

airwaves

For the Alpha-1 community • Brought to you by ARALAST and Baxter • Winter 2008

INSIDE THIS ISSUE



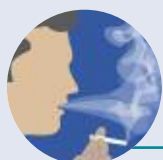
PAGE 3

Exercises to help you breathe easy



PAGE 5

Getting ready for CFC-free inhalers



PAGE 4

Smoking blamed for rise in COPD deaths

BACK PAGE



This month in Expert Attention

Developing a bond with your doctor

How being a better patient can lead to better care



In this interview, we sat down with Dr. Kyle Hogarth, director of the Alpha-1 Center at the University of Chicago. Here he discusses why it's important for Alphas to develop a strong doctor-patient relationship.

How should Alphas view their doctor-patient relationship?

You should treat your relationship with your doctor like any other relationship: you give, and you expect something in return. It's the same with anyone you hire: the relationship with your physician shouldn't be viewed any differently than your relationship with the guy who fixes your house. You're paying them money for good service.

How can I evaluate my doctor's commitment to my needs as an Alpha?

Say to your doctor, "I'm not a 'needy' patient, but I do have a unique disorder. I want to make sure I have an open line of communication with you." If your doctor's not comfortable with that, that's your first red flag to start looking for a new doctor.

Of course, the relationship works both ways. Doctors want to have an open line of communication with all their patients.

How can I avoid becoming "that patient"?

When you come to the clinic, come with a focused complaint. Understand that our time is limited.

How can I support my doctor's interest in Alpha-1?

Say to him or her, "Look, you probably haven't seen a lot of people with this disorder. Can I show you what I have learned about it?" Doctors are intrigued by rare diseases, because they usually spend their time dealing with more common illnesses. You can help spark their interest in what you have.

continued on page 2

ARALAST [Alpha₁-Proteinase Inhibitor (Human)] is indicated for chronic augmentation therapy in patients having congenital deficiency of A₁-PI with clinically evident emphysema. ARALAST is not indicated as therapy for lung disease patients in whom congenital A₁-PI deficiency has not been established.

Please see Important Safety Information on the last page of this newsletter and review the accompanying ARALAST Prescribing Information for full details. If you have any questions about ARALAST or your current treatment program, please talk with your physician.

National Heart Lung and Blood Institute funds largest-ever COPD genetics study

Group donates \$37 million for COPD research

Adapted from *PR Newswire*

DENVER, Oct. 10, 2007 – Researchers from National Jewish Medical and Research Center and Brigham and Women's Hospital have been awarded a \$37 million grant from the National Heart Lung and Blood Institute (NHLBI) to lead the most comprehensive study of COPD ever undertaken.

This multi-institutional study will seek to identify the genetic, epidemiological, and radiological characteristics of COPD, with a long-term goal of better understanding the disease and finding more effective treatments.

“COPD is the fourth-leading cause of death in the United States, and yet we know so little about the disease,” said James Crapo, MD, professor of medicine at National Jewish Medical and Research Center and co-principal investigator of the study. “This study will help us determine which smokers are most at risk of developing the disease, who is most likely to have progressive disease, and how to more effectively treat it.”

“Our goal with this massive project is to discover genes responsible for this chronic lung disease and to develop a comprehensive data-sharing plan so that this study will become a national resource for the scientific community,” said Edwin Silverman, MD, PhD, associate professor of medicine at Brigham and Women's Hospital and co-principal investigator of the study.

The 16 clinical study centers involved will enroll a total of 10,500 participants, 3,500 of whom will be African American, a population whose COPD rates are rapidly growing and whose risk factors have not been adequately studied.

The study will enroll smokers with and without COPD. Study participants with COPD will undergo a single study visit that will include pulmonary function tests, questionnaires about respiratory and general health, a six-minute walk test, a physical examination, and a chest CT scan. After participating, they will be contacted every six months.

