



Arthur Small, M.D.

Medical Director

The Prudential Insurance Company of America
Prudential Plus of the Bay Area
1400 Fashion Island Boulevard, Suite 210
San Mateo, CA 94404
415 345-5599

March 17, 1989

Mr. David Anthony Coppock
3909 17th Street, No. 3
San Francisco, CA 94114

Dear Mr. Coppock:

Thank you for your letter of March 15, 1989.

The Prudential has not changed it's policy on covering aerosolized pentamidine. We have always considered it an experimental treatment. Your treatments were paid for for the fourteen months by Prudential Plus because of our error. Your claims were processed by someone who either was not aware of what treatment was being given, or was not aware of our policy. We have paid for thousands of dollars of treatment which we should not have done. We apologize for our error.

The American system for approving new drugs and treatments for wide use has in the past saved our patients from widespread ill effects that were seen in European countries after introduction of new treatments through their less rigorous approval mechanism. The FDA, other insurance companies, and The Prudential are doing their best to streamline their approval mechanisms in the face of the AIDS epidemic, but these changes are difficult and certainly not nearly as rapid as many AIDS patients and their physicians would wish. I can only assure you that The Prudential's position is not taken as a money saving measure. As you yourself mentioned aerosolized pentamidine, if it is effective in preventing the onset of pneumocystis carinii pneumonia, will likely prevent long and expensive hospitalizations and lower overall health care costs.

Sincerely,

Arthur J. Small, M.D.
Medical Director
0015m/24



Carmelita Cass
Manager

Northern Group Health Claim Division
1450 Fashion Island Boulevard, Suite 200
San Mateo, CA 94404

April 7, 1989

Mr. David Anthony Coppock
3909 17th Street, Number 3
San Francisco, CA 94114

RE: Group Plan 17357

Dear Mr. Coppock:

It has come to our attention that all medical claims for your employer, Chase P. Young Company, are now handled in our Louisville Group Claim Operation. This change occurred recently. We were under the incorrect assumption that you were covered by our Prudential Plus Managed Medical Program.

We are forwarding your file complete with all correspondence between yourself and Dr. Small to Betty Nutt, Claim Consultant in Louisville, Kentucky.

Judy Penrod, Supervisor and Betty Nutt will be your contacts for claims. Their telephone number is (800)541-2037. You should be hearing from Ms. Nutt soon.

Sincerely,

A handwritten signature in cursive script that reads "Carmelita Cass".

Carmelita Cass
Manager
San Mateo Group Claim Complex

CC/pr

cc: Arthur Small, M.D.
Betty Nutt

David A. (Tony) Coppock

3909 17TH STREET #3
SAN FRANCISCO, CA 94114
415/553-4041

PAHT

p e n t a m i d i n e
a d v o c a t e s f o r
n e c e s s a r y
t r e a t m e n t



FOR FURTHER INFORMATION, CONTACT:
DAVID COPPOCK
(415) 553-4041

APRIL 10, 1989



FOR IMMEDIATE RELEASE

The Prudential Insurance Company of America recently notified clients with AIDS, ARC, or who are HIV-positive, that they will no longer pay for treatments for Aerosolized Pentamidine, an extremely promising treatment that preliminary study figures indicate can minimize recurrence or prevent initial onset of *Pneumocystis Carinii Pneumonia*. As reported in the Bay Area Reporter (March 30, 1989), the carrier sent out form letters informing clients receiving the treatments that it was discontinuing payment for the treatments, claiming that it was unproven and experimental, citing Aerosolized Pentamidine's status as an Investigational New Drug under FDA guidelines. The letter also indicated that other carriers may be following suit.

According to local hospital sources, who wished to remain anonymous, the exact number of patients receiving the treatment could not be revealed due to confidentiality concerns. The same sources did indicate that Prudential, while the primary carrier instigating the action, was not the only major U.S. carrier involved. Other carriers are either re-examining their policies or have already begun terminating benefits for the treatments.

In an effort to collect information on the number of people affected or possibly affected by the actions of these carriers, and to determine the best approach in dealing with these carriers, a grass-roots group has been formed, named PANT (Pentamidine Advocates for Necessary Treatment) in San Francisco.

Anyone who has been denied coverage for this treatment is urged to contact PANT at (415) 553-4041, or write them at 3909 17th St., No.3, San Francisco, CA 94114. Respondents need not give their names if

MORE---MORE---MORE

3909 17TH STREET #3
SAN FRANCISCO, CA 94114
415 553-4041

INSURANCE CUT OFF YOUR PENTAMIDINE?

Earlier this year, The Prudential Insurance Company sent out letters to AIDS, ARC and HIV-positive clients, informing them that it would no longer cover the cost of Aerosolized Pentamidine treatments.

Unconfirmed reports from local hospitals tell us that other large insurance carriers are following suit — but won't tell us any more than that. We still don't know which carriers are denying this coverage (besides Prudential), and exactly how many people have been affected by this inhumane decision. Naturally, the insurance companies would like to keep us all in the dark.

We are **PANT**. (PENTAMIDINE ADVOCATES FOR NECESSARY TREATMENT), a grass roots group of people with HIV disease and their friends. Our lives have been drastically affected by this cut off in insurance coverage. Life with HIV can be challenging and expensive enough as it is. How many people can afford an extra \$200-\$300 per month to cover the full costs associated with Aerosolized Pentamidine treatments?

At present, the National Gay Rights Action Alliance are preparing to fight this battle on the national front in the courts. This will take several years. We have been advised that the **fastest** way to solve this problem is pressure on elected officials in

Sacramento. The State Assembly could alter the language in existing insurance regulations, or write new legislation into the insurance code, which would **force** the insurance carriers to cover specifically-exempted treatments, such as Aerosolized Pentamidine, which they might otherwise decline to cover due to the FDA status as Investigational New Drugs. For this work to succeed, we need your help, fast.

WE NEED INFORMATION.

In order to channel our efforts most effectively and influence the people in power on national — and particularly state — levels, we need to know about you. **You need not give your name, if you prefer.** Just call or write us at the address below and tell us your situation: the name of your carrier, when they denied benefits to you, etc. Your quick action could save a life of your own. Please contact us today. Thanks.

