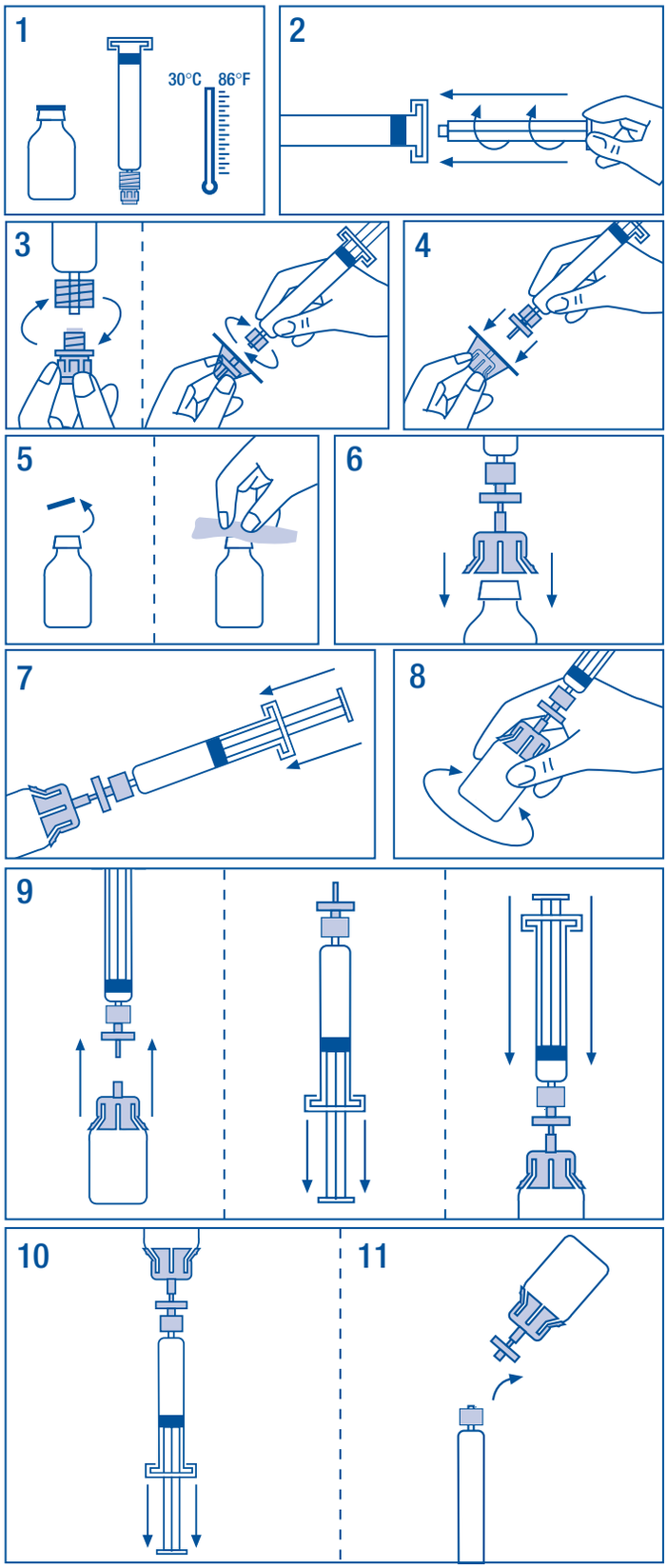

GRIFOLS

Anbinex® 500 I.U., 1000 I.U.

Powder and solvent for solution for infusion

Human antithrombin

QUALITATIVE AND QUANTITATIVE COMPOSITION

Human antithrombin.

Anbinex® is presented as a lyophilised powder containing nominally 500 I.U. or 1000 I.U. human plasma-derived antithrombin per vial.

The product contains approximately 500 I.U./10 ml or 1000 I.U./20 ml human plasma-derived antithrombin when reconstituted with 10 ml or 20 ml of water for injections.

The potency (I.U.) is determined using the European Pharmacopoeial chromogenic assay. The specific activity of Anbinex® is at least 5 I.U./mg protein.

For a full list of excipients, see section "List of excipients".

PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Vial containing a white, hygroscopic, friable solid or powder and a syringe pre-filled with water for injections.

CLINICAL PARTICULARS

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.

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.

