National Office
Private Bag 92071
Victoria Street West
Auckland 1142
New Zealand
Telephone: 64-9-523 5744

8th September 2023

Hospital Transfusion Committee Chairs
PLEASE CIRCULATE AS REQUIRED

Dear Colleagues

Re: THROMBOTROL-VF® to be discontinued and replaced by KYBERNIN® P (Section 29 – commercial product)

As part of the change to New Zealand's plasma products portfolio (https://www.nzblood.co.nz/assets/111I074-Poster-HCP-on-Process-Migration.pdf), THROMBOTROL-VF® (human antithrombin III) will no longer be manufactured for New Zealand Blood Service (NZBS) by CSL Behring. Production of THROMBOTROL-VF® ceased in May 2022 and the current batch of product expires in May 2024.

As a result, NZBS has sourced an alternative antithrombin III product to replace Thrombotrol-VF®, KYBERNIN® P from CSL Behring. KYBERNIN® P is made from plasma/blood donations from other countries and marketed in a number of European and other countries.

KYBERNIN® P does not have full New Zealand registration and so consultation with an NZBS Transfusion Medicine Specialist/ Medical Officer is required prior to product release. It is supplied by NZBS under Section 29, a provision in the Medicines Act 1981, whereby a medical practitioner can prescribe a medicine that is not registered with Medsafe.

We have pre-existing systems in place for cardiac bypass and the paediatric liver transplant that would allow release of KYBERNIN® P, in urgent situations, without TMS discussion. It will be important for clinicians who expect to use that pathway, to ensure that patients are informed of the unregistered status of KYBERNIN® P.

How does KYBERNIN® P differ from THROMBOTROL-VF®?

There are some important differences between KYBERNIN® P and THROMBOTROL-VF®, although both contain the active compound human antithrombin III.

KYBERNIN® P will be available in a 500 IU vial (not 1000 IU), which can be stored at room temperature (<25ºC), (THROMBOTROL-VF® required refrigeration). It is supplied with a Transofix® double spike (THROMBOTROL-VF® used a Mix2Vial®) to use when reconstituting the product.

Dosing with KYBERNIN® P is based on 1 IU/kg body weight raises plasma antithrombin activity by approximately 1.5% (THROMBOTROL-VF® raised AT III activity by 2.2%), and therefore uses a different equation to calculate the required dose:

Units required = body weight [kg] x (100 – actual antithrombin activity [%]) x 2/3.

KYBERNIN® P can be diluted with 5% albumin and some other solutions (for dilutions up to 1:5). The maximum infusion rate is 4mL/min. Dopamine, dobutamine or furosemide should not be administered via the same venous access.

KYBERNIN® P has a slightly higher sodium content than the equivalent THROMBOTROL-VF® vial and contains different excipients:

- Aminoacetic acid
- Sodium chloride
- Sodium citrate
- HCl or NaOH (in small amounts for pH adjustment)

Why is there a difference in the potency / IU to plasma activity ratio / dosing equation between KYBERNIN® P and THROMBOTROL-VF®?

The calculation for the KYBERNIN® P dose is based on the empirical finding (from clinical trials) that 1 International Unit (IU) antithrombin per kg body weight raises the plasma antithrombin activity by approximately 1.5 %. For THROMBOTROL-VF®, the equation was based on an expected incremental in vivo recovery above baseline levels for ATIII of 2.2% per IU per kg administered. For this reason, the equations for each product are unique.

When is THROMBOTROL-VF® currently used in New Zealand?

THROMBOTROL-VF® is sometimes used in replacement of Antithrombin III in cases of:

- Hereditary antithrombin III deficiency (licensed indication)
- Paediatric Liver Transplant cases
- Cardiac surgery with bypass
- Asparaginase-induced antithrombin III deficiency in Acute Lymphoblastic Leukaemia patients

THROMBOTROL-VF® is routinely stocked at five of the six NZBS operated Blood Banks (Dunedin, Christchurch, Wellington, Waikato, and Auckland) and available for Blood Banks to order from NZBS hub sites.

What to expect and timelines:

NZBS intends to introduce KYBERNIN® P in a phased manner, starting in the South Island in the latter part of 2023. NZBS is currently closely monitoring inventory levels of Thrombotrol-VF® and has designated stock level points at which the changeover will start for each region. NZBS will issue notification to the relevant Hospital Transfusion Committee of that region when KYBERNIN® P is to be introduced into each Blood Bank.

Information to assist with the update of local procedures and policies is attached as appendixes to this notification.

Please direct any queries to plasmaproductschange@nzblood.co.nz

Thank you for your support in ensuring a safe and effective move to these transitioned products.

