ARALAST NP
[Alpha$_1$-Proteinase Inhibitor (Human)]

Solvent Detergent Treated
Nanofiltered

DESCRIPTION

ARALAST NP is a sterile, stable, lyophilized preparation of purified human alpha$_1$-proteinase inhibitor (α_1-PI), also known as alpha$_1$-antitrypsin.[1] ARALAST NP is a similar product to ARALAST, containing the same active components of plasma α_1-PI with identical formulations.

ARALAST NP is prepared from large pools of human plasma by using the cold ethanol fractionation process, followed by purification steps including polyethylene glycol and zinc chloride precipitations and ion exchange chromatography. All U.S. licensed α_1-PI plasma derived products contain chemical modifications which arise during manufacturing and occur in varying levels from product to product.[11] ARALAST NP contains approximately 2% α_1-PI with truncated C-terminal lysine (removal of Lys394), whereas ARALAST contains approximately 67% α_1-PI with the C-terminal lysine truncation.[12] No known data suggest influence of these structural modifications on the functional activity and immunogenicity of α_1-PI.[13]

To reduce the risk of viral transmission, the manufacturing process includes treatment with a solvent detergent (S/D) mixture [tri-n-butyl phosphate and polysorbate 80] to inactivate enveloped viral agents such as human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV). In addition, a nanofiltration step is incorporated into the manufacturing process to reduce the risk of transmission of enveloped and non-enveloped viral agents. Based on *in vitro* studies, the process used to produce ARALAST NP has been shown to inactivate and/or partition various viruses as shown in Table 1 below.[2]

Table 1: Virus Log Reduction in ARALAST NP Manufacturing Process

Processing Step	Virus Log Reduction Factors				
	HIV-1	BVDV	PRV	HAV	MMV
Cold ethanol fractionation	4.6	1.4	2.1	1.4	≤ 1.0*
Solvent Detergent-treatment	> 5.8	> 6.0	> 5.5	N/A	N/A
15 N nanofiltration	> 5.3	> 6.0	> 5.6	> 5.1	4.9
Overall reduction factor	***> 15.7***	***> 13.4***	***> 13.2***	***> 6.5***	***4.9***

* Reduction factors ≤ 1.0 are not used for calculation of the overall reduction factor

N/A – Not applicable; study did not test for virus indicated

HIV-1: Human immunodeficiency virus-1, BVDV (Bovine Viral Diarrhea Virus, model for Hepatitis C Virus and other lipid-enveloped RNA viruses), PRV (Pseudorabies Virus, model for lipid-enveloped DNA viruses, to which Hepatitis B also belongs): HAV: Hepatitis A Virus, MMV (Mice Minute Virus, model for small non-lipid-enveloped DNA viruses)

The unreconstituted, lyophilized cake should be white or off-white to slightly yellow-green or yellow in color. When reconstituted as directed, the concentration of functionally active α_1-PI is ≥ 16 mg/mL and the specific activity is ≥ 0.55 mg active α_1-PI/mg total protein. The composition of the reconstituted product is as follows:

Component	Quantity/mL
Elastase Inhibitory Activity	≥ 400 mg Active α_1-PI/0.5 g vial * ≥ 800 mg Active α_1-PI/1.0 g vial **
Albumin	≤ 5 mg/mL
Polyethylene Glycol	≤ 112 µg/mL
Polysorbate 80	≤ 50 µg/mL
Sodium	≤ 230 mEq/L
Tri-n-butyl Phosphate	≤ 1.0 µg/mL
Zinc	≤ 3 ppm

* Reconstitution volume: 25 mL/0.5 g vial

** Reconstitution volume: 50 mL/1.0 g vial

Each vial of ARALAST NP is labeled with the amount of functionally active α_1-PI expressed in mg/vial. The formulation contains no preservative. The pH of the solution ranges from 7.2 to 7.8. Product must only be administered intravenously.

