Recombinant human antithrombin

PRESS RELEASE FROM THE MANUFACTURER (EDITED)
Framingham, MA, and Deerfield, IL, 06 Feb, 2009 – GTC Biotherapeutics and Ovation Pharmaceuticals, Inc. announced today that the U.S. Food and Drug Administration (FDA) approved ATryn® (Antithrombin [Recombinant]) 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. Recombinant human antithrombin is the first transgenically produced therapeutic protein, and the first recombinant antithrombin, approved in the United States.

With its approval, the FDA’s Center for Veterinary Medicine also approved GTC’s New Animal Drug Application, the first of its kind to regulate genetically engineered animals. This is now required for a recombinant technology used to develop transgenic animals, such as the goats that produce recombinant antithrombin.

GTC has granted Ovation the right to market recombinant human antithrombin in the United States and pursue further clinical development. The companies expect to sell it in the second quarter of 2009.

Humans with hereditary antithrombin deficiency are at increased risk for venous thromboembolic events, including pulmonary embolism and deep vein thrombosis, which can be life-threatening, particularly in high risk situations. Antithrombin is a natural anticoagulant with a role in controlling the formation of blood clots. Purified recombinant antithrombin has the same amino acid sequence as antithrombin derived from human plasma. This drug was developed to provide a safe and consistent supply of recombinant antithrombin.

Comparability of rhAT and hpAT

STRUCTURE
- Same primary and secondary structure
- Some glycosylation difference

FUNCTION
- Increased heparin binding of rhAT
- Same inhibitory activity for thrombin & Factor Xa

From FDA Advisory Board Meeting on 09 Jan 2009, http://www.fda.gov

Prescribing Information (PI) for Antithrombin III

“THROMBATE III is prepared from pooled units of human plasma from normal donors."

CLINICAL PHARMACOLOGY
Antithrombin III (AT-III), an alpha2-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL, and is the major plasma inhibitor of thrombin.

For Recombinant Antithrombin

“...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. Antithrombin (recombinant)... is a recombinant human antithrombin. It is a 432-amino acid glycoprotein...molecular weight approximately 57,215.”

This drug was developed to provide a safe and consistent supply of recombinant antithrombin.
events in the United States, Europe and Canada. During these studies, the drug prevented the formation of clinically overt thromboembolic events.

The prevalence of hereditary antithrombin deficiency in the general population is approximately 1 in 2,000 to 1 in 5,000.(4,5) Half these patients may experience a thrombosis before 25, and, up to 85% may suffer a thromboembolic event by 50.(6,7)

This is the first time recombinant antithrombin has been approved anywhere, and the first antithrombin product approved through the European Union’s EMEA regulatory approval authority.(8)

The serious adverse reaction 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.

Scientists produce recombinant human antithrombin by inserting DNA for the human antithrombin protein into a single-celled goat embryo. This embryo is implanted into a surrogate doe. The resulting transgenic offspring produce antithrombin in their milk. This protein is collected and purified from the milk, and once certified safe for human use, is given intravenously to patients.

REFERENCES
1. GTC Biotherapeutics, GTC Biotherapeutics and Ovations Pharmaceuticals close agreement to market and develop ATryn® in the United States

Edited abstract


Antithrombin (AT) is the principal inhibitor of thrombin and other serine proteases of the coagulation cascade. AT has previously been prepared from human plasma (hpAT), and a transgenic variant from goat milk (tgAT) is now available.

Two open-label, parallel pharmacokinetic studies in rats (n=18) and rabbits (n=18) compared plasma concentrations of hpAT and tgAT following intravenous administration; the efficacy of the 2 preparations in prolonging survival from bacterial-induced sepsis was compared in 2 open-label, randomised, placebo-controlled studies in rats (n=266). Maximum plasma concentrations were approximately dose-proportional and were similar for both hpAT and tgAT. The elimination of tgAT was faster than hpAT, and the t(1/2) of hpAT was longer than that of tgAT in both rats (0.85-1.92 h versus 0.17-0.73 h) and rabbits (19.38 h versus 1.5-2.2 h). Correspondingly, tgAT showed a lower area under the curve, mean residence time, pharmacokinetic response to dosing and a higher clearance rate. In a meta-analysis of the efficacy studies, the overall hazard ratio for death was 1.36 (tgAT:hpAT; p=0.06; 95% CI 0.99-1.86). HpAT and tgAT have differing pharmacokinetic properties in pre-clinical studies.

3. ATIII.com - A resource for information on hereditary antithrombin deficiency (HD)
8. GTC Biotherapeutics, European Commission approves ATryn

Edited by MJoTA Editors