3909 17TH STREET #3
SAN FRANCISCO CA 94114
415 553-4041



PANT

TAKE TWO--

NEWS RELEASE--

pentamidine
advocates for
necessary
treatment

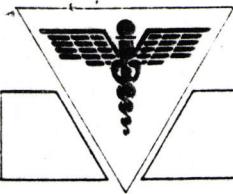
they prefer. With a clear idea of the number of people affected by the carriers' actions, and the names of all carriers involved, PANT hopes to monitor legal and political action against the insurance companies involved, using whatever resources are available and appropriate.

The National Gay Rights Advocates has begun preliminary work on a court case concerning this issue. Interested parties may contact them directly. A PANT legal advisor has suggested that political pressure applied at the state level could move the California State Assembly to act. The Assembly might be persuaded to rewrite parts of the state's insurance code to specifically exempt Aerosolized Pentamidine from the "experimental" status, thus forcing carriers to carry their share of the costs.

If you--or anyone you know-- has been denied benefits for these treatments, please contact PANT immediately.

-30-30-30-30-30-30-30-30-30-

3909 17TH STREET #3
SAN FRANCISCO, CA 94114
415 553-4041



Bay Area Physicians for Human Rights

2940 16th Street, Suite 309 San Francisco, CA 94103 (415) 558-9353

BAPHR

March 31, 1989

Prudential Insurance Company of America
1400 Fashion Island Blvd., Suite 210
San Mateo, CA 94402

Attn: Arthur Small, MD
Medical Director

Dear Dr. Small:

BAPHR, a membership association of several hundred physicians and dentists, urges you and Prudential Insurance to reconsider the policy of not reimbursing costs of prescribed pentamidine mist therapy.

The very much respected San Francisco County Community Consortium has been one of the co-principal investigators of the recent trial of aerosolized pentamidine and has demonstrated the efficacy of this modality. It is obvious that aerosolized pentamidine 300mg inhaled once monthly has been effective in preventing episodes of *Pneumocystis carinii* pneumonia, and is cost effective in the overall management and treatment of individuals with HIV infection. This therapy is rapidly becoming the standard of care for individuals who are immuno-compromised.

Again, we urge Prudential to reconsider its position and adopt a policy of reimbursing this cost effective treatment IND as well as the non-research patient care costs of this therapy.

Thank you for your consideration.

Yours very truly,

BAPHR

Richard L Andrews, MD
Richard Andrews, MD
President

Kenneth Mills, MD
Kenneth Mills, MD
Secretary

Robert Scott, MD

Robert Scott, MD
Vice President

Leonard A. Simpson, MD
Leonard A. Simpson, MD
Treasurer

cc: Nancy Pelosi, Rep., 450 Golden Gate Ave., SFCA 94102
Barbara Boxer, Rep., 450 Golden Gate Ave., SFCA 94102

LAS/as



Arthur Small, M.D.
Medical Director

The Prudential Insurance Company of America
Prudential Plus of the Bay Area
1400 Fashion Island Boulevard, Suite 210
San Mateo, CA 94404
415 345-5599

February 28, 1989

San Francisco, CA 94103

Dear Mr.

Your physician has prescribed Pentamidine by inhalation for you.

This medication has been well proven as a treatment for pneumocystis carinii pneumonia when used intravenously. It has been widely used as an aerosol by inhalation in an attempt to prevent further episodes of pneumocystis carinii pneumonia; however, no one has yet proven that it is effective when used in this way. There are several research projects currently underway attempting to demonstrate its effectiveness. Until these experiments are completed and the full risks and effectiveness of the aerosolized pentamidine are known, it is still considered an experimental drug. Experimental treatments are not covered by your Prudential Plus insurance policy, nor by most other insurance policies.

The Food & Drug Administration has given aerosolized pentamidine the status as an Investigational New Drug (IND). Under this provision, an experimental drug can be sold by the manufacturer outside of the confines of a strict research protocol. While this policy by the FDA does make aerosolized pentamidine more widely available, it does not change its status as an investigational drug.

We will be watching the progress of research in this area closely, and will be adding pentamidine by aerosol to our covered benefits as soon as it has been proven to be safe and effective.

Sincerely,

Art Small, MD

Arthur Small, M.D.
Medical Director

cc: Martin Mass

Insurer Stops Payment For Pentamidine Mist

Prudential Says Preventive Treatment Experimental; Will Pay For IV Treatment Only

by Dennis McMillan

A man with AIDS is up in arms because Prudential Insurance has cancelled coverage of his aerosol pentamidine treatments. David Anthony Coppock, who was due to receive 14 months of prescribed pentamidine mist therapy, was sent a form letter announcing Prudential's policy. He is now waging a personal war against the insurance company, starting off with a letter campaign.

Since the Food and Drug Administration has given aerosolized pentamidine the status of an Investigational New Drug (IND), Prudential Insurance Company of America has apparently been sending out form letters to clients who use the treatment, stating, "under this provision, an experimental drug can be sold by the manufacturer outside the confines of a strict research protocol, and while this policy by the FDA does make [the drug] more widely available, it does not change its status as an IND."

The letter stated that an exception existed for the intravenous form of the medication as a proven treatment for pneumocystis carinii pneumonia, but that the FDA has not yet accepted final proof of the aerosol's effectiveness in its current status.

Coppock pointed out that the IV form of the drug is far more expensive than the mist form and is used for treatment of the disease. The aerosol form is used to prevent the disease from developing.

The letter then flatly stated that since the aerosol is an experimental drug, such treatments "are not covered by the Prudential Plus insurance policy, nor by most other insurance policies."

It went on to say that they will be watching the progress of research of aerosol and will add its coverage "as soon as it has been proven safe and effective."

Coppock, with a very low count of 13 T-cells, responded angrily to Prudential's Feb. 28 letter, writing to Dr. Arthur Small, medical director of Prudential. Coppock wrote: "It is downright shameful that this semantic shift in the way the FDA views the drug is so quickly capitalized upon by insurance carriers to deny benefits."

He told the doctor that he could not imagine going more than six months without the mist until he developed pneumocystis.

"I am extremely saddened to see you, a physician who has presumably taken the Hippocratic oath to preserve life, should conspire with bureaucrats to endorse such a decision," Coppock wrote.

Small wrote back two days later that Prudential has not changed its policy, but there had been a clerical error in ever having paid for his mist treatments in the first place.

Coppock said that he knows of other people who have received this form letter. He said that the receptionist for Pacific Presbyterian stated he is not the only one to complain and that other insurance carriers are acting similarly.