Yours faithfully

DR SARAH MORLEY
Chief Medical Officer

cc: All NZBS Transfusion Team

Appendix

- *Kybernin® P Indonesia Leaflet May 2021*
- *Kybernin® P (500IU) & Thrombotrol-VF® (1000IU) Differences Comparison (from Datasheets)*

CSL Behring

1. NAME OF THE MEDICINAL PRODUCT

Kybernin P 500

500 IU

Powder and solvent for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kybernin is presented as a powder containing nominally 500 IU human plasma-derived antithrombin per vial.

The product contains approximately 50 IU/ml human plasma-derived antithrombin when reconstituted with 10 ml water for injections.

The potency (IU) is determined using the Chromogenic substrate method according to PH.Eur. The specific activity of Kybernin is approximately 5 IU/mg protein.

Excipients with known effect:
One vial of Kybernin 500 contains a maximum of 44.76 mg of sodium (found in table salt). This is equivalent to 2 % of the recommended maximum daily intake of sodium for an adult.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for intravenous injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of thromboembolic complications in

– hereditary deficiency of antithrombin III
– acquired deficiency of antithrombin III

4.2 Posology and method of administration

Posology
In congenital deficiency, dosage should be individualised for each patient taking into account the family history with regard to thromboembolic events, the actual clinical risk factors and the laboratory assessment.

The dosage and duration of the substitution therapy in acquired deficiency depend on the plasma antithrombin level, the presence of signs for increased turnover, the underlying disorder, and the severity of the clinical condition. The amount to be administered and the frequency of administration should always be based on the clinical efficacy and laboratory assessment in the individual case.

The number of units of antithrombin administered is expressed in International Units (IU), which are related to the current WHO standard for antithrombin. Antithrombin activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to the International Standard for antithrombin in plasma).

One international unit (IU) of antithrombin activity is equivalent to that quantity of antithrombin in one ml of normal human plasma. The calculation of the required dosage of antithrombin is based on the empirical finding that 1 International Unit (IU) antithrombin per kg body weight raises the plasma antithrombin activity by approximately 1.5 %.

The initial dose is determined using the following formula:

Required units = body weight [kg] × (100 - actual antithrombin activity [%]) × 2/3.

The initial target antithrombin activity depends on the clinical situation. When the indication for antithrombin substitution is established, the dosage should be sufficient to reach the target antithrombin activity, and to maintain an effective level. The dosage should be determined and monitored on the basis of laboratory measurements of the antithrombin activity, which should be performed at least twice a day until the patient is stabilized, thereafter once a day, preferably immediately before the next infusion. Correction of the dosage should take into account both signs of increased antithrombin turnover according to laboratory controls and clinical course. The antithrombin activity should be maintained above 80 % for the duration of the treatment, unless clinical particulars would indicate a different effective level.

It should be kept in mind that the half-life of antithrombin may be substantially shortened in certain clinical conditions, such as disseminated intravascular coagulation.

The usual starting dose in congenital deficiency would be 30 – 50 IU/kg.

Thereafter, dosage and frequency, as well as duration of treatment should be adjusted to the biological data and clinical situation.

Paediatric population
40 – 60 IU antithrombin per kg of body weight per day depending on the coagulation status. If required by the clinical condition higher dosages may be necessary in individual cases. The antithrombin activity must then be monitored more frequently and should not exceed 120 %.

Duration of therapy
In general therapy continues until antithrombin activity normalizes and symptoms resolve.

Method of administration
For instructions on reconstitution of the medicinal product before administration, see section 6.6.
Inject or infuse the solution slowly intravenously (max. 4 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Caution is advised in patients with known allergic reaction to constituents of the preparation.

4.4 Special warnings and precautions for use

Based on clinical investigations, the use of antithrombin for the treatment of IRDS (Infant Respiratory Distress Syndrome) in premature infants cannot be recommended.

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur after administration, they should contact their physician.

In case of shock, standard medical treatment should be administered.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV) and parvovirus B19 viruses.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived antithrombin products.

It is strongly recommended that every time that Kybernin is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Clinical and Biological surveillance when antithrombin is used together with heparin:
– In order to adjust heparin dosage and to avoid excessive hypocoagulability, controls of the extent of anticoagulation (APPT, and where appropriate anti-FXa activity) should be performed regularly, at close intervals and in particular in the first minutes/hours following the start of antithrombin use.
– Daily measure of antithrombin levels, in order to adjust the individual dose, because of the risk of diminution of antithrombin levels by prolonged treatment with non fractionated heparin.

