

**PULMOZYME- dornase alfa solution**  
**Genentech, Inc.**

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**Pulmozyme®**  
**(dornase alfa)**  
**Inhalation Solution**

**DESCRIPTION**

Pulmozyme is a sterile, clear, colorless, highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. The protein is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing DNA encoding for the native human protein, deoxyribonuclease I (DNase). Fermentation is carried out in a nutrient medium containing the antibiotic gentamicin, 100–200 mg/L. However, the presence of the antibiotic is not detectable in the final product. The product is purified by tangential flow filtration and column chromatography. The purified glycoprotein contains 260 amino acids with an approximate molecular weight of 37,000 daltons (1). The primary amino acid sequence is identical to that of the native human enzyme.

Pulmozyme is administered by inhalation of an aerosol mist produced by a compressed air driven nebulizer system (see Clinical Experience, DOSAGE AND ADMINISTRATION). Each Pulmozyme single-use ampule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.

**CLINICAL PHARMACOLOGY**

**General**

In cystic fibrosis (CF) patients, retention of viscous purulent secretions in the airways contributes both to reduced pulmonary function and to exacerbations of infection (2,3).

Purulent pulmonary secretions contain very high concentrations of extracellular DNA released by degenerating leukocytes that accumulate in response to infection (4). In vitro, Pulmozyme hydrolyzes the DNA in sputum of CF patients and reduces sputum viscoelasticity (1).

**Pharmacokinetics**

When 2.5 mg Pulmozyme was administered by inhalation to eighteen CF patients, mean sputum concentrations of 3 µg/mL DNase were measurable within 15 minutes. Mean sputum concentrations declined to an average of 0.6 µg/mL two hours following inhalation. Inhalation of up to 10 mg TID of Pulmozyme by 4 CF patients for six consecutive days, did not result in a significant elevation of serum concentrations of DNase above normal endogenous levels (5,6). After administration of up to 2.5 mg of Pulmozyme twice daily for six months to 321 CF patients, no accumulation of serum DNase was noted.

Pulmozyme, 2.5 mg by inhalation, was administered daily to 98 patients aged 3 months to ≤10 years, and bronchoalveolar lavage (BAL) fluid was obtained within 90 minutes of the first dose. BAL DNase concentrations were detectable in all patients but showed a broad range, from 0.007 to 1.8 µg/mL. Over an average of 14 days of exposure, serum DNase concentrations (mean ± s.d.) increased by 1.3 ± 1.3 ng/mL for the 3 months to <5 year age group and by 0.8 ± 1.2 ng/mL for the 5 to ≤10 year age group. The relationship between BAL or serum DNase concentration and adverse experiences and clinical outcomes is unknown.

**Clinical Experience**

Pulmozyme has been evaluated in a randomized, placebo-controlled trial of clinically stable cystic

fibrosis patients, 5 years of age and older, with baseline forced vital capacity (FVC) greater than or equal to 40% of predicted and receiving standard therapies for cystic fibrosis (7). Patients were treated with placebo (325 patients), 2.5 mg of Pulmozyme once a day (322 patients), or 2.5 mg of Pulmozyme twice a day (321 patients) for six months administered via a Hudson T Up-draft II<sup>®</sup> nebulizer with a Pulmo-Aide<sup>®</sup> compressor.

Both doses of Pulmozyme resulted in significant reductions when compared with the placebo group in the number of patients experiencing respiratory tract infections requiring use of parenteral antibiotics. Administration of Pulmozyme reduced the relative risk of developing a respiratory tract infection by 27% and 29% for the 2.5 mg daily dose and the 2.5 mg twice daily dose, respectively (see Table 1). The data suggest that the effects of Pulmozyme on respiratory tract infections in older patients (>21 years) may be smaller than in younger patients, and that twice daily dosing may be required in the older patients. Patients with baseline FVC >85% may also benefit from twice a day dosing (see Table 1). The reduced risk of respiratory infection observed in Pulmozyme treated patients did not directly correlate with improvement in FEV<sub>1</sub> during the initial two weeks of therapy.