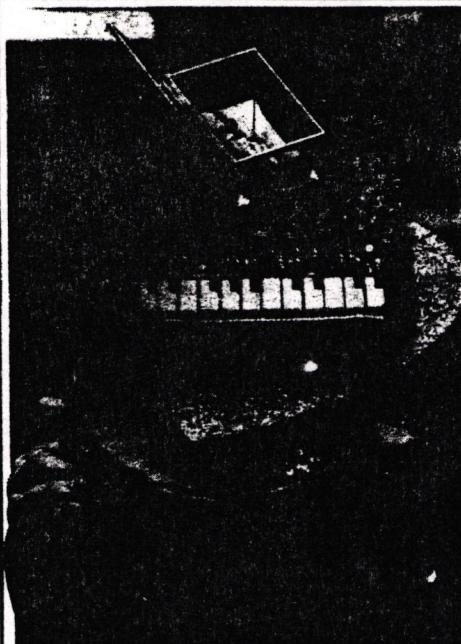
When the B.A.R. contacted Pacific Presbyterian, they were unable to reveal the number of clients affected by Prudential's policy because of the privacy act.

Ida Escarda, area supervisor of the representatives who handle insurance coverage, said that she understood that other insurance companies would likely follow suit.

National Gay Rights Advocates said they are looking into the matter and plan to take legal action against any carriers who adopt this policy of non-coverage of the mist therapy.

Dr. Small declined to speak over the phone concerning the policy, but sent a copy of the form letter stating, "Enclosed is the language sent to our members impacted by this policy."

Coppock encouraged concerned people to write Prudential Insurance Company of America at 1400 Fashion Island Blvd., Suite 210, San Mateo, CA 94404. ▼



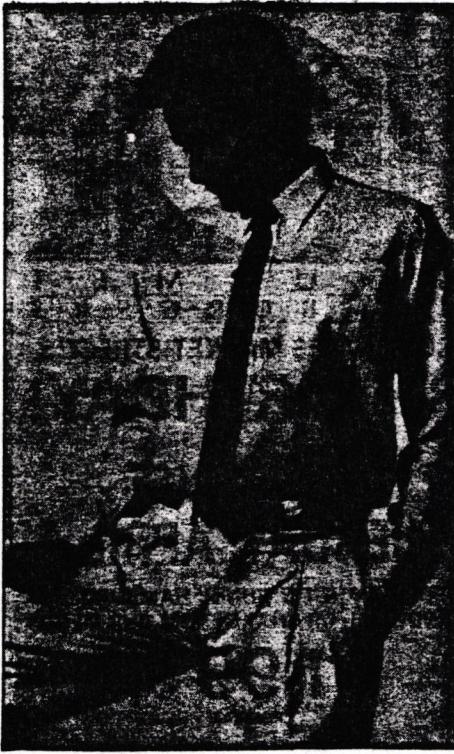
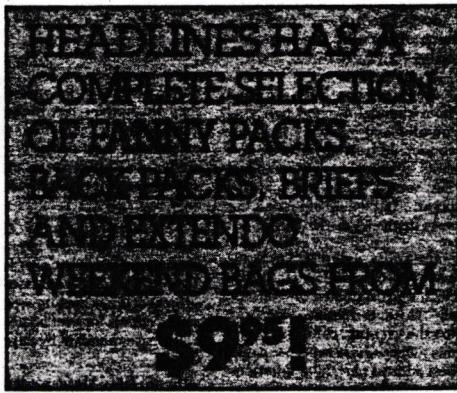
Flair At The Lily Street Fair

This Liberace Bonnet consists of a cowboy hat foundation heart stage holding a red sequined baby grand piano with open caskets containing a gold sequined Liberace lying in state.

(Photo: PhotoGraphics/Dark)

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RETAIL ENTERTAINMENT!



The New York Times/Marilynn K. Yee

Mark Tomita, a registered nurse, administering aerosol pentamidine to an AIDS patient, Robert Mony.

U.S. Permits AIDS Patients to Use Unproven Drug

By GINA KOLATA

The first drug that is thought to prevent a deadly pneumonia in AIDS patients will be made available to seriously ill patients next week without formal Federal approval for marketing.

The drug is being used under a Federal program to give the seriously ill access to promising new drugs before they receive marketing approval from the Food and Drug Administration.

The decision will send a signal to doctors that the drug agency is convinced by preliminary evidence that the drug will prove effective.

The drug, aerosol pentamidine, acts by stopping the growth of organisms

that cause *Pneumocystis carinii* pneumonia, a leading killer of AIDS patients. Several drugs, including an injected form of pentamidine, have been available to treat the pneumonia, but none have been proved effective in preventing it.

The drug agency has been strongly criticized by some advocates for AIDS patients for withholding promising drugs until it had strong evidence of their safety and efficacy. The new decision was perhaps the most significant one yet in an evolving policy under which the agency has said that it will make promising but still unproved drugs available to patients with life-

threatening illnesses.

"This could be a landmark decision," said Dr. Jerome Groopman, an AIDS researcher at New England Deaconess Hospital in Boston.

The agency's limited approval of the drug is expected to provide incentives for people who are at risk for AIDS virus infections to be tested and to have

Continued on Page B7, Column 1

their immune systems monitored. If their immune systems reach the critical danger point that places them at high risk for Pneumocystis pneumonia, they can use aerosol pentamidine to ward off the pneumonia.

The decision of the agency, to be officially announced next week, was reported yesterday by several newspapers. The agency would not comment on the prospects for full marketing approval of aerosol pentamidine.

Pneumocystis pneumonia "is the most common serious infection" to strike AIDS patients, said Dr. Edward M. Bernard of the Memorial Sloan-Kettering Cancer Center in New York. The once rare form of pneumonia strikes more than half of all AIDS patients and has been the most common immediate cause of death among people suffering from acquired immune deficiency syndrome.

Dr. Bernard said most patients survived their first bout with the disease if they went to treatment centers that are experienced in treating it. But treatment involves three weeks of hospitalization, and some patients who have had the disease two or three times are no longer able to tolerate the powerful drugs used to treat it, Dr. Bernard said.

The drug will be released under a program involving investigational new drugs for treatment, or treatment I.N.D.'s. These drugs can be legally prescribed, but their use must be monitored and more data on the drug's safety and effectiveness must be accumulated before the drugs can be licensed for general marketing.

The only drug licensed for use against the AIDS virus itself, azidothymidine, or AZT, was also initially released in late 1986 in an I.N.D. program after initial studies showed it prolonged life. The drug agency says it has since taken steps to further speed availability of promising drugs against serious diseases. It has also ruled that companies may charge patients for drugs distributed under the program. But critics have complained that the agency's policies remained too restrictive.

