

“TBSF” High Purity Factor IX Concentrate

Taiwan

**Imported Biological Product Permit
No. 000843 Department of Health**

NAME OF THE MEDICINE

Human coagulation factor IX, powder for injection.

DESCRIPTION

“TBSF” High Purity Factor IX Concentrate is prepared in cooperation with the “Self sufficiency” recommendation set forth by the Taiwan Department of Health, from pooled human plasma obtained from voluntary donors. “TBSF” High Purity Factor IX Concentrate is a sterile freeze-dried powder containing purified human coagulation factor IX. The factor IX in “TBSF” High Purity Factor IX Concentrate is purified using ion-exchange and heparin affinity chromatography to remove other vitamin K-dependent factors such as factors II, VII and X. The manufacturing process of “TBSF” High Purity Factor IX Concentrate includes a solvent detergent (tributyl phosphate and polysorbate 80) treatment and a viral filtration step to reduce the potential for viral transmission, particularly of hepatitis A virus.

When reconstituted as recommended, each vial nominally contains 500 IU of factor IX, 50–140 IU of heparin sodium, 12.5 IU of antithrombin III, ≤ 20 mg of plasma proteins, 120 mmol/L sodium, 20 mmol/L phosphate, 10 mmol/L citrate and 50 mmol/L chloride.

PHARMACOLOGY

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.

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.

The clinical trials and animal studies for “TBSF” High Purity Factor IX Concentrate are based on MonoFIX[®] and MonoFIX[®]-VF, the comparable purified human coagulation factor IX products manufactured by CSL Limited for distribution in Australia. 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 TRIALS

CSL has performed clinical trials with MonoFIX[®]-VF and MonoFIX[®]. MonoFIX[®]-VF includes a viral 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[®].

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.

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

ADVERSE EFFECTS.

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.

INDICATIONS

“TBSF” High Purity Factor IX Concentrate is indicated for the treatment of haemorrhages, and as prophylaxis in patients with haemophilia B.

“TBSF” High Purity Factor IX Concentrate is not indicated for the treatment of factor II, VII or X deficiencies because it does not contain therapeutic levels of these coagulation factors.

“TBSF” High Purity Factor IX Concentrate is not indicated for the treatment of haemophilia A patients with factor VIII inhibitors.

CONTRAINDICATIONS

None known.

PRECAUTIONS

“TBSF” High Purity Factor IX Concentrate 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 “TBSF” High Purity Factor IX Concentrate 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, virus removal and inactivation procedures are included in the manufacturing process.

It is more difficult to remove or inactivate some viruses, such as parvovirus B19 and hepatitis A virus. The influence of parvovirus B19 on pregnant and immunodeficient patients is more serious.

There is also the possibility that other known or unknown infectious agents may be present in such products. Hence, if patients are infected after using this product, it must be reported to the medical practitioner, the distributor or the manufacturer. Please discuss the risks and benefits of this product with your medical practitioner.

The procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses (HBV and HCV), and the non-enveloped viruses, such as hepatitis A (HAV). These procedures may have some effect against non-enveloped viruses such as human parvovirus B19.

Despite these measures, such products may still potentially transmit disease.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

WARNING

The symptoms of parvovirus B19 infection may include fever, drowsiness, chills and runny nose. Skin rash and arthralgia may appear two weeks after infection. Symptoms of hepatitis A infection may include loss of appetite in the first few days to a week, lethargy and fever. Thereafter nausea, vomiting and abdominal pain. Jaundice is also a general symptom. If these symptoms occur please contact your medical practitioner.

Check the following before use

Prior to using “TBSF” High Purity Factor IX Concentrate 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.

“TBSF” High Purity Factor IX Concentrate contains 50–140 IU heparin sodium in each reconstituted 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 “TBSF” High Purity Factor IX Concentrate are required.

Carcinogenicity, genotoxicity, impairment of fertility

The potential carcinogenicity, genotoxicity and reproductive toxicity of “TBSF” High Purity Factor IX Concentrate have not been established in appropriate studies.

