“TBSF” High Purity Factor VIII Concentrate
Taiwan

NAME OF THE MEDICINE

Human Coagulation Factor VIII, Freeze-dried

DESCRIPTION

“TBSF” High Purity Factor VIII 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 VIII Concentrate is a high purity, sterile, freeze-dried powder containing human coagulation factor VIII. It is intended for intravenous administration. The factor VIII in “TBSF” High Purity Factor VIII Concentrate is purified from cryoprecipitate using selective precipitation and chromatography steps. The manufacturing process of “TBSF” High Purity Factor VIII Concentrate includes solvent detergent (tributyl phosphate and polysorbate 80) treatment and dry heat treatment (80°C for 72 hours) steps to reduce the potential for viral transmission. The solvent detergent, dry heat treatment, and partitioning steps used in the manufacture of “TBSF” High Purity Factor VIII Concentrate have been demonstrated to be effective virus inactivation/removal steps in vitro for the relevant viruses HIV and hepatitis A (HAV), and also with model viruses for hepatitis B (HBV) and hepatitis C viruses (HCV). The virus inactivation/removal steps in “TBSF” High Purity Factor VIII Concentrate manufacture also have some effect on parvovirus B19.

“TBSF” High Purity Factor VIII Concentrate is presented in packs of 250 IU factor VIII for reconstitution with 5 mL Water for Injections. When reconstituted as recommended, each vial nominally contains 50 IU/mL factor VIII, approximately 100 IU/mL von Willebrand factor: Ristocetin co-factor (VWF:RCo) activity, 1 mg/mL human plasma proteins, 15 mg/mL sucrose, 5.8 mg/mL sodium citrate, 3.4-4.6 mg/mL sodium chloride, 2.4 mg/mL trometamol, 0.36 mg/mL calcium chloride and 0.28 mg/mL sodium octanoate, as well as 10 mg/mL albumin (≥ 99% pure) as a stabiliser. In the absence of the added albumin, the specific activity of “TBSF” High Purity Factor VIII Concentrate has been determined to be nominally 50 IU/mg total protein. When expressed as per mg clottable protein (fibrinogen), the specific activity of “TBSF” High Purity Factor VIII Concentrate in the absence of the added albumin averages 150 IU/mg. The levels of fibrinogen and other proteins such as fibronectin, immunoglobulins (IgA, IgM, IgG) and TGF-β in “TBSF” High Purity Factor VIII Concentrate are all significantly lower than the levels commonly found in plasma.

Although the product contains von Willebrand Factor (VWF) as measured by an in vitro indicator of its activity VWF:RCo, no clinical trials have been conducted with “TBSF” High Purity Factor VIII Concentrate in patients with von Willebrand’s disease (VWD).
SPECIAL PRECAUTION

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 virus markers.

In addition, virus removal and inactivation procedures are included in the manufacturing process. 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. 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 current procedures applied in the manufacture of this product are effective against enveloped viruses such as HIV (human immunodeficiency virus), hepatitis B and hepatitis C viruses, and the non-enveloped virus hepatitis A. They are also known to have some effect on the removal of the non-enveloped virus, parvovirus B19.

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.

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.

PHARMACOLOGY

Haemophilia A is an X-linked recessive blood coagulation disorder. It is caused by reduced factor VIII activity through either insufficient or abnormal synthesis of the factor VIII protein. Factor VIII is a cofactor for factor IXa, and accelerates the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Clinical symptoms of haemophilia A 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 administration of “TBSF” High Purity Factor VIII Concentrate provides an increase in the plasma levels of factor VIII and can temporarily correct the coagulation defect in these patients.