Prevention of Pneumonia

Patients who have already had one episode of Pneumocystis pneumonia are especially likely to get it again, said Dr. Gifford Leoung of San Francisco General Hospital and the University of California at San Francisco. He and his colleagues found that 45 percent of patients who develop the pneumonia will get it again within nine months if they do not take aero-

sol pentamidine to prevent it.

Preliminary evidence from Dr. Leoung's group and others indicates that aerosol pentamidine can prevent a second attack of the pneumonia in patients who have already had one bout with the disease.

Although these studies did not demonstrate that the drug also prevents a first episode of the pneumonia, the F.D.A. considered data from a Federal study showing that patients with seriously weakened immune systems, those with counts of a type of white blood cell called T-4 cells below 200 per milliliter of blood, are very likely to develop the pneumonia. The agency suspects that those patients too would benefit from the aerosol pentamidine and is making the drug available to them.

Aerosol pentamidine has been widely used over the last year or two by patients in research programs,

'This could be a landmark decision,' an AIDS researcher in Boston says.

and by some doctors and patients, concentrated in the East and West coasts, who have acted without Federal approval.

\$70 a Vial

Pentamidine is made by LyphoMed Inc. of Rosemont, Ill., which charges \$70 a vial for the drug, enough for one treatment. Some patients have received the drug at no cost in experiments, but doctors charge patients anywhere from \$100 to \$500 a treatment, said Martin Delaney, a director of Project Inform, a San Francisco-based group that lobbies for speedier approval of new drugs for AIDS patients..

The treatment involves breathing a mist of pentamidine through a mask, after the drug has been whipped into small droplets by a special nebulizing machine. The optimal schedule of treatments has not been determined; many patients are treated twice a month, while others inhale the drug once a week or once a month. The drug agency will recommend that patients take 300 milligrams every four weeks.

Up to now, patients taking the aerosol treatment usually have traveled to doctors' offices or to hospitals, although some patients have purchased their own nebulizers, which cost from about \$200 to \$700, Mr. Delaney said.

Some insurance companies have

paid for aerosol pentamidine, but others have refused, arguing that this use of the drug was not approved, and patients have had to pay for the monthly or twice-a-month treatments out of their own pockets. A legal expert said yesterday that it was unclear whether the limited form of approval now being granted, which explicitly labels a drug as still experimental, would force more insurance companies to pay the cost.

Many Are Surprised

The agency's decision came as a surprise to many researchers and advocates for AIDS patients who have long argued that aerosol pentamidine should be widely and legally available. The drug is now marketed for use intravenously and by injection.

Some doctors have hesitated to use aerosol pentamidine to prevent disease, waiting for more definitive data showing that it was effective. And others have used it only in patients who have already had one bout with Pneumocystis pneumonia.

"You can get aerosolized pentamidine in New York and San Francisco with ease, but beyond that the ease falls off quickly," Mr. Delaney said. "A lot of doctors and hospitals have been waiting until the F.D.A. approved it."

To receive the drug through the I.N.D. program, doctors will call LyphoMed and request it for their patients, according to an F.D.A. official. If the patients are eligible under the guidelines of the I.N.D. program, the company will send the drug. The doctor will report back to the company on the clinical progress of the patients taking the drug. LyphoMed declined to say whether it would charge for the drug, adding that it would make that announcement next week when the treatment I.N.D. is formally announced. An official of the drug agency said the company would set up a special hot line for doctors seeking the drug and would announce the number next week.

In making its decision, the agency relied heavily on a study directed by Dr. Donald Abrams and Dr. Leoung of San Francisco General Hospital, which involved 408 people infected with the AIDS virus and 75 doctors in San Francisco. About 250 of the participants in the study had had at least one bout with Pneumocystis pneumonia, and the others had either Kaposi's sarcoma, a cancer that often infects AIDS patients, or other illnesses that are common to carriers of the AIDS virus who have weakened immune systems.

The patients were randomly assigned to take one of three doses of aerosol pentamidine, once every two weeks or once a month. The researchers found that the patients who had already had pneumonia had significantly fewer subsequent bouts with pneumonia than expected. But they could not determine whether the drug was equally effective in patients who had not already had pneumonia.

Uncertainty Over Effect

Dr. Leoung said the uncertainty was because the researchers did not know how likely those patients were to develop the pneumonia in the first place, and so they could not estimate how effective they were in preventing it. The researchers said they felt they would not be able to find patients willing to serve as a comparison group, taking an inert substance rather than the drug.

Aerosolized Pentamidine for Treatment and Prophylaxis of *Pneumocystis carinii* Pneumonia: An Update

Kevin J Corkery BS RCP RRT, John M Luce MD, and A Bruce Montgomery MD

Introduction

The rapid increase in numbers of cases of *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome (AIDS) has led to a search for effective and less toxic antipneumocystosis therapy and prophylaxis. This short review is intended to summarize recent developments regarding aerosolized pentamidine and inspire further research in this promising modality.

Background

The first reports of *P. carinii* causing what was then known as interstitial plasma cell pneumonia originated in central Europe in the 1940's in infants suffering from malnutrition. Subsequently, PCP was diagnosed in patients with impaired host immunity, leading to the classification of the organism as an opportunist.¹ With few exceptions, PCP continued to be a sporadic opportunistic infection involving

mainly patients who had lymphomas or leukemias or who were receiving immunosuppressive therapy.¹ Beginning in 1979, however, the epidemiology of PCP changed drastically with the development of the AIDS epidemic. Since that year, more than 49,000 AIDS cases have been reported to the Centers for Disease Control (CDC).² *P. carinii* pneumonia is the most common life-threatening opportunistic infection reported among patients with AIDS. It is the initial opportunistic infection in 65% of HIV-infected patients and occurs in 20% of patients whose diagnosis of AIDS has been established by another process. An analysis of past trends projects a cumulative AIDS incidence of 270,000 by 1991, with 51,000 new cases occurring in that year alone.^{3,4} Hence, it is projected that, by 1991, more than 173,000 cases of PCP will have occurred in the United States alone.

