ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ATryn 1750 IU powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally 1750 IU* antithrombin alfa**.

After reconstitution, 1 ml of solution contains 175 IU antithrombin alfa.

The specific activity of ATryn is approximately 7 IU/mg protein.

* potency (IU) determined using European Pharmacopoeial chromogenic assay.

** recombinant human antithrombin produced in the milk of transgenic goats by recombinant DNA technology (rDNA).

Excipient with known effect
This medicine contains 38 mg (1.65 mmol) sodium per 10 ml vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion
The powder is white to off-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ATryn is indicated for the prophylaxis of venous thromboembolism in surgery of adult patients with congenital antithrombin deficiency. It is normally given in association with heparin or low molecular weight heparin.

4.2 Posology and method of administration

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

Posology

Due to differences in pharmacokinetics of antithrombin alfa and plasma-derived antithrombin, treatment should follow the specific dose recommendations described below. In the treatment of congenital antithrombin deficiency, the dose and duration of treatment 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 alfa administered is expressed in International Units (IU), which is related to the current WHO standard for antithrombin concentrate. Antithrombin (AT) activity in plasma is expressed either as a percentage (relative to 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 alfa is based on pre-treatment plasma antithrombin activity and body weight.

The therapeutic goal of treatment with antithrombin alfa is to increase to, and maintain antithrombin activity between 80 – 120% of normal (0.8 – 1.2 IU/ml) for the duration of treatment.

Initial treatment starts with a loading dose targeting an antithrombin activity level of 100%. This initial loading dose is based on body weight and on the pretreatment antithrombin activity level.

The required loading dose is determined using the following formula:

Loading dose (IU) = [(100 – patient's pre-treatment AT activity level in %) /2.28] x Body Weight in kg

The usual loading dose in surgical patients (baseline AT activity 50%, bodyweight 75 kg) with congenital antithrombin deficiency in clinical risk situations is 20-25 IU/kg bodyweight. The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion.

The required maintenance dose for surgical patients is given as a continuous infusion and is determined using the following formula:

Maintenance dose (IU/hour) = [(100 – patient's pre-treatment AT activity level in %) /10.22] x Body Weight in kg

The usual maintenance dose in surgical patients with congenital antithrombin deficiency in clinical risk situations is 4-5 IU/kg/h. During consumptive states (e.g. major surgery, concomitant use of heparin) the actual dose may be higher. See therapeutic monitoring and dose adjustment recommendations below. Treatment should be continued until the risk for venous thromboembolisms is reduced and/or when effective follow-on anticoagulation has been established.

Therapeutic Monitoring and Dose Adjustment

The dose should be adjusted on the basis of laboratory measurements of antithrombin activity. Response may vary in individual patients, achieving different levels of in vivo recovery and different half-lives. Frequent antithrombin activity assessments and dosing adjustments may be necessary when starting treatment and just after surgery.

After the start of the maintenance dose infusion, blood for AT activity levels should be drawn at 45 minutes after the start of the loading dose infusion. In case the AT activity level is between 80% and 120% (0.8 – 1.2 IU/ml), no dose adjustment is needed. In case the AT activity level is less than 80%, increase the maintenance infusion rate by 50%. In case the AT activity level is greater than 120% decrease the infusion rate by 30%. Check AT activity level 30 minutes after any change in infusion rate, or four hours after a value within the target range. Subsequently, antithrombin activity should be checked 1-2 times a day and dose adjustments made accordingly. The antithrombin activity level should be maintained above 80% for the duration of the treatment, unless clinical particulars would indicate a different effective level.

It is possible that the surgical procedure will influence AT activity levels. Therefore, an additional check of the AT activity level should be done after the surgery. In case the activity level is below 80% a 15 minutes bolus infusion of AT can be given to quickly restore the AT activity level. The dose can be calculated utilizing the post-surgical AT activity in the loading dose formula above.

Paediatric population

The safety and efficacy of ATryn in children and adolescents (<18 years) have not been established. No data are available. Paediatric antithrombin levels may be different from adult levels, particularly in neonates.

Method of administration
For intravenous use.
The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to goat proteins or goat milk components.

4.4 Special warnings and precautions for use

Hypersensitivity reactions
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, generalized 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.

Patients treated with this medicine should be monitored for possible clinical immunological reactions. Antibody status should be monitored and reported.

The experience from repeated treatment with this medicine is very limited. Close surveillance with regard to immunological reactions is especially important in such situations.

Pregnancy
Due to differences in pharmacokinetic characteristics of ATryn in pregnant versus non-pregnant patients, recommendations for dosing in pregnancy or in the peripartum period cannot be given.