“The National Heart, Lung, and Blood Institute is excited to fund what will be the largest study ever of the genetics of COPD. Identifying genetic factors that contribute to this devastating disease will help us understand the biological mechanisms involved, and will ultimately lead to better treatments and improved outcomes for patients,” said Elizabeth G. Nabel, MD, director of the NHLBI. The NHLBI is promoting better awareness of COPD through its public education campaign, Learn More Breathe Better. For more information, visit: <http://www.learnaboutcopd.org>.

A team from Johns Hopkins University, the Harvard School of Public Health (HSPH), Brigham and Women's Hospital, and the University of Colorado will provide statistical analysis.

National Jewish Medical and Research Center is known worldwide for treatment of patients with respiratory, immune, and related disorders, and for groundbreaking medical research. Brigham and Women's Hospital is a 747-bed nonprofit teaching affiliate of Harvard Medical School and a founding member of Partners HealthCare System, an integrated health care delivery network. ●

Developing a bond with your doctor, cont.



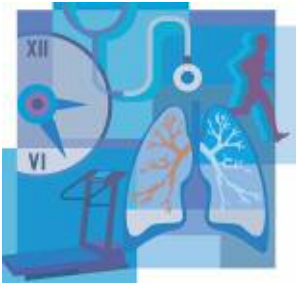
What do you think about the low level of awareness when it comes to Alpha-1?

As a doctor, you see about 25 patients a day. On average, three of them have COPD, and only one knows it. We can't even get people to diagnose COPD, let alone Alpha-1! There is a huge lack of awareness.

How can Alphas stay positive when awareness seems so low?

You can't allow yourself to say “Woe is me, I've got Alpha-1 and there's nothing I can do about it.” Again, that's where the relationship with your doctor comes in. He or she can help you get through this, and knows others you can go to for help.

A lot of people out there have emphysema, and we don't know why. Alpha-1 is different and we know we can find a way to help. Having a name to a disorder can be very empowering. ●



Exercises that can help you breathe easy

No matter what level of COPD you live with, you should make every effort to be active in some way. If your healthcare professional has already recommended an exercise plan that fits your ability and stamina, refer to that for guidance. If you don't have a healthcare professional-advised exercise program, ask for a referral to a pulmonary rehab program or a physical therapist. Here are some simple exercises you can do to make everyday breathing and activity easier.

Pursed-lip breathing

1. Inhale through your nose so that your stomach muscles move outward and your diaphragm pulls air into your lungs.
2. Exhale slowly and evenly through your mouth with your lips pursed, as if you were blowing bubbles.
3. Exhale twice as long as you inhale. This is very important, as it allows all the air to escape your lungs.
4. Try counting to 5 as you breathe out to develop a rhythm. Once you've mastered pursed-lip breathing, practice it whenever you're active or short of breath.

Knee extensions

1. Sit in a chair with your feet flat on the floor, slightly apart.
2. Take a breath in through your nose.
3. Breathe out through pursed lips as you straighten your knee and raise your lower leg.
4. Continue exhaling as you bend your knee and return your foot to the floor.
5. Do up to 15 repetitions, then repeat with your other knee.

Remember: You should NEVER hold your breath during any of these activities. Always breathe in before you begin your motion, and breathe out through pursed lips throughout the activity. This will help to provide oxygen to your muscles and allow carbon dioxide to leave your lungs.

If you need to stop, do so; take another breath in and breathe out as you continue the activity. Timing and rhythm will make exercising easier, so find the breathing technique that works for you and apply to all activities. ●

Derived from [ibrathe.com](http://www.ibrathe.com), available at: http://www.healthsmart.org/ibrathe/3_0_copd/3_3_5_exercise.htm.

Leg lifts

1. Sit in a chair with your feet flat on the floor, slightly apart.
2. Take a breath in through your nose.
3. Breathe out through pursed lips as you raise one of your knees toward your shoulder.
4. Continue exhaling as you return to the start position.
5. Do up to 15 repetitions, then repeat with your other leg.