4.5 Interaction with other medicinal products and other forms of interaction

Heparin: antithrombin replacement during administration of heparin in therapeutic dosage increases the risk of bleeding.
The effect of antithrombin is greatly enhanced by heparin.
The half-life of antithrombin may be considerably decreased with concomitant heparin treatment due to accelerated antithrombin turnover. Therefore, the concurrent administration of heparin and antithrombin to a patient with an increased risk of bleeding must be monitored clinically and biologically.

4.6 Fertility, pregnancy and lactation

Experience as to the safety of human antithrombin products for use in human pregnancy is limited.

The safety of Kybernin P for use in human pregnancy has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and pre- and postnatal development.

There is no negative experience with regard to the treatment during pregnancy and lactation. Therefore, Kybernin P should be administered to pregnant and lactating antithrombin deficient women only if clearly indicated taking into consideration that pregnancy confers an increased risk of thromboembolic events in these patients.

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

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticarial, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently, and may in some cases progress to severe anaphylaxis (including shock).

On rare occasions, fever has been observed

The following adverse reactions are based on postmarketing experience. In case data are available the following standard categories of frequency have been used:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10 000 to < 1/1000
Very rare	> 1/10 000 (including reported single cases)

System Organ Class	Preferred term	Frequency
Immune system disorders	Hypersensitivity / anaphylactic reactions including severe anaphylaxis and shock	Rare
General disorders and administration site conditions	Pyrexia	Rare

For information on viral safety see section 4.4

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions reactions.

4.9 Overdose

No symptoms of overdose with antithrombin have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group
Antithrombotic agents, heparin group
ATC-Code: B01A B02

Antithrombin, a 58 kD, 432 amino-acid glycoprotein, belongs to the serpin (serin protease inhibitor) superfamily. It is one of the most important natural inhibitors of blood coagulation. The factors most strongly inhibited are thrombin and factor Xa, but also factors of contact activation, intrinsic system and the factor VIIa/tissue factor complex. Antithrombin activity is greatly enhanced by heparin and the anticoagulant effects of heparin depend on the presence of antithrombin.

Antithrombin contains two functionally important domains. The first contains the reactive centre and provides a cleavage site for proteinases such as thrombin, a prerequisite for forming a stable proteinase-inhibitor complex. The second is a glycosaminoglycan binding domain responsible for the interaction with heparin and related substances, which accelerates the inhibition of thrombin. The inhibitor-coagulation enzyme complexes are removed by the reticulo-endothelial system.

Antithrombin activity in adults is 80 – 120 % and levels in neonates are about 40 – 60 %.

5.2 Pharmacokinetic properties

Intravenous administration means that the preparation is available immediately; bioavailability is proportional to the dose administered. The mean *in-vivo* recovery has found to be 65 % in 5 healthy test persons (quantified at t_{max} = 1.15 hours).

Kybernin is distributed and metabolized in the same way as the physiological inhibitor.

The biological half-life amounts to 2.5 days, but may, however, be decreased to hours in conditions with acute consumption. In these patients determination of antithrombin activity is required several times a day. For this purpose analysis using chromogenic substrate is suited.

5.3 Preclinical safety data

Toxicological properties
Human antithrombin III is a normal constituent of human plasma. Single dose toxicity testing is of little relevance and does not permit the estimation of toxic or lethal doses.
No signs of acute toxicity were found in animal models.

Repeated dose toxicity testing in animals is impracticable due to the formation of antibodies to heterologous protein in the animals.

Mutagenicity
Available clinical experience provides no hint for embryo-fetal toxicity. Neither oncogenic nor mutagenic effects were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aminoacetic acid
Sodium chloride
Sodium citrate
HCl or NaOH (in small amounts for pH adjustment)

Water for injections

6.2 Incompatibilities

The use of hydroxyethyl starch (HES), however, is not recommended as a diluent (for infusion) because a loss of antithrombin activity is observed.

This medicinal product must not be mixed with other medicinal products in the syringe/infusion set except those mentioned in section 6.6. Dopamine, Dobutamine and Furosemide should not be applied by the same venous access.

6.3 Shelf life

3 years.

Kybernin must not be used after the expiry date given on the pack and container.

After reconstitution the physico-chemical stability has been demonstrated for 8 hours at room temperature (max. +25 °C). From a microbiological point of view and as Kybernin contains no preservative, the reconstituted product should be used immediately. If it is not administered immediately, storage shall not exceed 8 hours at +25 °C.

Once the container has been opened, the contents have to be used immediately.

6.4 Special precautions for storage

Store at room temperature (max. +25 °C). Do not freeze.

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

6.5 Nature and contents of container

Powder (500 IU) in a vial (Type II glass) with a stopper (bromobutyl rubber), seal (aluminium) and flip-off cap (polypropylene).

