events beyond the first trimester.

If the gestational age is not known with certainty and the possibility exists that the gestational age is 13 weeks or more, 625 IU should be given.

In twin and multiple pregnancies in the first trimester, 625 IU should be given.

The dose should be given as soon as possible and within 72 hours of the event.

Sensitising events include normal delivery, miscarriage, termination of pregnancy, ectopic pregnancy, chorionic villus sampling, amniocentesis, cordocentesis, abdominal trauma considered sufficient to cause foeto-maternal haemorrhage, antepartum haemorrhage and external cephalic version.

Since evidence of the efficacy of these doses is limited, it is recommended that the magnitude of foeto-maternal haemorrhage is assessed and further doses given as necessary. As a guide, a dose of 625 IU will protect against a foeto-maternal haemorrhage of up to 6 mL of Rh(D) positive red blood cells. For haemorrhages greater than 6 mL, the recommended dose is 100 IU per mL Rh(D) positive red blood cells.

Transfusion of Rh(D) positive blood

The recommended dose of anti-D immunoglobulin is:

- 100 IU per mL Rh(D) positive red blood cells.

Administration

If the product appears to be turbid by transmitted light or contains any sediment it must not be used. **The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the vial. Any unused solution must be discarded appropriately.**

Rh(D) Immunoglobulin-VF should be brought to room temperature before use, and given slowly by deep intramuscular injection using an appropriate sized needle. If a large dose (more than 5 mL) is required, it is advisable to administer it in divided doses at different sites. Hyaluronidase and/or a suitable local anaesthetic may be added to the injection if desired.

OVERDOSAGE

The consequences of overdosage are not known.

PRESENTATION AND STORAGE CONDITIONS

Rh(D) Immunoglobulin-VF solution for intramuscular injection is available in single vials containing 625 IU or 250 IU anti-D antibody. The actual volume in the vial is stated on the label.

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Do not use after the expiry date shown on the label.

Note: Supplies of suitable plasma for Rh(D) Immunoglobulin-VF production are scarce. Individuals who have Rh(D) antibodies should be urged to enrol as voluntary blood donors.

NAME AND ADDRESS OF THE SPONSOR

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DISTRIBUTED BY

Australian Red Cross Blood Service

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF THERAPEUTIC GOODS ADMINISTRATION APPROVAL

15 October 2010

DATE OF MOST RECENT AMENDMENT

22 December 2014

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