CLINICAL TRIALS

Pharmacokinetics

The clinical trials presented for “TBSF” High Purity Factor VIII Concentrate were conducted on Biostate®. Biostate® is the trademark for the comparable purified human coagulation factor VIII product.
manufactured by CSL for distribution in Australia. Two clinical trials have been conducted with Biostate®. The first trial investigated the pharmacokinetics of Biostate® in 16 male patients with severe haemophilia A (up to or equal to 2% factor VIII) who each received a single dose of 50 IU factor VIII/kg body weight. All patients had been previously treated with factor VIII concentrates and were aged from 17 to 53 years. The pharmacokinetic data for the 16 patients is summarised in Table 1 in row labelled “1. Initial”.

To assess the potential for development of inhibitors to factor VIII which may not be detected by conventional laboratory assays, a repeat pharmacokinetic trial was performed on eight patients who participated in the first pharmacokinetic trial and continued treatment with Biostate® for 3-6 months. There was no significant difference in the half-life or recovery determined in this trial compared to the first pharmacokinetic trial (see Table 1), thus indicating no inhibitor development with the use of Biostate®. The data for the 8 patients in the repeat pharmacokinetic trial is summarised in Table 1 in row labelled “2. Repeat”.

Table 1: Pharmacokinetic Data (Mean Values)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Half-life (h)</th>
<th>Recovery (%)</th>
<th>Clearance (mL/h/kg)</th>
<th>Volume of Distribution (L/kg)</th>
<th>Mean Resident Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Initial</td>
<td>12.4</td>
<td>108</td>
<td>3.25</td>
<td>0.053</td>
<td>16.7</td>
</tr>
<tr>
<td>2. Repeat</td>
<td>14.1</td>
<td>110</td>
<td>2.98</td>
<td>0.053</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Efficacy and Safety

The second clinical trial with Biostate® investigated the safety, tolerability and efficacy of Biostate® in 30 male patients with severe haemophilia A, including the 16 patients who participated in the first trial. All patients had been previously treated with factor VIII concentrates, were aged from 16 to 62 years, and were treated with Biostate® in this trial on an as required basis for 6 months. The 30 patients received a total of 1,416,550 IU of factor VIII (1019 administrations) over the 6 month period, the total dose per person ranging from 6000 IU to 112,250 IU. Out of the 789 administrations which were graded by the patients for efficacy, 131 (17%) were graded as excellent, 490 (62%) as good, 137 (17%) as moderate and 31 (4%) as poor. No patients undergoing surgery were included in this trial. Biostate® was well tolerated by all patients. Inhibitor development was monitored during the trial using the Bethesda assay. Inhibitors were not detected in any of the 30 patients.

Adverse reactions encountered during the clinical trials are outlined under ADVERSE EFFECTS.

Biostate® has not been studied in previously untreated patients.

INDICATIONS

For the treatment and prophylaxis of bleeding associated with haemophilia A due to factor VIII deficiency.

CONTRAINDICATIONS

None known.

PRECAUTIONS

“TBSF” High Purity Factor VIII Concentrate should be used with caution in patients with a known allergy to factor VIII concentrates, or human albumin. Allergic, anaphylactic reactions or fever are rarely observed in patients receiving factor VIII preparations. If any adverse event occurs while “TBSF” High
Purity Factor VIII Concentrate is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Patients congenitally deficient in factor VIII may develop antibodies to factor VIII following treatment. The reported prevalence for the formation of neutralising antibodies (inhibitors) in patients receiving plasma derived factor VIII is approximately 10-20%, although inhibitor development was not detected in the 30 patients who participated in the safety and efficacy trial with Biostate®. If the patient’s plasma factor VIII level fails to reach expected levels or if bleeding is not controlled after adequate dosage, the presence of inhibitors should be suspected. The presence of inhibitors can be demonstrated by a laboratory test and the level of inhibitor quantified in terms of factor VIII levels neutralised by the plasma. If the inhibitor is present at levels less than 10 Bethesda Units per mL, administration of factor VIII may neutralise the inhibitor. In this circumstance the plasma factor VIII levels should be monitored by laboratory assay.

The product contains blood group antibodies derived from the starting plasma in amounts which are insignificant in the normal treatment of haemarthroses and moderate haemorrhage. If very high doses are used in patients with blood groups A, B, or AB, the patient should be monitored for signs of intravascular haemolysis.