Step-ups

1. Find a flight of stairs that has a banister you can hold onto.
2. Take a breath in through your nose.
3. Breathe out through pursed lips as you step up with one foot and then the other.
4. Continue breathing out as you step back down.
5. Do as many repetitions as you can, stopping at 15.



4 simple ways you can make infusing easier

Infusing can be painful when it isn't done right. Here are tips on how you can prepare your veins for infusion, and hopefully avoid unnecessary pain. If none of these seems to help, talk to your doctor about other infusion options, such as a venous access port.

1. **Have all your infusion supplies ready and at room temperature when your nurse arrives.**
2. **Wrap your hand and lower arm in a warm, wet towel for about 20 minutes before you infuse. This will help the veins "pop," making them easier to spot and access.**
3. **When infusing, alternate arms and puncture sites. Infusing into the same spot multiple times can cause irritation and discomfort.**
4. **You can also dangle your arm over the side of your chair for 5 to 15 minutes to increase blood flow to your arm.** ●

Derived from www.about.com, available at: http://ms.about.com/od/treatments/a/vein_prep.htm

Please see the Important Safety Information on the last page.

COPD mortality rates skyrocket while heart, stroke, and cancer rates decline

Smoking blamed for rise in COPD deaths

From *MedPage Today*

ATLANTA, Sept. 13, 2007 – The age-adjusted mortality rates attributed to four of the six leading causes of death in the U.S. declined during the past three decades except for one that’s on the rise: COPD.

The overall age-standardized death rate fell by 32%. For stroke, it dropped by 63%. The heart disease rate fell by 52% and the accident rate was down by 41%. Cancer squeezed onto the improvement list, although at only 2.7%.

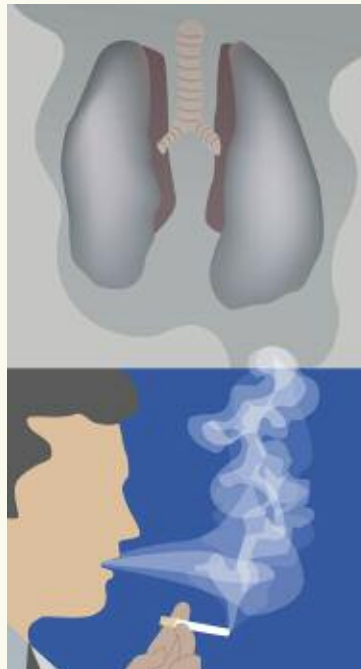
Then there was cigarette-fueled COPD, which rose by 102.8% from 1970 to 2002, according to Ahmedin Jemal, DVM, PhD, and colleagues of the department of epidemiology and surveillance research at the local American Cancer Society.

In 1970, the COPD age-standardized death rate (per 100,000 per year) was 21.4 deaths, while in 2002 it was 43.4 deaths, according to the death-trend data published in the Sept. 14 issue of the *Journal of the American Medical Association*.

The increase in COPD age-standardized death rates results largely from the long-term effects of tobacco smoking in an aging population, said the investigators. The increase in diabetes deaths, they wrote, “reflects dramatic increases in obesity.”

Causes of death vary by age and in 2002 the leading cause of death in people age 75 or older was heart disease, while cancer was the

leading cause of death for people ages 40 to 74, and accidents were the leading cause of deaths in those younger than 40.



The decrease in age-standardized death rates in four of the six leading causes of death represents “progress toward one of the fundamental goals of disease prevention by extending the number of years of potentially healthy life,” the researchers proclaim. That progress has been greater in heart disease than in cancer, but even the cancer death rate has been “decreasing by 1.1% per year since 1993.”

