PRODUCT MONOGRAPH

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN)

I.V. Injection

500, 1000 mg

Alpha$_1$ - Antitrypsin Replenisher

Manufactured by:
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Distributed and imported by:
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June 13, 2005

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THERAPEUTIC CLASSIFICATION

Alpha$_1$ - Antitrypsin Replenisher

ACTION AND CLINICAL PHARMACOLOGY

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is a sterile, stable, lyophilized preparation of purified human Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI), also known as alpha$_1$-antitrypsin. ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is intended for use in therapy of congenital alpha$_1$-antitrypsin deficiency.

Alpha$_1$-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal recessive disorder in which a low concentration of alpha$_1$-PI (alpha$_1$-antitrypsin) is associated with slowly progressive severe panacinar emphysema that most often manifests itself in the third to fourth decades of life.[2-9] [Although the terms "Alpha$_1$-Proteinase Inhibitor" and "alpha$_1$-antitrypsin" are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha$_1$-PI is conventionally referred to as "alpha$_1$-antitrypsin deficiency" while the deficient protein is referred to as "Alpha$_1$-Proteinase Inhibitor"[10]]. The emphysema is typically worse in the lower lung zones.[4,8,9] The pathogenesis of development of emphysema in alpha$_1$-antitrypsin deficiency is not well understood at this time. It is believed, however, to be due to a chronic biochemical imbalance between elastase (an enzyme capable of degrading elastin tissues, released by inflammatory cells, primarily neutrophils, in the lower respiratory tract) and alpha$_1$-

PI (the principal inhibitor of neutrophil elastase), which is deficient in alpha$_1$-antitrypsin disease.[11-15] As a result, it is believed that alveolar structures are unprotected from chronic exposure to elastase released from a chronic, low-level burden of neutrophils in the lower respiratory tract, resulting in progressive degradation of elastin tissues.[11-15] The eventual outcome is the development of emphysema. Neonatal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha$_1$-antitrypsin deficiency.[15] In some adults, alpha$_1$-antitrypsin deficiency is complicated by cirrhosis.[15]

A large number of phenotypic variants of alpha$_1$-antitrypsin deficiency exists.[15] The most severely affected individuals are those with the PiZZ variant, typically characterized by alpha$_1$-PI serum levels <35% normal.[15] Epidemiologic studies of individuals with various phenotypes of alpha$_1$-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha$_1$-PI $\leq$ 50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime.[3-6,8,9,16] However, individuals with endogenous alpha$_1$-PI levels >80 mg/dL, in general, do not manifest an increased risk for development of emphysema above the general population background risk.[5,15] From these observations, it is believed that the "threshold" level of alpha$_1$-PI in the serum required to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is about 80 mg/dL (based on commercial standards for immunologic assay of alpha$_1$-PI).[12,15,17]

In clinical studies of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN), 23 subjects with the PiZZ variant of congenital deficiency of alpha$_1$-antitrypsin deficiency and documented destructive lung disease participated in a study of acute and/or chronic replacement therapy with ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN).[18] The mean *in vivo* recovery of alpha$_1$-PI was 4.2 mg (immunologic) /dL per mg (functional) / kg body weight administered.[18,19] The half-life of alpha$_1$-PI *in vivo* was approximately 4.5 days.[18,19] Based on these observations, a program of chronic

replacement therapy was developed. Nineteen of the subjects in these studies received ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN), replacement therapy, 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of alpha$_1$-PI were maintained above 80 mg/dL (based on the commercial standards for alpha$_1$-PI immunologic assay).[18-20] Within a few weeks of commencing this program, bronchoalveolar lavage studies demonstrated significantly increased levels of alpha$_1$-PI and functional antineutrophil elastase capacity in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to commencing the program of chronic replacement therapy with ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN).[18-20]

All 23 individuals who participated in the investigations were immunized with Hepatitis B Vaccine and received a single dose of Hepatitis B Immune Globulin (Human) on entry into the investigation. Although no other steps were taken to prevent hepatitis, neither hepatitis B nor non-A, non-B hepatitis occurred in any of the subjects.[18,19] All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to alpha$_1$-PI or other serum protein.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) on the development of or progression of emphysema in patients with congenital alpha$_1$-antitrypsin deficiency have not been performed. Estimates of the sample size required of this rare disorder and the slow, progressive nature of the clinical course have been considered impediments in the ability to conduct such a trial.[21] Studies to monitor the long-term effects will continue as part of the postapproval process.