The effects of “TBSF” High Purity Factor VIII Concentrate on male fertility are unknown.

Any case of infection associated with the use of the product, including details of the batches given, should be reported to the distributor listed on the label.

Check the following before use
Prior to using “TBSF” High Purity Factor VIII Concentrate for the first time, the hepatitis A and hepatitis B antibody status of recipients should be tested. Immunisation with hepatitis A or hepatitis B vaccines is recommended for patients with no antibodies to these viruses.

Carcinogenicity/genotoxicity
The carcinogenic or genotoxic effects of “TBSF” High Purity Factor VIII Concentrate have not been established in appropriate studies.

Use in pregnancy or lactation
The safe use of “TBSF” High Purity Factor VIII 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 VIII 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 VIII Concentrate with other drugs has not been established in appropriate studies.

ADVERSE EFFECTS

Allergic, anaphylactic reactions or fever are rarely observed in patients receiving factor VIII preparations. If any adverse event occurs while “TBSF” High Purity Factor VIII Concentrate is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Twenty-one of the 30 patients who participated in the safety and efficacy clinical trial with Biostate® experienced 68 adverse events over a total of 1019 administrations (6.7% of administrations). Of the 68
adverse events, 21 events (2% of total administrations) were considered to be related or possibly related to Biostate®. These events were (total number of events, % of total administrations): headache (8, 0.8%), back pain (4, 0.4%), anxiety (2, 0.2%), chest pain (2, 0.2%), arthralgia (1, 0.1%), skeletal pain (1, 0.1%), dizziness (1, 0.1%), flushing (1, 0.1%) and fever (1, 0.1%). One of the patients who experienced back pain and skeletal pain during the safety and efficacy trial also experienced these symptoms during the first pharmacokinetics trial. All of these adverse events were considered to be mild.

**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 VIII concentrations are achieved.

**Table 2: Guidelines for Dosage**

<table>
<thead>
<tr>
<th>Indication a</th>
<th>Desired Plasma Concentration of Factor VIII (IU/dL)</th>
<th>Dose (IU/kg)</th>
<th>Frequency of Dosing (per day)</th>
<th>Duration of Treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor haemorrhage</td>
<td>peak 20-30</td>
<td>10-15</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Moderate to severe haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intracranial haemorrhage</td>
<td>peak 30-80</td>
<td>15-40</td>
<td>1-3</td>
<td>7-10</td>
</tr>
<tr>
<td>other e.g. haemarthroses</td>
<td>peak 30-80</td>
<td>15-40</td>
<td>1-3</td>
<td>7-10</td>
</tr>
<tr>
<td>Minor surgery:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loading dose</td>
<td>50-60</td>
<td>20-30</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>maintenance</td>
<td>20-50</td>
<td>15-30</td>
<td>1 b</td>
<td>8-9</td>
</tr>
<tr>
<td>Major surgery:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loading dose</td>
<td>80-100</td>
<td>40-50</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>maintenance</td>
<td>20-100</td>
<td>10-40</td>
<td>1-3 b</td>
<td>8-9</td>
</tr>
<tr>
<td>Dentistry c</td>
<td>e.g. invasive dental procedures, extractions, surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loading dose</td>
<td>70-80</td>
<td>35-40</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>maintenance</td>
<td>50-60</td>
<td>25-30</td>
<td>2 b</td>
<td>1-3</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>trough 1</td>
<td>25-40</td>
<td>3 times weekly</td>
<td>continuous</td>
</tr>
</tbody>
</table>

a Guidelines for all therapy except for prophylaxis are based on Rickard, 1995 1. Guidelines for prophylaxis refers to prophylaxis in children according to the protocol developed in Sweden by Nilsson's group 2.

b An alternative is to use a continuous infusion.

c For extensive dental clearance or surgery, higher levels (greater than 6-10 days) may be necessary for longer periods of time. The use of an antifibrinolytic agent in support of factor replacement is strongly recommended after dental extractions.