CLINICAL PHARMACOLOGY

ARALAST NP functions in the lungs to inhibit serine proteases such as neutrophil elastase (NE), which is capable of degrading protein components of the alveolar walls and which is chronically present in the lung. In the normal lung, α_1-PI is thought to provide more than 90% of the anti-NE protection in the lower respiratory tract.[3,4]

α_1-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of α_1-PI.[1,3,5,6] Severe forms of the deficiency are frequently associated with slowly progressive, moderate-to-severe panacinar emphysema that most often manifests in the third to fourth decades of life, resulting in a significantly lower life expectancy.[1,3,4,6,7] However, an unknown percentage of individuals with severe α_1-PI deficiency are not diagnosed with or may never develop clinically evident emphysema during their lifetimes. Individuals with α_1-PI deficiency have little protection against NE released by a chronic, low-level of neutrophils in their lower respiratory tract, resulting in a protease:protease inhibitor imbalance in the lung.[3,8] The emphysema associated with severe α_1-PI deficiency is typically worse in the lower lung zones.[5] It is believed to develop because there are insufficient amounts of α_1-PI in the lower respiratory tract to inhibit NE. This imbalance allows relatively unopposed destruction of the connective tissue framework of the lung parenchyma.[8]

There are a large number of phenotypic variants of this disorder.[1,3,4] Individuals with the PiZZ variant typically have serum α_1-PI levels less than 35% of the average normal level.[1,5] Individuals with the Pi(null)(null) variant have undetectable α_1-PI protein in their serum.[1,3] Individuals with these low serum α_1-PI levels, i.e., less than 11 µM, have an increased risk of developing emphysema over their lifetimes. In addition, PiSZ individuals, whose serum α_1-PI levels range from approximately 9 to 23 µM[14], are considered to have moderately increased risk for developing emphysema, regardless of whether their serum α_1-PI levels are above or below 11 µM. Two Registry studies have shown 54% and 72% of α_1-PI deficient individuals had emphysema and pulmonary symptoms such as cough, phlegm, wheeze, breathlessness, and chest colds, respectively.[9,10] The risk of accelerated development and progression of emphysema in individuals with severe α_1-PI deficiency is higher in smokers than in ex-smokers or non-smokers.[3]

Not all individuals with severe genetic variants of α_1-PI deficiency have emphysema. **Augmentation therapy with Alpha$_1$-Proteinase Inhibitor (Human) is indicated only in patients with congenital α_1-PI deficiency who have clinically evident emphysema.**

Augmenting the levels of functional α_1-proteinase inhibitor by intravenous infusion is an approach to therapy for patients with α_1-PI deficiency. However, the efficacy of augmentation therapy in affecting the progression of emphysema has not been demonstrated in randomized, controlled clinical trials. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. Whether augmentation therapy with ARALAST NP actually protects the lower respiratory tract from progressive emphysematous changes has not been evaluated. Although the maintenance of blood serum levels of α_1-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection, this has not been proven. Individuals with severe α_1-PI deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with α_1-PI above 11 µM have emphysema attributed to α_1-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of α_1-PI during augmentation therapy. The clinical benefit of the increased blood levels of Alpha$_1$-Proteinase Inhibitor at the recommended dose has not been established.

The clinical efficacy of ARALAST NP in influencing the course of pulmonary emphysema or the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated in randomized, controlled clinical trials.

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Pharmacokinetics

The pharmacokinetics of ARALAST NP were compared with ARALAST in a multicenter, single-dose, randomized, double-blind, crossover clinical study (Study 460501). Twenty-five subjects with congenital α_1-PI deficiency received a single intravenous (IV) infusion of 60 mg/kg ARALAST NP or ARALAST. The 25 subjects in this study were between 20 and 75 years old, with a median age of 59. Plasma α_1-PI concentrations were measured using an enzyme linked immunosorbent assay (ELISA). Figure 1 shows that the mean ± standard deviation (SD) plasma α_1-PI concentration-time profiles after a single IV infusion of ARALAST NP and ARALAST at 60 mg/kg were comparable. Table 2 summarizes the pharmacokinetic parameters of ARALAST NP and ARALAST. The 90% confidence intervals for C_{max} and $AUC_{0\text{-}inf}$/dose were well within the pre-defined acceptance limits of 80 to 125%.