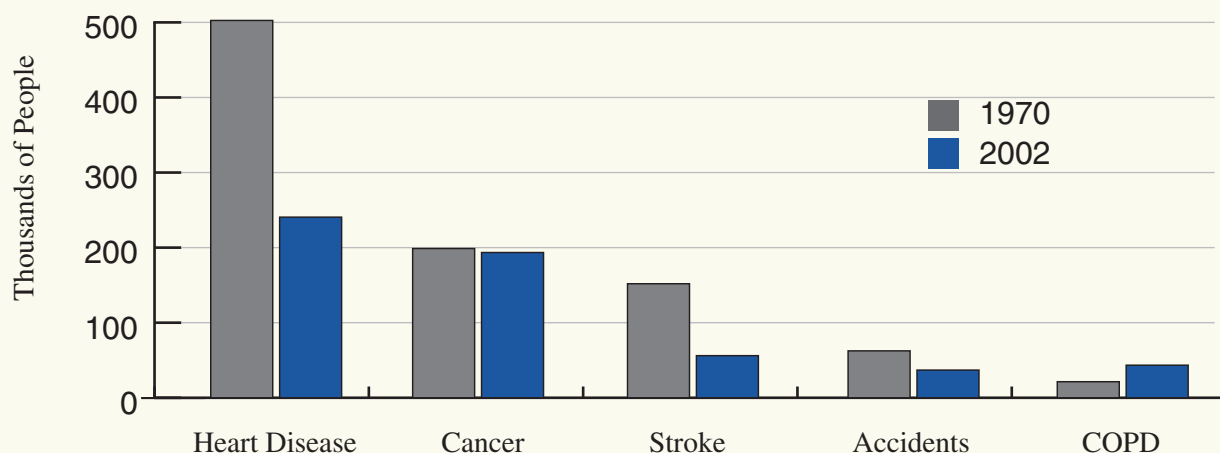
The researchers caution, however, that the rate of decline in the death rate for stroke and accidents has slowed since the 1990s, suggesting that this decline may be approaching a plateau.

At the same time, the “... trend in cancer mortality rates reflects both the impact of the tobacco epidemic on tobacco-related cancers through 1990, followed by reduction in cancer mortality through tobacco control and advances in early detection, in treatment, or in both.”

Finally, they point out that the flip side of declining death rates is an increase in the number of aging Americans who survive disease but require chronic treatment, which is likely to put ever-increasing demands on Medicare. ●

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Leading causes of death, 1970 to today





Getting ready for new CFC-free inhalers

Many people who use metered-dose inhalers are switching inhaler devices.

Manufacturers are phasing out one type of inhaler, called a chlorofluorocarbon (CFC) inhaler, and increasing production of another, called a hydrofluoroalkane (HFA) inhaler. This information may help you prepare for the switch:

Why are CFC inhalers being phased out?

The U.S. Food and Drug Administration (FDA) has told makers of inhalers that they must stop using CFCs, which are ozone-depleting propellants that send albuterol and other medications into the lungs.

Manufacturers have begun to make or ramp up production of HFA inhalers and powder

inhalers that are CFC-free in advance of the December 31, 2008 deadline.

What is albuterol?

Albuterol is a common drug found in many metered-dose inhalers, and is a short-acting beta₂-agonist. It quickly relaxes and opens airways for four to six hours. Some people with COPD also use albuterol inhalers.

What should I do?

Some people have already switched over to the new HFA inhalers, either because they want to get comfortable with the new product or because their CFC inhaler is no longer available. Everyone who uses an albuterol or other inhalers will have to stop using CFC inhalers by the end of 2008. So you may

want to speak with your doctor about making the change. To get an HFA inhaler, your doctor will need to write a new prescription. Your pharmacist can't simply substitute the new inhaler for your existing CFC inhaler prescription.

Will I see a price difference?

There may be a significant price difference between the CFC inhalers and the new HFA inhalers, particularly if you are using a generic CFC inhaler. The HFA inhalers cost from \$30 to \$60, compared with \$5 to \$25 for a generic CFC inhaler. The price difference is most likely to affect patients without health insurance.