Use in pregnancy or lactation

“TBSF” High Purity Factor IX Concentrate contains heparin sodium. An increased incidence of foetal loss and prematurity may be associated with heparin-induced maternal haemorrhage. The safe use of “TBSF” High Purity Factor IX Concentrate during human pregnancy or lactation has not been established in appropriate studies.

Paediatric use and use in the elderly

The use of “TBSF” High Purity Factor IX Concentrate in the paediatric and elderly populations has not been established in appropriate studies.

Interactions with other medicines

The interaction of “TBSF” High Purity Factor IX Concentrate with other drugs has not been established in appropriate studies.

Effect on laboratory tests

“TBSF” High Purity Factor IX Concentrate is formulated with heparin sodium and antithrombin III. Therefore, the results of anticoagulation tests should be interpreted with care.

ADVERSE EFFECTS

Allergic, anaphylactic reactions or fever are rarely observed in patients receiving factor IX preparations. If any adverse event occurs while “TBSF” High Purity Factor IX Concentrate 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.

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 1**.

Table1: 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)
Infection 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.

DOSAGE AND ADMINISTRATION

This product should be administered by a medical practitioner only.

Dosage

The following recommendations for doses are provided in **Table 2** as 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: Guidelines for dosage

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	40 to 60	40 to 60	-	-
Maintenance ^b	20 to 50	15 to 40	1 to 2 ^c	7 to 10
Major surgery:				
Loading dose	70 to 100	70 to 100	-	-
Maintenance	20 to 90	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 An alternative is to use a continuous infusion.

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

Continuous infusion

No studies using continuous infusion were carried out in patients. However, based on 24 hour stability studies conducted in the laboratory, it is suggested that this method is 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.

Reconstitution

1. Before reconstitution allow the vials of “TBSF” High Purity Factor IX Concentrate and Water for Injections to reach a temperature between 20°C and 30°C.
2. Remove the dust covers from the tops of the “TBSF” High Purity Factor IX Concentrate and Water for Injections vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both “TBSF” High Purity Factor IX Concentrate and Water for Injections 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 distributor listed on the label.** Place the Water for Injections 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 Water for Injections. See **Figure 1**.

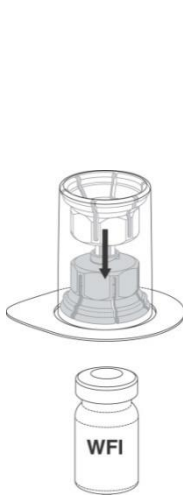


Figure 1

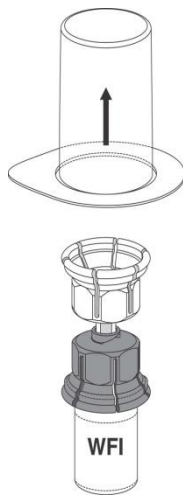


Figure 2

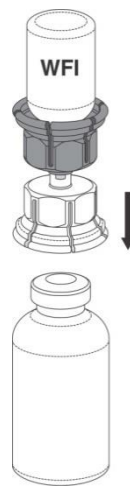


Figure 3

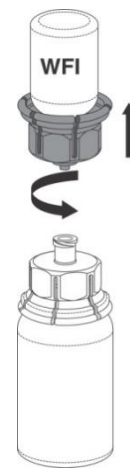


Figure 4

WFI = Water for Injections

5. While holding onto the vial of Water for Injections, carefully remove the outer package

from the Mix2Vial™, being careful to leave the Mix2Vial™ attached firmly to the Water for Injections vial. Ensure that only the package and not the Mix2Vial™ is removed. See **Figure 2**.