Figure 1. Mean (± SD) Plasma α_1-PI Concentration-Time Profiles After a Single Intravenous Infusion of ARALAST NP and ARALAST (60 mg/kg) in Subjects with Congenital α_1-PI Deficiency

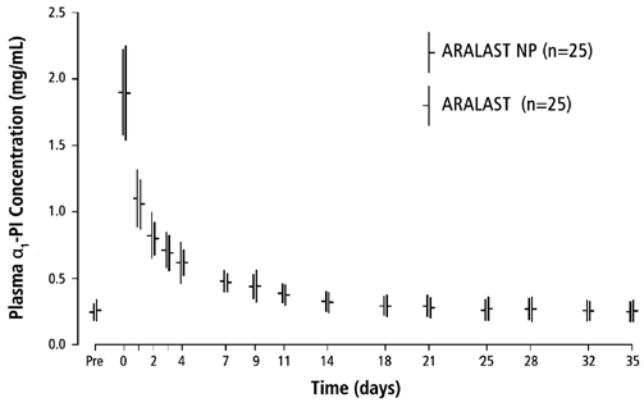

Table 2: Mean (± SD) Pharmacokinetic Parameters of ARALAST NP and ARALAST Following a Single IV infusion of 60 mg/kg (n=25)

Parameters	Units	ARALAST NP	ARALAST
C_{max}	mg/mL	1.6 ± 0.3	1.7 ± 0.3
$AUC_{0\text{-}inf}$/dose	days*kg/mL	0.0868 ± 0.0253	0.0920 ± 0.0238
Half-life	days	4.7 ± 2.7	4.8 ± 2.0
Clearance	mL/day	940 ± 275	862 ± 206
V_{ss}	mL	5632 ± 2006	5618 ± 1618

C_{max} = Maximum increase in plasma α_1-PI concentration following infusion; $AUC_{0\text{-}inf}$/dose = Area under the curve from time 0 to infinity divided by dose; Half-life = terminal phase half-life determined using non-compartmental method; V_{ss} = Volume of distribution at steady state.

A clinical study (ATC 97-01) was conducted to compare ARALAST to a commercially available preparation of α_1-PI (Prolastin®, manufactured by Bayer Corporation). All subjects were to have been diagnosed as having congenital α_1-PI deficiency and emphysema but no α_1-PI augmentation therapy within the preceding six months.

Twenty-eight subjects were randomized to receive either ARALAST or Prolastin®, 60 mg/kg intravenously per week, for 10 consecutive weeks. Two subjects withdrew from the study prematurely: 1 subject receiving ARALAST withdrew consent after 6 infusions; 1 subject receiving Prolastin® withdrew after 1 infusion due to pneumonia following unscheduled bronchoscopy to remove a foreign body. Trough levels of α_1-PI (antigenic determination) and anti-NE capacity (functional determination) were measured prior to treatment at Weeks 8 through 11. Following their first 10 weekly infusions, the subjects who were receiving Prolastin® were switched to ARALAST while those who already were receiving ARALAST continued to receive it. Maintenance of mean serum α_1-PI trough levels was assessed prior to treatments at Weeks 12 through 24. Bronchoalveolar lavages (BALs) were performed on subjects at baseline and prior to treatment at Week 7. The epithelial lining fluid (ELF) from each BAL meeting acceptance criteria was analyzed for the α_1-PI level and anti-NE capacity.

With weekly augmentation therapy with ARALAST or Prolastin®, a gradual increase in peak and trough serum α_1-PI levels was noted, with stabilization after several weeks. The metabolic half-life of ARALAST was 5.9 days. Serum anti-NE capacity trough levels rose substantially in all subjects by Week 2, and by Week 3, serum anti-NE capacity trough levels exceeded 11 µM in the majority of subjects. With few exceptions, levels remained above this recommended threshold level in individual subjects for the duration of the period Weeks 3 through 24 on study. Although only five of fourteen subjects (35.7%) receiving ARALAST had BALs meeting acceptance criteria for analysis at both baseline and Week 7, a statistically significant increase in the antigenic level of α_1-PI in the ELF was observed. No statistically significant increase in the anti-NE capacity in the ELF was detected.

