

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atenativ 50 IU/mL, powder and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenativ is presented as a powder and solvent for solution for infusion containing 500 IU, 1000 IU or 1500 IU lyophilised human plasma-derived antithrombin per vial.

The product contains 50 IU/mL human plasma-derived antithrombin when reconstituted with the accompanying solution (water for injections), i.e. 10 mL (500 IU), 20 mL (1000 IU), 30 mL (1500 IU).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Atenativ is supplied in freeze-dried form.

The concentrate is administered intravenously after reconstitution in the accompanying solution.

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 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.

Acquired antithrombin deficiency as in connection with heparin resistance associated with low antithrombin values, e.g. in surgery with the support of heart-lung machine (also see section 4.4 and 5.1)

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.

Physiology

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.

Dosage and duration of the substitution treatment depends on the severity of the disease and the clinical condition. The dosage is individually dependent on the patient's needs based on the doctor's medical assessment and laboratory values.

One antithrombin III unit corresponds to the quantity of antithrombin III present in 1 mL pooled normal human plasma. This concentration is established at 100 %. Administration of 1 IU antithrombin III per kg body weight increases the antithrombin III concentration (activity) by approximately 1 %.

The dose requirement is calculated according to the following formula:

Number of units (dose) = body weight (kg) x (100 – current antithrombin III activity (in %)).

Initially, an antithrombin III level of at least 100% should be achieved, and this should be kept beyond 80 % during the treatment.

The dose should be defined after determination of the patient's antithrombin III activity.

This should be determined at least twice a day until the patient is stabilised, then daily and always immediately before the next infusion. It should be remembered that the plasma half life of antithrombin III can be reduced considerably in certain clinical situations, such as disseminated intravascular coagulation.

Method of administration

Dissolve the preparation as described in section 6.6 and slowly inject or infuse the solution intravenously.

The infusion rate for adults should not exceed 300 IU/min.

The preparation should be administered within 12 hours.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Antithrombin should be administered restrictively in connection with acquired antithrombin deficiency and in consultation with a coagulation specialist (also see section 5.1).

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 allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. The applicable guidelines for shock treatment should be followed.

When medical products prepared from human blood or plasma are administered, infectious diseases due to the 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 medical interview and screening of 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 and HAV.

The viral inactivation/removal procedures may be of limited value against certain non-enveloped viruses such as 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 Atenativ 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 and considered very carefully. If it is decided to use heparin, only standard heparin in low doses should be given.

4.6 Pregnancy and lactation

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

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%.

Antithrombin should be administered restrictively in connection with acquired antithrombin deficiency and in consultation with a coagulation specialist. There are several smaller studies of consumption syndrome (DIC), sepsis, preeclampsia, L-asparaginase treatment of acute lymphoblastic leukaemia, veno-occlusive disease, surgery with heart-lung machine, where antithrombin administration has shown positive effects on coagulation parameters. Convincing effects on morbidity and mortality has not been documented in these occasions. In the so called Kybersept study, which included more than 2300 patients with sepsis, there was no difference in mortality in those treated with antithrombin compared to placebo.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with Atenativ have shown a mean biological half life of about 3 days. The half life may be reduced to approximately 1.5 days in the case of concurrent heparin treatment.

5.3 Preclinical safety data

Atenativ contains trace amounts of the chemicals tributyl phosphate and octoxynol, which are used during manufacturing for viral inactivation. In non-clinical studies, effects of these impurities were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, human albumin, acetyltryptophan and sodium caprylate.
Solvent/Diluent: water for injection.

6.2 Incompatibilities

Atenativ should not be mixed with other medicinal products.

6.3 Shelf life

36 months (infusion vial).
The reconstituted solution should be used within 12 hours.

6.4 Special precautions for storage

To be stored at 2°C to 8°C.
Within its shelf-life the product may be stored at 25°C for up to one month, without being refrigerated again during this period, and must be withdrawn if not used after this.

6.5 Nature and contents of container

Injection vial of type II glass (Ph.Eur.), 50 or 100 mL with a bromobutyl rubber stopper sealed with an aluminium pull-off cap.

6.6 Special precautions for disposal and other handling

The freeze-dried powder is reconstituted in sterile water for injection. After reconstitution Atenativ may be mixed with isotonic sodium chloride solution (9 mg/mL) and/or isotonic glucose solution (55 mg/mL) in glass infusion vials as well as plastic containers. Atenativ should not be used after the expiry date, as indicated on the packaging.

Normally, the solution is clear or slightly opalescent. Do not use solutions that are cloudy or contain sediment.

The reconstitution time is 5 minutes at the most. After reconstitution, the product should be used as soon as possible and within 12 hours.

Discard any unused solution.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

02/2007