Public Assessment Report
Scientific discussion

Prolastin
Bayer Vital GmbH

Mutual Recognition Procedure
DE/H/472/01

This module reflects the scientific discussion for the approval of Prolastin. The procedure has been finalised at 2006-03-21. For information on changes after this date please refer to the module 'Update'.

Table of Content

1. INFORMATION OF THE INITIAL PROCEDURE

1. **Type of application**
   Full application according article 8.3 (i) Directive 2001/83/EC

2. **Active substance**
   Alpha-1-Proteinase inhibitor

3. **Form**
   Powder and solvent for solution for infusion

4. **Strength**
   1000 mg

5. **Marketing Authorisation Holder**
   Bayer Vital GmbH
   D51368 Leverkusen
   Germany

6. **Reference Member State**
   Paul-Ehrlich-Institut
   Germany

7. **Concerned Member States**
   Austria, Belgium, Denmark, Greece, Spain, Finland, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Sweden,

8. **Procedure-number**
   DE/H/472/01

9. **Timetable**

submission of application:	2005-12-07
start of procedure:	2005-12-21
termination of procedure:	2006-03-21

2. SCIENTIFIC DISCUSSION

I. INTRODUCTION

Prolastin is a plasma-derived alpha 1-proteinase inhibitor (alpha1-PI). The approved indication is long-term augmentation therapy in patients with alpha$_1$-proteinase inhibitor deficiency (phenotypes PiZZ, PiZ(null), Pi (null,null) and PiSZ) within the limits of moderate airflow obstruction (FEV1 35-60%) and the evaluation of the clinical condition (disability).

The national marketing authorisation for Prolastin was granted on 12.12.1988. In order to meet the requirements of Alpha1-Proteinase Inhibitor-deficient patients, Prolastin has been marketed under exceptional circumstances because no alternative medicinal product existed at that time. In addition, the marketing authorisation has been associated with the condition that the company should report about the clinical development and use of Prolastin at regular intervals.

Within the Mutual Recognition Procedure in 2006 supplementary information has been requested concerning quality and clinical aspects. The applicant provided this information in-line with the default timetable and the Marketing Authorisation application was accomplished on day 90 for all Concerned Member States.

II. QUALITY ASPECTS

II.1 Introduction

Alpha1-PI is the most abundant serine proteinase inhibitor in human plasma. It consists of 394 amino acids and has a molecular weight of 51 kDa. Alpha1-PI exhibits no disulfide bonds, the proper processing and the inhibitor activity are maintained by salt bridges. This inhibitor is highly structured into eight helices and three β-sheets. Approximately 12 % of the molecule consists of carbohydrates linked to aspartate residues. Its target enzyme is leucocyte elastase, which recognises a specific methionine in the reaction centre loop of the inhibitor molecule.

Prolastin is presented as a sterile, lyophilized powder for injection presented in glass vials with rubber stoppers containing 1000 mg of alpha 1-proteinase inhibitor. The powder is reconstituted with 40 ml Water for Injection (WFI) prior to intravenous administration. Product and solvent vials are provided in the final package.

II.2 Drug Substance

Material Source

The active substance of Prolastin is derived from pooled human plasma that complies with the monograph of the European Pharmacopoeia "Human plasma for fractionation". All information regarding the source material is laid down in a certified plasma master file (EMEA/H/PMF/000004/04). Individual donations and plasma pools are tested for viral markers (HBsAg, anti-HIV1/2, and anti-HCV) using qualified test kits and, in addition, plasma mini-pools are tested for HIV-1, HBV and HCV by NAT. A Parvovirus B19 DNA limit of 10^5 genomes per mL has been implemented for all plasma pools. An adequate look-back procedure is established from a single donation to drug product batches and vice-versa.

Purification

The manufacturing process consists of two separate stages, the Cohn-Oncley fractionation of plasma as starting material, followed by two PEG precipitation steps and one chromatography step. Major residual product-related impurities of alpha1-PI sterile final bulk are Ig A, Ig E and albumin which represent ~10-15 % of total protein. After addition of sodium citrate, citric acid and glucose, the active substance is subjected to pasteurization as a viral inactivation step. The sterile final bulk has a potency

of not less than 20 mg/ml. The manufacture of alpha1-PI from plasma to the drug product does not include a prolonged storage of the sterile final bulk in a frozen condition but the final bulk may be stored at 2-5 °C for up to 2 weeks prior to processing.

II.3 Medicinal Product

Composition

Prolastin is available in a single dosage form with 1000 mg alpha1-PI/vial and is administered in a relatively large volume of 40 ml, requiring a well tolerable solvent. After reconstitution with water for injection (WFI), the product nominally contains active $Alpha_1$-PI, 0.1 M sodium chloride and 0.02 M sodium monophosphate. The sodium chloride and sodium monophosphate provide the correct tonicity and pH for intravenous administration.