6. With the “TBSF” High Purity Factor IX Concentrate vial held firmly on a level surface, invert the Water for Injections with the Mix2Vial™ attached and push the transparent plastic cannula end of the Mix2Vial™ firmly through the “TBSF” High Purity Factor IX Concentrate 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 distributor listed on the label.**
7. With the Water for Injections and “TBSF” High Purity Factor IX Concentrate 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. The solution should be used immediately as described below under **“Administration”**.
8. Once the contents of the “TBSF” High Purity Factor IX Concentrate 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 Water for Injections 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 “TBSF” High Purity Factor IX Concentrate only. If multiple vials of “TBSF” High Purity Factor IX Concentrate are to be administered, a separate Mix2Vial™ must be used for each vial.

Do not refrigerate “TBSF” High Purity Factor IX Concentrate once it has been reconstituted.

CAUTION

The product does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. If a clot or gel forms, do not use the product but return it to the distributor listed on the label.

Administration

1. With the “TBSF” High Purity Factor IX Concentrate vial upright, attach a plastic disposable syringe to the Mix2Vial™ (transparent plastic part). Invert the system and draw the reconstituted “TBSF” High Purity Factor IX Concentrate into the syringe by pulling the plunger back slowly. One large syringe may be used to pool several vials of reconstituted “TBSF” High Purity Factor IX Concentrate.
2. Once the “TBSF” High Purity Factor IX Concentrate 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 “TBSF” High Purity Factor IX Concentrate vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted “TBSF” High Purity Factor IX Concentrate. 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.

Spillage or 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.

OVERDOSAGE

High doses of products containing factor IX have been associated with instances of myocardial infarction, DIC, venous thrombosis and pulmonary embolism. Overdosage with “TBSF” High Purity Factor IX Concentrate may potentially enhance the risk of these complications.

PRESENTATION

“TBSF” High Purity Factor IX Concentrate is available in vials containing 500 IU of factor IX. Each single pack contains one vial of product, one 10 mL vial of Water for Injections and one Mix2Vial™ filter transfer set.

STORAGE CONDITIONS

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

Do not use after the expiry date.

NAME AND ADDRESS OF THE MANUFACTURER

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“國血製劑益康”高純度第九凝血因子注射劑

“TBSF” High Purity Factor IX Concentrate

台灣

衛署菌疫輸字第 000843 號

成分名稱

人類第九凝血因子，凍晶乾燥劑

說明

本產品係配合行政院衛生署執行「推動我國血漿製劑方案」所製造，是由台灣血液基金會自國人自願、無償捐血者收集之血漿原料，經製備而得之高純度第九凝血因子注射劑。

“國血製劑益康”高純度第九凝血因子注射劑是一種無菌冷凍乾燥製劑，含有純化之人類第九凝血因子。“國血製劑益康”高純度第九凝血因子注射劑含有的第九因子是利用離子交換技術和肝素親和層析法純化並去除其它維他命 K 依賴因子，如第二因子，第七因子和第十因子而得。”國血製劑益康”高純度第九凝血因子注射劑的製造過程包括溶媒清潔劑(tributyl phosphate and polysorbate 80)處理和病毒的過濾步驟以減少病毒傳染的風險，尤其是 A 型肝炎。

依照指示調配之後，每一小瓶內含有 500IU 的第九因子，50–140 IU 肝素，12.5 IU 抗凝血酶 III。此外含有少於或等於 20 毫克的血漿蛋白，120 mmol/L 的鈉，20 mmol/L 的磷，10 mmol/L 的檸檬酸鹽以及 50 mmol/L 的氯。

藥理學

人類第九凝血因子是一種單鏈的醣蛋白，分子量為 68 千道爾頓，在肝臟合成。就如其它維他命 K 依賴性蛋白質一樣參與內生性凝血路徑。因子 XIa 激活因子 IX 後，在因子 VIIIa 存在的情況下激活因子 X。這樣可導致凝血酶原轉化成凝血酶並形成纖維栓塞。

B 型血友病 (又名聖誕節病) 是一種 X-性聯遺傳性凝血異常疾病。它是由於第九凝血因子蛋白質合成之不足或不正常所導致降低第九凝血因子活性所造成的。B 型血友病的臨床症狀是皮膚瘀斑，受傷後過量出血以及自發性關節、肌肉和內臟出血等。大量和嚴重的出血會導致骨骼畸形，器官功能不良甚至死亡。

