NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Tetanus Immunoglobulin-VF 250 IU, solution for intramuscular injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Tetanus Immunoglobulin

Tetanus Immunoglobulin-VF is a sterile solution containing 160 mg/mL human plasma proteins and 22.5 mg/mL glycine. At least 98% of the protein is immunoglobulins (mainly IgG), with a tetanus antitoxin activity of not less than 100 IU/mL.

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

Tetanus Immunoglobulin-VF (for intramuscular use (IM)) contains no preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for intramuscular injection.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tetanus prophylaxis

Tetanus Immunoglobulin-VF 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.

4.2 Dose and method of administration

Dose

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 (IM) 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.

Table 1: Guide to tetanus prophylaxis in wound management

History of active immunisation	Type of wound			
	Clean, minor wound		All other wounds	
	Tetanus Vaccine*	Tetanus Immunoglobulin-VF	Tetanus Vaccine*	Tetanus Immunoglobulin-VF
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.

Paediatric population

Children and adults are to receive the same dose.

Method of administration

Tetanus 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 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.

Although Tetanus Immunoglobulin-VF and vaccine can be given at the same time, they should be administered in opposite limbs, using separate syringes.

For further instructions, see section 6.6.

4.3 Contraindications

Tetanus 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

Tetanus Immunoglobulin-VF (IM) 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).

Tetanus 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.

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. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B (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.

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 Tetanus Immunoglobulin-VF. There have been no reports of such effects associated with the use of CSL Behring’s plasma-derived 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. There is no evidence to date that parvovirus B19 can be transmitted by Tetanus 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).

4.5 Interaction with other medicines and other forms of interaction

Tetanus 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.

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.

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. Tetanus 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. Tetanus 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 Tetanus Immunoglobulin-VF.

Fertility

No reproductive toxicity studies have been conducted with Tetanus 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.

Clinical studies

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 immunoglobulin products.

Elderly population

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 Behring's intramuscular immunoglobulin products.

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 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, human tetanus immunoglobulin.

ATC code: J06BB02

Tetanus Immunoglobulin-VF (IM) is prepared from human plasma. Donations are selected on the basis that they contain high levels of specific antibodies against the toxin of *Clostridium tetani*. The manufacturing process for Tetanus Immunoglobulin-VF contains specific steps to reduce the possibility of viral transmission including pasteurisation for viral inactivation and nanofiltration for virus removal.

Mechanism of action

Tetanus Immunoglobulin-VF contains high levels of antibodies (mainly IgG) against tetanus toxin.

Clinical efficacy and safety

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 has not been conducted.

5.2 Pharmacokinetic properties

Absorption and Distribution

Human tetanus immunoglobulin for intramuscular administration is bioavailable in the recipient's circulation after a delay of 2 to 3 days. Human tetanus 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

Tetanus Immunoglobulin-VF (IM) with tetanus immunoglobulin 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, carcinogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines, diluents, or solvents except those mentioned in section 4.2.

6.3 Shelf life

3 years

Shelf life 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 conditions of the medicine after first opening, see section 6.3.

6.5 Nature and contents of container

Solution in a single glass vial, with a rubber stopper, an aluminium seal and a plastic flip-top cap.

Pack size

1 vial with 250 IU human tetanus antitoxin

The actual volume in the vial is stated on the label.

Tetanus Immunoglobulin-VF is packaged in latex free materials.

6.6 Special precautions for disposal and other handling

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

If the product appears to be turbid by transmitted light or contains any sediment it must not be used.

Any unused solution must be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

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8 SPONSOR

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10 December 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Data sheet reformatted to the SPC format
5.2	New section added
5.3	New section added
8	Sponsor contact information amended.