For more information about transitioning to HFA inhalers or

assistance programs that may help you pay for your prescriptions, including a coupon offer, call the American Lung Association Lung HelpLine at 1-800-LUNGUSA, and press "2" to speak to a nurse or respiratory therapist. ●

Derived from www.lungusa.org, available at: <http://www.lungusa.org/site/apps/s/content.asp?c=dvLUK900E&b=34706&ct=3224093>



4 THINGS YOU SHOULD DO AT EVERY CHECKUP

- Have a spirometry test done, so you can know your lung function.
- Make sure you're up to date on vaccinations, such as flu and pneumonia.
- If you haven't already, ask about a pulmonary rehab program.
- Make sure the rest of your body is healthy. If you're in good shape for a lung transplant, you will have less trouble getting one. ●

Resource: Dr. Kyle Hogarth, University of Chicago

HFA vs. CFC INHALERS



Ozone-friendly HFA inhalers share many similarities with CFC inhalers, but there are some differences. Talk to your doctor, pharmacist, or other healthcare professional about the metered-dose inhaler.

How CFC and HFA are the same

- Safe and effective for the same FDA-approved uses
- Similar shape
- Similar size
- Convenient to use

How HFA is different

- Ozone-friendly
- Slight difference in smell and taste
- Mist is warmer and less forceful
- May need to be cleaned and cared for differently ●

Please see the Important Safety Information on the last page.

Poor indoor air quality may worsen lung disease

Cigarette smoke is main culprit for home air pollution

From *Reuters Health*

NEW YORK—A smog-filled sky can make it hard to breathe, but air pollution in the home may also be hard on people with lung disease.

In a study of 148 adults with COPD, investigators concluded that those who lived in homes with poor air quality tended to have worse symptoms. Cigarette smoke was the major air-polluting culprit.

“The importance of knowing this for people with COPD and their families is that indoor smoking is under our control,” lead study author Dr. Liesl M. Osman told *Reuters Health*.

“We can immediately very much improve air quality by stopping smoking in the home,” said Osman, a senior research fellow at the University of Aberdeen in Scotland.

To investigate, Osman’s team measured air quality in the homes of 148 Scottish adults with severe COPD. They also questioned them about their respiratory symptoms and smoking habits.

Thirty-nine percent of the subjects were smokers and 49 percent lived in a household where someone smoked.

In general, the researchers found, patients’ homes had high levels of particulate matter – the fine airborne particles that constitute pollution. Smokers’ homes had especially high concentrations.

Homes with the highest levels of particulate matter exceeded the maximum levels recommended by the EPA by about four-fold. Overall, the greater the level of particulate matter, the more advanced patients’ COPD symptoms were.

A number of factors, including outdoor air pollution, can affect indoor air quality, according to Osman. However, the current findings show that smoking is “a big contributor.”

“Our study shows that environmental tobacco smoke exposure worsens symptoms among people with COPD,” Osman said. It’s reasonable to assume that poor indoor air quality also worsens the long-term prognosis for COPD patients, she added, but long-range studies are needed to confirm this. ●

Derived from MedicineOnline.com, available at: <http://www.medicineonline.com/news/12/9901/Poor-indoor-air-quality-may-worsen-lung-disease.html>.

ARALAST AATmosphere Answers

Still have questions about Alpha-1? Our Aralast AATmosphere registered nurse answers frequently asked questions from Alphas like you.

Q. If I go on vacation, how can I keep up on infusions?

A. When traveling in the U.S., your homecare pharmacy has branch offices nationwide and can arrange for you to have your infusions. Ask your doctor or nurse to arrange for you to have your infusions at a site near where you will be staying. If possible, travel with someone who knows how to infuse.

If you take your own medication, contact your hotel to make sure it suits your needs. For example, will your room have a refrigerator where you can store your ARALAST? Better to plan ahead than risk ruining your vacation.