“國血製劑益康”高純度第九凝血因子之臨床及動物試驗係根據 MonoFIX[®]-VF 及 MonoFIX[®]。MonoFIX[®]-VF 及 MonoFIX[®]係為由 CSL Limited 生產並在澳洲銷售之高純度第九凝血因子。動物試驗顯示 MonoFIX[®]-VF 引發血栓形成的潛在危險低於複合的凝血酶原(PPCs)。在一項試驗中，以大鼠活體產生纖維蛋白酶 A 作為血栓形成的標記，每公斤體重按 300IU 劑量給予 MonoFIX[®]-VF，注入 60 分鐘後未見血漿纖維蛋白酶 A 的濃度升高，結果與使用 20% 人血清蛋白的陰性對照組相同。相反的，若以 PPCs 作為陽性對照組則可把輸注前的纖維蛋白酶濃度提高 30 至 70 倍。

在一項改良了的 Wessler 兔子對照模式中，按每公斤體重 200 IU 第九因子劑量的試驗中沒有任何一項試驗顯示 MonoFIX[®]-VF 有血栓形成的證據。相較於陽性對照組，使用活化濃縮的第九因子，則在所有的試驗中都引起血栓形成。

臨床試驗

CSL Limited 對 MonoFIX[®]-VF and MonoFIX[®]進行了臨床試驗。MonoFIX[®]-VF 包含病毒過濾的步驟，而此步驟是不包括在 MonoFIX[®]的生產過程內的。其他實驗分析顯示，MonoFIX[®]-VF 內的主成份的生化特性與 MonoFIX[®]是相等的。

MonoFIX[®]-VF 的藥物動力學已在一項開放性多中心試驗後決定。在對 12 位超過 12 歲的 B 型血友病患者注射單一劑量 50 IU/Kg 的 MonoFIX[®]-VF 後，估計第九因子的半衰期和回復率分別是 24 個小時和 60%。

使用 MonoFIX[®]的臨床試驗研究臨床上的有效性及安全性。包括 11 位年齡介於 2–52 歲之間，免疫功能健全，患有中度到嚴重出血 B 型血友病患者。所有的病人均曾經接受過濃縮第九因子的治療。病患使用 MonoFIX[®]為期六個月，均不曾接受過手術。某些證據顯示接受過手術的患者的第九因子回復率可能減低。

在六個月的試驗之後，在全部 233 次給藥 MonoFIX[®]當中有 218 次被評估為有效的。有 98%的治療被病患或其監護人認為是有效的。有關安全性的資料請參閱**不良反應**。

沒有進行人體因使用 MonoFIX[®]-VF 而產生抗體的研究。但在 MonoFIX[®]的一項臨床研究裡，曾有一位病人在研究後期階段發生暫時性抗體出現的證據。重複的藥物動力學研究則沒有進行。

適應症

“國血製劑益康”高純度第九凝血因子注射劑是用以治療 B 型血友病患者之出血及預防。“國血製劑益康”高純度第九凝血因子注射劑不適用於治療第二、第七或第十因子缺乏症，因為本品不含有具治療濃度的這些凝血因子。”國血製劑益康”高純度第九凝血因子注射劑亦不適用於治療有第八因子抗體的 A 型血友病患。

禁忌

目前尚未知。

特殊警語

曾對第九因子濃縮劑有嚴重過敏的患者應小心使用”國血製劑益康”高純度第九凝血因子注射劑。

大劑量使用 PCCs 可能會引起瀰漫性血管內凝血(DIC)。儘管”國血製劑益康”高純度第九凝血因子注射劑含有純化的第九因子，血栓形成和 DIC 的潛在風險還是應當加以小心。有纖維蛋白溶解症，心肌梗塞，DIC 或肝病病史的患者，使用含有第九因子的製劑可能是有害的。

