1 PRODUCT NAME

Thrombotrol®-VF 1000 IU powder and diluent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Thrombotrol®-VF is a sterile, freeze-dried preparation of purified human antithrombin III (ATIII).

Thrombotrol®-VF is manufactured from plasma donated by voluntary and non-remunerated donors from New Zealand. Each vial of Thrombotrol®-VF contains 1000 International Units (IU) of ATIII. The potency assignment has been determined with a standard calibrated against a World Health Organisation (WHO) ATIII reference preparation.

Each vial of Thrombotrol®-VF contains up to 300 mg human plasma proteins.

Excipients with known effect

Sodium 76 mg (3.3 mmol) per 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

Thrombotrol®-VF is indicated in patients with hereditary deficiency of ATIII under the following circumstances:

(a) Prophylactic administration for the prevention of thrombosis and pulmonary embolism in surgery, pregnancy and childbirth (see section 4.6).

(b) Therapeutic administration in thrombosis or pulmonary embolism.

4.2 Dose and method of administration

Dose

Each vial of Thrombotrol®-VF nominally contains 1000 IU of ATIII.

An individual patient's dose should be determined using the pre-treatment and desired plasma ATIII levels, according to the following formula:

$$\text{Dose required (IU)} = \frac{[\text{desired} - \text{pre-treatment ATIII level*}] \times \text{weight (kg)}}{2.2}$$

* expressed as % normal level based on functional ATIII assay.

The above formula is based on an expected incremental *in vivo* recovery above baseline levels for ATIII of 2.2% per IU per kg administered. Thus, if a 70 kg individual has a pre-treatment ATIII level of 57%, in order to increase plasma ATIII to 120%, the initial Thrombotrol®-VF dose required would be [(120–57) x 70] /2.2 = 2000 IU.

However, recovery may vary, and initially levels should be determined pre-treatment and 20 minutes post-infusion. Subsequent doses can be calculated based on the recovery of the first dose. These recommendations are intended only as a guide for therapy. The exact loading dose and maintenance intervals should be individualised for each patient, based on the individual's clinical condition, response to therapy and actual plasma ATIII levels achieved.

It is recommended that following an initial dose of Thrombotrol®-VF plasma levels of ATIII are monitored at least every 12 hours and before the next infusion of Thrombotrol®-VF to maintain plasma ATIII levels at greater than 80%. In some situations, e.g. following surgery, haemorrhage or acute thrombosis, and during intravenous heparin administration, the half-life of ATIII has been reported to be shorter. In such conditions, plasma ATIII levels should be monitored more frequently, and Thrombotrol®-VF administered as necessary.

When an infusion of Thrombotrol®-VF is indicated for a patient with hereditary deficiency to control an acute thrombotic episode or prevent thrombosis following surgical or obstetrical procedures, it is desirable to raise the ATIII levels to normal. This level should generally be maintained for 2 to 8 days but will depend on the indication for treatment, type and extent of surgery, patient's medical condition, past history and physician's judgement. Concomitant administration of heparin in each of these situations should be based on the medical judgement of the physician.

Method of administration

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

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

2. Once the Thrombotrol®-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 Thrombotrol®-VF vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted Thrombotrol®-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. 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. Any unused portion remaining in the vial must be discarded appropriately.

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

Monitoring

It is recommended that ATIII plasma levels be monitored during the treatment period. Functional levels of ATIII in plasma may be measured by amidiolytic assays using chromogenic substrates or by clotting assays.

4.3 Contraindications

Thrombotrol®-VF should not be used if there is a history of allergy to this type of product, or its excipients (see section 6.1).

4.4 Special warnings and precautions for use

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 Thrombotrol®-VF manufacturing process includes pasteurisation (60ºC for 10 hours) and nanofiltration as dedicated virus inactivation and removal steps to reduce the possibility of virus transmission. 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 viruses (HCV), 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 (e.g. hepatitis A and hepatitis B) should be considered where appropriate, for patients in receipt of medicinal products manufactured from human plasma.

Paediatric population

Safety and effectiveness in children have not been established. The ATIII level in neonates of parents with hereditary ATIII deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported).

Plasma levels of ATIII are lower in neonates than adults, averaging approximately 60% in normal term infants. ATIII levels in premature infants may be much lower. Low plasma ATIII levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with Thrombotrol®-VF in neonates be discussed with an expert on coagulation.

