

**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'.

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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 alpha₁-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 (EMA/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 10⁵ 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 Alpha₁-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 1-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.



Prolastin[®]

1. NAME OF THE MEDICINAL PRODUCT

Prolastin[®]

1000 mg, powder and solvent for solution for infusion

2. QUALITATIVE UND QUANTITATIVE COMPOSITION

1 vial contains:

1000 mg alpha₁-proteinase inhibitor, human.

1 ml of the reconstituted solution contains 25 mg alpha₁-proteinase inhibitor (human).

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion

White to beige powder

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prolastin is indicated for long-term augmentation therapy in subjects with alpha₁-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).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY

Adults, including elderly patients

Unless otherwise prescribed, a once-weekly dose of 60 mg active ingredient/kg body weight (equivalent to 180 ml reconstituted solution for infusion containing 25 mg/ml alpha₁-proteinase inhibitor (human) in the case of a patient weighing 75 kg) as a short-term infusion is usually sufficient to keep the serum alpha₁-proteinase inhibitor level constantly over 80 mg/dl which correlates with pulmonary levels of 1.3 µM. Theoretically this serum and epithelial-lining fluid levels are estimated protective levels against further worsening of the pulmonary emphysema.

Children and adolescents

No experience is available on use of Prolastin in children and adolescents below the age of 18.

Method of administration

The dry substance should be brought into contact with and dissolved in the solvent (40 ml water for injections) as described in section 6.6. "Instructions for use and handling".

The reconstituted solution should be administered by slow intravenous infusion, using a suitable infusion set. The infusion rate should not exceed 0.08 ml/kg body weight per minute (equivalent to 6 ml per minute in a patient weighing 75 kg).

The prepared solution must be used within 3 hours of its preparation.

The duration of treatment is at the discretion of the attending physician. A specific limit on the duration of treatment is not envisaged.

Physicians experienced with chronic obstructive lung diseases should treat or supervise the treatment of patients who have alpha₁-proteinase inhibitor deficiency.

4.3 CONTRAINDICATIONS

Prolastin must not be used in patients with

- selective IgA deficiency who are known to have antibodies against IgA, as allergic reactions to the point of anaphylactic shock may occur in such cases,
- known hypersensitivity to alpha₁-proteinase inhibitors or any of the excipients.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

In the event of a severe hypersensitivity reaction (with a fall in blood pressure to < 90 mmHg, dyspnoea or even anaphylactic shock), Prolastin should be discontinued immediately and suitable therapy, with treatment for shock as necessary, should be instituted.

Since Prolastin can cause a transient increase in blood volume, particular caution is necessary in patients with severe heart failure and patients at risk of circulatory overload.

Standard measures to prevent infections resulting from use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular repeated receipt of human plasma-derived proteinase inhibitors.

It is strongly recommended that every time that Prolastin is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Prolastin contains 4.8 mmol sodium per vial (equivalent to a dose of 21.6 mmol sodium in the case of a patient weighing 75 kg). This should be taken into consideration in the case of patients who have to follow a sodium-restricted diet.

PROLASTIN THERAPY CANNOT BE DENIED TO SMOKERS. HOWEVER SINCE THE EFFICACY OF PROLASTIN WILL BE COMPROMISED BY TOBACCO SMOKE IN THE LUNGS, CESSATION OF SMOKING IS STRONGLY RECOMMENDED.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There are no known interactions between Prolastin and other medicinal products.

4.6. Pregnancy and lactation

Pregnancy:

For Prolastin no clinical data on exposed pregnancies are available. Animal studies have not been conducted. Caution should be exercised when prescribing to pregnant women.

Lactation:

It is unknown whether α 1-P inhibitor is excreted in human breast milk. The excretion of α 1-P inhibitor in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Prolastin should be made taking into account the benefit of breast-feeding to the child and the benefit of Prolastin therapy to the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no indications that Prolastin impairs the ability to drive or use machines.

4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed during treatment with Prolastin:

System organ class	Uncommon > 0.1% to <1%	Rare >0.01% to <0.1%	Very rare < 0.01%
Cardiac disorders		Tachycardia	
General disorders and administration site conditions	Chills, fever, flu-like symptoms, chest pain		
Immune system disorders	Urticaria	Hypersensitivity reactions	Anaphylactic shock
Nervous system disorders	Dizziness / dazed state headache		
Respiratory, thoracic and mediastinal disorders	Dyspnoea		
Skin and subcutaneous tissue disorders	Rash		
Vascular disorders		Hypotension Hypertension	
Gastrointestinal disorders	Nausea		
Musculoskeletal and connective tissue disorders	Joint pain / arthralgia	Back pain	

Treatment with Prolastin may result in known reactions as fever, flu-like symptoms, dyspnoea, urticaria, nausea, etc. However, uncommon or rare immunological reactions may occur as with any protein treatment. This would include allergic reactions such as urticaria or dyspnoea, arthralgia, very rarely anaphylaxis. Symptoms which are of possible immunological origin should be evaluated before patients are re-challenged with therapy.