曾有報導指出患者接受血漿製劑的第九因子者，第九凝血因子抗體(抑制物)的發生率大約是 4%。病患應被監控第九凝血因子抗體的形成。如果使用適當劑量的高純度第九凝血因子注射劑之後，血漿中第九凝血因子達不到預期濃度，或出血情況未獲控制，則應分析是否有第九凝血因子抗體的出現。當病患有大量的第九凝血因子抗體，則第九凝血因子治療可能不會有效，而應考慮其他治療選項。此類病患應由有照護血友病患經驗的醫生直接管理。

對於以前未曾接受過治療之患者使用 MonoFIX[®]-VF 而產生抗體的情況則沒有臨床方面的經驗。

注意事項

本品係由人類血漿製得，自人類血漿所製得之產品，可能存在著某些感染原，例如致病性之病毒和庫賈氏病 (Creutzfeldt-Jakob Disease, CJD)之病原；藉由篩檢血漿之捐血

者，檢驗某些現有病毒感染原標記，再經由去活化及，或去除某些病毒，即可降低此產品傳染感染原之危險性。

某些病毒，例如 parvovirus B19 或 A 型肝炎病毒，特別難去除或去活化。Parvovirus B19 對孕婦或免疫不全的人影響較嚴重。由於仍有可能存在某些未知的感染原，因此使用本產品後，若有感染之病人，均應直接向診療醫師及製造廠或代理商報告。請與你的醫師討論使用此產品之風險及利益。

本產品製造過程所採用的方法，可有效地對抗含外套膜的病毒，如 HIV (人類免疫缺乏病毒)、B 型及 C 型肝炎病毒，及不含外套膜的 A 型肝炎病毒。這些方法對抗不具外套膜的 parvovirus B19 之效果可能有限。

惟縱然採取上述措施，此類產品仍有可能傳染疾病。

使用血漿製品時可考慮給予適當之疫苗注射。

警語

Parvovirus B19 之感染症狀為發燒、昏睡、發寒及流鼻水，接著大約二週後會產生發疹及關節痛。A 型肝炎則包含幾天至一週之食慾不振、倦怠及發燒，接著噁心、嘔吐及肚子痛。深色尿及面色略黃亦為一般症狀，如果這些症狀產生，請向醫生諮詢。

請先檢查以下資訊再使用本產品

首次使用“國血製劑益康”高純度第九凝血因子注射劑之前，患者應先接受 A 型及 B 型肝炎抗體檢查，對於體內不含這些肝炎抗體的患者，建議應先接種 A 型或 B 型肝炎疫苗。

每小瓶“國血製劑益康”高純度第九凝血因子注射劑含有 50-140 國際單位的肝素。肝素已知會引起血小板減少，在治療過程中出現血小板減少情況時，應當考慮其關聯性。如果需要大劑量使用“國血製劑益康”高純度第九凝血因子注射劑，要考慮到肝素的臨床作用。

致癌性，基因毒性和損害生殖能力

“國血製劑益康”高純度第九凝血因子注射劑的致癌性，基因毒性及損害生殖能力的潛在毒性尚未於適當的研究中被證實。

懷孕與哺乳期的使用

“國血製劑益康”高純度第九凝血因子注射劑含有肝素。胎兒流產或早產可能與肝素導致的母體出血有關。在婦女懷孕期和哺乳期間使用“國血製劑益康”高純度第九凝血因子注射劑的安全性尚未有對照的臨床研究證明。

小兒使用或老年人使用

小兒及老年人族群的使用“國血製劑益康”高純度第九凝血因子注射劑尚未建立適當的研究。

與其他藥物的交互作用

“國血製劑益康”高純度第九凝血因子注射劑與其它藥物的相互作用方面尚未有適當的研究報告。

對實驗室試驗的影響

“國血製劑益康”高純度第九凝血因子注射劑含有肝素和抗凝血酶 III，因此，對抗凝血試驗的結果要小心評估。

不良反應

使用第九因子製劑的病人很少發生過敏、過敏性反應、或發燒現象。在給予“國血製劑益康”高純度第九凝血因子注射劑若出現任何不良反應時，應減慢注射速度或停止注射，以緩解症狀。

