NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Normal Immunoglobulin-VF, 160 mg/mL, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin

Normal Immunoglobulin-VF is a sterile solution with no preservatives containing 160 mg/mL human plasma proteins. At least 98% of the protein is immunoglobulins (mainly IgG).

Normal Immunoglobulin-VF is presented in single vials as follows:

- 2 mL of solution containing 320 mg of human normal immunoglobulin.
- 5 mL of solution containing 800 mg of human normal immunoglobulin.

Normal Immunoglobulin-VF is manufactured from human plasma donated by New Zealand's voluntary and non-remunerated donors.

Excipients with known effect

Glycine (22.5 mg/mL)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

The pH of the solution is 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary and secondary hypogammaglobulinaemia

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

Dose

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.

Method of 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.**

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 Behring 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.

For further instructions, see section 6.6.

4.3 Contraindications

Normal Immunoglobulin-VF is contraindicated in individuals:

- with isolated immunoglobulin A (IgA) deficiency, unless they have been tested and shown not to have circulating anti-IgA antibodies.
- 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, virus removal and inactivation procedures are included in the manufacturing process to reduce the possibility of viral transmission. This includes 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.

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 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.

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).

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 and carcinogenicity

No genotoxicity or carcinogenicity studies have been conducted with Normal Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL Behring's plasma-derived products.

4.5 Interaction with other medicines and other forms of interaction

Normal Immunoglobulin-VF should not be mixed with other pharmaceutical products, except as indicated (see section 4.2).

Vaccinations with 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.

Vaccinations with 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.

Interference with laboratory testing

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.

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

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.

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 Behring's plasma-derived products.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Summary of the safety profile

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.

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.

Adverse reactions from clinical trials

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).

Paediatric population

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 Behring's intramuscular therapeutic medicines.

Elderly population

The use of this product in the elderly populations 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 Behring's intramuscular therapeutic medicines.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The consequences of overdosage are not known.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration

ATC code: J06BA01

Mechanism of action

Normal Immunoglobulin-VF consists mainly of IgG with a broad spectrum of antibodies against various infectious agents. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

Clinical efficacy and safety

A clinical trial with Normal Immunoglobulin-VF has not been conducted.

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.

5.2 Pharmacokinetic properties

Absorption and Distribution

The immunoglobulin after intramuscular administration is slowly absorbed into the recipient's circulation and reaches a maximum after a delay of 2 to 3 days. The immunoglobulin has a half-life of about 3 to 4 weeks. This half-life may vary from patient to patient.

Elimination

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

Animal reproduction studies have not been conducted with Normal Immunoglobulin-VF.

Normal Immunoglobulin-VF with normal human IgG as the active ingredient is derived from human plasma and acts like an endogenous constituent of plasma. Preclinical studies with repeated dose applications (chronic toxicity and carcinogenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine (22.5 mg/mL)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Storage after first opening:

The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the vial.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

For storage after first opening, see section 6.3.

6.5 Nature and contents of container

Normal Immunoglobulin-VF for intramuscular injection is available in single dose glass vials containing 2 mL or 5 mL of solution. 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.

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.

6.6 Special precautions for disposal and other handling

Normal Immunoglobulin-VF is a sterile, ready-to-use solution.

Any unused solution must be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11 February 1999

10 DATE OF REVISION OF THE TEXT

23 April 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Sponsor contact details amended. Manufacturer and Distributor addresses added.