Container/closure

The primary packaging materials of the product (type I clear glass vials and isoprene rubber blend stoppers) and solvent (type II glass vial with chlorobutyl rubber stopper) are in accordance with European Pharmacopoeia requirements.

Manufacturing process

Prolastin is manufactured using validated manufacturing methods and processes. The solution is sterilized by filtration through a 0.22 µm membrane filter prior to filling into the sterilized vials. Formulation, aseptic filling, freeze-drying and stoppering are performed at Talecris Biotherapeutics, Inc. Clayton, North Carolina, USA. The final product release testing (except pyrogenicity) and secondary packaging are performed by Bayer Biologicals S.r.l., Torri-Sovicille, Italy. The test methods used at the European site are validated and shown to be reproducible. Satisfactory information is provided that the manufacturing process is in compliance to current requirements for this kind of biological medicinal products.

Final product specification

Since no pharmacopoeia monograph exists for alpha 1-PI, appropriate release criteria have been established by the manufacturer. The respective control tests have been adequately described. The potency of alpha1-PI is determined by measuring the inhibitory potential for porcine pancreatic elastase in a chromogenic assay. In lack of an international standard for alpha1-PI, the manufacturer has assigned potency in mg/ml to an in house primary standard derived from a production batch. Finished product testing includes tests for process-related impurities (albumin and globulins), for components added during manufacture (sucrose, PEG, TRIS) and for the excipients sodium chloride and sodium monophosphate. Prolastin contains alpha1-PI at a concentration of not less than 70 % of the total protein. Albumin is not more than 20 %. The sum of alpha2, beta and gamma globulins is not more than 20 %. The concentration of alpha1-PI in the reconstituted drug product is not less than 20 mg/ml (800-1250 mg per vial). Tests on final container samples for residual solvents (acetic acid, ethanol and methanol) have shown that the medicinal product complies with the ICH guideline *Note for guidance on Impurities: Residual solvents* (CPMP/ICH/283/95).

Batch analyses

Analysis data from 3 batches demonstrated compliance with final product specifications.

Final product stability

The primary packaging material of the product for stability testing and for commercial lots is identical. As recommended in the ICH guideline Q5C real time/real temperature stability studies have been performed, which justify the claimed shelf life of 24 month at not more than 25 °C. Once reconstituted, the product is stable for at least 3 hours. The reconstituted product should not be refrigerated again.

Viral safety and safety with respect to TSEs

Prolastin is produced from human Plasma of U.S. origin. No animal materials conferring to a risk for animal TSE have been identified. The risk for (v)CJD is minimised by adequate donor exclusion measures according to current regulations and a substantial removing capacity for TSE-agents at the precipitation steps has been demonstrated. An adequate mini-pool–plasma pool NAT strategy has been implemented for HIV-1, HBV and HCV. Further, a Parvovirus B19 DNA limit of 10^5 genomes per mL has been implemented for all plasma pools.It was convincingly demonstrated that the production process of Prolastin HS contains two effective steps for inactivation/removal of enveloped viruses (i. e. pasteurisation and the 11.5% PEG-Precipitation/depth filtration). Non-enveloped viruses are effectively removed during 11.5 % PEG-Precipitation/depth filtration-step. The Cold-Ethanol precipitation of Fraction II+III is considered to contribute to enveloped and non-enveloped virus safety by moderate virus removal. Robustness of virus inactivation/removal with regard to variation of critical process parameters has been extensively investigated and demonstrated.

III. NON-CLINICAL ASPECTS

In general, the non clinical investigation program for human Plasma Proteins is limited by the immune response triggered in the heterologous animal species utilized for evaluation. The safety profile of Prolastin has been investigated by conducting general pharmacology, pharmacokinetic, acute and sub-chronic toxicity studies. In addition, the non clinical part of the dossier has been supplemented by scientific literature.
Pharmacokinetic results suggest that Alpha1-Proteinase Inhibitor circulates with a plasma residence time within the expected half life and does enter the lung in quantities proportional to plasma levels.
The results of the pharmacological and toxicological studies revealed no evidence of adverse effects in the different animal species exposed to Alpha1-Proteinase Inhibitor.