For information on viral safety, see 4.4.

4.9 OVERDOSE

Consequences of overdose are not known.

In the event of overdose, the patient should be observed closely for the occurrence of undesirable effects and supportive measures should be available as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proteinase inhibitor

ATC code: B02AB02

Alpha₁-proteinase inhibitor is a normal constituent of human blood that inhibits the activity of neutrophil elastase, amongst other enzymes. Alpha₁-proteinase inhibitor has a molecular weight of 51kDa and belongs to the family of serine protease inhibitors.

It is currently assumed that the pathogenesis of emphysema in alpha₁-proteinase inhibitor deficiency is attributable to a chronic biochemical imbalance between elastase and alpha₁-proteinase inhibitor. Elastase, which is synthesised by pro-inflammatory cells in the lower respiratory tract, is capable of breaking down elastic tissue. One of the principal inhibitors of elastase is alpha₁-proteinase inhibitor, which is lacking in congenital alpha₁-proteinase inhibitor deficiency. As a result, the alveolar structures remain unprotected against the elastin that is released by the neutrophils in the lower respiratory tract and to which they are therefore chronically exposed. This leads to progressive degradation of the elastic tissue and when serum alpha₁ antitrypsin levels decrease below 80 mg/dl, this is associated with an increased risk for development of emphysema. In two controlled observational registries, the most significant slowing of reduction in the rate of FEV1 has been observed in patients with FEV1 35 to 60 % of predicted.

5.2 Pharmacokinetic properties

After intravenous administration, virtually 100% of the alpha₁-proteinase inhibitor dose is immediately available in the patient's bloodstream. The mean in vivo recovery rate is 4.2 mg/dl per kg body weight. The in vivo half life is approximately 4.5 days.

5.3 Preclinical safety data

The active ingredient of Prolastin, alpha₁-proteinase inhibitor, is obtained from human plasma and behaves like endogenous plasma constituents. Administration of a single dose of Prolastin to various animal species, as well as administration of daily doses during five consecutive days to rabbits, showed no indications of toxic effects. Additional preclinical studies with repeated dosing (chronic toxicity, carcinogenicity, reproduction toxicity) were not conducted. These studies cannot usefully be performed in conventional animal models, as antibodies are expected to be formed as a result of administration of heterologous human proteins.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder:
Sodium chloride
Sodium dihydrogen phosphate
Solvent:
Water for injection

The powder for solution for infusion contains 4.8 mmol sodium.

6.2 INCOMPATIBILITIES

Prolastin must not be mixed with medicinal products or other solutions for infusion.

6.3 SHELF LIFE

2 years.

The reconstituted solution should always be used within 3 hours of its preparation.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Do not freeze. Once prepared, the solution for infusion should not be stored in a refrigerator. Discard any unused solution according to local requirements.

6.5 NATURE AND CONTENTS OF CONTAINER

Powder:

Type I glass vial with isoprene rubber stopper and aluminium cap.

Solvent:

Type II glass vial with chlorobutyl rubber stopper.

1 original pack containing 1 x 1000 mg alpha₁-proteinase inhibitor (human) and 1 x 40 ml solvent.

6.6 INSTRUCTIONS FOR USE AND HANDLING

The dry substance is to be brought into contact with and dissolved in the contents of one vial containing 40 ml water for injections, as described below.

Preparation of the reconstituted solution for infusion

Aseptic technique should be used.

1. Both vials (dry substance and solvent) should be at room temperature (20-25°C).
2. Remove the protective caps from the vials and clean the rubber stoppers of both vials, using a separate sterile swab for each (or spray with disinfectant).
3. Remove the protective cap from one end of an appropriate transfer device and insert the transfer device into the stopper of the solvent vial.
4. Remove the protective cap from the other end of the transfer device and, with the free spike of the transfer device, carefully pierce at an angle of 90° the centre of the stopper of the vial containing the dry substance.
5. Allow the solvent to flow onto the dry substance. Remove and discard the solvent vial plus transfer device.
6. Dissolve the dry substance fully with slow circular movements.