Viral serology of all subjects was determined periodically throughout the study, including testing for antibodies to hepatitis A (HAV) and C (HCV), presence of circulating HBsAg, and presence of antibodies to HIV-1, HIV-2, and Parvovirus B-19. Subjects who were seronegative to parvovirus B-19 at enrollment were retested by PCR at Week 2. There were no seroconversions in subjects treated with ARALAST through Week 24. None of the subjects became HBsAg positive during the study, although five of 13 (38%) evaluable subjects treated with ARALAST and eight of 13 (62%) treated with Prolastin® had not been vaccinated to hepatitis B. No patient developed antibodies against α_1-PI.

It was concluded that at a dose of 60 mg/kg administered intravenously once weekly, ARALAST and Prolastin® had similar effects in maintaining target serum α_1-PI trough levels and increasing antigenic levels of α_1-PI in epithelial lining fluid (ELF) with maintenance augmentation therapy.

INDICATIONS AND USAGE

Congenital Alpha$_1$-Proteinase Inhibitor Deficiency

ARALAST NP is indicated for chronic augmentation therapy in patients having congenital deficiency of α_1-PI with clinically evident emphysema. Clinical and biochemical studies have demonstrated that with such therapy, ARALAST is effective in maintaining target serum α_1-PI trough levels and increasing α_1-PI levels in epithelial lining fluid (ELF). ARALAST NP pharmacokinetics are comparable with the pharmacokinetics of ARALAST after single-dose administration in 25 subjects with congenital deficiency of α_1-PI. Clinical data demonstrating the long-term effects of chronic augmentation or replacement therapy of individuals with ARALAST NP or ARALAST are not available.

The effect of augmentation therapy with ARALAST NP on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials.

ARALAST NP is not indicated as therapy for lung disease patients in whom congenital α_1-PI deficiency has not been established.

CONTRAINDICATIONS

ARALAST NP is contraindicated in IgA deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.

WARNINGS

Because ARALAST NP is derived from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma through the application of viral elimination/reduction steps such as ethanol fractionation, PEG precipitation, solvent detergent treatment, and nanofiltration. Despite these measures, such products can still potentially transmit disease; therefore, the risk of infectious agents cannot be totally eliminated. ALL infections thought by a physician possibly to have been transmitted by this product should be reported to the manufacturer at 1-800-423-2090 (US). The physician should weigh the risks and benefits of the use of this product and should discuss these with the patient.

ARALAST NP may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. ARALAST NP is contraindicated in patients with antibodies against IgA due to risk of severe hypersensitivity.

The rate of administration specified in DOSAGE AND ADMINISTRATION should be closely followed, at least until the physician has had sufficient experience with a given patient. Vital signs should be monitored continuously and the patient should be carefully observed throughout the infusion. **IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, THE INFUSION SHOULD BE DISCONTINUED IMMEDIATELY.** Epinephrine and other appropriate supportive therapy should be available for the treatment of any acute anaphylactic or anaphylactoid reaction.

PRECAUTIONS

General

ARALAST NP should be administered at room temperature within three (3) hours after reconstitution. Partially used vials should be discarded and not saved for future use. The solution contains no preservative.

ARALAST NP should be administered alone, without mixing with other agents or diluting solutions.

Pregnancy Category C

Animal reproduction studies have not been conducted with ARALAST NP. It is also not known whether ARALAST NP can cause fetal harm when administered to pregnant women or can affect reproductive capacity.

Nursing Mothers

It is not known whether alpha$_1$-proteinase inhibitor is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARALAST NP is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of ARALAST NP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation. Safety and effectiveness in patients over age 65 years of age have not been established.