Q. How do I go about telling my family I have Alpha-1?

A. Telling your family you have Alpha-1 can be difficult. Aralast AATmosphere advocates are available to help you prepare for that conversation, and can provide you with literature, support groups, and web sites.

It’s important to tell your children and siblings that you have Alpha-1, and that it is a genetic disease. They should speak with their physician about being tested. Any physician can request a complimentary test kit by calling the Aralast AATmosphere program at 1-866-ARALAST.

Q. What else do I need to be aware of when it comes to Alpha-1?

A. Know that there is no shame in asking for help if you feel sad or anxious. Talk to your doctor if you experience depression, and know that support systems like Aralast AATmosphere are there to help.

It’s also important to assert yourself, and demand answers from healthcare professionals. Make sure your healthcare providers communicate with you and with each other in order to make the best decisions in your treatment plan. ●

Are you looking for answers? Call 1-866-ARALAST to get advice from a registered nurse, reimbursement specialist, or patient advocate.

Please see the Important Safety Information on the last page.



Traveling in style with Alpha-1

Holly Lockwood, founder of LifeBack Carriers and *Everything Respiratory* magazine, provides 10 easy ways you can avoid hassles while you travel.

1. Plan your travel arrangements at least 6 weeks prior to your flight and, above all, be patient.
2. Bring your own portable oxygen concentrator (POC) with you, unless you would rather pay for airline-supplied oxygen.
3. Contact your airline to confirm they will allow a POC.
4. Also contact your oxygen provider to obtain a POC that is approved for air travel (Inogen One, Airsep Lifestyle and Freestyle, Sequal Eclipse and Repsironics Evergo are approved for most commercial airlines).
5. Contact your physician for your current prescription, and fill out your airline medical form.
6. Have a list of contact names with you at all times.
7. Carry your oxygen prescription and medications with you at all times; never check them with your baggage.
8. Stow or check oxygen cylinders according to airline regulations (make sure each one is empty and the regulator is removed).
9. Bring enough extra batteries and an extra power strip to last at least 50% longer than your scheduled flight time (I recommend the "Power Squid", which I found at Radio Shack).
10. If you are given a seating option, always choose one that is close to the bathroom. ●

Important: If you get sick while you travel

- Be proactive. Call your doctor as soon as symptoms start
- If you act too slowly, complications such as pneumonia can result
- Under no circumstances should you let your symptoms "run their course"



Surrounding you with online support

Here at the Knowledge Network, we're constantly looking for new ways to surround you with support.

We're currently in the process of refreshing our website to help you get information faster and more efficiently. In addition to the one-on-one support and insurance information you expect from AATmosphere, you'll soon be able to gain support from a wider range of experts, learn more ways you can receive financial assistance, and have access to more health and legislative news.

Feel free to check our website periodically as we find new ways to extend our AATmosphere. ●

www.aatmosphere.com

How ARA-ASSIST revolves around you

ARA-ASSIST is an easy way to make sure that you keep receiving ARALAST therapy in the event of a lapse in insurance. Any ARALAST user who has third-party insurance, is on a state-sponsored program, or is on Medicaid or Medicare is eligible to participate in the program. **To enroll in ARA-ASSIST, fill out an online enrollment form at www.alpha1health.com, or call 1-888-229-8379.**

How does the program work?

Once you're enrolled, you will receive one ARA-ASSIST

Certificate of Participation for every four months you use ARALAST.

To remain active in the program, every four months you complete a utilization form to verify your continued use of ARALAST and mail it to PAREXEL, the independent program administrator for the ARA-ASSIST Program.

After one year of continuous use of ARALAST, you can redeem each certificate for a one-month supply (based on your usage) of augmentation therapy, should you have an insurance lapse.

Up to 12 certificates (representing four years of continuous use of ARALAST) can be collected. A maximum of twelve certificates can be redeemed in one calendar year.

If you remain on ARALAST therapy, your ARA-ASSIST certificates are good for five years from when you receive them.