**Continuous Infusion**
No studies using continuous infusion were carried out in patients. However, 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 administered 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 VIII concentrations be determined in patient’s plasma at suitable intervals and during the treatment of severe haemorrhage.

**Reconstitution**
1. Before reconstitution allow the vials of “TBSF” High Purity Factor VIII 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 VIII 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 VIII 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. (5 mL Water for Injections is provided for 250 IU vial).

![Figure 1](image1)
![Figure 2](image2)
![Figure 3](image3)
![Figure 4](image4)

**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 VIII 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 VIII 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 VIII 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 within 2 to 5 minutes. The solution should be used immediately as described below under **Administration.**
8. Once the contents of the “TBSF” High Purity Factor VIII 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 VIII Concentrate only. If multiple vials of “TBSF” High Purity Factor VIII Concentrate are to be administered, a separate Mix2Vial™ must be used for each vial.

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

CAUTION
The product does not contain an antimicrobial preservative. It must, therefore, be used within 3 hours 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 VIII 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 VIII 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 VIII Concentrate.
2. Once the “TBSF” High Purity Factor VIII 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 VIII Concentrate vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted “TBSF” High Purity Factor VIII Concentrate. Do not use the Mix2Vial™ for injection.
3. Give the dose slowly (usually within 5 minutes, or as tolerated by the patient) by the intravenous route. 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. This product is for single use only and 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.

Medical personnel, family carers and patients should be adequately trained in the techniques for the preparation and the administration of “TBSF” High Purity Factor VIII Concentrate.

OVERDOSAGE

No symptoms of overdose with human plasma coagulation factor VIII concentrate are known.

PRESENTATION

“TBSF” High Purity Factor VIII Concentrate is available in one pack size: 250 IU. Each single pack contains:
• 250 IU vial of “TBSF” High Purity Factor VIII Concentrate, 5 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.

REFERENCES


NAME AND ADDRESS OF THE MANUFACTURER

CSL Limited ABN 99 051 588 348
189-209 Camp Road
Broadmeadows VIC 3047
AUSTRALIA

MANUFACTURER OF THE DILUENT

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

NAME AND ADDRESS OF THE DISTRIBUTOR

Taiwan Blood Services Foundation
3 Fl. No.3 Nan-Hai Road
Taipei 100
Taiwan, R.O.C.
(02) 23511600

NAME AND ADDRESS OF THE CONSIGNER

BioTrust International Corporation
9F, 201 Tung-Hwa North Road
Taipei 105
Taiwan, R.O.C.
(02) 25458877

® Registered Trademark of CSL Limited
™ Trademark of Medimop Medical Projects Ltd
“國血製劑益康”高純度第八凝血因子注射劑
“TBSF” High Purity Factor VIII Concentrate

成分

人類第八凝血因子，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八凝血因子注射劑。

“國血製劑益康”高純度第八凝血因子注射劑是一種含有人類第八凝血因子的高純度、無菌、冷凍乾燥粉末藥劑，由匯集的人類血漿製備而來，用於靜脈注射。

高純度第八凝血因子注射劑裡的第八凝血因子是由冷凍沉澱品經過選擇性沉澱與色層分析法等步驟純化而來。

“國血製劑益康”高純度第八凝血因子注射劑的製程，包括溶媒清潔劑【磷酸三丁酯 (tributyl phosphate) 和 polysorbate 80】處理，以及乾熱處理 (80℃ 72 小時)，以降低病毒感染的可能性。製程裡面包括的這些溶媒清潔劑處理、乾熱處理、以及分隔沉澱等步驟，已經在體外試驗中獲得證實，能有效地移除愛滋病毒 (HIV)、A 型肝炎病毒 (HAV)、B 型肝炎病毒 (HBV)、C 型肝炎病毒 (HCV) 等相關的病毒，或去除其活性。製程中這些病毒移除或去活化步驟，對 B19 型小病毒 (parvovirus B19) 也有一些效果。

