1 PRODUCT NAME

MonoFIX®-VF 500 IU powder and diluent (10 mL) for solution for injection

MonoFIX®-VF 500 IU powder and diluent (5 mL) for solution for injection

MonoFIX®-VF 1000 IU powder and diluent (10 mL) for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MonoFIX®-VF is a sterile freeze-dried powder containing purified human coagulation factor IX.

MonoFIX®-VF is manufactured from human plasma donated by New Zealand's voluntary and non-remunerated donors. The factor IX in MonoFIX®-VF is purified using ion-exchange and heparin affinity chromatography to remove other vitamin K-dependent factors such as factors II, VII and X.

MonoFIX®-VF is presented in two different concentrations (strengths): 50 IU/mL and 100 IU/mL, and in three different presentations as detailed in **Table 1**.

Table 1: MonoFIX®-VF presentations

Presentation	**500 IU (50 IU factor IX/mL)**	**500 IU (100 IU factor IX/mL)**	**1000 IU (100 IU factor IX/mL)**
Active ingredient IU/vial (nominal)			
Factor IX	500	500	1000
Reconstitution volume (mL)	10	5	10
Concentration	**50 IU/mL**	**100 IU/mL**	**100 IU/mL**
Plasma proteins (mg/mL)	≤ 2	≤ 4	≤ 4

Not all registered presentations may be supplied.

Excipients with known effect

MonoFIX®-VF contains 28 mg (1.2 mmol) sodium in each 500 IU vial and 56 mg (2.4 mmol) sodium in each 1000 IU vial.

MonoFIX®-VF contains 50–140 IU heparin in each 500 IU vial and 100–280 IU heparin in each 1000 IU vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection

Powder: white

Diluent (Water for Injections): clear, colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MonoFIX®-VF is indicated for the treatment of haemorrhages, for use in surgery, and as prophylaxis in patients with haemophilia B. MonoFIX®-VF is not indicated for the treatment of factor II, VII or X deficiencies because it does not contain therapeutic levels of these coagulation factors. MonoFIX®-VF is not indicated for the treatment of haemophilia A patients with factor VIII inhibitors.

4.2 Dose and method of administration

Dose

The dosage recommendations in **Table 2** are a general guideline for therapy. The exact loading and maintenance doses and dosing intervals should be based on the patient's clinical condition and response to therapy. Laboratory tests should be performed to ensure that the desired plasma factor IX concentrations are achieved.

Table 2: Dosage guidelines

Indication	Desired plasma concentration of factor IX (IU/dL)	Dose (IU/kg)	Frequency of dosing (per day)	Duration of treatment (days)
Minor haemorrhage	20 to 30	20 to 30	1	1 to 2
Moderate to severe haemorrhage e.g. haemarthroses	30 to 50	30 to 50	1 to 2	1 to 5
Minor surgery[a]: Loading dose Maintenance[b]	 40 to 60 20 to 50	 40 to 60 15 to 40	 - 1 to 2[c]	 - 7 to 10
Major surgery: Loading dose Maintenance	 70 to 100 20 to 90	 70 to 100 20 to 90	 - 1 to 2[c]	 - 10 to 12
Prophylaxis*	1 (trough)	25 to 40	twice weekly	continuous

[a] Includes dental extraction.

[b] Initially (days 1 to 3) aim for levels at the higher end of this range. Gradually reduce to lower level during subsequent days.

[c] Continuous infusion, administered after an initial bolus infusion, may be used as an alternative to maintain desired factor IX plasma levels.

* This refers to prophylaxis in children according to the protocol developed in Sweden by Nilsson's group.

Paediatric population

The use of MonoFIX®-VF in the paediatric population has not been established in appropriate studies.

Continuous infusion

Limited clinical data exists on the use of MonoFIX®-VF administered by continuous infusion. Based on a 24 hour stability study conducted in the laboratory, it is suggested that this method may be suitable for covering surgical procedures. The product required should be reconstituted to the same

volume and in the same diluent as for bolus infusion, and infused using an infusion pump suitable for this volume. Reconstitution should be done under aseptic conditions, and sterile integrity of the delivery device should be maintained.