Use in the elderly

The safety of this product for use in the elderly population has not been established in appropriate studies.

Other

Thrombotrol®-VF contains 76 mg sodium per vial, equivalent to 3.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Concurrent therapy with ATIII Concentrates may enhance the anticoagulant effect of heparin (see section 5).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this product for use in human pregnancy has not been established in appropriate studies, therefore it should be given to pregnant women only if clearly needed, taking into consideration that pregnancy confers an increased risk of thromboembolic events in these patients.

The published literature contains several reports relating to the use of ATIII Concentrates in ATIII deficient women during pregnancy, at delivery and post-partum. These reports support the clinical efficacy and safety of the product in this indication.

Lactation

The safety of this product for use during lactation has not been established in appropriate studies, therefore it should be given to nursing mothers only if clearly needed.

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

The clinical study in six asymptomatic subjects with hereditary ATIII deficiency reported only one adverse event of transient rash which occurred 90 minutes after the start of the intravenous infusion and resolved spontaneously within 3 hours.

Adverse reactions associated with other ATIII Concentrates include dizziness, chest tightness, foul taste in mouth, abdominal cramps, shortness of breath, light-headedness, hives, fever, and haematoma formation. If adverse reactions are experienced, the infusion rate should be decreased or, if indicated, the infusion should be interrupted until symptoms abate.

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

No cases of overdose with ATIII Concentrate have been reported.

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: Antithrombotic agents: heparin group

ATC code: B01AB02

Mechanism of action

Antithrombin III, an alpha$_2$-glycoprotein of molecular weight 58,000 daltons, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by ATIII occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the active serine of thrombin and an arginine reactive site of ATIII. ATIII also inactivates other components of the coagulation cascade including factors IXa, Xa, XIa and XIIa, as well as plasmin.

Pharmacodynamic effects

The neutralisation rate of serine proteases by ATIII is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect of heparin is mediated by ATIII, the effectiveness of heparin as an anticoagulant may be reduced in the absence or near absence of ATIII.

The prevalence of the hereditary deficiency of ATIII is estimated to be one per 2000 to 5000 in the general population. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with ATIII levels of 40%–60% of normal. These episodes usually appear after the age of 20, the risk increasing with age in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary antithrombin III deficiency during pregnancy has been reported to be 70%. Greater than 85% of individuals with hereditary ATIII deficiency have had at least one thrombotic episode by the age of 50 years. Thromboses may be recurrent and in many cases no precipitating factor is identified. In some individuals, treatment with oral anticoagulants leads to a minor increase in endogenous levels of ATIII.

Clinical efficacy and safety

In clinical studies, patients with hereditary ATIII deficiency and histories of thromboembolism, treated prophylactically with ATIII Concentrates for high thrombotic risk situations (surgery, delivery) have not developed thrombotic complications. Patients with hereditary ATIII deficiency have also been treated therapeutically with ATIII Concentrates as well as heparin for major thrombotic or thromboembolic complications, with good results. Treatment with ATIII Concentrates reversed heparin resistance in patients with hereditary ATIII deficiency being treated for thrombosis or thromboembolism.

CSL has performed a pharmacokinetic and safety clinical study in six asymptomatic subjects with hereditary deficiency of ATIII. The study used the ATIII product prior to the introduction of a virus filtration (nanofiltration) step. The product supplied with this leaflet, Thrombotrol®-VF, includes a nanofiltration step in the manufacturing process to enhance viral safety. This product has been the subject of extensive biochemical characterisation which has demonstrated that the active ingredient is equivalent to, and the concentrate more pure than the product investigated in the clinical study. The pharmacokinetic parameters from this clinical study are described in section 5.2.

Under conditions of acute consumption, the biological half-life of ATIII may only be a few hours. In such patients the ATIII activity level should be determined several times a day. Underlying pathological states such as hepatic insufficiency (failure of synthesis) and the nephrotic syndrome (renal losses) must also be considered when calculating expected ATIII plasma increases.