INDICATIONS AND CLINICAL USE

Congenital Alpha$_1$-Antitrypsin Deficiency

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha$_1$-PI (alpha$_1$-antitrypsin deficiency) with clinically demonstrable panacinar emphysema. Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha$_1$-PI, and that levels of functionally active alpha$_1$-PI in the lung epithelial lining fluid are increased proportionately.[18-20] As some individuals with alpha$_1$-antitrypsin deficiency will not go on to develop panacinar emphysema, only those with evidence of such disease should be considered for chronic replacement therapy with ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN).[22] Subjects with the PiMZ or PiMS phenotypes of alpha$_1$-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for panacinar emphysema.[22] Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha$_1$-antitrypsin deficiency with ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN). Only adult subjects have received ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) to date.

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is not indicated for use in patients other than those with PiZZ, PiZ (null) or Pi (null) (null) phenotypes.

CONTRAINDICATIONS

Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) should not receive ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.

WARNINGS

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Bayer Inc. at 1-800-622-2937, ext. 5425.

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient.

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) has been heat-treated in solution at 60°C for 10 hours in order to reduce the potential for transmission of infectious agents.[1] No cases of hepatitis, either hepatitis B or hepatitis C have been recorded to date in individuals receiving ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN).[18] However, as all individuals received prophylaxis against hepatitis B, no conclusion can be drawn at this time regarding potential transmission of hepatitis B virus.

PRECAUTIONS

General

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

2. Administer only by the intravenous route.

3. As with any colloid solution, there will be an increase in plasma volume following intravenous administration of $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN).[23] Caution should therefore be used in patients at risk for circulatory overload.

4. It is recommended that in preparation for receiving $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) recipients be immunized against hepatitis B using a licensed Hepatitis B Vaccine, according to the manufacturer's recommendations. Should it become necessary to treat an individual with $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN), and time is insufficient for adequate antibody response to vaccination, individuals should receive a single dose of Hepatitis B Immune Globulin (Human), 0.06 mL/kg body weight, intramuscularly, at the time of administration of the initial dose of Hepatitis B Vaccine.

5. $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) should be given alone, without mixing with other agents or diluting solutions.

6. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) product in accordance with biohazard procedures.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility have not been conducted.

Pregnancy

Animal reproduction studies have not been conducted with $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN). It is also not known whether $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population has not been established.

ADVERSE REACTIONS

Therapeutic administration of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) 60 mg/kg weekly, has been demonstrated to be well-tolerated. In clinical studies, six reactions were observed with 517 infusions of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN), or 1.16%. None of the reactions was severe.[18] The adverse reactions reported included delayed fever (maximum temperature rise was 38.9°C, resolving spontaneously over 24 hours) occurring up to 12 hours following treatment (0.77%), light-headedness (0.19%), and dizziness (0.19%).[18] Mild transient leukocytosis and dilutional anemia several hours after infusion have also been noted.[18] Since market entry, occasional reports of other flu-like symptoms, allergic-like reactions, chills, dyspnea, rash, tachycardia, and, rarely, hypotension have also been received.

DOSAGE AND ADMINISTRATION

Each bottle of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) has the functional activity, as determined by inhibition of porcine pancreatic elastase,[1] stated on the label of the bottle.

The "threshold" level of alpha$_1$-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha$_1$-PI immunologic assay).[12,15,17] However, assays of alpha$_1$-PI based on commercial standards measure antigenic activity of alpha$_1$-PI, whereas the labeled potency value of alpha$_1$-PI is expressed as actual functional activity, i.e., actual capacity to neutralize porcine pancreatic elastase. As functional activity may be less than antigenic activity, serum levels of alpha$_1$-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha$_1$-PI levels.