Use of concomitant anticoagulation
Clinical and biological surveillance when antithrombin is used together with heparin, low molecular weight heparin or other anticoagulants which potentiate the anticoagulant activity of antithrombin:

- In order to properly adjust the dose of the anticoagulant and to avoid excessive hypocoagulability, controls of the extent of anticoagulation (APTT, and where appropriate anti-Factor Xa activity) should be performed regularly, at close intervals and in particular in the first minutes/hours following the start of antithrombin use.
- Antithrombin levels should be measured daily, in order to adjust the individual dose. The risk of diminution of antithrombin levels by prolonged treatment with a non-fractionated heparin should be taken into account.

Sodium content
This medicinal product contains 1.65 mmol (or 37.9 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Antithrombin replacement during administration of anticoagulants that potentiate the anticoagulant activity of antithrombin (e.g., heparin, low molecular weight heparin), may increase the risk of bleeding. The half-life of recombinant antithrombin may be altered with concomitant treatment with these anticoagulants due to an altered antithrombin turnover. Thus, concurrent administration of antithrombin with heparin, low molecular weight heparin, or other anticoagulants that potentiate the anticoagulant activity of antithrombin to a patient with increased risk of bleeding must be monitored clinically and biologically.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited clinical data are available on the use of antithrombin alfa in pregnant women. Available data do not suggest harmful effects to the mother or infant. Animal studies performed in rats did not indicate harmful effects on parturition, embryonal/foetal and post-natal development. However due to the difference in pharmacokinetic characteristics of this medicine in pregnant versus non-pregnant patients no recommendation for dosing in pregnancy can be given at this time (see section 4.4). Antithrombin alfa should therefore not be used in pregnant women.

Breast-feeding
It is unknown whether antithrombin alfa or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ATryn therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No information is available on the possible effects of antithrombin alfa on male and female fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions observed in clinical trials are dizziness, headache, haemorrhage, nausea, venipuncture site haemorrhage, post procedural haemorrhage and wound secretion. The most serious reported adverse reactions observed in clinical trials are haemorrhage and post procedural haemorrhage.

Tabulated list of adverse reactions

In clinical trials involving congenital antithrombin deficient patients (n=35) one mild undesirable effect of "application site pruritis" was reported as related to treatment with ATryn.

In other clinical trials with acquired antithrombin deficient cardiac surgery patients (n=118) and healthy volunteers (n=102), undesirable effects reported to be related to treatment with ATryn that were observed more than once are listed by System Organ Class in the table below.

Adverse reactions are presented below by system organ class and absolute frequency. Frequencies are defined as: common (≥ 1/100 to < 1/10) and uncommon (≥1/1,000 to <1/100).

MedDRA SOC	**Frequency category**	**Adverse reactions**
Nervous system disorders	Common	Dizziness headache
Vascular disorders	Common	Haemorrhage

Gastrointestinal disorders	Common	Nausea
General disorders and administration site conditions	Common	Venipuncture site haemorrhage
	Uncommon	Feeling hot Infusion site erythema Infusion site pain Infusion site rash Venipuncture site bruise
Injury and poisoning and procedural complications	Common	Post procedural haemorrhage Wound secretion

No antibodies to antithrombin alfa have been detected up to 90 days following treatment with ATryn.

Reporting of suspected adverse reactions
Reporting 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 via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antithrombotic agents: heparin group; ATC code: B01AB02.
Mechanism of action

Antithrombin, a 58 kD, 432 amino-acid glycoprotein, belongs to the serpin (serine 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.

Normal antithrombin activity in adults is 80 - 120% (0.8-1.2 IU/ml) and levels in neonates are about 40 - 60% (0.4-0.6 IU/ml).

Clinical efficacy and safety
In a formal clinical trial employing serial Duplex ultrasound examinations, antithrombin alfa was shown to be effective in the prevention of thromboembolic events in fourteen congenital antithrombin deficient patients in clinical high risk situations. Some additional data have been obtained from a number of patients in a compassionate use programme.

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease, it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

After intravenous administration of ATryn (intravenous bolus dose of 50 IU/kg or 100 IU/kg body weight) to congenital antithrombin deficient patients without clinical symptoms of thrombosis, and not using heparin, the incremental recovery was 2.07 ± 1.54 %/IU/kg body weight (mean ± SD). Population pharmacokinetic parameters for ATryn derived from the same study revealed (mean ± SD):

- Area under the curve: 587.88 ± 1.63 (% x h)
- Distribution half-life: 1.74 ± 1.28 h, elimination half-life: 10.16 ± 1.28 h.
- Mean residence time (MRT): 8.57 ± 1.24 h
- Clearance: 0.665 ± 0.0493 l/h (Mean ± SE)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium citrate
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials: 4 years.