高純度第八凝血因子注射劑組含有 250 IU 的第八凝血因子及 5 mL 的注射用水。依照指示調配之後，每個玻璃小瓶會含有 50 IU/mL 濃度的第八凝血因子、濃度約為 100 IU/mL 的 VWF:RCo (von Willebrand factor: Ristocetin co-factor; VWF:RCo)、1 mg/mL 人血漿蛋白質、15 mg/mL 蔗糖、5.8 mg/mL 檸檬酸鈉、3.4~4.6 mg/mL 氯化鈉、2.4 mg/mL 氨丁三醇、0.36 mg/mL 氯化鈣與 0.28 mg/mL 正辛酸鈉、以及當作穩定劑的 10 mg/mL 白蛋白 (albumin，純度≧99%)。不包括白蛋白時，“國血製劑益康”高純度第八凝血因子注射劑的特異活性度 (specific activity) 約為 50 IU/mg 總蛋白質。如果是以可被凝結的蛋白質 (纖維蛋白原; fibrinogen) 來表示的話，“國血製劑益康”高純度第八凝血因子注射劑的特異活性度平均為 150 IU/mg (不包括白蛋白的情況下)。”國血製劑益康”高純度第八凝血因子注射劑裡面所含的纖維蛋白原及其他蛋白質，例如纖維結合蛋白 (fibronec tin)、免疫球蛋白 (immunoglobulins; IgA, IgM, IgG)、和 β 型轉化生長因子 (TGF-β)，其含量都遠低於血漿中的含量。

雖然在體外試驗的測量方法，測得本產品含有 von Willebrand 因子 (VWF) (VWF:Rco 活性)，還沒有臨床試用進行“國血製劑益康”高純度第八凝血因子注射劑在類血友病 (又名 von Willebrand 氏病，VWD) 病患的治療上。

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。惟縱然採取上述措施，此類產品仍有可能傳染疾病。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。這些方法對抗不含外套膜的 parvovirus B19 之效
可能有限。

**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。

使用血漿製品時可考慮給予適當之疫苗注射。

### 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。就市面上買到的漂白水加以稀釋，即可得到這個濃度。

### 藥理學
A型血友病 (haemophilia A) 是一種 X–性聯遺傳性凝血異常疾病，它是由於第八凝血因子蛋白質合成之不足或不正常所導致降低第八凝血因子活性所造成的。第八凝血因子是第九凝血因子 (IXa) 的輔因子，可一起將第十凝血因子活化。活化的第十凝血因子可將凝血酵素原 (prothrombin) 轉化為凝血酵素 (thrombin)。而凝血酵素再將纖維蛋白原 (fibrinogen) 轉化為纖維蛋白 (fibrin)，以形成血凝塊。A 型血友病的臨床症狀包括：皮膚淤青、外傷後的過多出血、以及自發性的關節、肌肉、或內臟出血。嚴重的出血會造成骨骼的畸形、器官功能障礙、或死亡。使用“國血製劑益康”高純度第八凝血因子注射劑可以提高血液中第八凝血因子的濃度，能夠暫時矯正病人的凝血缺陷。

### 臨床試驗

#### 藥物動力學

\[ \text{Biostate®} \] 係由 CSL Limited 生產並在澳洲銷售之高純度第八凝血因子之商標。以 \[ \text{Biostate®} \] 進行兩個臨床試驗。第一個是以 16 個患有 A 型血友病男性病人（第八凝血因子的濃度低於或等於 2%），研究 \[ \text{Biostate®} \] 的藥物動力學。每一個病人均接受單一劑量的第八凝血因子 50 IU/kg。所有病人之前都接受過第八凝血因子治療過，年齡介於 17 ~ 53 歲之間。這 16 個病人的藥物動力學研究結果總結於表一，標示為 (1. 初次使用)。