Solvent (10 ml) in a vial (Type I glass) with a stopper (chlorobutyl or bromobutyl rubber), seal (aluminium) and flip-off cap (polypropylene).

Transfer spike

Pack size of 1.

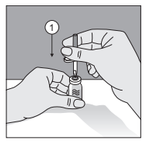
6.6 Special precautions for disposal and other handling

General instructions
The dried substance is to be completely reconstituted under aseptic conditions with the supplied diluent. A clear to slightly opalescent solution is obtained.

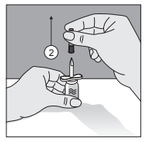
For administration as an infusion, human albumin 5 % solution is suited as diluent. For preparing dilutions of up to 1:5, the following may also be used: Ringer lactate solution, physiological saline solution, 5 % glucose solution, or polygelin.

The reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

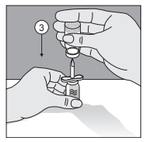
Reconstitution
For correct handling of the Transofix® double spike follow the below steps:



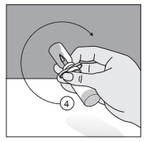
1. After removal of one of the two protection caps push the laid bare spike perpendicularly into the rubber stopper of the solvent vial.



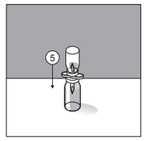
2. Remove the protection cap from the second spike



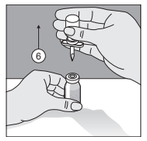
3. Pierce the product vial head first into this spike.



4. Turn the whole unit through 180°



5. Place it on the bottom of the product vial. The solvent now runs into the product vial.



6. The Transofix® double spike together with the solvent vial is pulled from the product vial and subsequently Kybernin is dissolved. The reconstituted Kybernin can be withdrawn into a syringe and administered.

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

7. MANUFACTURER

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Imported by
PT Dexa Medica
Palembang - Indonesia

8. MARKETING AUTHORIZATION NUMBER

DKI9794900244A1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 2008 / 23 October 2018

10. DATE OF REVISION OF THE TEXT

May 2021

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Kybernin-P (500IU) & Thrombotrol-VF (1000IU) Differences Comparison (from Data Sheets)

Characteristic	Kybernin-P	Thrombotrol-VF
Vial strength	500 IU	1000 IU
Sodium content	44.76mg (89.72mg in 1000 IU)	76mg
Dose formula	Body weight (kg) x (100 – actual antithrombin activity (%)) x 2/3	Desired ATIII (IU) – Pretreatment ATIII level (IU) x Body weight (kg) / 2.2
Dose basis	1 IU/kg = 1.5% increase AT III	1 IU/kg = 2.2% increase AT III
Indication	Prophylaxis & treatment of thromboembolic complications in hereditary or acquired deficiency of antithrombin III	In patients with hereditary deficiency of antithrombin III, to prevent thrombosis/ pulmonary embolism in surgery, pregnancy & childbirth and to treat thrombosis or pulmonary embolism
Paediatric population	40-60 IU/kg per day depending on coagulation status. Higher doses can be considered for individual clinical cases. Antithrombin activity must be monitored more frequently and should not exceed 120%.	Recommended that treatment in neonates should be discussed with an expert in coagulation.
Warnings/Precautions	Use in Infant Respiratory Distress Syndrome	None
Adverse events	Hypersensitivity/allergic reactions/anaphylaxis; pyrexia (all rare)	Transient rash; others (hypersensitivity-like but not described as such)
PK t½	2.5 days	2.8-3.2 days
Pre-clinical data	Single dose animal toxicity study	No toxicity studies
Clinical data	None included	PK/safety study in 6 subjects
Excipients	Amino acetic acid Sodium chloride Sodium citrate HCl or NaOH (pH adjust)	Sodium Citrate Chloride
Shelf life	3 years	2 years
Storage	Room temperature (<25ºC)	2º- 8ºC
Reconstituted storage	Up to 8 hours at 25ºC if not used immediately	Use immediately
Solvent	10mL per 500 IU WFI	20mL WFI
Reconstitution kit	Transofix spike	Mix2Vial
Reconstitution steps	Significant differences	
Administration	Rate: max 4mL/min Can dilute with 5% albumin, some other solutions. Do not administer dopamine, dobutamine or furosemide by the same venous access.	Do not mix with other fluids Rate: approx. 3mL/min or as tolerated

References:

- Kybernin-P information from Core Company Data Sheet 2016
- Kybernin-P Indonesian Product Leaflet 2021
- Thrombotrol information from New Zealand Datasheet 2018

Disclaimer: *the above information is based on a comparison of available information. It may not include all differences, including clinically important ones. The Product Information/DataSheet for each product should be reviewed in detail before prescribing*