During the clinical investigation none of the 6 subjects monitored for 9 months after receiving a single dose showed evidence of seroconversion to the following viruses: human immunodeficiency virus (HIV-1, HIV-2), hepatitis A, B or C, cytomegalovirus, Epstein-Barr virus, human herpes virus 6 and human parvovirus B19. A clinical investigation of viral safety on the product with enhanced virus safety from the additional virus filtration step was not regarded as necessary, since the product with a single virus inactivation step had shown no evidence of viral transmission in clinical trials.

5.2 Pharmacokinetic properties

In the pharmacokinetic and safety clinical study, six volunteers with asymptomatic congenital ATIII deficiency were administered a single, variable dose of Thrombotrol® (ATIII product prior to the introduction of a virus filtration step).

The mean *in vivo* recovery of ATIII was 3.1% per IU per kg administered based on immunological ATIII assay, and 2.2% per IU per kg administered based on functional ATIII assay. The half-life ($t_{½}$) of ATIII was 3.2 days based on immunological assays and 2.8 days based on functional assays of ATIII. These values are similar to the pharmacokinetic parameters reported for other ATIII Concentrates in the literature.

5.3 Preclinical safety data

No toxicology studies (including genotoxicity and carcinogenicity studies) have been conducted with Thrombotrol®-VF.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sodium
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 to 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 Thrombotrol®-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

Thrombotrol®-VF is available in vials containing 1000 IU of ATIII. Each Thrombotrol®-VF single pack contains:

- One glass vial of 1000 IU ATIII, with a latex-free rubber stopper closed with an aluminium seal and a plastic flip-top cap
- One glass vial of 20 mL Water for Injections, with a latex-free rubber stopper closed with an aluminium seal and a plastic flip-top cap
- One Mix2Vial™ filter transfer set.

6.6 Special precautions for disposal and other handling

Reconstitution

1. Before reconstitution, allow the vials of Thrombotrol®-VF and Water for Injections (WFI) to reach a temperature between 20°C and 30°C.
2. Remove the caps from the top of the Thrombotrol®-VF and WFI vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both Thrombotrol®-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**.

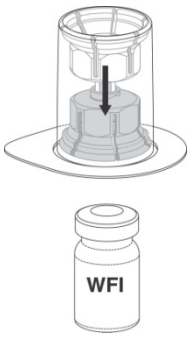

Figure 1

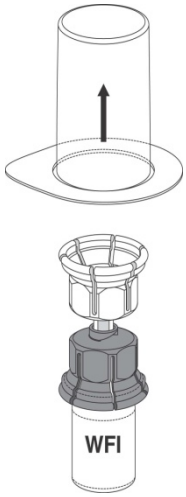

Figure 2

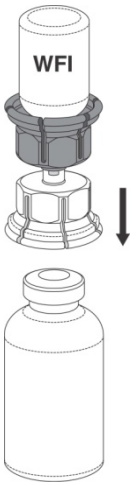

Figure 3

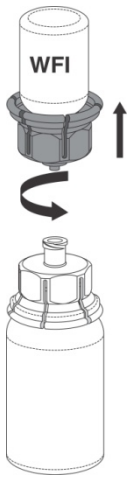

Figure 4

WFI = Water for Injections

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**.
6. With the Thrombotrol®-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 Thrombotrol®-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 Thrombotrol®-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 Thrombotrol®-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 Thrombotrol®-VF only. If multiple vials of Thrombotrol®-VF are to be administered, a separate Mix2Vial™ must be used for each vial.

Do not refrigerate Thrombotrol®-VF after 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.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

CSL Behring (NZ) Limited
P O Box 62590
Greenlane
Auckland 1546
New Zealand

For Medical/Technical Enquiries: TOLL FREE: 0800 640 677
For Customer Service Enquiries: TOLL FREE: 0800 841 532

customerservice@cslbehring.com.au
www.cslbehring.com.au

Manufacturer

CSL Behring (Australia) Pty Ltd
189-209 Camp Road
Broadmeadows VIC 3047
Australia

Distributor

New Zealand Blood Service
71 Great South Road
Epsom
Auckland
New Zealand

9 DATE OF FIRST APPROVAL

11 November 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
5.2	Section 5.2 Pharmacokinetic properties added
6.2	Information about incompatibilities added
6.5	Information about nature of container added
8	Sponsor's address and phone numbers updated

® Registered trademark of CSL Limited

™ Mix2Vial is a trademark of West Pharmaceutical Services, Inc. or a subsidiary thereof.