Pneumocystis carinii pneumonia in AIDS patients may have protean manifestations but classically presents with symptoms of fever, cough, and dyspnea.¹ Diagnostic tests characteristically reveal arterial hypoxemia, diffuse radiographic infiltrates, and evidence of restrictive lung disease.¹ Unlike common pathogens that cause bacterial pneumonia, *P. carinii* is an extracellular protozoan that inhabits predominantly the alveolar spaces, with close approximation to the surfaces of alveolar epithelial cells or alveolar macrophages.⁵ Extrapulmonary *P. carinii* infections are rare, suggesting that the alveolar environment is usually necessary for growth of the pathogen.⁵ Optimal therapy would produce adequate antipneumocystosis drug levels in alveoli while limiting systemic side effects, this being the theoretical advantage of aerosol therapy that targets the lungs.

Mr Corkery is Assistant Technical Director, Respiratory Care Service, University of California at San Francisco General Hospital, San Francisco, California. Dr Luce is Associate Professor of Medicine and Anesthesia, University of California, San Francisco, and Associate Director, Medical-Surgical Intensive Care Unit, San Francisco General Hospital. Dr Montgomery is Assistant Professor of Medicine, University of California, San Francisco, Chest Service, San Francisco General Hospital.

Reprints: Kevin J Corkery BS RCP RRT, Respiratory Care Service, 1001 Potrero Ave, Room GA 2, San Francisco General Hospital, San Francisco CA 94110.

particles and half in smaller particles.²² Geometric standard deviation is a unitless measurement calculated by dividing the MMAD by particle size at the 84th percentile of the total mass.²³ Generally, a geometric standard deviation greater than 2 indicates a wide range of particle sizes.²³ The size range of pentamidine aerosols that have been used clinically has varied from 0.25 to greater than 12 μ (Table 1).

Aerosol deposition is determined by three interdependent processes—inelastic impaction, gravitational sedimentation, and Brownian motion—each affecting different size ranges of particles.^{22,23,25-27} Inertial impaction occurs at areas of nonlaminar flow in the oropharynx and large central airways. Nonlaminar conditions are created by turns and bifurcations or increased flowrates. Larger particles generally impact from inertia in the oropharynx; almost all particles $> 10 \mu$ do not reach the alveoli, and most are impacted in the oropharynx. Likewise,

the majority of particles $> 5 \mu$ do not reach beyond the central airways. The second process, gravitational sedimentation, is determined by low-flow states of particles between 0.5 and 10 μ in small airways and alveoli. Brownian motion, the third process of particle deposition, causes particles $< 0.5 \mu$ to deposit randomly throughout the lung. The relatively large surface area of alveoli compared to airway surface area determines that more submicronic particles deposit in the alveoli.^{22,23,25-27} Approximately 80% of particles in this size range remain suspended and are exhaled.^{23,27}

Particle size, therefore, is a major determinant of location of deposition. The optimal size of particles for alveolar deposition is between 1 and 2 μ , and for tracheobronchial deposition it is between 4 and 7 μ .²² Many patient factors affect aerosol deposition, including inspiratory flowrates, frequency of respiration, breath-holding, and tidal volumes. Airway narrowing from bronchospasm, emphysema, mucus,

Table 1. Features of Nebulizers Used To Deliver Aerosolized Pentamidine

	MMAD*	GSD†	Reservoir for Aerosol during Exhalation?	Expiratory Filter?	Comments
Jet Nebulizers					
Aerotech II	2.0	$\pm 2.5\ddagger$	No	Optional	10-15 L/min flow
Centimist	1.1	$\pm 2.2\$$	Yes	No	9 L/min flow
Fan Jet	4.3	$\pm 2.5\ddagger$	No	Optional	7 L/min flow
Respirgard II	0.93	$\pm 1.8\ddagger$	Yes	Yes	7 L/min flow
System 22	1.3	N.A.	No	No	7 L/min flow
Ultra Vent	0.25	$\pm 2.0^{\#}$	No	Yes	11-14 L/min flow
Ultrasonic Nebulizers					
Fisoneb	5.0	$\pm 2.0\ddagger$	Yes	No	Intermittent use trigger
"Green Machine"	> 12.0	N.A.	Yes	No	Intermittent use trigger
Portosonic	1.6	$\pm 2.2\ddagger$	Yes	Optional	Continuous flow
Pulmosonic	4.2	$\pm 2.3\ddagger$	Yes	No	Continuous flow

*MMAD = mass median aerodynamic diameter. This was measured by noted methods under various conditions and may not be directly comparable.

†GSD = geometric standard deviation.

‡Particle size measured as in Ref 31, with 7 L/min flow to jet nebulizer or to flush chamber on ultrasonic nebulizer.

§Particle size measured under conditions of simulated breathing (Ref 24).

||Particle size measured by Malvern 2400 laser diffraction particle sizer (Ref 34).

#Particle size measured by cascade impactor (Ref 29).

N.A. = not available (not noted or not measured).

and/or alveolar-filling processes such as PCP also can limit aerosol delivery to the alveoli.^{22,25,26}

Two types of nebulizers, ultrasonic and jet, have been employed to deliver aerosolized pentamidine. Ultrasonic nebulizers operate by generating an ultra-high-frequency sound from a piezoelectric crystal that creates a geyser from which particles are expelled.²⁸ The particle size of aerosols from ultrasonic nebulizers is a function of the frequency of the signal to the piezoelectric crystal²⁸ and of flowrates. A higher frequency ultrasonic nebulizer will produce smaller initial particles, but when flow through the nebulizer is discontinuous, as with tidal breathing, larger particles are created because the small particles rapidly coalesce into larger particles.²³ It will not be surprising if different measurements of output and particle size are reported, because of different operating conditions. Jet nebulizers work by high-flow gas shearing liquid strands from a thin layer of solution maintained by surface tension. The liquid strands hit a baffle, and a wide variety of particle sizes is created. The larger particles generally fall by gravity and are reincorporated into the solution. Smaller particles can be created by higher gas pressures. Due to the inherent continuous flow, output, and particle-size distribution, jet nebulizers are relatively more constant than ultrasonic nebulizers.²⁸

Commercially available ultrasonic nebulizers currently in use are the Fisoneb, Pulmosonic, and Portosonic (Table 1).* The Fisoneb and Pulmosonic both operate at a frequency of 1.3 mHz, which predicts a MMAD of 4 to 6 μ .²⁸ The Pulmosonic has been reported to deliver few particles $< 2 \mu$ and therefore may be unsuitable for applications requiring high yields to peripheral lung areas.²⁸ The Portosonic nebulizer is a 2.3-mHz ultrasonic nebulizer and may offer the combination of a 1.3 μ MMAD with a high output. Output and particle size of ultrasonic nebulizers need to be periodically sampled, as the frequency of the piezoelectric crystal may alter with age.²⁸

