**AUSTRALIAN PRODUCT INFORMATION**

# Tetanus Immunoglobulin-VF (for Intramuscular Use)

## (Human tetanus immunoglobulin) – Solution for intramuscular injection

## 1 NAME OF THE MEDICINE

Human Tetanus Immunoglobulin

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tetanus Immunoglobulin-VF (for Intramuscular Use) is a sterile, preservative-free solution containing 160 mg/mL human plasma protein of which at least 98% is immunoglobulin G (IgG), with a tetanus antitoxin activity of not less than 100 IU/mL.

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

Tetanus Immunoglobulin-VF (for Intramuscular Use) is manufactured from human plasma collected by Australian Red Cross Lifeblood.

Tetanus Immunoglobulin-VF (for Intramuscular Use) contains 22.5 mg/mL of glycine.

## 3 PHARMACEUTICAL FORM

Solution for intramuscular injection.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Tetanus Immunoglobulin-VF (for Intramuscular Use) is indicated for the passive protection of individuals who have sustained a tetanus-prone wound and who have either not been actively immunised against tetanus or whose immunisation history is doubtful. It should also be given to the fully immunised patient with a tetanus-prone wound if more than 10 years have elapsed since the last vaccine dose. In all the above instances, active immunisation with a tetanus vaccine should be commenced at the same time (refer to **Table 1**) according to current recommendations. Although Tetanus Immunoglobulin-VF (for Intramuscular Use) and vaccine can be given at the same time, they should be administered in opposite limbs, using separate syringes.

**Table 1: Guide to tetanus prophylaxis in wound management (refer to Therapeutic indications)**

| History of active immunisation | Type of wound | | | |
|---|---|---|---|---|
| | Clean, minor wound | | All other wounds | |
| | Tetanus vaccine* | Tetanus Immunoglobulin- VF (for Intramuscular Use) | Tetanus vaccine* | Tetanus Immunoglobulin- VF (for Intramuscular Use) |
| Not immunised or less than 3 doses | Yes | No | Yes | Yes |
| 3 doses or more: <5 years since last dose | No | No | No | No |
| 5 to 10 years since last dose | No | No | Yes | No |
| >10 years since last dose | Yes | No | Yes | Yes |

* For children less than 8 years old, use of a combined diphtheria/tetanus/pertussis (DTPa) vaccine is recommended in preference to tetanus vaccine alone. For persons 8 years of age or older use a combined diphtheria/tetanus (dT) vaccine in preference to tetanus vaccine alone.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Dosage

Good medical care is essential in the prevention of tetanus from fresh wounds. Thorough cleansing and removal of all foreign and necrotic material from the site of injury is important.

The minimum routine prophylactic dose of Tetanus Immunoglobulin-VF (For Intramuscular Use) for adults or children is 250 IU. The dose should be doubled if the wound is grossly contaminated or if more than 24 hours have elapsed between wounding and the seeking of medical attention.

### 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.**

Tetanus Immunoglobulin-VF (for Intramuscular Use) 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.

An intravenous preparation of tetanus immunoglobulin (Tetanus Immunoglobulin for intravenous use) is available for patients where large doses are indicated (i.e. treatment of tetanus), or when the patient has a significant haemostatic defect which may cause bleeding following intramuscular injection.

## 4.3 CONTRAINDICATIONS

Tetanus Immunoglobulin-VF (for Intramuscular Use) 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.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Route of administration

**Tetanus Immunoglobulin-VF (For Intramuscular Use) 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, (Tetanus Immunoglobulin for intravenous use is available when an intravenous product is required).

### Hypersensitivity

Tetanus Immunoglobulin-VF (for Intramuscular Use) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

Tetanus Immunoglobulin-VF (for Intramuscular Use) contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with Tetanus Immunoglobulin-VF (for Intramuscular Use) against the potential risks of hypersensitivity reactions.

Rarely human tetanus immunoglobulin can induce a precipitous fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with normal

human 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 Tetanus Immunoglobulin-VF (for Intramuscular Use). 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 Tetanus Immunoglobulin-VF (for Intramuscular Use) 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 Tetanus Immunoglobulin-VF (for Intramuscular Use) 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

Tetanus Immunoglobulin-VF (for Intramuscular Use) 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.

*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 Tetanus Immunoglobulin-VF (for Intramuscular Use). There have been no reports of effects on fertility associated with the use of CSL's plasma-derived therapeutic medicines.

### Use in pregnancy

The safety of Tetanus Immunoglobulin-VF (for Intramuscular Use) for use in human pregnancy has not been established in controlled clinical trials and therefore it should only be given to pregnant women with caution.

### Use in lactation

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

## 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

Tetanus Immunoglobulin-VF (for Intramuscular Use) contains high levels of antibodies (mainly IgG) against tetanus toxin. Donations are selected on the basis that they contain high levels of specific antibodies against the toxin of *Clostridium tetani*.

## 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 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 Tetanus Immunoglobulin-VF (for Intramuscular Use) 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 Tetanus Immunoglobulin-VF (for Intramuscular Use). 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 Tetanus Immunoglobulin-VF (for Intramuscular Use). 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

Tetanus Immunoglobulin-VF (for Intramuscular Use) solution is available in single vials containing 250 IU human tetanus antitoxin. 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

07 April 2005

## 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 for large doses. |
| **4.3** | Addition of contraindication for history of anaphylaxis. |
| **4.4** | Updated for consistency with other Ig 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. |