



ATryn® (Antithrombin [Recombinant]) Development Process Facts

ATryn® (Antithrombin [Recombinant]) is approved by the U.S. Food and Drug Administration (FDA) for the prevention of peri-operative and peri-partum thromboembolic events in patients with hereditary antithrombin deficiency. It is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients. Administered by intravenous infusion, ATryn is developed through recombinant technology. ATryn was developed with the objective to provide a safe and reliable supply of recombinant antithrombin. Purified recombinant antithrombin has the same amino acid sequence as antithrombin derived from human plasma. Antithrombin (Recombinant) and plasma-derived antithrombin both contain six cysteine residues forming three disulphide bridges and 3-4 linked carbohydrate moieties. The glycosylation profile of ATryn is different from plasma-derived antithrombin, which results in an increased heparin affinity. When assayed in the presence of excess of heparin the potency of the recombinant product is not difference from that of plasma-derived product. ⁴ GTC Biotherapeutics has developed a strict process to develop and purify ATryn, while maintaining the health and compassionate care of the animals used in its development. GTC has granted Lundbeck Inc. the right to market ATryn in the U.S. ¹ and pursue further clinical development.

The Process

- GTC develops and uses transgenic technology to enable development of protein-based human therapeutics that would be difficult to express or cost prohibitive to manufacture utilizing traditional recombinant DNA technologies, such as E. coli, fungal, baculovirus, and mammalian cell cultures.³
- ATryn was developed using microinjection. Microinjection involves inserting the transgene into a fertilized egg and re-implanting the resulting embryo in a surrogate doe to carry to term. Offspring born using this process are transgenic, normal and healthy.³
- The goat's mammary gland efficiently expresses high levels of different types of proteins during milk production. GTC's select herd of transgenic goats express the desired therapeutic protein in their milk in addition to the many other standard milk proteins. A single goat typically produces three liters of milk per day and will yield up to three kilograms of therapeutic protein per year. ³

Product Purity

- GTC Biotherapeutics has developed a highly efficient proprietary process for the recovery of biologically active proteins from this milk. The proteins can be efficiently purified from the goats' milk to meet the exacting FDA standards.³ In addition, the protein is purified using viral removal filtration.
- This process typically begins with direct filtration of raw milk under specific conditions that remove fat, casein, cells and particulates. This is followed by a capture chromatography step that is specific for the particular protein. Additional chromatography steps are then used to achieve high level purity of the protein.³

Health and Care of the Goats

- Over the last 10 years, GTC has put considerable effort into evaluating the general health and well being of its goats.³
- All of GTC's procedures involving the goats are monitored by mandate of the USDA (United States Department of Agriculture) and periodically by the AAALAC International (Association for Assessment and Accreditation of Laboratory Animal Care International).³
- In addition to these external oversight authorities that perform inspections and/or site visits, GTC includes two non-company affiliated members (one outside expert and one lay member) on its own internal Institutional Animal Care and Use Committee (IACUC). The IACUC reviews all of the company's animal protocols before implementation, performs annual re-assessments of protocols, reviews the animal care and use and veterinary care programs and performs inspections of all animal facilities and animals in residence a minimum of twice annually.³

Indications and Usage:

ATryn [Antithrombin (Recombinant)] is indicated for the prevention of peri-operative and peri-partum 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 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. Adding ATryn to or withdrawing ATryn from anticoagulants that use antithrombin to exert their anticoagulative effects may alter this effect. 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. In such situations, patients should be monitored for the occurrence of bleeding or thrombosis.

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 $\geq 5\%$ are hemorrhage and infusion site reaction.

For more information, please see full Prescribing Information at www.lundbeckinc.com.

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About Lundbeck Inc.

Lundbeck Inc. was established in March 2009 following the acquisition of Ovation Pharmaceuticals, Inc. by H. Lundbeck A/S in Copenhagen, Denmark, and has proven success in developing and commercializing high-need treatments. The company is committed to providing innovative therapies that fulfill unmet medical needs of people with severe, and often rare, disorders for which few, if any, effective treatments are available. Lundbeck Inc. has been recognized for excellence in the global pharmaceutical and biotechnology industries with the 2009 North American Frost & Sullivan Award for Entrepreneurial Company of the Year and with the Scrip 2006 and 2007 “Pharma Company of the Year” award for small to mid-sized enterprises. More information about the company, its products and full prescribing information may be found at www.lundbeckinc.com.

About GTC Biotherapeutics

GTC Biotherapeutics (Nasdaq: GTCB) develops, supplies, and commercializes therapeutic proteins produced through transgenic animal technology. In addition to ATryn, GTC is developing a portfolio of recombinant human plasma proteins with known therapeutic properties. These proteins include recombinant forms of human coagulation factors VIIa, VIII, and IX, which are being developed for the treatment of hemophilia, and alpha-1 antitrypsin. GTC also has a monoclonal antibody portfolio that includes a monoclonal antibody to CD20 and a monoclonal antibody to CD137. GTC’s intellectual property includes a patent in the United States through 2021 for the production of any therapeutic protein in the milk of any transgenic mammal. GTC’s transgenic production platform is particularly well suited to enabling cost effective development of proteins that are difficult to express in traditional recombinant production systems as well as proteins that are required in large volumes. Additional information is available on the GTC web site, <http://www.gtc-bio.com>.

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References:

1. GTC Biotherapeutics, FDA Accepts BLA Filing <http://www.gtc-bio.com/pressreleases/pr100608.html>. Last accessed on 12/17/2008.
2. ATIII.Com – A Resource for Information on Hereditary Antithrombin Deficiency (HD) <http://www.atiii.com/>. Last accessed on 12/17/08.
3. GTC Biotherapeutics. Data on file.
4. ATryn Package Insert. February 2009.