Monitoring

It is recommended that plasma factor IX concentrations be monitored during treatment for more severe haemorrhage. Monitoring of plasma factor IX concentrations is also recommended for patients undergoing surgery.

Method of administration

For instructions on reconstitution of the medicine before administration, see section 6.6.

1. With the reconstituted MonoFIX®-VF vial upright, attach a plastic disposable syringe to the Mix2Vial™ (transparent plastic part). Invert the system and draw the reconstituted MonoFIX®-VF into the syringe by pulling the plunger back slowly. One large syringe may be used to pool several vials of reconstituted MonoFIX®-VF.

2. Once the MonoFIX®-VF has been transferred into the syringe, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and detach the Mix2Vial™ from the syringe. Discard the Mix2Vial™ (transparent plastic part) and empty MonoFIX®-VF vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted MonoFIX®-VF. Do not use the Mix2Vial™ for injection.

3. Give the dose slowly (approximately 3 mL per minute or as tolerated by the patient) by the intravenous route. Slow the rate of infusion or stop the infusion if any sign of intolerance is recognised. When the contents of more than one vial are to be given, it will be convenient to pool the total amount prior to administration in a large syringe or sterile bag. This must be done aseptically.

4. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. The solution must not be stored and, unless reconstitution has been done under aseptic conditions and sterile integrity of the delivery device has been maintained, infusion should be completed within three hours of reconstitution in the case of routine use. For use in surgery, the conditions described under **Continuous infusion** can apply. Any unused portion remaining in the vial must be discarded appropriately.

5. The solution must not be added or mixed with any other fluids to be given, including whole blood.

4.3 Contraindications

MonoFIX®-VF is contraindicated in patients with a known hypersensitivity to factor IX concentrates or any of the excipients in MonoFIX®-VF.

4.4 Special warnings and precautions for use

MonoFIX®-VF should be used with caution in patients with a previous or known severe allergy to factor IX concentrates.

High doses of PCCs have been associated with disseminated intravascular coagulation (DIC). Although MonoFIX®-VF contains purified factor IX, the potential risk of thrombosis and DIC should be recognised. The use of products containing factor IX could be hazardous in patients with a history of fibrinolysis, myocardial infarction, DIC or liver disease.

The reported prevalence for the formation of neutralising antibodies (inhibitors) in patients receiving plasma derived factor IX is approximately 4%. Patients should be monitored for the development of factor IX inhibitors. If the expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor IX inhibitor is present. In patients with high levels of inhibitor, factor IX replacement therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.

There has been no clinical experience with MonoFIX®-VF with respect to inhibitor development in previously untreated patients.

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 of MonoFIX®-VF includes solvent detergent (tributyl phosphate and polysorbate 80) treatment and nanofiltration as dedicated virus inactivation and removal steps to reduce the possibility of virus transmission, particularly of hepatitis A virus.

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 (HCV) viruses, and the non-enveloped virus hepatitis A (HAV). They are also known to have some effect on the removal of the non-enveloped virus, parvovirus B19.

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.

Check the following before use

Prior to using MonoFIX®-VF for the first time, the hepatitis A and hepatitis B antibody status of recipients should be tested. Immunisation with hepatitis A and hepatitis B vaccine is recommended for patients with no antibodies to these viruses.

MonoFIX®-VF contains 50–140 IU heparin sodium in each 500 IU vial and 100–280 IU in each 1000 IU vial. Heparin is known to cause thrombocytopenia and this possibility should be considered if thrombocytopenia develops during treatment. Consideration should be given to the clinical effect of heparin if high doses of MonoFIX®-VF are required.

MonoFIX®-VF 500 IU contains 28 mg sodium per vial, equivalent to 1.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

MonoFIX®-VF 1000 IU contains 56 mg sodium per vial, equivalent to 2.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

The use of MonoFIX®-VF in the paediatric population has not been established in appropriate studies.