為了評估病人對第八凝血因子的治療產生抑制物的可能性（傳統的實驗室分析方法可能無法偵測），對試驗當中的 8 個受試病人重複再進行一次藥物動力學試驗，並且持續以 \[ \text{Biostate®} \] 治療 3~6 個月。比較這兩次試驗的結果發現，並沒有明顯的差異存在，包括，半衰期或回復率 (half-life or recovery) (表一)。因此，\[ \text{Biostate®} \] 的使用並不會產生抑制物。這 8 個病人的重複藥物動力學研究結果總結於表一，標示為 (2. 重複使用)。

表一、藥物動力學數據 (平均值)

<table>
<thead>
<tr>
<th>臨床試驗</th>
<th>半衰期 (小時)</th>
<th>回復率 (%)</th>
<th>血漿中的清除 (mL/h/kg)</th>
<th>容積分佈 (L/kg)</th>
<th>平均停留時間 (小時)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.初次使用</td>
<td>12.4</td>
<td>108</td>
<td>3.25</td>
<td>0.053</td>
<td>16.7</td>
</tr>
<tr>
<td>2.重複使用</td>
<td>14.1</td>
<td>110</td>
<td>2.98</td>
<td>0.053</td>
<td>17.8</td>
</tr>
</tbody>
</table>

### 有效性與安全性 (Efficacy and Safety)

第二個臨床試驗在研究 \[ \text{Biostate®} \] 的安全性、病人耐受性與有效性。受試者為 30 個患有嚴重 A型血友病男性病人，包括第一個臨床試驗中的 16 個受試病人。所有病人之前都接受過第八凝血
因子治療，年齡介於16～62歲之間。只有在需要用藥的情況出現時才用藥。在持續6個月的治療期間，這30位病人總共接受了1,416,550 IU（約計1019次）。每個病人接受到的總劑量介於6000 IU到112,250 IU之間。在治療效果由病人自己評定的789次給藥當中，131（17%）次治療效果良好，137（17%）次治療效果普通，31（4%）次治療效果不佳。本試驗中的所有病人都沒有接受手術治療。所有病人對Biostate®的耐受性良好，以Bethesda分析法監測抑制物的產生與否，在所有30位受試病人當中，都沒有偵測到抑制物的產生。

本試驗中所發生的任何不良副作用都記錄在「不良反應」一節當中。

Biostate®未曾試用於沒有接受過任何治療的病人。

適應症

治療和預防因缺乏第八凝血因子而引起之A型血友病相關的出血病症。

禁忌

目前未知

特殊警語

對第八凝血因子或白蛋白過敏的病人，使用“國血製劑益康”高純度第八凝血因子注射劑時必須特別小心。第八凝血因子的使用很少造成過敏、過敏性反應、或發燒。正在使用“國血製劑益康”高純度第八凝血因子注射劑的病人如果發生不良反應，應該減慢注射速度或終止注射，以減緩症狀。

先天性缺少第八凝血因子的病人，在使用第八凝血因子製劑治療之後，有可能會對它產生抗體（抑制物）。雖然在參與Biostate®安全性與有效性試驗的30位病人當中，並沒有發生因使用第八凝血因子製劑而對其產生抗體，但根據文獻的報告，這現象發生機率大約是10～20%。如果使用適當劑量的“國血製劑益康”高純度第八凝血因子注射劑之後，血中第八凝血因子達不到預期濃度，或出血情況未獲控制，則很可能就是產生了抗體的緣故。憑藉著具有中和第八凝血因子的能力，該血漿中的抗體可用實驗室方法測知，其濃度也可以定量出。如果該抗體的濃度是每毫升低於10 Bethesda單位，則第八凝血因子的使用，可以有效地中和該抗體。在這種情況下，應該以實驗室分析方法，追蹤血中第八凝血因子濃度。

本產品含有來自捐血人血漿中的各種血型抗體，但其含量極微，在一般關節腔出血或中度出血情況下的用量，不致造成影響。但是，如果在A、B、或AB血型的病人，使用大的劑量，則必須注意並監控病人是否出現血管內溶血的徵兆。