Information for Patients

Inform patients that administration of ARALAST NP has been demonstrated to raise the plasma level of α_1-PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

ADVERSE REACTIONS

The safety of ARALAST NP was evaluated with ARALAST after a single-dose IV infusion in a multicenter, randomized, double-blind, crossover clinical PK comparability study (Study 460501). The number of subjects with one or more adverse events, regardless of causality, was 23 of 25 (92%) when receiving ARALAST NP and 19 of 25 (76%) when receiving ARALAST. Treatment-related adverse events were reported in 8 of 25 subjects (32%) for ARALAST NP and 7 of 25 subjects (28%) for ARALAST. Of a total of 61 adverse events reported for ARALAST NP, 43 (70%) were mild, 16 (26%) moderate, and 2 (3%) severe. Seventeen of 61 (28%) adverse events were deemed possibly or probably related to ARALAST NP of which 14 (82%) were mild and 3 (18%) were moderate. Of a total of 60 adverse events reported for ARALAST, 45 (75%) were mild, 12 (20%) moderate, and 3 (5%) severe. Eleven of 60 (18%) adverse events were deemed possibly or probably related to ARALAST of which 8 (73%) were mild and 3 (27%) were moderate. No serious adverse events or deaths were reported in the study. No clinically significant changes in the peri-infusion vital signs (blood pressure, heart rate, or respiratory rate) were reported. The most common adverse events deemed related to ARALAST NP included: headache (4 of 61 [7%] events) and musculoskeletal discomfort (4 of 61 [7%] events). These adverse events, as well as most of the other adverse events, were also reported in subjects treated with ARALAST.

In Clinical Study ATC 97-01, ARALAST was evaluated for up to 96 weeks in 27 subjects with a congenital deficiency of α_1-PI and clinically evident emphysema. The number of subjects with an adverse event, regardless of causality, was 22 of 27 (81.5%). The number of subjects with an adverse event deemed possibly, probably, or definitely related to study drug was 7 of 27 (25.9%).

The frequency of infusions associated with an adverse event, regardless of causality, was 108 of 1127 (9.6%) infusions administered per protocol. The most common symptoms were pharyngitis (1.6%), headache (0.7%), and increased cough (0.6%). Symptoms of bronchitis, sinusitis, pain, rash, back pain, viral infection, peripheral edema, bloating, dizziness, somnolence, asthma, and rhinitis were each associated with $\geq$ 0.2% but $<$ 0.6% of infusions. All symptoms were mild to moderate in severity.

The overall frequency of adverse events deemed to be possibly, probably, or definitely related to study drug was 15 of 1127 (1.3%) infusions. The most common symptoms included headache (0.3%) and somnolence (0.3%). Symptoms of chills and fever, vasodilation, dizziness, pruritus, rash, abnormal vision, chest pain, increased cough, and dyspnea were each associated with one (0.1%) infusion. Five (5) of 27 (18.5%) subjects experienced eight (8) serious adverse reactions during the study. None of these serious adverse events were considered to be causally related to the administration of ARALAST.

Twenty-six (26) of 27 (96.3%) subjects experienced a total of 94 upper and lower respiratory-tract infections during the 96-week study (median: 3.0; range: 1 to 8; mean $\pm$ SD: 3.6 $\pm$ 2.3 infections). Twenty-eight (29.8%) of the respiratory infections occurred in 19 (70.4%) subjects during the first 24 weeks of the 96-week study suggesting that the risk of infection did not change with time on ARALAST. In a post-hoc analysis, subjects experienced a range of 0 to 8 exacerbations of COPD over the 96-week study with a median of less than one exacerbation per year (median: 0.61; mean $\pm$ SD: 0.83 $\pm$ 0.87 exacerbations per year).

Treatment-emergent elevations (> two times the upper limit of normal) in aminotransferases (ALT or AST), up to 3.7 times the upper limit of normal, were noted in 3 of 27 (11.1%) subjects. Elevations were transient lasting three months or less. No subject developed any evidence of viral hepatitis or hepatitis seroconversion while being treated with ARALAST, including 13 evaluable subjects who were not vaccinated against hepatitis B.