Therefore, although it may be helpful to monitor serum levels of alpha$_1$-PI in individuals receiving ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN), using

currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage.

The recommended dosage of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is 60 mg/kg body weight administered once weekly. This dose is intended to increase and maintain a level of functional alpha$_1$-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency.

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 30 minutes to infuse.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution

1. Warm the unopened diluent and concentrate to room temperature (NMT 37°C, 99°F).

2. After removing the plastic flip-top caps (Fig. A), aseptically cleanse rubber stoppers of both bottles.

3. Remove the protective cover from the plastic transfer needle cartridge with tamper-proof seal and penetrate the stopper of the diluent bottle (Fig. B).

4. Remove the remaining portion of the plastic cartridge. Invert the diluent bottle and penetrate the rubber seal on the concentrate bottle (Fig. C) with the needle at an angle.

Alternate method of transferring sterile water: with a sterile needle and syringe, withdraw the appropriate volume of diluent and transfer to the bottle of lyophilized concentrate.

5. The vacuum will draw the diluent into the concentrate bottle. For best results, and to avoid foaming, hold the diluent bottle at an angle to the concentrate bottle in order to direct the jet of diluent against the wall of the concentrate bottle (Fig. C).

6. After removing the diluent bottle and transfer needle (Fig. D), gently swirl the concentrate bottle until the powder is completely dissolved (Fig. E).

7. Swab top of reconstituted bottle $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) again.

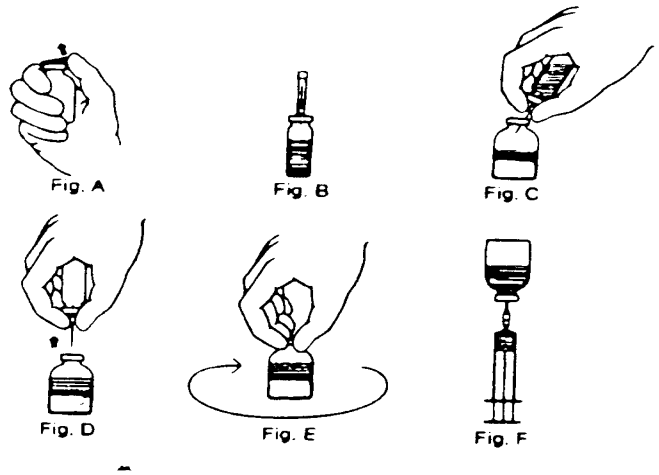
8. Attach the sterile filter needle provided to syringe. With filter needle in place, insert syringe into reconstituted bottle of $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) and withdraw $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) solution into syringe (Fig. F).

9. To administer $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) replace filter needle with appropriate injection needle and follow procedure for I.V. administration.

10. The contents of more than one bottle of $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) may be drawn into the same syringe before administration. If more than one bottle of $ALPHA_1$-PROTEINASE INHIBITOR (HUMAN) is used, withdraw contents from bottles using aseptic technique. Place contents into an administration container (plastic minibag or glass bottle) using a syringe.* Avoid pushing an I.V.

administration set spike into the product container stopper as this has been known to force the stopper into the vial, with a resulting loss of sterility.

* For a patient of average weight (about 70 kg), the volume needed will exceed the limit of one syringe.



PHARMACEUTICAL INFORMATION

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol method of Cohn.[1] Plasma used in the manufacture of this product has been collected in Canada from volunteer donors. In order to reduce the potential risk of transmission of infectious agents, ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) has been heat-treated in solution at 60 ± 0.5°C for not less than 10 hours. However, no procedure has been found to be totally effective in removing viral infectivity from plasma fractionation products.

The specific activity of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is ≥ 0.35 mg functional alpha$_1$-PI/mg protein and when reconstituted as directed, the concentration of alpha$_1$-PI is ≥ 20 mg/mL. When reconstituted, ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) has a pH of 6.6-7.4, a sodium content of 100-210 mEq/L, a chloride content of 60-180 mEq/L, a sodium phosphate content of 0.015-0.025 M, a polyethylene glycol content of not more than (NMT) 5 ppm, and NMT 0.1% sucrose. ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) contains small amounts of other plasma proteins including alpha$_2$-plasmin inhibitor, alpha$_1$-antichymotrypsin, C$_1$-esterase inhibitor, haptoglobin, antithrombin III, alpha$_1$-lipoprotein, albumin and IgA.[1]

Each vial of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) contains the labeled amount of functionally active alpha$_1$-PI in milligrams per vial (mg/vial), as determined by capacity to neutralize porcine pancreatic elastase.[1] ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) contains no preservative and must be administered by the intravenous route.