The number of units of antithrombin administered is expressed in International Units (I.U.), which are related to the current WHO standard for antithrombin. Antithrombin activity 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 (I.U.) 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 (I.U.) antithrombin per kg body weight raises the plasma antithrombin activity by approximately 1.1% to 1.6%.

The initial dose is determined using the following formula:

Required units = bodyweight (kg) x (100 - basal antithrombin activity [%]) x 0.8

The initial target of 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 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 I.U./kg.

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

Paediatric patients

Anbinex® is not recommended for use in children below 6 due to insufficient data on safety and efficacy.

Method of administration

Dissolve the preparation as described in section "Special precautions for disposal and handling". The product should be administered via the intravenous route.

Administration rate should not exceed 0.08 ml/kg/min.

Contraindications

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

Special warnings and special 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.

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 the 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 HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

It is strongly recommended that every time that Anbinex® 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.

Appropriate vaccination (hepatitis A and B) should be considered for patients receiving regularly human plasma-derived antithrombin products.

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 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.

Interaction with other medicaments and other forms of interactions

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.

Pregnancy and lactation

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

Anbinex® 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.

Effects on ability to drive and use machines

Anbinex® has no or negligible influence on the ability to drive and use machines.

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 safety with respect to transmissible agents, see section "Special warnings and special precautions for use".

Overdose

No case of overdose has been reported.

PHARMACOLOGICAL PROPERTIES

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%.

Pharmacokinetic properties

Pharmacokinetic studies on antithrombin show a mean biological half-life of approximately 3 days. Half-life may be decreased to approximately 1.5 days by concurrent heparin treatment. The half-life may be decreased to hours in conditions with heavy consumption.

The results obtained in the Clinical trial with Anbinex® in patients with congenital antithrombin deficiency estimated by an independent analysis model were:

- Incremental recovery 1.3 ± 0.2 with a range between 1.1 to 1.6% based on functional analysis.
- Area under curve (AUC) = 66,461 ± 15,445 I.U. h/l.
- Terminal half-life = 98.1 ± 45.0 h based on functional analysis.
- Mean residence time (MRT) = 121.7 ± 52.1 h.
- Clearance = 0.931 ± 0.214 ml/h/kg.

Preclinical safety data

Antithrombin 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 or of a dose-effect relationship.

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

No signs of acute toxicity have been described in animal models.

PHARMACEUTICAL PARTICULARS

List of excipients

D-Mannitol

Sodium chloride

Sodium citrate

Water for injections (solvent)

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Shelf life of the product not reconstituted is 3 years.

Chemical and physical in-use stability has been demonstrated for 12 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Do not store above 30 ºC.

Do not freeze.

For storage conditions of the reconstituted product see section "Shelf life".

Nature and contents of container

Anbinex® 500 I.U. powder and solvent for solution for infusion.

Anbinex® 1000 I.U. powder and solvent for solution for infusion.

Anbinex® is supplied in a type II glass vial containing 500 I.U. or 1000 I.U. of human antithrombin (powder for infusion) closed with a bromobutyl-rubber stopper, and a type I glass pre-filled syringe with a plunger stopper (bromobutyl-rubber) containing 10 ml (500 I.U.) or 20 ml (1000 I.U.) of water for injections (solvent).

Accessories supplied with Anbinex® for reconstitution of the product are: vial adaptor and filter.

Each pack size contains: 1 vial of lyophilisate, 1 pre-filled syringe with water for injections and accessories for reconstitution.

Not all pack sizes may be marketed.

Special precautions for disposal and handling

To prepare the solution:

1. Warm the vial and syringe but not above 30 ºC.
2. Attach plunger to syringe containing diluent.
3. Remove filter from packaging. Remove cap from syringe tip and attach syringe to filter.
4. Remove vial adaptor from packaging and attach to syringe and filter.
5. Remove cap from vial and wipe stopper with an antiseptic wipe.
6. Pierce vial stopper with adaptor needle.
7. Transfer all diluent from syringe to vial.
8. Gently shake vial until all product is dissolved.
9. Separate the syringe/filter from vial/adaptor. Pull back the plunger to draw a volume of air similar to the total volume of the solution. Rejoin the syringe/filter to vial/adaptor.
10. Invert vial and aspirate solution into syringe.
11. Separate syringe and administer the solution slowly intravenously. The flow rate should not surpass 0.08 ml/kg/min.

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.

Left-over product must never be kept for later use.

Do not re-use administration sets.

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

NAME AND ADDRESS OF MANUFACTURER

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