AUSTRALIAN PRODUCT INFORMATION

Hepatitis B Immunoglobulin-VF

(Human hepatitis B immunoglobulin) – Solution for intramuscular injection

1 NAME OF THE MEDICINE

Human Hepatitis B Immunoglobulin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hepatitis B Immunoglobulin-VF is a sterile, preservative-free solution containing 160 mg/mL human plasma protein of which at least 98% is immunoglobulin (mainly IgG), with a hepatitis B antibody titre of not less than 100 IU/mL.

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

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

Hepatitis B Immunoglobulin-VF contains 22.5 mg/mL glycine.

3 PHARMACEUTICAL FORM

Solution for intramuscular injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hepatitis B Immunoglobulin-VF is indicated for post-exposure prophylaxis in persons who did not receive prior vaccination, or whose prior vaccination regimen is incomplete, or when the hepatitis B antibody level is inadequate (<10 IU/L).

Post-exposure prophylaxis should be considered following percutaneous or permucosal exposure to HBsAg-positive or suspected HBsAg-positive material, for example, by needle stick, oral ingestion or sexual exposure.

Hepatitis B Immunoglobulin-VF is also indicated for prophylaxis in infants born to HBsAg-positive mothers.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Prophylaxis with Hepatitis B Immunoglobulin-VF in adults following percutaneous or permucosal exposure to HBsAg-positive or suspected HBsAg-positive material: Refer to **Table 1**.

Table 1: Prophylaxis with Hepatitis B Immunoglobulin-VF in adults following percutaneous or permucosal exposure to HBsAg-positive or suspected HBsAg-positive material

Source material	Vaccination history	
	No prior vaccination or incomplete vaccination regimen	Completed vaccination regimen
Confirmed positive for HBsAg	Give a single dose of 400 IU Hepatitis B Immunoglobulin-VF immediately* and initiate hepatitis B vaccination regimen at the same time.	Test exposed person for HBs antibody. If level is inadequate (<10 IU/L), give a single dose of 400 IU Hepatitis B Immunoglobulin-VF immediately plus a hepatitis B vaccine booster.
High risk for HBsAg, but not confirmed	Initiate hepatitis B vaccination regimen. Test source material for HBsAg and, if positive, give a single dose of 400 IU Hepatitis B Immunoglobulin-VF.	Test exposed person for HBs antibody. If level is inadequate (<10 IU/L), test source material for HBsAg and, if positive, give a single dose of 400 IU Hepatitis B Immunoglobulin-VF plus a hepatitis B vaccine booster.
Uncertain or low risk	Initiate hepatitis B vaccination regimen.	Nothing required.

* Hepatitis B Immunoglobulin-VF must be administered within 72 hours of exposure to the virus.

Prophylaxis in infants born to HBsAg-positive mothers: Give infant 100 IU Hepatitis B Immunoglobulin-VF at birth and initiate hepatitis B vaccination regimen at the same time by giving first vaccine dose in a different limb.

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.**

Hepatitis B 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.

Active immunisation with hepatitis B vaccine should always be commenced in conjunction with administration of Hepatitis B Immunoglobulin-VF in patients exposed to hepatitis B virus (see Table 1). In such case the immunoglobulin and the vaccine should be administered at different sites of the body.

4.3 CONTRAINDICATIONS

Hepatitis B Immunoglobulin-VF is contraindicated in patients:

- who have had a true anaphylactic reaction to the active substance or to any of the components of the product
- 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
- who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections
- who are HBsAg-positive.

Hepatitis B Immunoglobulin-VF is unnecessary in those who already have adequate circulating hepatitis B antibody (≥10 IU/L).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Route of administration

Hepatitis B 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

Hepatitis B Immunoglobulin-VF contains trace amounts of IgA which may provoke anaphylaxis in patients with anti-IgA antibodies, such as those with IgA deficiency.

Hepatitis B 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, human Hepatitis B immunoglobulin can induce a precipitous fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human Hepatitis B immunoglobulin. In case of anaphylactic reaction, the injection 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 Hepatitis B Immunoglobulin-VF. Particularly in cases of inadvertent intravenous injection, patients should be observed for longer term (at least 1 hour) after 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 Hepatitis B Immunoglobulin 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 Hepatitis B 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

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. Passive transmission of antibodies to erythrocyte antigens (e.g., anti-A, anti-B, anti-D) may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs' test).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Hepatitis B Immunoglobulin-VF should not be mixed with other pharmaceutical products, except as indicated (see section 4.2 Dose and method of administration).

Hepatitis B vaccine: If hepatitis B vaccine is administered at the same time as Hepatitis B Immunoglobulin-VF it should be given in a different limb/site.

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. If Hepatitis B Immunoglobulin-VF is administered within two weeks of vaccination with a live attenuated virus vaccine, the efficacy of the vaccine may be compromised. Consideration should be given to re-vaccination approximately three months after Hepatitis B Immunoglobulin-VF was given.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive toxicity studies have been conducted with Hepatitis B 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. Hepatitis B 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. Hepatitis B 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 Hepatitis B Immunoglobulin-VF.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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

Hepatitis B Immunoglobulin-VF contains specific neutralising antibodies (mainly IgG) against hepatitis B surface antigen (HBsAg). Donations are selected on the basis that they contain high levels of antibody to HBsAg. Pharmacological data is presented under Clinical trials.

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.). The IgG levels remained at protective levels for at least 6 weeks. These values are consistent with ranges observed with other intramuscular immunoglobulin products.

A clinical trial with Hepatitis B 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 Hepatitis B 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 Hepatitis B 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

Hepatitis B Immunoglobulin-VF solution for intramuscular injection is available in single vials containing 100 IU or 400 IU hepatitis B antibody. The actual volume in the vial is stated on the label.

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

08 November 2006

10 DATE OF REVISION

22 June 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Clarification of use of different administration sites
4.3	Addition of contraindication for history of anaphylaxis
4.4	Updated for consistency with other IVIg products. Interference with tests for red cell allo-antibodies added.
4.5	Effect on measles vaccine for up to one year added.
6.2	Instruction to not mix with other substances, except as indicated.