After reconstitution, from a microbiological pointy of view, this medicinal product should be used immediately. However, chemical and physical stability has been demonstrated for 3 hours after reconstitution and 8 hours after dilution at a temperature not above 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in glass vial (type I) with a stopper (siliconized bromobutyl rubber) and capped with a seal (aluminium) and flip-off cap (plastic).

Pack sizes of 1, 10 or 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicine is intended for single use only.

Reconstitution/dilution
Vials should be brought at temperature not above 25°C prior to reconstitution. The powder should be reconstituted with 10 ml of water for injections (WFI) injected along the side wall of the vial and gently swirled (not shaken) to prevent foaming.

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

The reconstituted solution should be used immediately and no longer than 3 hours after reconstitution.

Normal sodium chloride solution 9 mg/ml (0.9%) may be added to dilute to a concentration convenient for administration.

Administration
Upon complete dissolution, the reconstituted product may be drawn up into a sterile disposable syringe. The reconstituted product should be administered by intravenous infusion using a sterile disposable syringe or an infusion bag with a 0.22 micron pore size in-line filter. The contents of the syringes should be administered immediately and no longer than 3 hours after reconstitution. If diluted, the solution prepared in infusion bags should be administered immediately and no longer than 8 hours after dilution. Compatibility with PVC infusion lines with in-line filters has been established.

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

7. MARKETING AUTHORISATION HOLDER

Laboratoire Français du Fractionnement et des Biotechnologies
3 Avenue des Tropiques
ZA de Courtaboeuf
91940 Les Ulis
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/355/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 July 2006
Date of latest renewal: 15 July 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Therapure Biopharma Inc.
2585 Meadowpine Blvd.
Mississauga, Ontario, Canada L5N 8H9

Name and address of the manufacturer(s) responsible for batch release

LFB-BIOTECHNOLOGIES
3 Avenue des Tropiques
ZA de Courtaboeuf
91940 Les Ulis
France

MedImmune Pharma BV
Lagelandseweg 78
6545 CG Nijmegen, The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Atryn in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material for healthcare professionals is aimed at increasing the awareness about the potential efficacy issues resulting from off-label use of Atryn.

The MAH shall ensure that in each Member State where Atryn is marketed, all healthcare professionals who are expected to prescribe and use Atryn have access to/are provided with the following educational package:

- Physician educational material (guide)
- The Summary of Product Characteristics

The Physician educational material shall contain the following key elements:

- Information about the currently registered indications and population, including that the product is not indicated in the paediatric population.
- Information regarding the resulting efficacy issues associated with off-label use of ATryn, especially in the paediatric population.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Protocol GTC AT HD 012-04: A Multicenter, Multinational Study to Assess the Safety and Efficacy of Antithrombin alfa in Hereditary Antithrombin (AT) Deficient Patients in High-Risk Situations for Thrombosis. The results of completed study GTC AT HD 012-04 and in particular the results of investigations in pregnant women treated during the peri-partum period have been submitted. A marketing authorization variation will be submitted to seek to expand the indication and dosing of pregnant women.	31/03/2020
Post-marketing surveillance a) Prior to launch in any EU Member State, the MAH will set up a post-marketing surveillance programme to collect the following information about congenital AT deficient patients treated with ATryn • Demographics • Indication • Posology • Length of treatment • Prior treatment with ATryn • Use of anti-coagulants • Adverse drug reactions including lack of efficacy • Development of antibodies Physicians should be encouraged to enrol patients in the surveillance programme and results of the surveillance should be provided in the update to the EU-RMP or at the time of the annual reassessment, whichever comes first. b) Prior to launch in any EU Member State, the MAH will set up an immunosurveillance programme and provide antibody testing for anti-ATryn antibodies to physicians. This antibody testing should be provided upon request of a physician and when the MAH receives a report suggestive of a possible immune	31/03/2018

Description	Due date
reaction or lack of efficacy. c) The MAH will ensure that material provided to physicians provides information on the post-marketing surveillance programme and the immunosurveillance programme. This post-marketing surveillance will run up until such time as 40 patients are enrolled.	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1, 10 OR 25 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

ATryn 1750 IU powder for solution for infusion
antithrombin alfa (rDNA)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains nominally 1750 IU antithrombin alfa*. After reconstitution, 1 ml of solution contains 175 IU antithrombin alfa.

* recombinant human antithrombin.