Only clear solutions should be used. The reconstituted solution must always be used within 3 hours of its preparation. Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

BAYER VITAL GMBH

D-51368 Leverkusen

Tel.: (02 14) 30-51 55 7

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8. MARKETING AUTHORISATION NUMBER

12944.01.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation

12.12.1988

Renewal of the authorisation

12.12.2003

10. DATE OF REVISION OF THE TEXT

March 2006



Prolastin[®]

1000 mg, powder and solvent for solution for infusion
Active ingredient: alpha₁-proteinase inhibitor, human

Read all of this package leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Prolastin is and what it is used for
2. Before you use Prolastin
3. How to use Prolastin
4. Possible side effects
5. How to store Prolastin
6. Further information

1. WHAT *Prolastin* IS AND WHAT IT IS USED FOR

Prolastin belongs to the class of compounds known as proteinase inhibitors.

Alpha₁-proteinase inhibitor (alpha₁-PI) is a substance formed in the body to inhibit substances known as elastases that damage the lungs. Where there is a congenital deficiency of alpha₁-PI, there is an imbalance between alpha₁-PI and elastases. This may lead to progressive destruction of lung tissue and development of pulmonary emphysema. Pulmonary emphysema is an abnormal enlargement of the lungs, accompanied by destruction of the lung tissue. Prolastin is used to restore the balance between alpha₁-PI and elastases in the lung and consequently to prevent a further deterioration in the pulmonary emphysema.

Prolastin is used as long-term therapy in patients with alpha₁-proteinase inhibitor deficiency in particular forms as determined by your doctor.

2. BEFORE YOU USE *Prolastin*

Do not use *Prolastin*:

- if you are allergic (hypersensitive) to the active substance, alpha₁-proteinase inhibitor, or any of the other ingredients of *Prolastin*.
- if you are known to have a deficiency of particular immunoglobulins (IgA), as severe allergic reactions, even to the point of anaphylactic shock, may occur in such cases.

Take special care with *Prolastin*:

- If you experience a severe hypersensitivity reaction with a fall in blood pressure, dyspnoea or even anaphylactic shock, *Prolastin* should be discontinued immediately and your doctor will initiate suitable treatment.
- If you have a severely weakened heart (heart failure) special caution is necessary, as *Prolastin* can lead to a temporary increase in blood volume.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus HIV, hepatitis B virus and hepatitis C virus. The measures taken may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

It is strongly recommended that every time you receive a dose of *Prolastin* the name and batch number of the product are recorded in order to maintain a record of the batches used.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived proteinase inhibitors.

Since the efficacy of *Prolastin* will be compromised by tobacco smoke in the lungs, cessation of smoking is strongly recommended.

Using other medicines

To date, there are no known interactions between *Prolastin* and other medicines.

Please nevertheless tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

There is no experience of use of *Prolastin* during pregnancy. Tell your doctor if you are pregnant or plan to become pregnant. It is not known whether *Prolastin* passes into breast milk. Ask your doctor for advice if you are breastfeeding.

Driving and using machines

There are no indications that Prolastin impairs the ability to drive or use machines.

Important information about some of the ingredients of Prolastin

Prolastin contains 4.8mmol sodium per vial (equivalent to a dose of 21.6mmol sodium in the case of a patient weighing 75 kg). You must take this into consideration if other diseases require you to follow a sodium-restricted diet.

3. HOW TO USE *Prolastin*

Prolastin is used by your doctor as follows:

A once-weekly dose of 60 mg active substance/kg body weight (equivalent to 180 ml reconstituted solution for infusion containing 25 mg/ml alpha₁-proteinase inhibitor, human, in the case of a patient weighing 75 kg) as a short-term infusion is usually sufficient.

Physicians experienced with chronic obstructive lung diseases should treat or supervise the treatment of patients with Prolastin.

The doctor in charge of your treatment will decide on its duration. There are no indications to date of any need to limit the duration of treatment.

How and when should Prolastin be used?

The dry substance should be dissolved in the contents of 1 vial containing 40 ml water for injections under sterile conditions, and given as an intravenous infusion.

If you have the impression that the effect of Prolastin is too strong or too weak, talk to your doctor or pharmacist.

If more Prolastin is used than should have been

Consequences of overdose are not known to date.

If use of Prolastin has been forgotten

Your doctor will decide when Prolastin should next be used. Please discuss this with the doctor in charge of your treatment.

If use of Prolastin has been stopped:

If treatment with Prolastin is stopped, your condition may worsen. Please talk to the doctor in charge of your treatment if you wish treatment with Prolastin to be ended prematurely.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Prolastin can cause side effects, although not everybody gets them.