肝素已知會引起血小板減少，如果在治療過程中出現血小板減少情況時，應當聯想其相關性。

在 MonoFIX®-VF 的藥物動力學試驗中曾監控不良反應，然而沒有任何不良反應的報告。

在一項以 11 位中度到嚴重的 B 型血友病患者的二部份安全性、效力、耐受性的臨床試驗當中，也曾經監控不良反應。在第二部份的試驗中，按照需求輸注 MonoFIX® 達六個月，在全部 233 次給藥記錄中，發現 31 項不良反應。這些事件發生在 11 病患中的 9 位，並以表一表示。

表一、MonoFIX®的安全性、效力、耐受性臨床試驗之不良反應報告

不良反應	MonoFIX®臨床試驗 (n=病病人數)	
	相關性的不良反應 (n)	無相關性的不良反應(n)
感染及寄生蟲		
感冒	-	6(4)
扁桃腺炎(咽喉炎)	-	3(2)
敗血性關節炎	-	3(1)

精神疾病		
憂鬱症	-	1(1)
失眠	-	2(1)
憂鬱症/失眠	-	1(1)
胃腸疾病		
腹瀉	-	1(1)
呼吸、胸、縱膈疾病		
鼻塞	-	1(1)
神經系統疾病		
頭痛	-	5(4)
血液及淋巴系統疾病		
貧血	-	1(1)
皮膚、皮下組織疾病		
皮膚發疹	-	2(1)
一般疾病及輸注部位反應		
臨床潮紅反應	1(1)	-
外科及內科療程		
因有第九凝血因子抑制因子病史且不遵守抑制因子耐受性治療醫囑所導致之住院	2(1)	-
無法在家輸注 MonoFIX [®] 的病患因需治療外傷出血的住院	-	1(1)
因內視鏡檢查缺鐵性貧血所導致之住院	1(1)	-

在 MonoFIX[®]-VF 的上市後監控，亦曾有下列不良反應報告：注射部位反應、皮膚濕冷、嘔心、暈眩和味覺失調。

劑量和用法

本藥限由醫師使用

劑量

建議劑量列於表二，當作一般的治療準則。確切的首劑劑量、維持劑量、以及用藥間隔，必須視病人的臨床狀況，與其治療反應而定。必須進行實驗室測試，以確保病人的血漿第九凝血因子達到預期的濃度。

表二、使用劑量準則

適應症	第九凝血因子預期達到的血漿濃度(IU/dL)	劑量(IU/kg)	用藥頻率 (每天)	治療期間 (天數)
輕微出血	20–30	20–30	1	1–2
中度到嚴重出血如： haemarthroses 關節腔內出血	30–50	30–50	1–2	1–5
小手術 ^a ： 首劑劑量 維持劑量 ^b	40–60 20–50	40–60 15–40	- 1–2 ^c	- 7–10
大手術： 首劑劑量 維持劑量	70–100 20–90	70–100 20–90	- 1–2 ^c	- 10–12
病症預防*	低點 (trough) 1	25–40	每週兩次	持續

^a 包括拔牙。

^b 開始時(第 1-3 天)取該濃度範圍的上限值。其後的數天裏逐漸下降至下限值。

^c 另一種選擇是使用持續性點滴注入。

* 依據瑞典 Nilsson's 手冊針對兒童的預防性用藥。

連續性靜脈輸注 (Continuous infusion)