Nebulizers are commercially available in the United States that produce a MMAD between 0.25 and 2.0 μ (Table 1). The Respigrad II, currently used in studies at San Francisco General Hospital, has one-

way valves that control a drug reservoir, that allow entrainment of room air in patients whose minute ventilation is high, that act as a baffle to decrease particle size, and that direct expired air to a filter that scavenges remaining drug, preventing environmental contamination. The Centimist is a similar device with a larger reservoir but no expiratory filter. The Aerotech II has internal baffles in the jet nebulizer and therefore may allow recycling of the drug; however, because it requires a high gas flowrate between 10 and 15 L/min and lacks an aerosol reservoir, much of the drug is not available to the patient for inhalation. Experience with the Aerotech II is limited. Although efficacy is not known, anecdotal reports of coughing at high doses above 100 mg have led to use of a 40-mg dose for prophylaxis studies (Tom Boylen MD: personal communication.) Three factors could account for the increased incidence of airway reactivity at higher doses: increased flows from the higher inherent flow-rate of the device, a larger particle size, or higher output from the nebulizer. The Ultra Vent has a MMAD of 0.25 μ .²⁹ This would predict random deposition by Brownian motion throughout the lung, with most of the particles being exhaled.^{25,27}

The present state of knowledge cannot allow determination of the most effective device because comparative pharmacokinetic studies have not been conducted in human beings. The device should maximize alveolar deposition and keep large-airway deposition to a minimum because pentamidine isethionate, containing a SO₃ moiety, is an airway irritant.³⁰ The optimal particle size for alveolar deposition is between 1 and 2 μ , with 1 μ achieving more peripheral distribution and less airway distribution.^{22,23,25-27} Other features such as reservoirs, operating flowrates, and external filters may also be important.

A pharmacokinetic study that allows estimates of the dose of pentamidine needed in treatment trials using the Respigrad II has been conducted in eight patients with diffuse alveolar infiltrates undergoing fiberoptic bronchoscopy for suspected PCP.³¹ Bronchoalveolar lavage (BAL) sediment and supernatant concentrations of pentamidine were compared between 18 and 24 hours after administration of 4 mg/kg I.V (n = 3) and aerosolized (n = 5) pentamidine isethionate to different groups of patients. An aerosol containing 300 mg of

*Suppliers are identified in the Product Sources section at the end of the text.

Conventional and Experimental Systemic Therapy

Two drugs, trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine isethionate, have been conventional therapy for PCP. TMP-SMX is administered intravenously (I.V.) or orally, whereas pentamidine isethionate is usually administered I.V. or intramuscularly (IM).⁶ Both intravenous pentamidine and TMP-SMX are at least 80% effective in the treatment of first-time episodes of PCP in patients with AIDS.⁷ However, both conventional therapies have a 50% or greater incidence of adverse reactions that necessitate a change in drug therapy.⁷⁻⁹

Common adverse reactions seen with administration of TMP-SMX involve rash, fever, nausea, leukopenia, thrombocytopenia, and hepatitis.^{7,9} The adverse effects of parenteral pentamidine include pain, swelling, and sterile abscesses at the site of IM injection, and thrombophlebitis and urticarial eruptions with I.V. administration.^{10,11} Severe hypotension may develop with a single IM dose or after rapid I.V. infusion.^{10,11} Hypoglycemia has been reported in up to 62% of patients;¹¹ subsequent diabetes mellitus occurs rarely.¹² Impaired renal function has been described in up to 25% of patients receiving systemic pentamidine.^{11,12} Other side effects attributed to pentamidine include elevated liver enzymes, neutropenia, thrombocytopenia, fever, hypocalcemia, hallucinations, arrhythmias, and pancreatitis.¹²

Although not approved by the Food and Drug Administration (FDA), oral dapsone-trimethoprim has been shown to be as effective as, but less toxic than, oral TMP-SMX in AIDS patients with first-time episodes of PCP of mild severity in both a pilot study¹³ and a double-blind trial.¹⁴ The adverse reactions seen with dapsone-trimethoprim are nausea, vomiting, skin rash, decreased hematocrit, elevated creatinine, methemoglobinemia, elevated liver enzymes, neutropenia, and thrombocytopenia.^{13,14}

Trimetrexate is another experimental agent for PCP that has been approved by the FDA for use on a compassionate basis. Trimetrexate is a potent inhibitor of mammalian and protozoal dihydrofolate reductase.¹⁵ Due to its solubility in lipids, this agent easily enters both the protozoan and mammalian cells.

antifolate effects.¹⁶ Leucovorin, which is not lipid-soluble, is actively transported into mammalian cells but not into *P. carinii* cells.¹⁵ A pilot study with trimetrexate-leucovorin and trimetrexate-leucovorin with sulfadiazine revealed a 70% positive-response rate.¹⁶ Adverse reactions were less severe in the trimetrexate-leucovorin therapy than in conventional therapy, but they were similar to the reactions to TMP-SMX in patients receiving trimetrexate-leucovorin with sulfadiazine.¹⁶ Adverse reactions seen with trimetrexate-leucovorin are neutropenia, thrombocytopenia, elevated creatinine, elevated liver enzymes, and rash.¹⁶ Particularly promising results were seen in salvage therapy after failure to respond to standard therapy. Eleven of 16 patients survived, a considerable improvement compared with what has been reported in similar patients in other studies. Patients who received trimetrexate-leucovorin alone as initial therapy had a significant relapse rate of PCP within 6 weeks of ending therapy.¹⁶

Aerosol Pentamidine Therapy

Because of the high frequency of adverse reactions seen with current therapies for PCP, novel therapies are needed. Two approaches are possible: use new agents as noted earlier or target delivery of known agents. Due to the intra-alveolar location of *P. carinii*, aerosolization of pentamidine should provide an effective, site-specific, and hence less-systemically toxic method of therapy^{17,18} or prophylaxis.¹⁹ Studies of aerosolized pentamidine in rats with PCP have documented efficacy in both prophylaxis and treatment and suggest that the half-life of the drug is long—probably weeks—with increased clearance in ill animals.¹⁷⁻¹⁹ Debs and colleagues reported negligible clearance in 48 hours in normal mice,¹⁷ in rats the elimination half-life from the lungs has been reported to be 36 days.²⁰ A recent study of prolonged tissue concentrations after parenteral administration in AIDS patients suggests that an effective aerosol-delivery device should achieve high lung concentrations of pentamidine.²¹