STORAGE

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) should be stored under refrigeration (2°-8°C; 36°- 46°F) or at temperatures not to exceed 25°C (77°F). Freezing should be avoided as breakage of the diluent bottle might occur.

AVAILABILITY OF DOSAGE FORMS

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) is supplied in the following single use vials with the total alpha$_1$-PI functional activity, in milligrams, stated on the label of each vial.

A suitable volume of Sterile Water for Injection, USP, a sterile double-ended transfer needle and a sterile filter needle are provided.

Approximate Alpha$_1$-PI		
Product Code	Functional Activity	Diluent
XXX-XX	500 mg	20 mL
XXX-XX	1000 mg	40 mL

PHARMACOLOGY

a) Human Studies

In Vivo

i) Pharmacokinetic Studies

Gadek et al have treated several individuals with the PiZ phenotype of alpha$_1$-antitrypsin deficiency with a partially purified preparation of alpha$_1$-PI.[17] Using this material, five adults with severe serum alpha$_1$-antitrypsin deficiency (PiZ phenotype) and advanced emphysema received 4 grams of alpha$_1$-PI, intravenously, at weekly intervals for four doses. During this period of weekly replacement therapy alpha$_1$-PI serum levels were maintained at ≥ 70 mg/dL, the level likely required for effective antielastase protection of the lung.[15,17,24]

In a subsequent study[19], nineteen subjects with alpha$_1$-antitrypsin deficiency received ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) intravenously 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of alpha$_1$-PI were maintained above 80 mg/dL. Please refer to section "Action and Clinical Pharmacology" for more details.

A further study[25] evaluated an intravenous dosage of 250 mg/kg of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) administered every 28 days in an attempt to assess whether the intervals between dosing could be increased beyond one week, while still retaining protective anti-neutrophil elastase alpha$_1$-PI levels in the serum and the epithelial lining fluid (ELF). Nine subjects were included. Analysis of the repeated dosage data indicated that overall, the serum alpha$_1$-PI levels fell to below 80 mg/dL at about 18-21 days after the administration of the 250 mg/kg ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) dosage, reaching a nadir of about 50 mg/dL at 28 days. A serum level of 70 to 80 mg alpha$_1$-PI/dL equates to a pulmonary alveolar ELF level of 1.2 μmol. This is the ELF level which is considered protective against elastase activity in the normal subject.

ii) Pharmacodynamic Studies

No drug attributable pharmacodynamic changes were observed in any of the clinical studies to date.[19,25] As mentioned in the section on Pharmacokinetics, increased anti-neutrophil elastase activity is achieved in both serum and ELF following intravenous administration. Development of antibodies directed against alpha$_1$-PI has not been reported in any of the studies. Similarly transmission of viral disease has not been seen.

b) Animal Studies

In Vivo

i) Pharmacokinetic Studies

The half-life of ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) administered intravenously in rabbits was determined to be 20.1 hours.[18]

ii) Pharmacodynamic Studies

A series of studies was conducted in rats and rabbits to determine the effect of a single intravenous dose of alpha$_1$-PI, 100 mg/kg, infused rapidly, 8 mL (168 mg)/min in rats and 6 mL (126 mg)/min in rabbits, on a number of clinical and biochemical parameters.[18] Rats were studied both with and without an inhibitor of kininase II/angiotensin converting enzyme in order to potentiate any peptide-mediated cardiovascular effects which might be present. In rats, no significant cardiovascular or hematologic effects were observed, but a slight fall in fibrinogen 30 minutes following infusion of the alpha$_1$-PI was noted. In rabbits, a marginal fall in leukocytes was observed, but this proved to be not statistically significant. No significant hematologic changes were detected.