And for a limited time, if you enroll in ARA-ASSIST you will be issued 3 bonus certificates redeemable for 3 months of ARALAST in the event of an insurance lapse. ●



Knowledge Network Conference Call Series

On October 30, Dr. Kyle Hogarth from the University of Chicago Medical Center spoke with Alphas across the country on our monthly conference call. The Alpha-1 specialist answered callers' questions and provided insight into how Alphas can stay healthy during the cold and flu season.

On December 14, Holly Lockwood from LifeBack Carriers and *Everything Respiratory* magazine shared travel tips for Alphas and educated us about some exciting and important pending legislation.

For registration information, visit www.AATmosphere.com or call 1-886-ARALAST. ●

ARALAST [Alpha₁-Proteinase Inhibitor (Human)]

ARALAST [Alpha₁-Proteinase Inhibitor (Human)] is indicated for chronic augmentation therapy in patients having congenital deficiency of A₁-PI with clinically evident emphysema. ARALAST is not indicated as therapy for lung disease patients in whom congenital A₁-PI deficiency has not been established.

Important Safety Information

ARALAST is contraindicated in individuals with selective IgA deficiencies (IgA level less than 15mg/dL) who have known antibody against IgA, since they may experience severe

reactions, including a severe, potentially life-threatening allergic reaction to IgA, which may be present.

ARALAST is made from human plasma. It may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most common symptoms during the clinical study were headache (0.3%) and sleepiness (0.3%). Post market adverse event data have indicated reports of infusion site pain associated with the administration of ARALAST.

Please see accompanying ARALAST Prescribing Information for full prescribing details.

Baxter

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Brought to you by
Aralast
[alpha₁-proteinase inhibitor (human)]

ARALAST NP [alpha₁-proteinase inhibitor (human)]

Solvent Detergent Treated
Nanofiltered

DESCRIPTION

ARALAST NP is a sterile, stable, lyophilized preparation of purified human alpha₁-proteinase inhibitor (α₁-PI), also known as alpha₁-antitrypsin.¹ ARALAST NP is a similar product to ARALAST, containing the same active components of plasma α₁-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 α₁-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% α₁-PI with truncated C-terminal lysine (removal of Lys394), whereas ARALAST contains approximately 67% α₁-PI with the C-terminal lysine truncation.¹² No known data suggest influence of these structural modifications on the functional activity and immunogenicity of α₁-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 also hepatitis B 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 α₁-PI is ≥ 16 mg/mL and the specific activity is ≥ 0.55 mg active α₁-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 α₁-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, α₁-PI is thought to provide more than 90% of the anti-NE protection in the lower respiratory tract.^{3,4}

α₁-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of α₁-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 α₁-PI deficiency are not diagnosed with or may never develop clinically evident emphysema during their lifetimes. Individuals with α₁-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 α₁-PI deficiency is typically worse in the lower lung zones.⁵ It is believed to develop because there are insufficient amounts of α₁-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 α₁-PI levels less than 35% of the average normal level.^{1,5} Individuals with the Pi(null)(null) variant have undetectable α₁-PI protein in their serum.^{1,3} Individuals with these low serum α₁-PI levels, i.e., less than 11 µM, have an increased risk of developing emphysema over their lifetimes. In addition, PiSZ individuals, whose serum α₁-PI levels range from approximately 9 to 23 µM¹⁴, are considered to have moderately increased risk for developing emphysema, regardless of whether their serum α₁-PI levels are above or below 11 µM. Two Registry studies have shown 54% and 72% of α₁-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 α₁-PI deficiency is higher in smokers than in ex-smokers or non-smokers.³

Not all individuals with severe genetic variants of α₁-PI deficiency have emphysema. **Augmentation therapy with Alpha₁-Proteinase Inhibitor (Human) is indicated only in patients with congenital α₁-PI deficiency who have clinically evident emphysema.**

Augmenting the levels of functional α₁-proteinase inhibitor by intravenous infusion is an approach to therapy for patients with α₁-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 α₁-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 α₁-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 α₁-PI above 11 µM have emphysema attributed to α₁-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of α₁-PI during augmentation therapy. The clinical benefit of the increased blood levels of Alpha₁-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.