“國血製劑益康”高純度第八凝血因子注射劑對男性生殖力的影響，還沒有相關研究。

若因使用本產品而感染任何傳染性疾病，包括該產品批號的所有細節，都必須向標籤上標示的代理商報告。

請先檢查以下資訊再使用本產品

第一次使用“國血製劑益康”高純度第八凝血因子注射劑之前，使用者必須先檢查其A型和B型肝炎病毒抗體的狀況，沒有這些抗體的人，最好先施打A型和B型肝炎病毒預防疫苗，再使用本產品。

致癌性與基因毒性

“國血製劑益康”高純度第八凝血因子注射劑在致癌性與基因毒性方面的作用，還沒有相關研究。
懷孕與哺乳期的使用
懷孕與哺乳期的使用
懷孕與哺乳期的使用
懷孕與哺乳期的使用

小兒及老人使用
小兒及老人使用
小兒及老人使用
小兒及老人使用

與其他藥物的交互作用
“國血製劑 益康”高純度第八凝血因子注射劑與其它藥物的交互作用情形，還沒有相關研究。

不良反應
極少病人因為使用第八凝血因子而產生過敏、過敏性反應、發燒現象。正在使用“國血製劑 益康”高純度第八凝血因子注射劑的病人如果發生不良反應，應該減緩注射速度或終止注射，以減緩症狀。

在參與 Biostate®安全性與有效性的臨床試驗的30位受試者當中，其中21位發生過68次不良副作用事件，占所有1019次給藥的6.7%。在這68次當中的21次(總給藥次數的2%)，被認為與Biostate®有關係或可能有關係。這些不良反應包括(不良反應次數，占總給藥次數%)：頭痛(8, 0.8%)、背痛(4, 0.4%)、不安(2, 0.2%)、胸痛(2, 0.2%)、關鍵痛(1, 0.1%)、骨骼疼痛(1, 0.1%)、橈眩(1, 0.1%)、潮紅(1, 0.1%)、發燒(1, 0.1%)。其中一個參與這次安全性與有效性臨床試驗，而發生背痛與骨骼疼痛的病人，在其參與第一次藥物動力學試驗的時候，也發生這些症狀。全部這些症狀都屬輕微。

劑量與用法

本藥限由醫師使用

劑量
建議劑量列於表二，作為一般的治療準則。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八凝血因子達到預期的濃度。

表二、使用劑量準則

<table>
<thead>
<tr>
<th>適應症</th>
<th>第八凝血因子預期達到的血漿濃度 (IU/dL)</th>
<th>副量 (IU/kg)</th>
<th>用藥頻率 (每天次數)</th>
<th>治療期間 (天數)</th>
</tr>
</thead>
<tbody>
<tr>
<td>輕微出血</td>
<td>高峰 20-30</td>
<td>10-15</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>中度到嚴重出血</td>
<td>頭痛 (8, 0.8%)</td>
<td>15-40</td>
<td>1-3</td>
<td>7-10</td>
</tr>
<tr>
<td>頭痛 (8, 0.8%)</td>
<td>15-40</td>
<td>1-3</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td>關節腔內出血</td>
<td>關節疼痛 (1, 0.1%)</td>
<td>15-30</td>
<td>10-40</td>
<td>1-3</td>
</tr>
<tr>
<td>小手術：</td>
<td>50-60</td>
<td>20-30</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>首劑劑量</td>
<td>50-60</td>
<td>20-30</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>維持劑量</td>
<td>20-30</td>
<td>15-30</td>
<td>1-3</td>
<td>8-9</td>
</tr>
<tr>
<td>大手術：</td>
<td>80-100</td>
<td>40-50</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>首劑劑量</td>
<td>80-100</td>
<td>40-50</td>
<td>stat</td>
<td>-</td>
</tr>
<tr>
<td>維持劑量</td>
<td>20-100</td>
<td>10-40</td>
<td>1-3</td>
<td>10-12</td>
</tr>
<tr>
<td>牙科</td>
<td>例如，侵入性牙醫治療、拔牙、手術</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

