For patients with hereditary antithrombin deficiency who are at increased risk for VTE

A chain is only as strong as its weakest link

ATryn is designed to help prevent VTE through precise dosing

- In clinical studies, ATryn normalized and maintained antithrombin (AT) activity levels to help prevent venous thromboembolism (VTE)[1,2]
  - The most common adverse events associated with ATryn are hemorrhage and infusion site reaction[2]
- 85% of patient samples* demonstrated normalized AT activity levels (80%-120%)[1]
  - To help maintain AT activity levels, ATryn was administered as a continuous infusion for at least 3 days, starting 1 day prior to surgery or delivery[2]
- ATryn is not derived from human blood and is not formulated with human plasma proteins[2]

Make a recombinant connection with ATryn, the therapeutic alternative to plasma-derived AT

*27 samples obtained on last day of dosing from 23 patients with hereditary AT deficiency treated in the peri-operative and peri-partum periods.[1]

Indications and Usage

ATryn is a recombinant antithrombin indicated for the *prevention* of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients.

It is not indicated for *treatment* of thromboembolic events in hereditary antithrombin deficient patients.

Important Safety Information

ATryn is contraindicated in patients with known hypersensitivity to goat and goat milk proteins. Allergic-type hypersensitivity reactions, including anaphylaxis, 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 during administration, treatment must be discontinued immediately and emergency treatment should be administered.

The anticoagulant effect of drugs that use antithrombin to exert their anticoagulation may be altered when ATryn is added or withdrawn. To avoid excessive or insufficient anticoagulation, coagulation tests suitable for the anticoagulant used (e.g., aPTT and anti-Factor Xa activity) are to be performed regularly, at close intervals, and in particular in the first hours following the start or withdrawal of ATryn. Additionally, patients should be monitored for the occurrence of bleeding or thrombosis in such situations.

The serious adverse reaction that has been reported in clinical studies is hemorrhage (intra-abdominal, hemarthrosis, and post procedural). The most common adverse events reported in clinical trials at a frequency of ≥5% are hemorrhage and infusion site reaction.

For more information, please see Brief Summary of Prescribing Information on next page and full Prescribing Information available at www.lundbeckinc.com.

References: 1. Data on file, GTC Biotherapeutics. **2.** ATryn [package insert]. Framingham, MA: GTC Biotherapeutics; 2009.

Lundbeck

ATRYN® Antithrombin (Recombinant) FOR INJECTION

Antithrombin (Recombinant), ATryn®
Lyophilized powder for reconstitution

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ATryn® is a recombinant antithrombin indicated for the *prevention* of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients.

It is not indicated for *treatment* of thromboembolic events in hereditary antithrombin deficient patients.

CONTRAINDICATIONS

ATryn is contraindicated in patients with known hypersensitivity to goat and goat milk proteins.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

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 during administration, treatment must be discontinued immediately and emergency treatment should be administered.

Coagulation Monitoring Tests

The anticoagulant effect of drugs that use antithrombin to exert their anticoagulation may be altered when ATryn is added or withdrawn. To avoid excessive or insufficient anticoagulation, coagulation tests suitable for the anticoagulant used (e.g., aPTT and anti-Factor Xa activity) are to be performed regularly, at close intervals, and in particular in the first hours following the start or withdrawal of ATryn. Additionally, monitor the patients for the occurrence of bleeding or thrombosis in such situation.

ADVERSE REACTIONS

The serious adverse reaction that has been reported in clinical studies is hemorrhage (intra-abdominal, hemarthrosis and post procedural). The most common adverse events reported in clinical trials at a frequency of ≥ 5% are hemorrhage and infusion site reaction.

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions that occurred in clinical trials with hereditary AT deficient patients are shown in Table 1 by System Organ Class.

Table 1: Adverse Reactions in Hereditary AT Deficient Patients (one event per patient, 2% of total population, n=47)

Gastrointestinal Disorders: Intra-abdominal Hemorrhage
General Disorders and Administration Site Disorders: Application Site Pruritus, Feeling Hot, Non-cardiac Chest Pain
Investigations: Hepatic Enzyme Abnormal
Musculoskeletal and Connective Tissue Disorders: Hemarthrosis
Renal and Urinary Disorders: Hematuria
Vascular Disorders: Hematoma

Immunogenicity

For ATryn, a potential safety issue is the development of an immunological reaction to the recombinant protein or any of the potential contaminating proteins. Assays were developed and used to detect antibodies directed against antithrombin (Recombinant), goat AT, or goat-milk proteins. No confirmed specific immunological reaction was seen in any of the patients tested, nor were there any clinical adverse events that might indicate such a response.

A post-marketing patient registry has been established to collect additional data on the immunogenic potential of ATryn in patients treated with ATryn on more than one occasion. Physicians are encouraged to participate in the registry by collecting pre- and post-treatment serum samples from patients according to instructions provided by Lundbeck Inc. and submitting them to Lundbeck Inc. for analysis for the development of antibodies to antithrombin (Recombinant). Serum samples should be collected within one week before initiation of treatment and on days 1, 7 and 28 days from initiation of treatment. Physicians wanting to participate in this program are encouraged to contact Lundbeck Inc. at 1-800-455-1141. Lundbeck Inc. will provide detailed instructions for the collection, processing and shipping of samples, as well as all tubes and labels that are necessary for the collection and processing of samples.