Use in the elderly

The use of MonoFIX®-VF in the elderly population has not been established in appropriate studies.

Effects on laboratory tests

MonoFIX®-VF is formulated with heparin sodium and antithrombin III. Therefore, the results of coagulation tests should be interpreted with care.

4.5 Interaction with other medicines and other forms of interaction

The interaction of MonoFIX®-VF with other medicines has not been established in appropriate studies.

4.6 Fertility, pregnancy and lactation

Fertility

The potential reproductive effect of MonoFIX®-VF has not been established in appropriate studies.

Pregnancy or lactation

Pregnancy Category C. MonoFIX®-VF contains heparin sodium. An increased incidence of foetal loss and prematurity may be associated with heparin-induced maternal haemorrhage. The use of MonoFIX®-VF during human pregnancy or lactation has not been established in appropriate studies.

4.7 Effects on ability to drive and use machines

MonoFIX®-VF has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Allergic, anaphylactic reactions or fever are rarely observed in patients receiving factor IX preparations. If any adverse event occurs while MonoFIX®-VF is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Heparin is known to cause thrombocytopenia and this possibility should be considered if thrombocytopenia develops during treatment.

Tabulated summary of adverse reactions

Adverse events were monitored in a pharmacokinetic study with MonoFIX®-VF, however none were reported.

Adverse events were also monitored during a two-part safety, efficacy and tolerability clinical trial for MonoFIX® in 11 patients with moderate to severe haemophilia B. In the second part of the trial where MonoFIX® was administered on an as required basis for a period of 6 months, 31 adverse events were recorded from a total of 233 administrations. These events occurred in 9 of the 11 patients and have been presented in **Table 3**.

Table 3: Adverse events reported in MonoFIX® safety, efficacy & tolerability clinical trial

Adverse event	MonoFIX® clinical trial (n = No. of patients)	
	Related events (n)	Non related events (n)
Infections and infestations		
Cold/Flu (influenza-like symptoms)	-	6 (4)
Tonsillitis (pharyngitis)	-	3 (2)
Septic arthritis	-	3 (1)
Psychiatric disorders		
Depression	-	1 (1)
Insomnia	-	2 (1)
Depression/insomnia	-	1 (1)
Gastrointestinal disorders		
Diarrhoea	-	1 (1)
Respiratory, thoracic and mediastinal disorders		
Nose congestion	-	1 (1)
Nervous system disorders		
Headache	-	5 (4)
Blood and lymphatic system disorders		
Anaemia	-	1 (1)
Skin and subcutaneous tissue disorders		
Rash	-	2 (1)
General disorders and administration site conditions		
Clinical flare reaction	1 (1)	-
Surgical and medical procedures		
Hospitalisation related to previous history of inhibitor to Factor IX and patient's non-compliance with prescribed inhibitor tolerance therapy.	2 (1)	-
Hospitalisation required for treatment of traumatic haematoma with MonoFIX® due to patient's inability to administer home therapy.	-	1 (1)
Hospitalisation required for endoscopy to investigate iron deficiency anaemia.	1 (1)	-

During post-marketing surveillance of MonoFIX®-VF the following adverse events also have been reported: injection site reactions, cold clammy skin, nausea, dizziness and taste disturbances.

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

High doses of products containing factor IX have been associated with instances of myocardial infarction, DIC, venous thrombosis and pulmonary embolism. Overdose with MonoFIX®-VF may potentially enhance the risk of these complications.

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: Antihaemorrhagics: Blood coagulation factor IX.

ATC code: B02BD04

Mechanism of action

Human factor IX is a single chain glycoprotein with a molecular weight of 68 kilodalton. It is synthesised in the liver, like other vitamin K-dependent proteins, and participates in the intrinsic blood coagulation pathway. Factor XIa activates factor IX, which then, in the presence of factor VIIIa, activates factor X. This leads to the conversion of prothrombin to thrombin and the formation of a fibrin clot.