連續性靜脈輸注法尚未在病人身上做過研究。但是根據在實驗室裡所做的 24 小時安定性試驗顯示，建議這種給藥方法可適用於外科手術。配製方法與靜脈大量注射時的配

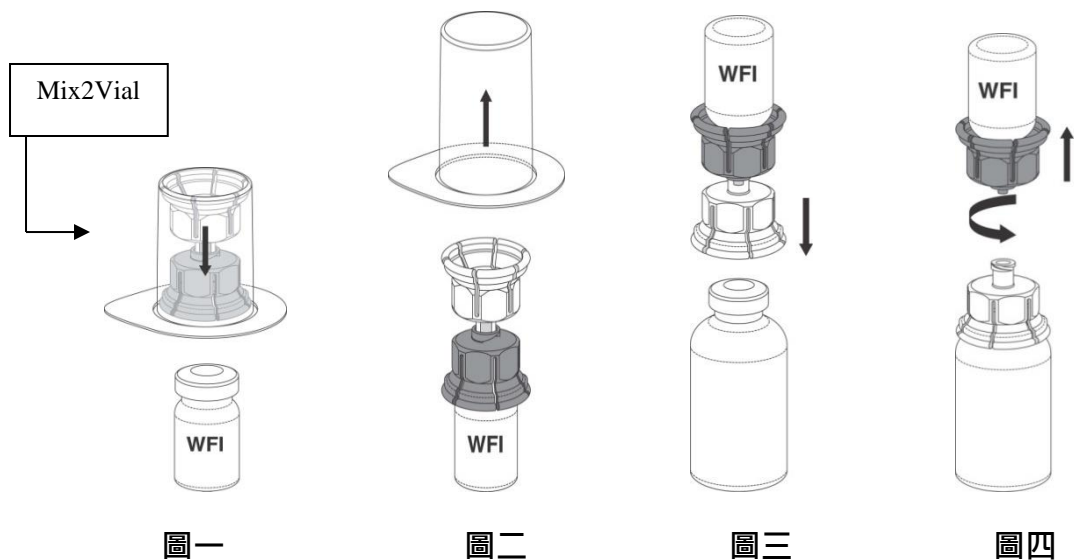
製法相同，並以適用此體積的輸液幫浦來給藥。藥液配製應當在無菌狀態下進行，且全部輸注用具均應保持在無菌狀態。

監視追蹤

對於治療較為嚴重的出血，建議監測第九因子的血漿濃度。接受手術的病人也應當監測第九因子的血漿濃度。

調配 (Reconstitution)

1. 配製前，先使”國血製劑益康”高純度第九凝血因子注射劑瓶和注射用水達到溫度 20°C 至 30°C。
2. 除去”國血製劑益康”高純度第九凝血因子注射劑和注射用水之瓶上防塵蓋。
3. 使用適當的消毒劑塗抹”國血製劑益康”高純度第九凝血因子注射劑和注射用水露出來的橡皮塞部份，並乾燥。
4. 剝開蓋子以打開 Mix2Vial™ 過濾轉接器的外包裝。假如密封不緊密或是有任何 **Mix2Vial™** 完整性的疑慮時，切勿使用並將之退回標籤上標示的代理商。將注射用水放在一平台上並緊握住，連外包裝一起拿著 Mix2Vial™ 並將之反轉過來，用力將藍色塑膠導管推入穿透注射用水的橡皮塞，如圖一。



WFI=注射用水

5. 握著注射用水，小心將 Mix2Vial™的外包裝移開，並小心的留住 Mix2Vial™使之緊密接靠著注射用水。確認被移開的只有外包裝而不是 Mix2Vial™，如圖二。
6. 將”國血製劑益康”高純度第九凝血因子注射劑放在一平台上並緊握住，將附有 Mix2Vial™的注射用水反轉過來，再將 Mix2Vial™尾端的透明塑膠導管用力推入穿透”國血製劑益康”高純度第九凝血因子注射劑的橡皮塞。如圖三。水應當被瓶內的真空負壓自動吸入。**通常不會發生，但若瓶內不呈真空負壓，切勿使用該瓶藥品，並將它退回標籤上標示的代理商。**
7. 當注射用水和”國血製劑益康”高純度第九凝血因子注射劑還連在一起時，輕輕搖動藥瓶溶解裏面的藥粉，直到完全溶解為止，避免產生過多的泡沫。十分鐘內應當得到澄清或稍呈半透明的液體。配製後之溶液應依以下”**使用方法**”一節之描述儘快使用。