例如，侵入性牙醫治療、拔牙、手術

### 資料來源

- Biostate®安全性與有效性的臨床試驗
- 使用“國血製劑 益康”高純度第八凝血因子注射劑的病人
- 不良反應事件的統計
- 藥物交互作用的評估

### 額外說明

- 胎兒及老人的使用
- 其他藥物的交互作用
- 不良反應的監控
- 使用劑量的建議
除了病症預防項目以外，其它治療準則都是根據 Rickard, 1995。病症預防準則，請參考瑞典 Nilsson 氏的兒童病症預防。

另一種選擇是使用持續性點滴注射。

大範圍的口腔清理或手術時，需用長一點的時間，6-10 天或更久及更高的標準。拔牙後，我們強烈建議使用抗纖維蛋白原溶解藥物 (antifibrinolytic agent)，進行凝血因子替補治療。

連綿性靜脈輸注 (Continuous Infusion)
連綿性靜脈輸注法尚未在病人身上做過研究。但是建議這種給藥方法適用於外科手術。配製方法與靜脈大規模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
在治療嚴重出血病人期間，或每隔一段適當時間，應該要監視病人血漿的第八凝血因子濃度。

調配 (Reconstitution)
1. 配製前，先使“國血製劑益康”高純度第八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”高純度第八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”高純度第八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。(5 毫升的注射用水是供每小瓶 250IU 使用)

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”高純度第八凝血因子注射器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”
使用過量之人類第八凝血因子，是治療人類的療法。注意5. 3. 4. 7.

高純度第八凝血因子注射劑的裝置。如圖三。使用應當使用軟瓶內的真空自體型吸入。通常不會發生，但若瓶內不呈真空自體型，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”高純度第八凝血因子注射劑混在一起時，輕輕搖動藥瓶溶解面的藥粉，直到完全溶解為止，避免產生過多的泡沫。二至五分鐘內應當得到澄清或略呈半透明的液體。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”高純度第八凝血因子注射劑混於的含物完全溶解時，分別緊握住Mix2Vial™的藍色與透明部份，並將之旋鬆成兩段(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”高純度第八凝血因子注射劑而設計。如需要使用多瓶“國血製劑益康”高純度第八凝血因子注射劑時，每一瓶均應使用新的Mix2Vial™。

一旦完成配製後，切勿將“國血製劑益康”高純度第八凝血因子注射劑再冷凍。

小心：

本品不含有抗微生物防腐劑。因此，配製後溶液應在3小時內使用。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，立即退回給標籤上標示的代理商。

使用說明

1. 將“國血製劑益康”高純度第八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”高純度第八凝血因子注射劑吸入注射器。一隻大注射器可用於混合多瓶配製好的“國血製劑益康”高純度第八凝血因子注射劑。

2. 當“國血製劑益康”高純度第八凝血因子注射劑已轉移到注射器內，緊握住注射器的管筒(保持活塞朝下)，旋鬆並移開Mix2Vial™。將“國血製劑益康”高純度第八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。套上合適的輸注針頭打配製好的“國血製劑益康”高純度第八凝血因子注射劑。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5分鐘內完成或視病人耐受情況調整)。如果需要注射超過一瓶以上，用藥前先把全量抽取在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”一節所述的情形是可適用的。本產品為單次使用，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。

醫療人員、居家照護人員及病患為了配製及注射“國血製劑益康”高純度第八凝血因子注射劑應該接受適當的技術訓練。

過量使用

使用過量之人類第八凝血因子，是否會造成任何徵狀，並不清楚。

包裝型式

“國血製劑益康”高純度第八凝血因子注射劑之包裝為250 IU。每個單劑包裝內含：
250 IU 国血製剤益康”高纯度第八凝血因子注射剂一瓶、5 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。

文献


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