Pharmacodynamic effects

Haemophilia B (also known as Christmas disease) is an X-linked recessive blood coagulation disorder. It is caused by reduced factor IX activity through either insufficient or abnormal synthesis of the factor IX protein. Clinical symptoms of haemophilia B include skin bruising, excessive haemorrhage after trauma, and spontaneous haemorrhage into joints, muscles or internal organs. Excessive and severe haemorrhage can cause orthopaedic deformity, organ dysfunction or death.

Studies in animals indicate that the potential thrombogenicity of MonoFIX®-VF is lower than prothrombin complex concentrates (PCCs). In a study where the *in vivo* generation of rat fibrinopeptide A was used as a marker of thrombogenicity, MonoFIX®-VF administered at a dose of 300 IU factor IX per kg body weight did not elevate plasma fibrinopeptide A concentration 60 minutes post infusion and was equivalent to the negative control, 20% human albumin. In contrast, PCCs used as positive controls raised plasma fibrinopeptide A concentration by a factor of 30 to 70 times over pre-infusion values. In a modified Wessler rabbit stasis model of thrombogenicity MonoFIX®-VF showed no evidence of thrombogenicity in any of the experiments when tested at a dose of 200 IU factor IX per kg body weight. In comparison, activated factor IX concentrates used for positive control were thrombogenic in all experiments.

Clinical efficacy and safety

CSL has performed clinical trials with MonoFIX®-VF and MonoFIX®. MonoFIX®-VF includes a virus filtration step. This step is not included in the manufacturing process for MonoFIX®.

MonoFIX®-VF has been the subject of extensive biochemical characterisation to demonstrate that the active ingredient is equivalent to MonoFIX®.

Clinical efficacy and safety were studied in a clinical trial using MonoFIX®. The trial included 11 immunocompetent male patients with moderate to severe haemophilia B. All patients had been previously treated with factor IX concentrates and were aged from 2 to 52. Patients used MonoFIX® on an as required basis for a period of 6 months. No patients undergoing surgery were included in the trial. There is some evidence that recovery of factor IX in patients undergoing surgery may be reduced.

During the 6 months of the trial, there were a total of 233 administrations of MonoFIX® of which 218 were assessed for effectiveness. Treatment was considered to be effective by the patient or his guardian in 98% of administrations. For safety data from this trial, see section 4.8.

No inhibitor studies have been carried out in humans using MonoFIX®-VF. However, in the clinical trial of MonoFIX®, one patient had evidence of transient inhibitor development in the post study period. Repeat pharmacokinetic studies were not performed.

5.2 Pharmacokinetic properties

The pharmacokinetics of MonoFIX®-VF have been determined in an open multicentre study, following a single intravenous infusion of 50 IU/kg in 12 participants over the age of 12 years with haemophilia B. The estimated half-life and recovery of factor IX were approximately 24 hours and 60% respectively.

5.3 Preclinical safety data

The potential carcinogenicity and genotoxicity of MonoFIX®-VF have not been established in appropriate studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Heparin sodium
Antithrombin III
Sodium
Phosphate
Citrate
Chloride

Diluent:
Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

The reconstituted solution must not be added or mixed with any other fluids to be given, including whole blood.

6.3 Shelf life

24 months

Reconstituted product

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

Do not refrigerate MonoFIX®-VF once it has been reconstituted.

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.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Each presentation includes MonoFIX®-VF powder for injection and Water for Injections in glass vials with latex free rubber closures closed with an aluminium seal and a plastic flip-top cap.

Each presentation is supplied with a Mix2Vial™ filter transfer set.

- 500 IU vial of MonoFIX®-VF, 10 mL vial of Water for Injections
- 500 IU vial of MonoFIX®-VF, 5 mL vial of Water for Injections
- 1000 IU vial of MonoFIX®-VF, 10 mL vial of Water for Injections

Not all registered presentations may be supplied.

