AUSTRALIAN PRODUCT INFORMATION

Rh(D) Immunoglobulin-VF

(Human anti-D Rh_o immunoglobulin) – Solution for intramuscular injection

1 NAME OF THE MEDICINE

Human Anti-D Rh_o Immunoglobulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rh(D) Immunoglobulin-VF is a sterile, preservative-free solution containing human plasma protein of which at least 98% is immunoglobulin (mainly IgG), with an anti-D (Rh_O) antibody content of 625 IU per vial/ ≥10 mg/mL human plasma proteins or 250 IU per vial/ ≥10 mg/mL human plasma proteins.

The pH value of the ready-to-use solution is 6.6.

Rh(D) Immunoglobulin-VF is manufactured from human plasma collected by Australian Red Cross Lifeblood.

Rh(D) Immunoglobulin-VF contains 22.5 mg/mL glycine.

3 PHARMACEUTICAL FORM

Solution for intramuscular injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF 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 is required, it is advisable to administer it in divided doses at different sites. This applies in the case of doses above 2 mL for children up to 20 kg body weight and doses above 5 mL for persons above 20 kg body weight.

Hyaluronidase and/or a suitable local anaesthetic may be added to the injection if desired.

4.3 CONTRAINDICATIONS

Rh(D) Immunoglobulin-VF is contraindicated in:

- an Rh(D) positive or D^u positive individual
- 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 the product is given to a woman who is not sensitised

- patients who have had a true anaphylactic reaction to the active substance or to any of the components of the product
- patients with Immunoglobulin A (IgA) deficiency, unless they have been tested and shown not to have circulating anti-IgA antibodies, since these patients may experience severe reactions to the IgA which is present in trace amounts
- patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Route of administration

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.

Hypersensitivity

Rh(D) Immunoglobulin-VF contains trace amounts of IgA which may provoke anaphylaxis in patients with anti-IgA antibodies, such as those with IgA deficiency.

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. Rarely, Rh(D) Immunoglobulin-VF can induce a precipitous fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human immunoglobulins. In case of anaphylactic reaction, the treatment should be stopped immediately.

In the case of shock, treatment should follow the guidelines of shock therapy.

Patients should be observed for at least 20 minutes after administration of Rh(D) Immunoglobulin-VF. Particularly in cases of inadvertent intravenous injection, patients should be observed for longer term (at least 1 hour) after administration.

Obesity

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, 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. 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.

There is reassuring clinical experience regarding the lack of parvovirus B19 transmission with immunoglobulins and the nanofiltration step of the manufacturing process has been shown to remove such viruses (or viruses of similar size). The product is known to contain antibodies to the virus.

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.

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.

It is strongly recommended that every time that Rh(D) Immunoglobulin-VF 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 the product.

Use in the elderly

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

Paediatric use

In case of postnatal use, Rh(D) Immunoglobulin-VF must not be given to the newborn infant. Babies born of women given Rh(D) Immunoglobulin-VF antepartum may have a weakly positive Coombs' test at birth.

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

Effects 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 through passive transmission of antibodies to erythrocyte antigens (e.g. anti-A, anti-B, anti-D) particularly in Rh(D) positive neonates whose mothers have received antepartum prophylaxis. **When performing red cell antibody screening, take blood prior to the administration of Rh(D) Immunoglobulin-VF.**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Rh(D) Immunoglobulin-VF should not be mixed with other pharmaceutical products, except as indicated (see section 4.2 Dose and method of 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. In the case of measles, the decrease in efficacy may persist for up to one year. Therefore, patients receiving measles vaccine should have their antibody status checked. By the same token, immunoglobulins should not be administered for at least two weeks after such a vaccine has been given.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No 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 therapeutic medicines.

Use in pregnancy

The safety of this medicinal product for use in human pregnancy 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.

Use in lactation

The safety of this medicinal product for use during lactation has not been established in controlled clinical trials. Immunoglobulins are excreted in breast milk, however, it is not known whether this applies to passively administered Rh(D) Immunoglobulin-VF.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rh(D) Immunoglobulin-VF has no influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The consequences of overdosage are not known.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Rh(D) Immunoglobulin-VF is manufactured from human plasma donated 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'.

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 trials

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.

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.

5.2 PHARMACOKINETIC PROPERTIES

Refer to Section 5.1 Pharmacodynamic Properties.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity 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 therapeutic medicines.

Carcinogenicity

No carcinogenicity 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 therapeutic medicines.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products, diluents or solvents, except as indicated (see section 4.2 Dose and method of administration).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Rh(D) Immunoglobulin-VF solution for intramuscular injection is available in single vials containing 625 IU or 250 IU anti-D antibody.

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Not applicable

CAS Number

None assigned

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 October 2010

10 DATE OF REVISION

14 January 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Specified limit of human plasma proteins for 625 IU vial changed to ≥10 mg/mL
6.5	Variable volume statement removed, as product is now filled to a fixed volume