No clinically relevant alterations in blood pressure, heart rate, respiratory rate, or body temperature occurred during infusion of ARALAST. Mean hematology and laboratory parameters were little changed over the duration of the study, with individual variations not clinically meaningful.

During the initial 10 weeks of the study, subjects were randomized to receive either ARALAST or a commercially available preparation of α_1-PI (Prolastin®). The overall frequency, severity and symptomatology of adverse reactions were similar in both the ARALAST and Prolastin® groups. There were two serious adverse events in the Prolastin® group, both of which were considered to be possibly related to Prolastin®. These included chest pain, dyspnea and bilateral pulmonary infiltrates in one individual that withdrew from the study prematurely following an unscheduled bronchoscopy to remove a foreign body and the other, a positive seroconversion to Parvovirus B-19. There were no serious adverse events or seroconversions reported for the ARALAST group during the 96 week study period. No subject developed an antibody to α_1-PI.

DOSAGE AND ADMINISTRATION

Dose ranging studies using efficacy endpoints have not been performed.

Chronic Augmentation Therapy

FOR INTRAVENOUS USE ONLY. The recommended dosage of ARALAST NP is 60 mg/kg body weight administered once weekly by intravenous infusion. Each vial of ARALAST NP has the functional activity, as determined by inhibition of porcine pancreatic elastase, stated on the label. Administration of ARALAST NP within three hours after reconstitution is recommended to avoid the potential ill effect of any inadvertent microbial contamination occurring during reconstitution. Discard any unused contents.

Infusion Rate

ARALAST NP should be administered at a rate not exceeding 0.08 mL/kg body weight/minute. If adverse events occur, the rate should be reduced or the infusion interrupted until the symptoms subside. The infusion may then be resumed at a rate tolerated by the subject.

RECONSTITUTION

Use Aseptic Technique

1. ARALAST NP and diluent should be at room temperature before reconstitution.
2. Remove caps from the diluent and product vials.
3. Swab the exposed stopper surfaces with alcohol.
4. Open the package of the BAXJECT II Hi-Flow device by peeling away the lid without touching the inside contents (Fig. A). Do not remove the transfer system from the package. Do not touch the clear spike.
5. Turn the package over and insert the clear plastic spike through the diluent vial by pressing straight down (Fig. B).
6. Grip the BAXJECT II Hi-Flow package at the edges and pull the package off the device (Fig. C). Do not remove the blue protective cap from the BAXJECT II Hi-Flow device. Do not touch the purple spike.
7. Turn the system over so that the diluent vial is on top. Press the purple spike of the BAXJECT II Hi-Flow device into the ARALAST NP vial. The vacuum will draw the diluent into the ARALAST NP vial (Fig. D).
8. Let the vial stand until most of the contents is in solution, then GENTLY swirl until the powder is completely dissolved. Reconstitution requires no more than five minutes for a 0.5 gram vial and no more than 10 minutes for a 1.0 gram vial.
9. DO NOT SHAKE THE CONTENTS OF THE VIAL. DO NOT INVERT THE VIAL UNTIL READY TO WITHDRAW CONTENTS.
10. Use within three hours of reconstitution.

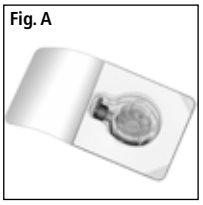
Fig. A

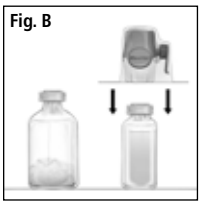
Fig. B


Fig. C

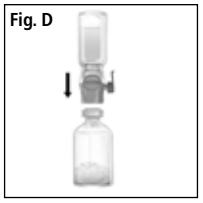
Fig. D

For Intravenous Injection/Infusion

1. After reconstituting the product as described under **Reconstitution,** inspect parenteral drug products visually for particulate matter and discoloration prior to administration. The reconstituted product should be a colorless or slightly yellowish to yellowish-green solution and be essentially free of visible particles.
2. Remove the blue protective cap from the BAXJECT II Hi-Flow device. Connect the syringe to the BAXJECT II Hi-Flow device (DO NOT DRAW AIR INTO THE SYRINGE) (Fig. E).
3. Invert the system (with the ARALAST NP concentrate vial on top). Draw the dissolved product into the syringe by pulling the plunger back SLOWLY (Fig. F).
4. Disconnect the syringe. Reconstituted product from several vials may be pooled into an empty, sterile IV solution container by using aseptic technique.