6.6 Special precautions for disposal and other handling

Reconstitution

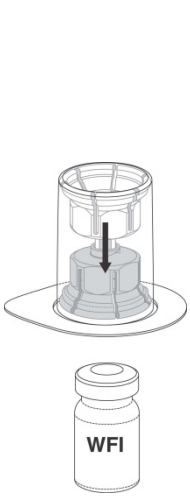
1. Before reconstitution allow the vials of MonoFIX®-VF and Water for Injections (WFI) to reach a temperature between 20°C and 30°C.

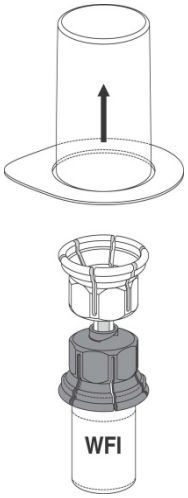
2. Remove the caps from the tops of the MonoFIX®-VF and WFI vials.

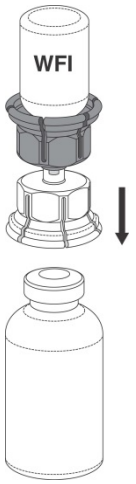
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both MonoFIX®-VF and WFI vials and allow to dry.

4. Open the outer package of the Mix2Vial™ filter transfer set by peeling away the lid. If the seal of the lid is not intact or there are any concerns about the integrity of the Mix2Vial™, do not use it but return it to the New Zealand Blood Service. Place the WFI vial on a level surface and hold the vial firmly. Take the Mix2Vial™ together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial™ firmly through the rubber stopper of the WFI vial. See **Figure 1.**

5. While holding onto the vial of WFI, carefully remove the outer package from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the WFI vial. Ensure that only the package and not the Mix2Vial™ is removed. See **Figure 2.**







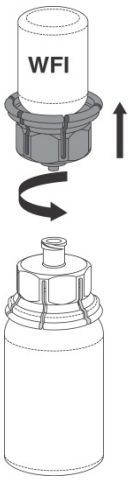


Figure 1 **Figure 2** **Figure 3** **Figure 4**

WFI = Water for Injections

6. With the MonoFIX®-VF vial held firmly on a level surface, invert the WFI vial with the Mix2Vial™ attached and push the transparent plastic cannula end of the Mix2Vial™ firmly through the MonoFIX®-VF stopper. See **Figure 3.** The water will be drawn into the vial by the vacuum within. **In the unlikely event that the vial does not contain a vacuum, do not use the product, but return it to the New Zealand Blood Service.**

7. With the WFI and MonoFIX®-VF vials still attached, gently swirl the product vial to ensure the product is fully dissolved. Avoid excessive frothing. A clear or slightly opalescent solution is usually obtained in 10 minutes or less.

8. Once the contents of the MonoFIX®-VF vial are completely dissolved, firmly hold both the transparent and blue parts of the Mix2Vial™. Unscrew the Mix2Vial™ into two separate pieces (see **Figure 4**), and discard the empty WFI vial and the blue part of the Mix2Vial™ in an appropriate waste container.

Note: The Mix2Vial™ is intended to filter the contents of a single vial of MonoFIX®-VF only. If multiple vials of MonoFIX®-VF are to be administered, a separate Mix2Vial™ must be used for each vial.

Do not refrigerate MonoFIX®-VF once it has been reconstituted.

The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution. Use in one patient on one occasion only. If a clot or gel forms, do not use the product but return it to the New Zealand Blood Service.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Spillage and breakages

Should a break in the container or spillage occur, due precautions should be taken to avoid contamination of cuts and abrasions, as well as to avoid inhalation or swallowing of the spillage. Adequate disinfection can be obtained with the application of 1% sodium hypochlorite for 15 minutes. Commercial bleaches may be diluted appropriately to obtain this concentration.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

12 August 1999

10 DATE OF REVISION OF THE TEXT

22 November 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Data sheet reformatted to the SPC format
2	Information about excipients with known effect added
4.7	Information about effects on ability to drive and use machines added
6.2	Information about incompatibilities added
6.5	Information about nature of container added
8	Sponsor's address and phone numbers updated

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