IV. CLINICAL ASPECTS

Alpha1-Proteinase Inhibitor deficiency is a chronic, hereditary often fatal disorder, in which a low concentration of serum Alpha1-Proteinase Inhibitor is associated with progressive emphysema that most often manifests itself by the fourth decade of life. The deficiency occurs as a result of inheritance of two abnormal Alpha l-Proteinase Inhibitor alleles from the Alpha1-Proteinase Inhibitor locus on chromosome 14. The discovery of this clinical association, together with the demonstration that enzymes with elastase activity experimentally induced emphysema when instilled into the lower respiratory tract of animals, have led to the "protease-antiprotease" concept of emphysema. This concept suggests that the alveolar structures of the lower respiratory tract in healthy individuals are protected from proteolytic attacks by proteases released by inflammatory cells through an antiprotease shield. The pathogenesis of emphysema in Alpha1-Proteinase Inhibitor deficiency is assumed to be a result of a chronic biochemical imbalance between elastase (an enzyme capable of degrading elastin, released by inflammatory cells, primarily neutrophils) and its counteracting inhibitor, Alpha1-Proteinase Inhibitor. Alpha1-Proteinase Inhibitor deficiency is a rare disease and the progression of emphysema is a slow process. Traditionally, emphysema progression is measured by the rate of annual decline in forced expiratory volume (FEV1). However, the quantitation of this decline on an individual basis is hampered by the high intra-individual variability of FEV1 measurements. Clinical studies investigating biochemical pharmacodynamics and pharmacokinetics demonstrated that weekly intravenous doses of 60 mg/kg Prolastin treatment provided protective levels of Alpha1-Proteinase Inhibitor in both plasma and epithelial lung lining fluid.

A retrospective review of the disease process in well documented long-term patient registries, especially in the US and Germany, compared to historical controls (i.e. registered patients without API therapy) gave evidence of significant benefit of Prolastin therapy. This could be shown for the subset of patients within the limits of moderate airflow obstruction (FEV1 35-60%) which led to corresponding changes in the indication section of Prolastin.
Furthermore the MAH is conducting an exploratory study for the detection of feasible endpoints regarding the measurement of stealthy lung destruction over time which may contribute to the conduct of a Phase IV efficacy evaluation of Alpha1-PI augmentation therapy. Depending on the outcome of the EXACTLIE trial a respective phase IV efficacy evaluation study protocol is expected.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Reference Member State considered that the application for Prolastin, in the treatment of progressive, pulmonary emphysema in hereditary Alpha 1-Proteinase Inhibitor deficient patients, could be approved.

According to new legislative requirements a user testing of the package leaflet has been performed.

During the mutual recognition procedure, the applicant has made commitments regarding quality and clinical aspects:

LETTER OF COMMITMENT:

Quality

Commitment 1:

The marketing authorisation holder commits to establish in-process controls for potency and specific activity for the Alpha-1 Proteinase Inhibitor purification process based on a statistical analysis of manufacturing process data and in accordance with ICH guideline Q6B "*Specifications: Test procedures and acceptance criteria for biotechnological/biological products*". Potency and Specific Activity will be monitored at the 11.5% Polyethylene Glycol filtrate, the concentrated column eluate, and the final bulk solution. Additionally, the applicant commits to set action levels for each of these steps to assess the consistency of the purification process and to present the IPCs post-approval as soon as the statistical analysis of the manufacturing process data has been completed.

Commitment 2:

The marketing authorisation holder commits to establish a program that will specify the requirements for periodic re-validation of the manufacturing process.

Commitment 3:

Regarding sterility testing, the applicant commits to implement a two stage incubation procedure. The first stage incubation will consist of 7 days within the 20-27°C range, and the second stage incubation will consist of 7 days within the 30-35°C range.

Following the implementation of the new procedure in 2006, all prospective aseptic filling validations will be performed with the two stage incubation procedure. The applicant commits to provide a revised T.08.04, *Manufacturing In-Process Controls* (section 3.2.P.3.3), post-approval following the implementation of the two stage incubation procedure. The revised document will describe the two stage incubation procedure that will be used to provide ongoing validation of the aseptic filling process.

Commitment 4:

The applicant commits to re-validate post-approval the SEC HPLC method in order to assess the entire molecular weight distribution of the finished product in more detail.

Commitment 5:

Water for injection
Bayer commits to label the storage condition “do not store above 25°C”

Commitment 6:

Sterilized water for parenteral use in 50 mL bottle (IT d90)
The marketing authorisation holder commits to give in depth explanation on the validation of the manufacturing process of the solvent.

Clinical aspects

Commitment 7:

Post marketing surveillance data
Bayer commits to provide PSUR covering the period of January 1, 2004 to December 31, 2004 and January 1, 2005 to December 31, 2005 when available.

Commitment 8:

Pharmacovigilance Programme Greece
Bayer commits to submit to EOF any post marketing surveillance data and PSUR on a regular basis. Greece will be included in a Pharmacovigilance Programme following approval.

Commitment 9:

EXACTLE trial
The EXACTLE trial is a double-blinded, placebo-controlled exploratory study to evaluate the potential utility of CT lung scans as a measure of effectiveness of Alpha1-PI over two years. The results of the EXACTLE trial may contribute to a more robust assessment of the value of lung density measurements with CT scanners as clinical trial endpoints for the conduct of a future efficacy evaluation of Alpha1-PI augmentation therapy. Clean data and biometrical analysis of the results are expected to be available in the first quarter 2007. Bayer commits to provide the final study report as soon as it is available. Depending on the outcome of the EXACTLIE trial a clinical Phase IV efficacy study protocol will be provided.