DRUG INTERACTIONS

The anticoagulant effect of heparin and low molecular weight heparin (LMWH) is enhanced by antithrombin. The half-life of antithrombin may be altered by 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 use antithrombin to exert their anticoagulant effect must be monitored clinically and biologically. To avoid excessive anticoagulation, regular coagulation tests (aPTT, and where appropriate, anti-Factor Xa activity) are to be performed at close intervals, with adjustment in dosage of the anticoagulant as necessary.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C: In rats, a dose of 210 mg/kg/day ATryn (5-6 times the human dose for pregnant women) administered during most of the pregnancy and entire lactation showed a slight but statistically significant increase in pup mortality in day one through day four when compared to concurrent control (90% compared to 94% viability index for 210 mg/kg/day versus control). This slight statistical difference does not reflect a true treatment-related effect. This same dose was shown to be safe in a second rat study when administered around parturition and during lactation where the no adverse effect level for dam and pups was 210 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Studies in pregnant women have not shown that ATryn increases the risk of fetal abnormalities if administered during the third trimester of pregnancy. In clinical trials in hereditary AT deficient patients, 22 pregnant women have been treated with ATryn around parturition.

No adverse reactions were reported in 22 neonates born from pregnant women treated with ATryn during clinical trials.

Labor and Delivery

ATryn is indicated for the treatment of pregnant women during the peri-partum period. Pregnant patients who need a surgical procedure other than Cesarean section are to be treated according to the dosing formulae for pregnant patients.

Nursing Mothers

ATryn will be present in breast milk at levels estimated to be 1/50 to 1/100 of its concentration in the blood. This level is the same as that estimated to be present in breast milk of normal lactating women which is not known to be harmful to breastfed neonates. However, caution should be exercised when ATryn is administered to a nursing woman. Use only if clearly needed.

In 2 reproductive toxicology studies performed in rats, antithrombin (Recombinant) was administered to pregnant dams at doses up to 210 mg/kg/day, resulting in supraphysiologic plasma levels of antithrombin. Pups were allowed to breastfeed and were monitored for changes in prothrombin (PT) or aPTT, as well as pup viability, body weight at birth, growth, and development. In these studies, there were no adverse effects in offspring who consumed milk from dams treated with ATryn.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of ATryn did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: No carcinogenicity data for ATryn are available in animals or humans.

Mutagenesis and Genotoxicity: ATryn was not mutagenic when tested in the Ames bacterial test and in *in vitro* cytogenetic assays nor was it shown to be genotoxic when tested in an *in vivo* test to assess chromosomal aberration.

Impairment of Fertility: No studies have been conducted to evaluate the effects of ATryn on fertility in humans.

Animal Toxicology and/or Pharmacology

Pharmacokinetic and toxicokinetic (1 single, 2 repeated dose) studies of antithrombin (Recombinant) were performed in mice, rats, dogs and monkeys. In toxicokinetic studies in monkeys the area under the curve was 3-4 times greater than in the rat at all doses used.

The toxicological profile of antithrombin (Recombinant) administered by the intravenous route as bolus injections and infusions has been evaluated in both single- and repeat-dose studies performed in rats, dogs, and monkeys across a range of doses from 2.1 to 360 mg/kg. The highest doses in the single dose toxicity studies in rats and dogs were 360 mg/kg and 210 mg/kg, respectively. Toxicities observed were limited to transient injection site swelling observed in rats and dogs at the highest doses tested, and increased AST at highest dose in the dog study, both resolved during recovery period.

The highest dose in the 28-day repeated-dose toxicity study in rats was 360 mg/kg/day. The toxicity at this dose was limited to transient limb swelling and local injection site bruising and swelling. The highest dose in the 14-day repeated-dose toxicity study in monkeys was 300 mg/kg/day or approximately 7-8 times human dose. Toxicities observed in female monkeys at this dose included internal bleeding, hematological changes and liver toxicity, with one out of three female animals showing multifocal hepatic necrosis. Both sexes showed increased AST and ALK on day 15, with both parameters returning to normal by day 22. There was no adverse effect in monkeys dosed with 120 mg/kg/day.

HOW SUPPLIED/STORAGE AND HANDLING

Dosage Form

NDC 67386-521-51

Approximately 1750 IU/vial in a sterile white to off-white lyophilized powder for reconstitution. Each carton contains one single dose vial of ATryn.

The actual potency of ATryn is stated on the vial label and carton.

Storage and Handling

Store ATryn refrigerated at between 2-8°C (36-46°F).

Do not use product beyond the expiration date printed on the package. Discard unused portions.

PATIENT COUNSELING INFORMATION

Inform patients that allergic-type hypersensitivity reactions are possible and instruct them to inform their physicians about any past or present known hypersensitivity to goats or goat milk proteins prior to treatment with ATryn. Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis and to notify their health care provider immediately if these events develop.

Inform patients about the risk of bleeding when ATryn is administered with other anticoagulants and instruct them to notify their physicians of any bleeding events while on treatment with ATryn.

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Revised: April 2009