Pentamidine has been nebulized only as a heterodispersed aerosol. Aerosol size is described by mass median aerodynamic diameter (MMAD), and the size range is described by geometric standard

pentamidine isethionate in 6 ml of distilled water was inhaled for 35 to 40 minutes. In patients with diffuse alveolar infiltrates, significantly higher concentrations of aerosolized pentamidine reached the airspaces than did the I.V. form of the drug; BAL pentamidine concentrations in sediment were 9.34 ± 1.74 ng/ml post-I.V. administration vs 705 ± 242 ng/ml post-aerosol (mean \pm SEM, $P < 0.05$).³¹ Serum pentamidine levels were low or undetectable after aerosolization. The large variation in BAL levels following aerosol but not I.V. administration suggests that the variability is due to aerosol deposition and not to BAL technique.³¹

Conte and colleagues, using another aerosol device (the Ultra Vent nebulizer), have conducted a similar study and reached similar conclusions.³² The efficiency of the two nebulizers in the studies could not be directly compared due to different methods of BAL analysis.

Three pilot studies of aerosolized pentamidine as treatment have been conducted. In one study,³³ Montgomery and colleagues used 600 mg of pentamidine in the Respigrad II nebulizer in order to at least match the dose used in the pharmacokinetic study cited earlier³¹ and to shorten the duration of therapy. Montgomery et al had noted that aerosol administration for longer than 30 minutes was not well tolerated and that the nebulizer became progressively less efficient. They estimated the deposited dose to be between 30 and 60 mg because the nebulizer probably delivers about 5 to 10% of the dose to the lungs.²² In this study, 15 AIDS patients with initial episodes of mild to moderate PCP received a 25-minute daily inhalation of aerosol pentamidine for 21 days. Thirteen of the 15 patients responded to therapy. In successfully treated patients, mean P_{aO_2} was 67.9 torr before therapy and 80.1 torr after therapy; mean vital capacity was 50.8% of predicted value before therapy and 67.9% of predicted value after therapy. No adverse systemic reactions (such as renal, liver, and hematologic abnormalities, hypoglycemia, or hypotension) were observed during therapy. Serum pentamidine concentrations were less than 10 ng/ml in 12 of 14 patients. In two patients, serum pentamidine concentrations were 22 and 32 ng/ml at the end of therapy. Coughing was noted in 12 patients and was successfully treated in 9 patients by administration of an aerosolized bronchodilator prior to aerosolization of pentamidine or by lowering

the gas flowrate to the pentamidine aerosol delivery device.³³ Three patients who had persistent cough had a history of bronchospasm or smoking.³³ After one year of follow-up, only two relapses have occurred.

In a second study, Conte and colleagues studied inhaled or reduced-dose pentamidine for treatment of PCP.³² Nine of the 13 patients inhaling aerosolized pentamidine for treatment of mild PCP had a satisfactory response in this study; three patients could not be evaluated due to early withdrawal, and one had treatment failure. Two of the nine patients who could be evaluated had neutropenia, but these patients had been receiving zidovudine (azidothymidine, AZT) and had low pretreatment leukocyte counts. Other mild adverse reactions involved cough, bronchospasm, rash in one patient, and temperature elevations. The nebulizer (Ultra Vent) dose was 4 mg/kg body weight; this was nebulized over a 30- to 60-minute period.³² Serum pentamidine concentrations were greater than 20 ng/ml in 5 of 13 patients. The higher serum pentamidine concentrations in this study as compared to that of Montgomery and colleagues are unexplained but may be due to the increased airway deposition, resulting in systemic absorption. Three of the successfully treated patients experienced early relapse.³² Based on dose, duration of treatment, particle size, deposition estimates, higher nebulizer flowrate, and lack of a nebulizer reservoir, the total dose delivered to the alveoli in this study was probably one half to one fourth the dose used by Montgomery and colleagues; whether this explains the difference in patient outcome in the two studies is not known.

The third study was by Godfrey-Faussett and colleagues.³⁴ An acorn nebulizer (System 22) that lacks a drug reservoir was used with or without a bead filter at two different doses in 13 patients (4 mg/kg in the first 6 patients and 8 mg/kg in the other 7 patients). Only two patients responded; the others were removed for failure to respond or cough. The MMAD of aerosol from their nebulizer system was 1.3μ for the first 10 patients and 0.8μ for the remainder. They concluded that the optimum characteristics of the best delivery system need to be determined prior to recommendation that aerosolized pentamidine be used for treatment.³⁴

Other side effects of aerosolized pentamidine therapy include hypoglycemia, reported in one patient

the episode. The number of relapses in the control group has been 37, compared to 6 in the 152 patients receiving aerosolized pentamidine ($P < 0.01$).⁴⁸ The efficacy over longer periods and toxicity other than airway irritation of each dosing group have yet to be determined.

In another San Francisco study, Fallat and colleagues have treated 211 patients with a dose of 30 mg of aerosolized pentamidine delivered by the Fan Jet nebulizer.⁴⁹ These investigators have estimated that relapse was delayed an average of 5 months in their patients.⁴⁹ Lowery and colleagues have reviewed the radiographic pattern of relapse in patients on aerosol pentamidine and found a striking increase of relapses in the upper lobes.⁵⁰ This correlates with the predicted deposition of most of the drug in the lower lobes and suggests that patients respond to the aerosol. In order to achieve more even distribution of the aerosol throughout all lung zones, it may be efficacious to have the patient breathe at a fast rate, breathe higher doses, and/or periodically breathe from residual volume during the aerosol administration.⁵⁰

Other data on aerosol prophylaxis have been reported by Bernard and colleagues from Sloan Kettering Medical Center.⁵¹ Aerosolized pentamidine has been administered using a Siemens "Green Machine"** hand-held ultrasonic nebulizer in this protocol. In the first trials, 30 mg of pentamidine was administered bi-weekly; in the next set of trials, patients were randomized to 30, 45, or 60 mg weekly for the first month and then bi-weekly.⁵¹ The 30- and 45-mg doses were discontinued because of prophylaxis breakthrough. They reported that a total of 120 patients with AIDS and PCP had been treated for an average of 5 months. Five episodes of PCP have been reported in patients receiving 30 mg, two episodes in patients receiving 45 mg, and one episode in patients receiving 60 mg.⁵¹ It is unclear how much of the pentamidine actually reached the lung periphery of these patients since the "Green Machine" ultrasonic nebulizer used in this study produces a median particle size $> 12 \mu$ (Table 1). Because of this large particle

size, most of the drug probably is delivered to the oropharynx.^{22,25,26} Bernard and colleagues are now doing dose-ranging studies with a Fisoneb ultrasonic nebulizer.