3. LIST OF EXCIPIENTS

Excipients:
Glycine
Sodium chloride
Sodium citrate

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion (1750 IU)
1 vial
10 vials
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only.
Any unused medicinal product should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoire Français du Fractionnement et des Biotechnologies
3 Avenue des Tropiques
ZA de Courtaboeuf
91940 Les Ulis
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/355/001
EU/1/06/355/002
EU/1/06/355/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ATryn 1750 IU powder for solution for infusion
antithrombin alfa (rDNA)
For intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1750 IU of antithrombin alfa

6. OTHER

Store in a refrigerator.

Laboratoire Français du Fractionnement et des Biotechnologies, Les Ulis, France

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ATryn 1750 IU powder for solution for infusion
antithrombin alfa (rDNA)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ATryn is and what it is used for

ATryn contains antithrombin alfa which is similar to the naturally occurring human antithrombin. In the body, antithrombin blocks thrombin, a substance that plays a central role in the process of blood clotting.

If you have an inborn deficiency of antithrombin, your blood level of antithrombin is lower than normal. This may result in a higher tendency to form clots in your blood vessels. This may be in the vessels of your legs (deep vein thrombosis) or in other vessels of your body (thromboembolism). Around major surgical procedures this tendency to clot is even more increased. Therefore, it is important that your antithrombin blood level be maintained at sufficient levels in these situations.

This medicine is used in patients who have 'congenital antithrombin deficiency' (inherited low levels of the protein antithrombin). It is used when the patients are having surgery, to prevent problems due to the formation of blood clots in the vessels. It is normally given in association with heparin or low molecular weight heparin (another medicine that helps to prevent blood clots).

2. What you need to know before you use ATryn

Do not use ATryn:
- if you are allergic to antithrombin alfa or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to goat products as antithrombin alfa is produced in the milk of transgenic goats by recombinant DNA technology (rDNA).

Warnings and precautions
If you experience hives, itchy welts or wheals all over the skin, tightness of the chest, wheezing (difficulty breathing), you should immediately contact your physician since these might be symptoms of a severe

allergic reaction. To test whether you developed an allergic reaction, blood may be collected and tested before and some time after you have been treated with ATryn.

Children and adolescents

No information on the use of ATryn in patients less than 18 years is available. This medicine should therefore not be used if you are less than18 years.

Other medicines and ATryn
Tell your doctor if you are taking, have recently taken or might take any other medicines.
When ATryn is used together with heparin (an anti-clotting medicine), or some other anti-clotting medicines, this may increase the risk of bleeding. Therefore your doctor will carefully monitor the use of this medicine when administered together with these anti-clotting medicines.

Pregnancy and breast-feeding
ATryn is not indicated for use in pregnant women. It is unknown whether it is present in breast milk. Therefore it is not recommended to breastfeed whilst being treated with this medicine.

ATryn contains sodium
This medicinal product contains 1.65 mmol (or 37.9 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. How to use ATryn

Your treatment will be initiated under the supervision of a physician experienced in the care of patients with an inborn deficiency of antithrombin.
Your health care provider will prepare a solution of antithrombin alfa to be administered to you through your vein. To protect you from developing blood clots the medicine will continue to be administered to you until your doctor determines it safe to stop treatment.

If you use more ATryn than you should

The doctor will treat you, as appropriate, if you have any particular side effects.

If you stop using ATryn

Please discuss possibility of stopping the treatment with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you experience hives, itchy welts or wheals all over the skin, tightness of the chest, wheezing (difficulty breathing), you should immediately contact your physician since these might be symptoms of a severe allergic reaction.

In studies with ATryn the following side effects were reported:
Common side effects (may affect up to 1 in 10 people) are:

- itching at the site of infusion
- dizziness
- headache
- bleeding (at site of infusion or after surgery)
- nausea

Uncommon side effects (may affect up to 1 in 100 people) are:

- feeling hot
- infusion site reactions such as pain, bruising and redness

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ATryn

Keep out of the sight and reach of children.

Unopened vials:
Store in a refrigerator (2°C – 8°C).
Do not use this medicine after the expiry date stated which is stated on the carton and vial label after EXP. The expiry date refers to the last date of that month.

Reconstituted/diluted solutions:
After reconstitution, from a microbiological pointy of view, this medicinal product should be used immediately. However, chemical and physical stability has been demonstrated for 3 hours after reconstitution and 8 hours after dilution at a temperature not above 25°C.

6. Contents of the pack and other information

What ATryn contains

The active substance is antithrombin alfa*: 1750 IU. After reconstitution, 1 ml of solution contains 175 IU antithrombin alfa.

The specific activity of ATryn is approximately 7 IU/mg protein.

* recombinant human antithrombin produced in the milk of transgenic goats by recombinant DNA technology (rDNA).