TOXICOLOGY

a) Human Studies

Weekly infusions of alpha$_1$-PI at 60 mg/kg body weight intravenously (iv)[19] as well as monthly infusions of 250 mg/kg (iv)[25] were well tolerated. Administration of 507 infusions of alpha$_1$-PI in 21 subjects[19] did not cause any severe adverse reactions. There were no acute reactions. One subject developed low-grade fever persisting for 48 hours. This had commenced 12 hours after an intravenous dose of 90 mg/kg and was self-limiting. The patient continued on treatment for a further six months without problems. When utilizing the higher dosage of 250 mg alpha$_1$-PI per kg every 28 days, no side effects were observed.

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN) was licensed on September 19, 1988 and since that time has been generally available for intravenous administration to subjects with congenital alpha$_1$-antitrypsin deficiency. Side effects reported have included chills and shivering, fever,

headache, nausea and vomiting, dyspnea and shortness of breath, bronchospasm and wheezing (chest tightness); urticaria (hives, rashes), itching, chest pain, back pain, muscle and joint pain, flushing, clamminess, sweating, dizziness, diarrhea, fatigue, and less frequently anxiety, cyanosis, hypotension, malaise, swelling of hands and feet, angio-, facial and lip edema, nasal congestion, sinusitis, abdominal pains or cramps, pallor, and weakness[18]. Generally, reactions are mild to moderate in severity. The product is heated in solution at 60°C for 10 hours against the possibility of transmitting viral infection. As of this time, none of the clinical studies nor spontaneous reporting has suggested transmission of any viral disease[18].

b) Animal Studies

i) Acute Toxicity

The acute toxicity of alpha$_1$-PI administered intravenously, was determined in mice, rats, and rabbits and compared to the acute toxicity of the excipient control substance.[18] At an infusion rate of 3 mL/min, the LD_{50} of alpha$_1$-PI in mice was 150 ± 6 mL/kg (3,750 mg/kg) and that of the control was > 156 mL/kg. In rabbits, there was no indication of any toxicity at the highest dose of alpha$_1$-PI tested, 20.7 mL/kg, which was infused at a rate of 6 mL/kg (517 mg/kg) although one of three rabbits each in the groups receiving 6.9 mL and 20.7 mL/kg, respectively, of alpha$_1$-PI died during the observation period. These two deaths were not related to administration of Alpha-PI. An additional three rabbits were administered alpha$_1$-PI at a dose of 20.7 mL/kg without any sign of adverse effect throughout the 14-day observation period.

ii) Subacute Toxicity

A series of rabbits also received alpha$_1$-PI or excipient control substance, 9.1 mL/kg (227 mg/kg), administered intravenously at a rate of 6 mL/min, daily on five successive days. All rabbits in the study gained weight and there

were no significant differences in weight gain on the 6th day or 33rd day of the study between animals receiving alpha$_1$-PI compared to those receiving control substance. No significant hematologic abnormalities were noted on the 6th or 33rd days of the study following five consecutive days of administration of alpha$_1$-PI. An unexplained decrease in the cholesterol level of animals receiving alpha$_1$-PI was seen on day six in one series of animals but was not seen when repeated in another group. Two rabbits died during the course of the study, both of which were receiving alpha$_1$-PI. One rabbit died on day 4, with diarrhea present, and its death was felt to be related to infection. The other rabbit died on day 27 (three weeks after the infusion period) and histopathology revealed no probable cause of death. Overall, no effects directly ascribable to administration of alpha$_1$-PI were detected in animals undergoing necropsy and histopathologic analysis on days 6 or 33 of the study. No studies were performed regarding subchronic, chronic and reproductive toxicity or genotoxicity.

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors it is important that this product be stored properly, that the directions be followed carefully during use, and that the risk of transmitting viruses be carefully weighed before the product is prescribed. No warranty, express or implied, including any warranty of merchantability or fitness is made. Representatives of the Company are not authorized to vary the terms or the contents of the printed labeling, including the package inserts for this product, except by printed notice from the Company's headquarters. The prescriber and user of this product must accept the terms hereof.

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