Baxter

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 \pm 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 $AUC_{0-\infty}/dose$ were well within the pre-defined acceptance limits of 80 to 125%.

Figure 1. Mean (\pm 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

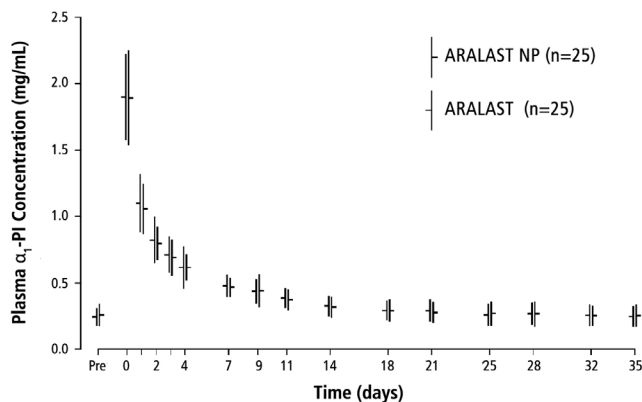


Table 2: Mean (\pm SD) Pharmacokinetic Parameters of ARALAST NP and ARALAST Following a Single IV infusion of 60 mg/kg (n=25)

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

C_{max} = Maximum increase in plasma α_1 -PI concentration following infusion; $AUC_{0-\infty}/dose$ = 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 μ M 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 Alpha₁-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 alpha₁-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 alpha₁-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 alpha₁-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 alpha₁-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 alpha₁-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 alpha₁-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.

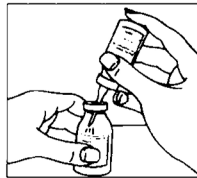
Infusion Rate

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. Remove cover from one end of the double-ended transfer needle. Insert the exposed end of the needle through the center of the stopper in the DILUENT vial.
5. Remove plastic cap from the other end of the double-ended transfer needle now seated in the stopper of the diluent vial. To reduce any foaming, invert the vial of diluent and insert the exposed end of the needle through the center of the stopper in the PRODUCT vial at an angle, making certain that the diluent vial is always above the product vial. The angle of insertion directs the flow of diluent against the side of the product vial. Refer to Figure below. The vacuum in the vial is sufficient to allow transfer of all of the diluent.
6. Disconnect the two vials by removing the transfer needle from the diluent vial stopper. Remove the double-ended transfer needle from the product vial and discard the needle into the appropriate safety container.
7. 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.
8. DO NOT SHAKE THE CONTENTS OF THE VIAL. DO NOT INVERT THE VIAL UNTIL READY TO WITHDRAW CONTENTS.
9. Use within three hours of reconstitution.
10. Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. The reconstituted product should be a colorless or slightly yellow to yellowish-green solution. When reconstitution procedure is strictly followed, a few small visible particles may occasionally remain. These will be removed by the microaggregate filter.
11. Reconstituted product from several vials may be pooled into an empty, sterile IV solution container by using aseptic technique. A sterile 20 micron filter is provided for this purpose.



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HOW SUPPLIED

ARALAST NP is supplied as a sterile, non-pyrogenic, lyophilized powder in single-dose vials. The following product packages are available: 0.5 g (NDC 0944-2802-01) and 1 g (NDC 0944-2802-02). A suitable volume of Sterile Water for Injection, USP diluent is provided (25 mL/0.5 g vial; 50 mL/1 g vial). Each vial is labeled with the total α_1 -PI functional activity in mg. ARALAST NP is packaged with a sterile double-ended transfer needle and a sterile 20-micron filter.

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

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Made by the method of U.S. Patent No. 5,616,693 and 5,981,715.

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