The other ingredients are: glycine, sodium chloride, sodium citrate

What ATryn looks like and contents of the pack

ATryn is supplied as a powder for solution for infusion (1750 IU powder in vial).

The powder is white to off-white.

Pack sizes of 1, 10 or 25 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Laboratoire Français du Fractionnement et des Biotechnologies, 3 Avenue des Tropiques, ZA de Courtaboeuf, 91940 Les Ulis, France

Manufacturer
LFB-BIOTECHNOLOGIES, 3 Avenue des Tropiques, ZA de Courtaboeuf, 91940 Les Ulis, France

MedImmune Pharma BV Lagelandseweg 78 6545 CG Nijmegen, The Netherlands.

This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

This medicine is intended for single use only.

Reconstitution/dilution
Vials should be brought at temperature not above 25°C prior to reconstitution. The powder should be reconstituted with 10 ml of water for injections (WFI) injected along the side wall of the vial and gently swirled (not shaken) to prevent foaming.

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

The vials should be used immediately and no longer than 3 hours after reconstitution.

Normal sodium chloride solution 9 mg/ml (0.9%) may be added to dilute to a concentration convenient for administration.

Administration
Upon complete dissolution, the reconstituted product may be drawn up into a sterile disposable syringe. The reconstituted product should be administered by intravenous infusion using a sterile disposable syringe or an infusion bag with a 0.22 micron pore size in-line filter. The contents of the syringes should be administered immediately and no longer than 3 hours after reconstitution. If diluted, the solution prepared in infusion bags should be administered immediately and no longer than 8 hours after dilution. Compatibility with PVC infusion lines with in-line filters has been established.

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

The therapeutic goal of treatment with antithrombin alfa is to increase to, and maintain antithrombin activity between 80 - 120% (0.8 – 1.2 IU/ml) for the duration of treatment.

Initial treatment starts with a loading dose targeting an antithrombin activity level of 100%. This initial loading dose is based on body weight and on the pretreatment antithrombin activity level.

The required loading dose is determined using the following formula:

Loading dose (IU) = [(100 – patient's pre-treatment AT activity level in %) /2.28] x Body Weight in kg

The usual loading dose in surgical patients (baseline AT activity 50%, bodyweight 75 kg) with congenital antithrombin deficiency in clinical risk situations is 20-25 IU/kg bodyweight. The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion.

The required maintenance dose for surgical patients is given as a continuous infusion and is determined using the following formula:

Maintenance dose (IU/hour) = [(100 – patient's pre-treatment AT activity level in %) /10.22] x Body Weight in kg

The usual maintenance dose in surgical patients with congenital antithrombin deficiency in clinical risk situations is 4-5 IU/kg/h. During consumptive states (e.g. major surgery, concomitant use of heparin) the actual dose may be higher. See therapeutic monitoring and dose adjustment recommendations below. Treatment should be continued until the risk for venous thromboembolisms is reduced and/or when effective follow-on anticoagulation has been established.

Therapeutic Monitoring and Dose Adjustment

The dose should be adjusted on the basis of laboratory measurements of antithrombin activity. Response may vary in individual patients, achieving different levels of in vivo recovery and different half-lives. Frequent antithrombin activity assessments and dosing adjustments may be necessary when starting treatment and just after surgery.

After the start of the maintenance dose infusion, blood for AT activity levels should be drawn at 45 minutes after the start of the loading dose infusion. In case the AT activity level is between 80% and 120% (0.8 - 1.2 IU/ml), no dose adjustment is needed. In case the AT activity level is less than 80%, increase the maintenance infusion rate by 50%. In case the AT activity level is greater than 120% decrease the infusion rate by 30%. Check AT activity level 30 minutes after any change in infusion rate, or four hours after a value within the target range. Subsequently, antithrombin activity should be checked 1-2 times a day and dose adjustments made accordingly. The antithrombin activity level should be maintained above 80% for the duration of the treatment, unless clinical particulars would indicate a different effective level.

It is possible that the surgical procedure will influence AT activity levels. Therefore, an additional check of the AT activity level should be done after the surgery. In case the activity level is below 80% a 15 minutes bolus infusion of AT can be given to quickly restore the AT activity level. The dose can be calculated utilizing the post-surgical AT activity in the loading dose formula above.

<u>*Paediatric population*</u>
The safety and efficacy of ATryn in children and adolescents (<18 years) have not been established. No data are available. Paediatric antithrombin levels may be different from adult levels, particularly in neonates.

<u>*Method of administration*</u>
For intravenous use.
The loading dose should be given as a 15 minute infusion immediately followed by initiation of the maintenance infusion.