AUSTRALIAN PRODUCT INFORMATION

Normal Immunoglobulin-VF
(Human normal immunoglobulin)

1 NAME OF THE MEDICINE

Human Normal Immunoglobulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Normal Immunoglobulin-VF is a sterile, preservative-free solution containing 160 mg/mL human plasma proteins and 22.5 mg/mL glycine. At least 98% of the protein is immunoglobulins (mainly IgG).

Normal Immunoglobulin-VF contains less than 0.5 mg/mL immunoglobulin A (IgA).

Normal Immunoglobulin-VF is manufactured from human plasma collected by Australian Red Cross Lifeblood.

3 PHARMACEUTICAL FORM

Solution for intramuscular injection.

The solution has a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Normal Immunoglobulin-VF is indicated in the management of congenital and acquired forms of primary hypogammaglobulinaemia. It may also be of value in treating secondary forms of this disorder as in leukaemia, nephrosis and acute protein-losing enteropathy, particularly when there is a tendency to recurrent infection.

In susceptible contacts of hepatitis A, measles and poliomyelitis, Normal Immunoglobulin-VF may be of value in preventing or modifying the disease. In general, the earlier in the incubation period of these diseases Normal Immunoglobulin-VF is given, the greater its effectiveness.

Hepatitis A

Routine passive protection is recommended in persons exposed less than one week previously for the following categories of individuals:

- Household contacts of an index case, who have not already had hepatitis A or have no serological evidence of immunity to the virus.

- Common source exposures. When a vehicle such as food or water is identified as a common source of infection for multiple hepatitis cases, administration of Normal Immunoglobulin-VF should be considered for all those exposed to the source.
- Institutional contacts.
- Staff in institutions where hepatitis is endemic.

Routine prophylaxis is not recommended for school, office, factory or hospital contacts.

Rubella

Although Normal Immunoglobulin-VF can prevent or modify the clinical disease in susceptible rubella contacts if given within 72 hours of exposure, it does not prevent viraemia in such patients. It should, therefore, not be relied upon to prevent congenital malformations due to rubella if given to susceptible pregnant women during the first trimester.

Measles (Morbilli)

Normal Immunoglobulin-VF is indicated for protection against measles in persons exposed less than one week previously. It is recommended in children under six months of age whose mothers have not had the disease, in children between six months and three years of age who have not been actively immunised and in immunosuppressed contacts of the index case.

Poliomyelitis

Normal Immunoglobulin-VF is recommended for susceptible contacts who have not been immunised against poliomyelitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The following dosages are recommended:

Hepatitis A

Household contacts, common source exposures: A dose of Normal Immunoglobulin-VF equivalent to 0.06 mL/kg body weight should be given for long term protection or 0.03 mL/kg body weight for short term protection. For prophylaxis long term, the injections should be given 5-monthly but serological checks should be made to assess if active immunity has developed.

The following doses of Normal Immunoglobulin-VF are recommended for persons who plan to travel in areas where hepatitis A is common*. Length of stay less than 3 months, 0.03 mL/kg body weight; 3 months or longer, 0.06 mL/kg body weight (repeat every 4–6 months).

Institutional contacts:* 0.06 mL/kg body weight.

Staff in institutions where hepatitis is endemic:* A large dose (0.06 mL/kg body weight) should be offered at the time of employment, and this should be repeated at six-monthly intervals if the risk persists.

* The use of hepatitis A vaccine may be more appropriate for these individuals, provided there is adequate time for active immunity to develop (7 to 10 days).

Measles

0.2 mL/kg body weight for prevention.

Poliomyelitis

0.3 mL/kg body weight.

Hypogammaglobulinaemia

0.6 mL/kg body weight at intervals of one month. An additional dose should be given during the first month of treatment.

Administration

If the product appears to be turbid by transmitted light or contains any sediment, it must not be used. **The product contains no antimicrobial preservative. It must, therefore, be used immediately after opening the vial. Any unused solution must be discarded appropriately.**

Normal 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.

An intravenous preparation is available from CSL when large doses of immunoglobulin need to be given, or when the patient has a significant haemostatic defect which may cause bleeding following intramuscular injection.

4.3 CONTRAINDICATIONS

Normal Immunoglobulin-VF is contraindicated in individuals:

1. With isolated immunoglobulin A (IgA) deficiency, unless they have been tested and shown not to have circulating anti-IgA antibodies.
2. Who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Normal 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.

Normal 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.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. These events may be associated with Normal Immunoglobulin-VF when it is used for primary or secondary hypogammaglobulinaemia. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

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 Normal 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. Additionally, the product contains specific antibodies directed against human parvovirus B19.

There is no evidence to date that parvovirus B19 can be transmitted by Normal 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).

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.

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

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Normal 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. By the same token, immunoglobulins should not be administered for at least two weeks after a vaccine has been given.

Inactivated vaccines: Inactivated vaccines may be administered concurrently with passive antibody (although in separate syringes) to induce active immunity as is sometimes done for tetanus-prone wounds.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive toxicity studies have been conducted with Normal 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. Normal Immunoglobulin-VF should therefore only be given with caution to pregnant women.

Use in lactation

The safety of this medicinal product for use during lactation has not been established in controlled clinical trials. Normal Immunoglobulin-VF should therefore only be given with caution to breast-feeding mothers. Immunoglobulins are excreted in breast milk, however, it is not known whether this applies to passively administered Normal Immunoglobulin-VF.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

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

Normal Immunoglobulin-VF consists mainly of IgG with a broad spectrum of antibodies against various infectious agents.

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 Normal 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 Normal 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 Normal 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

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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

Normal Immunoglobulin-VF solution for intramuscular injection is available in single vials containing 2 mL or 5 mL. Both presentations contain 160 mg/mL human plasma proteins and 22.5 mg/mL glycine.

NOTE: The following specific immunoglobulins are also available:

Tetanus Immunoglobulin-VF (for intramuscular use) for passive prophylactic immunisation against tetanus.
Tetanus Immunoglobulin-VF (for intravenous use) for the treatment of clinical tetanus.

Zoster Immunoglobulin-VF (for intramuscular use) for prevention of varicella/zoster infection in high-risk patients, e.g. patients with malignant disease or on immunosuppressive therapy.
Hepatitis B Immunoglobulin-VF (for intramuscular use) to prevent infection of persons accidentally exposed to hepatitis B virus.
Rh(D) Immunoglobulin-VF (for intramuscular use) for prevention of haemolytic disease of the newborn.
CMV Immunoglobulin-VF (for intravenous use) for prevention of CMV infections following bone marrow or renal transplants.

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

07 April 2005

10 DATE OF REVISION

08 July 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Addition of immunoglobulin A value.