The optimal dose, particle size, and frequency of administration for prophylactic aerosol pentamidine are not known. A change in the distribution, severity of occurrence, and frequency is apparent even at low doses delivered to the alveoli, but whether higher doses prove more efficacious without significant side effects is yet to be determined. It will be difficult to compare specific doses with those achieved at other centers using different nebulizers because the amount of pentamidine deposited in the alveoli is so dependent upon equipment and patient factors. Furthermore, uncontrolled studies may involve patients with different rates of relapse because the incidence of recurrent PCP is dependent on time between episodes of PCP and the start of prophylaxis.⁵²

Administration

Lyophilized pentamidine must be reconstituted with sterile water, because saline solutions cause the pentamidine to precipitate out of solution. We have chosen the volume of the diluent to be 6 ml because 100 mg/ml is the saturation concentration, and also to standardize therapy. After reconstitution, pentamidine is stable at 20°C for 24 hours, at 4°C for 104 hours, and at -10°C for 5 months (Abu Alam PhD, LyphoMed Inc: unpublished data).

We cannot comment on other nebulizer systems used to deliver aerosolized pentamidine because we have personal experience with only the Respigrad II Nebulizer System. However, if one uses the Respigrad II Nebulizer System, the nebulizer flowrate should be 5-7 L/min using a pressure-compensated flowmeter attached to a 50-psi dry-gas source; this generates a nebulizer-line pressure of 20 to 25 psi. If the 50-psi dry-gas source is not available for prophylactic administration of non-acutely ill patients, we recommend the BUNN BA 400 air compressor or equivalent with a variable pressure (20-50 psi) regulating knob. The Respigrad II Nebulizer System should be attached to a PALL BRO-1 nebulizer-line bacterial filter or equivalent, which is attached to a nipple adapter on the oxygen DISS connector of the air compressor. The variable-psi knob must be adjusted between 23 and 25 psi to match the pressure

**"Green Machine" is a nickname bestowed on the device by researchers, not a commercial name. The nebulizer is not available in the U.S., and Siemens would not recognize the name.

March 15, 1989

Dr. Arthur Small, M.D.
Medical Director
The Prudential Insurance Company of America
1400 Fashion Island Boulevard, Suite 210
San Mateo, California 94404

Dear Dr. Small:

I have just received your letter of February 28, 1989, regarding your company's decision to drop payment benefits for aerosolized pentamidine treatments.

That the FDA has blundered again in its decision to classify Pentamidine administered via mist as an Investigational New Drug is certainly no surprise, considering the agency's historic inability to do anything in a pragmatic, humane or logical way. But it is downright shameful that this semantic shift in the way the FDA views the drug has been so quickly capitalized upon by U.S. insurance carriers to deny benefits, and maximize their profits at the expense of people's lives and futures. If this weren't so, how can you explain that your company paid for this treatment for FOURTEEN MONTHS before suddenly changing its mind?

I am just one man, and I don't earn enough money to pay for these treatments without the help of insurance. You're a doctor, you tell me: I had 13 T-Helper cells in my last blood draw a week ago, and that count has been below 50 for more than six months now. Without this treatment, just how long do you think it will be before I develop Pneumocystis? Six months, maybe a year? And your company will save how much--\$3,000--by denying these benefits?

How much will the standard 21 hospital days with the drug administered IV cost you? \$12,000? \$14,000? \$16,000? You tell me, since you have the statistics and the hospital bills of other patients. It certainly doesn't make any fiscal sense in the short term, does it? But then, I think there's a larger agenda going on here. If, by not preventing the onset of Pneumocystis with these treatments, I actually get the disease, I will probably lose 10 to 20% of my total body weight, all my strength, and my system will less able to fight off future infections. Plus there's the good chance that my system will be desensitized to Pentamidine as a result of IV infusion on that scale. All of this can only set me up to get sick again, sooner, and more frequently, thereby decreasing my actual lifespan. And the shorter my lifespan, the fewer months or years that Prudential will have to pay for the various other exotic and costly infections this syndrome produces. Thus, in the long term, the decision to not provide benefits for this treatment in effect shortens my life and saves you money.

While I am appalled by this decision, I am not particularly surprised, in light of my past difficulties in dealing with your company. I am, however, extremely saddened to see that you, a physician who has presumably taken the Hippocratic Oath to preserve life, should collude with actuaries and conspire with bureaucrats in endorsing such a decision, particularly in the face of recent and mounting evidence that Aerosolized Pentamidine does, indeed, seem to minimize the recurrence of PCP, and would thus by logical extension, tend to prevent or minimize its onset in severely immunocompromised patients. Shame on you. I just wish that you were the one that had to write my mother back in Mississippi and explain why benefits to pay for a treatment that would likely prolong my life are being denied.

David Anthony Coppock



Arthur Small, M.D.
Medical Director

The Prudential Insurance Company of America
Prudential Plus of the Bay Area
1400 Fashion Island Boulevard, Suite 210
San Mateo, CA 94404
415 345-5599

February 28, 1989

David Coppock
59 Albion St.
San Francisco, CA 94103

Dear Mr. Coppock:

Your physician has prescribed Pentamidine by inhalation for you.

This medication has been well proven as a treatment for pneumocystis carinii pneumonia when used intravenously. It has been widely used as an aerosol by inhalation in an attempt to prevent further episodes of pneumocystis carinii pneumonia; however, no one has yet proven that it is effective when used in this way. There are several research projects currently underway attempting to demonstrate its effectiveness. Until these experiments are completed and the full risks and effectiveness of the aerosolized pentamidine are known, it is still considered an experimental drug. Experimental treatments are not covered by your Prudential Plus insurance policy, nor by most other insurance policies.

The Food & Drug Administration has given aerosolized pentamidine the status as an Investigational New Drug (IND). Under this provision, an experimental drug can be sold by the manufacturer outside of the confines of a strict research protocol. While this policy by the FDA does make aerosolized pentamidine more widely available, it does not change its status as an investigational drug.

We will be watching the progress of research in this area closely, and will be adding pentamidine by aerosol to our covered benefits as soon as it has been proven to be safe and effective.

Sincerely,

Art Small, MD

Arthur Small, M.D.
Medical Director

cc: Martin Mass