



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 17 January 2002
CPMP/BPWG/3226/99

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

CORE SPC FOR HUMAN PLASMA DERIVED ANTITHROMBIN

DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	February 2000 September 2000 November 2000
TRANSMISSION TO THE CPMP	December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	June 2001
DISCUSSION IN THE BLOOD PRODUCTS WORKING GROUP	September 2001 November 2001
TRANSMISSION TO THE CPMP	January 2002
FINAL ADOPTION BY THE CPMP	January 2002
DATE FOR COMING INTO OPERATION	July 2002

**CORE SPC
FOR
HUMAN PLASMA-DERIVED ANTITHROMBIN**

The QRD Product Information template with explanatory notes and the convention to be followed for QRD templates** provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*

* (<http://www.emea.eu.int/htms/human/qrd/qrdplt/01aspc52exp.pdf>)

** (<http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv5.pdf>)

1. NAME OF THE MEDICINAL PRODUCT

{(Trade) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Product specific information on quantitative composition as nominal potency per container and nominal potency per ml <after reconstitution> and nominal potency per x ml <after reconstitution>. Volume of solvent for reconstitution. Method of potency determination. Specific activity.]

{(Trade) name of product} is presented as a {pharmaceutical form} containing nominally {x} *[as per labelled content]* IU human plasma-derived antithrombin per {container}.

The product contains approximately {x} IU/ml ({y}IU/{z}ml) human plasma-derived antithrombin *[the exact volume for reconstitution of the powder has to be indicated.]* <when reconstituted with {z} ml of *[define solvent]*>.

The potency (IU) is determined using the European Pharmacopoeial chromogenic assay. The specific activity of {(Trade) name of product} is approximately {x} IU/mg protein.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Patients with congenital deficiency:
 - a) Prophylaxis of deep vein thrombosis and thromboembolism in clinical risk situations (especially during surgery or during the peri-partum period), in association with heparin if indicated
 - b) Prevention of progression of deep vein thrombosis and thromboembolism in association with heparin as indicated
- *[Product specific: Indications in acquired deficiency will be defined by the supporting clinical data.]*

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of patients with deficiency of antithrombin.

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.

[Product specific]

<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 {x% to y%}.

The initial dose is determined using the following formula:

Required units = body weight (kg) x (Target level - actual antithrombin activity [%]) x {correction factor}

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 stabilised, 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.

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.

[Where indicated in children, provide information on whether dose and frequency of administration differs. Where there are insufficient data to recommend use in children include the following: <There are insufficient data to recommend the use of {(trade) name of the product} in children less than 6 years of age>]

Method of administration

Dissolve the preparation as described under 6.6. The product should be administered via the intravenous route. *[A recommendation for maximal rate of infusion should be given.]*

4.3 Contra-indications

Hypersensitivity to any of the constituents.

[Product specific]

<Known history of heparin induced thrombocytopenia.>

4.4 Special warnings and precautions for use

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.

[The choice of text indicated between <> depends on whether inactivation/removal procedures in the production process are effective for the specified virus.]

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of individual donations and plasma pools for HBsAg and antibodies to HIV and HCV.
- testing of plasma pools for HCV genomic material;
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, HBV <, HAV> <and> <parvovirus B19>.

<The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as <HAV or> parvovirus B19.>

<Appropriate vaccination (hepatitis A and B) for patients with congenital deficiency in regular receipt of plasma derived antithrombin concentrates should be considered.>

In the interest of patients, it is recommended that, whenever possible, every time {name of the product} is administered to them, the name and batch number of the product is recorded.

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 Pregnancy and lactation

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

[A short paragraph describing the experience of antithrombin treatment in pregnant or lactating women should be added.]

{(trade) name of product} 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 urticaria, 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.

[product specific for heparin containing products:]

<Heparin induced antibody mediated thrombocytopenia (type II) might occur in rare cases. Thrombocyte count of less than 100 000/ µl or a decrease in thrombocyte count of 50% might be observed.>

For information on viral safety see 4.4.

4.9 Overdose

No symptoms of overdose with antithrombin have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antithrombotic agents: heparin group. ATC Code: B01AB02

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

[Product specific]

[Description of:

- *incremental recovery in antithrombin deficient patients without clinical symptoms of thrombosis*
- *area under the curve (AUC)*
- *half-life (both the initial phase and elimination half life) /half-life under heparin treatment, half life under certain clinical conditions (consumption)*
- *mean residence time (MRT)*
- *clearance]*

5.3 Preclinical safety data

[Product specific]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

[Product specific]

This medicinal product must not be mixed with other medicinal products.

<Only the provided <injection> <infusion> sets should be used because treatment failure can occur as a consequence of human antithrombin adsorption to the internal surfaces of some <injection> <infusion> equipment.>

[If an injection/infusion set is not provided, information should be included on suitable injection /infusion sets].

6.3 Shelf life

[Product specific:

- *shelf life of the medicinal product as packaged for sale*
- *shelf life after dilution or reconstitution according to directions]*

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Instructions for use and handling, and disposal

[Product specific]

[Product specific: {instructions for reconstitution}]

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

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.

7. MARKETING AUTHORISATION HOLDER

[Product specific]

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

10. DATE OF REVISION OF TEXT

[Product specific]