8. 當”國血製劑益康”高純度第九凝血因子注射劑瓶子的內含物完全溶解後，分別緊握住 Mix2Vial™ 的藍色與透明部份，將其旋鬆分成兩段(如圖四)。將注射用水的瓶子及 Mix2Vial™ 的藍色部份丟入適當的廢棄物桶內。

注意：Mix2Vial™ 是針對過濾單瓶”國血製劑益康”高純度第九凝血因子注射劑而設計，如需要使用多瓶”國血製劑益康”高純度第九凝血因子注射劑時，每一瓶均應使用新的 Mix2Vial™。

一旦完成配製後應儘快使用，切勿將”國血製劑益康”高純度第九凝血因子注射劑冷藏。

小心

本品不含有抗微生物防腐劑。因此，配製後溶液應立即使用。任何未用完的液體均應作適當棄置。每次僅可使用於單一病人。如果有塊狀或膠狀物出現，切勿使用該瓶製品，立刻退回給標籤上標示的代理商。

使用說明

1. 將”國血製劑益康”高純度第九凝血因子注射劑直立，並接上一塑膠可拋式注射器到 Mix2Vial™ (透明塑膠部份)。將整個系統反轉過來並緩慢的拉回注射器活塞，使配製好的”國血製劑益康”高純度第九凝血因子注射劑吸入注射器內。一隻大注射器可用於混合多瓶配製好的”國血製劑益康”高純度第九凝血因子注射劑。
2. 當”國血製劑益康”高純度第九凝血因子注射劑已轉移到注射器內，緊握住注射器的筒管(保持活塞朝下)，旋鬆並移開 Mix2Vial™。將”國血製劑益康”高純度第九凝血因子注射劑的空瓶及 Mix2Vial™ 的透明部份丟入適當的廢棄物桶內。套上合適的輸注針施打配製好的”國血製劑益康”高純度第九凝血因子注射劑。切勿使用 Mix2Vial™ 直接注射。

3. 緩慢地通過靜脈途徑注射給藥(大約每分鐘 3 毫升或視病人耐受情況調整)。如果發現有任何無法忍受的徵兆，降低注射速度或停止注射。如果需要注射超過一瓶以上，用藥前先把全量抽放在一個無菌瓶或袋裏再給予可能比較方便，但是要保證無菌操作。
4. 為減少微生物污染的危險，溶液配製後應立刻使用。該溶液不可存放，除非溶液配製是在無菌條件下進行，且所有用具均保持無菌狀態。配製後三個小時內必須輸注完畢。用於手術時，“**連續性靜脈輸注**”一節所描述的情形是可適用的。任何剩餘在瓶裏的溶液必須適當棄置。
5. 該溶液切勿與其它需要輸注的液體混合或加入其它液體中，包括全血。

破損或溢出

當發生打破容器或濺溢時，必須採取適當的處理措施，以避免割傷和擦傷造成的污染，也要避免吸入或吞入濺溢出的物質。以 1% 次氯酸鈉 (漂白水) 處理 15 分鐘，能獲得適當的消毒作用。就市面上買得到的漂白水加以稀釋，即可得到這個濃度。

過量使用

高劑量使用第九凝血因子產品可能導致心肌梗塞，血管內瀰漫性凝血，血栓形成和肺栓塞。過量使用可能會增加這些併發症的風險。

包裝型式

“國血製劑益康”高純度第九凝血因子注射劑是小瓶裝，含有 500 國際單位的第九凝血因子。每一盒內裝有本產品一小瓶，10 毫升注射用水一小瓶和 Mix2Vial™ 過濾轉接器一支。

儲存

儲存於 2°C~8°C 之間 (冷藏，勿冷凍)。避光、超過效期切勿使用。

製造廠

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藥商

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