The following side effects have been observed during treatment with Prolastin. Evaluation of side effects has been based on the following frequency data:

Uncommon:	less than 1 per 100 but more than 1 per 1,000 subjects treated
Rare:	less than 1 per 1,000 but more than 1 per 10,000 subjects treated
Very rare:	less than 1 per 10,000, including isolated cases

Uncommon:

- chills, fever, flu-like symptoms, pain in the chest
- hives (urticaria)
- dizziness, dazed state, headache
- difficulty breathing (dyspnoea)
- rash
- nausea
- joint pain (arthralgia)

Rare:

- hypersensitivity reactions
- fast pulse (tachycardia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- back pain

Very rare:

- allergic shock

What action should be taken if side effects occur?

If side effects occur during infusion of Prolastin, the infusion should be suspended or discontinued, depending on the nature and severity of the side effect.

In the event of a severe hypersensitivity reaction (with a fall in blood pressure, dyspnoea or even anaphylactic shock), treatment with Prolastin should be discontinued immediately and suitable therapy, with treatment for shock as necessary, should be instituted.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE *Prolastin*

Do not store above 25°C! Do not freeze.

The reconstituted solution should not be refrigerated and should always be used within 3 hours of its preparation. Unused solution should be discarded.

Keep out of the reach and sight of children.

Do not use Prolastin after the expiry date which is stated on the vial label and the carton.

Do not use Prolastin if you notice that the reconstituted solution is not clear.

6. FURTHER INFORMATION

What Prolastin contains

- The active substance is α_1 -proteinase inhibitor, human (i.e. derived from human blood or plasma)
- The other ingredients are sodium chloride, sodium dihydrogen phosphate, water for injection

What Prolastin looks like and contents of the pack

α_1 -proteinase inhibitor is a white to beige powder.

The reconstituted solution is clear.

The Prolastin carton contains

- 1 vial containing 1000 mg α_1 -proteinase inhibitor, human, with a rubber stopper and an aluminium tear-off seal
- 1 vial containing 40 ml solvent.
1 ml of the reconstituted solution contains 25 mg α_1 -proteinase inhibitor.

Marketing Authorisation Holder and Manufacturer

Bayer Vital GmbH
D-51368 Leverkusen
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VI.

VII.

VIII. MANUFACTURER

Bayer Biologicals S.r.l.
Viale Certosa, 130
I-20156 Milan
Italy

This leaflet was last approved in March 2006

The following information is intended for medical and health-care professionals only:

Preparation of reconstituted solution for infusion by healthcare professionals under aseptic conditions.

1. Both vials (dry substance and solvent) should be at room temperature (20-25°C).
2. Remove the protective caps from the vials and clean the rubber stoppers of both vials, using a separate sterile swab for each (or spray with disinfectant).
3. Remove the protective cap from one end of an appropriate transfer device and insert the transfer device into the stopper of the solvent vial.
4. Remove the protective cap from the other end of the transfer device and, with the free spike of the transfer device, pierce at an angle of 90° the centre of the stopper of the vial containing the dry substance.
5. Allow the solvent to flow onto the dry substance. Remove and discard the solvent vial plus transfer device.
6. Dissolve the dry substance fully with slow circular movements.

Only clear solutions should be used. Prolastin should not be mixed with other solutions for infusion.

The reconstituted solution should be administered by slow intravenous infusion, using a suitable infusion set (“drip”). The infusion rate should not exceed 0.08 ml/kg body weight (equivalent to 6 ml in a patient weighing 75 kg) per minute.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING: Prolastin

1. NAME OF THE MEDICINAL PRODUCT

Prolastin
1000 mg, Powder and solvent for solution for infusion
Active substance: Alpha-1-Proteinase inhibitor, human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 1000 mg Alpha-1-Proteinase inhibitor, human

3. LIST OF EXCIPIENTS

Powder:
Sodium chloride,
Sodium dihydrogen phosphate,
Solvent:
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial containing powder for solution for infusion
1 vial containing 40 ml water for injections

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous administration

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Vital
D-51368 Leverkusen

12. MARKETING AUTHORISATION NUMBER(S)

MA no. 12944.01.00

13. BATCH NUMBER

Lot
Lot documentation necessary

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE Prolastin bottle label :

1. NAME OF THE MEDICINAL PRODUCT

Prolastin
1000 mg, Powder and solvent for solution for infusion
Active substance: Alpha-1-Proteinase inhibitor, human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1000 mg Alpha-1-Proteinase inhibitor, human

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial containing powder for solution for infusion

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous administration

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Vital
D-51368 Leverkusen

12. MARKETING AUTHORISATION NUMBER(S)

MA no. 12944.01.00

13. BATCH NUMBER

Lot
Lot documentation necessary

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE Bottle label:

Water for injection

WATER for Injection

40 ml water for injections

EXPIRY DATE

Exp

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Vital,
53136 Leverkusen

MARKETING AUTHORISATION NUMBER(S)

MA no. 12944.01.00

BATCH NUMBER

Lot