

Issue Summary
Blood Products Advisory Committee
Gaithersburg, Maryland
November 3, 2005

Topic II: Heterogeneity of Commercial Alpha-1-Proteinase Inhibitor (Human) Products – Implications for Longer-Term Safety and Efficacy?

Issue: FDA seeks to be advised how best to address any new safety and efficacy concerns raised by the discovery, post approval, of modifications to the primary structure of Alpha-1-Proteinase Inhibitor (Human) [A₁PI] products, which were present at the time of the original clinical studies.

Background:

Following licensure, differences among the isoelectric focusing (IEF) patterns for the three alpha-1-proteinase inhibitor (A₁PI) products commercially available in the U.S. (Prolastin, Aralast, and Zemaira) and between these patterns and that of alpha-1-proteinase inhibitor (α_1 -PI) in normal plasma were discovered, thereby suggesting heterogeneity with respect to the type and extent of modifications of the primary structure of the active α_1 -PI moiety in the commercial products. These licensed products also contain varying levels of polymers of α_1 -PI. Some structural modifications are known to occur both naturally *in vivo* as well as *in vitro*, and some may be present in the starting plasma pools used to manufacture the product. In contrast, other modifications may occur only during manufacturing. No major changes to the manufacturing processes have occurred since licensure for any of the three licensed A₁PI products.

U.S.-licensed A₁PI products were approved by the FDA on the basis of surrogate endpoints: serum and calculated epithelial lining fluid (ELF) levels of α_1 -PI and anti-neutrophil elastase inhibitory capacity (functional inhibitory activity). ZLB Behring and Baxter agreed to conduct two-stage post marketing commitment studies to evaluate the longer-term effects of their A₁PI products on several clinically meaningful endpoints, including the frequency and severity of pulmonary exacerbations and lung density by computerized tomography. In addition to the post-marketing studies, the safety of long-term use of these products is being tracked by two monitoring programs (AlphaNet and the Coram study). Active and passive post-marketing surveillance of patients receiving all A₁PI products is ongoing.

Discussion:

Preliminary evidence indicates that all functionally active α_1 -PI molecules in all products retain full *in vitro* activity as determined by a functional activity assay (ability to inhibit a serine protease). Furthermore, the available information indicates that there have not been any changes in the type(s) or extent of structural modifications to any of the A₁PI products since licensure. As of June 2005, available pre- and postmarketing clinical data have not suggested clinically meaningful differences in the safety, tolerability, or

immunogenicity of the commercially available A₁PI products, despite quantitative differences in the percentage of the active α_1 -PI moiety that is modified.

Because the logic of relying on the surrogate endpoints of serum and ELF levels of α_1 -PI rests in part on an assumption that one is measuring the native protein as it exists in normal plasma, the discovery that α_1 -PI in commercial products differs by varying degrees both qualitatively and quantitatively from α_1 -PI present in normal plasma leads us to ask the Committee to evaluate the possible implications of these differences with regard to the safety and efficacy of the licensed A₁PI products.

To provide a larger context in which to consider the clinical significance of similar protein modifications, examples of therapeutic protein products with known modifications to primary structure, including Anti-Hemophilic Factor (Human) and Anti-Hemophilic Factor/von Willebrand Factor (Human), that were licensed based on safety and clinical efficacy data, will be presented.

QUESTIONS FOR THE COMMITTEE:

1. Based on the differences in primary structure of α_1 -PI and the concentrations of polymers in A₁PI products, does the Committee have any comments and/or recommendations regarding:
 - a. The adequacy of the requested/planned post-marketing commitment studies to evaluate the longer-term safety and efficacy of A₁PI products, as measured by specified clinically meaningful endpoints?
 - b. The adequacy of the proposed safety monitoring programs?
 - c. Any other suggested actions (e.g., additional communications through labeling or other venues)?