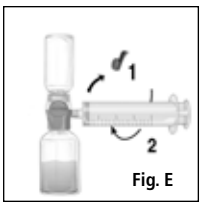

Fig. E

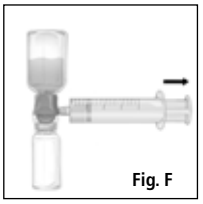
Fig. F

HOW SUPPLIED

ARALAST NP is supplied as a sterile, non-pyrogenic, lyophilized powder in single-dose vials. The following product packages are available:

Fill Size	NDC
0.5 g	0944-2812-01
1.0 g	0944-2822-02

ARALAST NP is packaged with a suitable volume of Sterile Water for Injection, USP diluent (25 mL/0.5 g vial; 50 mL/1.0 g vial), one BAXJECT II Hi-Flow Needleless Transfer Device and one package insert.

STORAGE

ARALAST NP should be stored at temperatures not to exceed 25°C (77°F). Do not freeze. Do not use after the expiration date printed on the label.

Rx only

REFERENCES

1. Brantly M, Nukiwa T, Crystal RG. Molecular basis of alpha-1-antitrypsin deficiency. *Am J Med* 1988 (Suppl 6A);84:13–31.
2. Data on file at Baxter Healthcare Corporation.
3. Crystal RG, Brantly ML, Hubbard RC, Curiel DT, et al. The alpha1-antitrypsin gene and its mutations: Clinical consequences and strategies for therapy. *Chest* 1989;95:196–208.
4. Crystal RG. α_1-Antitrypsin deficiency: pathogenesis and treatment. *Hospital Practice* 1991;Feb.15:81–94.
5. Hutchison DCS. Natural history of alpha-1-protease inhibitor deficiency. *Am J Med* 1988;84(Suppl 6A):3–12.
6. Hubbard RC, Crystal RG. Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin deficiency. *Am J Med* 1988;84(Suppl 6A):52–62.
7. Buist SA, Burrows B, Cohen A, et al. Guidelines for the approach to the patient with severe hereditary alpha-1-antitrypsin deficiency. *Am Rev Respir Dis* 1989;140:1494–1497.
8. Gadek JE, Fells GA, Zimmerman RL, et al. Antielastases of the human alveolar structures: Implications for the protease-antiprotease theory of emphysema. *J Clin Invest* 1981;68:889-898.
9. Stoller JK, Brantly M, Fleming LE, et al. Formation and current results of a patient-organized registry for α_1-antitrypsin deficiency. *Chest* 2000; 118(3):843-848.
10. McElvaney NG, Stoller JK, Buist AS, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of α_1-antitrypsin deficiency. *Chest* 1997;111:394-403.
11. FDA/CBER "Heterogeneity of Alpha-1-Proteinase Inhibitor Products" 27 Mar 2006 <http://www.fda.gov/cber/infosheets/alph1pi.htm>
12. Kolarich D, et al. Biochemical, molecular characterization, and glycoproteomic analyses of α_1-proteinase inhibitor products used for replacement therapy. *Transfusion* 2006;46:1959-1977.
13. Transcript of Blood Products Advisory Committee (BPAC) 85th Meeting; 3-4 Nov 2005.
14. Turino GM, Barker AF, Brantly ML, *et al:* Clinical features of individuals with Pi*SZ phenotype of α_1-antitrypsin deficiency. *Am J Respir Crit Care Med* 154: 1718-25, 1996.

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