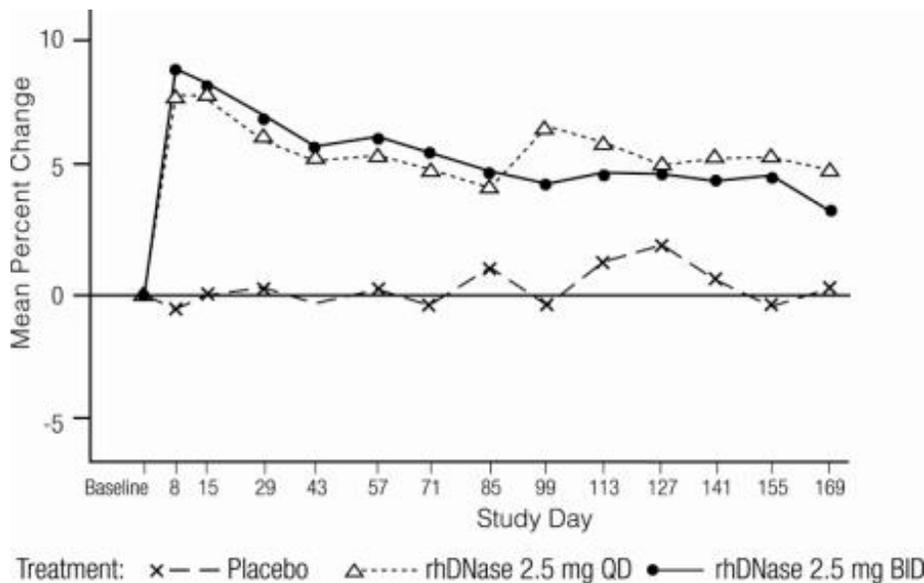
Within 8 days of the start of treatment with Pulmozyme, mean FEV<sub>1</sub> increased 7.9% in those treated once a day and 9.0% in those treated twice a day compared to the baseline values. The overall mean FEV<sub>1</sub> during long-term therapy increased 5.8% from baseline at the 2.5 mg daily dose level and 5.6% from baseline at the 2.5 mg twice daily dose level. Placebo recipients did not show significant mean changes in pulmonary function testing (see Figure 1).

For patients 5 years of age or older, with baseline FVC greater than or equal to 40%, administration of Pulmozyme decreased the incidence of occurrence of first respiratory tract infection requiring parenteral antibiotics, and improved mean FEV<sub>1</sub>, regardless of age or baseline FVC.

**Table 1: Incidence of First Respiratory Tract Infection Requiring Parenteral Antibiotics in Patients with FVC ≥40% of Predicted**

	Placebo N=325	2.5 mg QD N=322	2.5 mg BID N=321
<u>Percent of Patients Infected</u>	43%	34%	33%
Relative Risk (vs placebo)		0.73	0.71
p-value (vs placebo)		0.015	0.007
<u>Subgroup by Age and Baseline FVC</u>	Placebo (N)	2.5 mg QD (N)	2.5 mg BID (N)
<u>Age</u>			
5-20 years	42% (201)	25% (199)	28% (184)
21 years and older	44% (124)	48% (123)	39% (137)
<u>Baseline FVC</u>			
40-85% Predicted	54% (194)	41% (201)	44% (203)
>85% Predicted	27% (131)	21% (121)	14% (118)

Figure 1 Mean Percent Change from Baseline FEV<sub>1</sub> in Patients with FVC ≥40% of Predicted



Pulmozyme has also been evaluated in a second randomized, placebo-controlled study in clinically stable patients with baseline FVC <40% of predicted (8). Patients were enrolled and treated with placebo (162 patients) or Pulmozyme 2.5 mg QD (158 patients) for twelve weeks. In patients who received Pulmozyme, there was an increase in mean change (as percent of baseline) compared to placebo in FEV<sub>1</sub> (9.4% vs. 2.1%, p <0.001) and in FVC (12.4% vs. 7.3%, p <0.01). Pulmozyme did not significantly reduce the risk of developing a respiratory tract infection requiring parenteral antibiotics (54% of Pulmozyme patients vs. 55% of placebo patients had experienced a respiratory tract infection by 12 weeks, relative risk = .93, p=0.62).

The effect of Pulmozyme on exercise tolerance has not been established in adults and children.

### Other Studies

Clinical trials have indicated that Pulmozyme therapy can be continued or initiated during an acute respiratory exacerbation.

Short-term dose ranging studies demonstrated that doses in excess of 2.5 mg BID did not provide further improvement in FEV<sub>1</sub>. Patients who have received drug on a cyclical regimen (i.e., administration of Pulmozyme 10 mg BID for 14 days, followed by a 14 day wash out period) showed rapid improvement in FEV<sub>1</sub> with the initiation of each cycle and a return to baseline with each Pulmozyme withdrawal.

### INDICATIONS AND USAGE

Daily administration of Pulmozyme<sup>®</sup> (dornase alfa) Inhalation Solution in conjunction with standard therapies is indicated in the management of cystic fibrosis patients to improve pulmonary function. In patients with an FVC ≥40% of predicted, daily administration of Pulmozyme has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

Safety and efficacy of daily administration have not been demonstrated in patients for longer than twelve months.

### CONTRAINDICATIONS

Pulmozyme is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.

## **WARNINGS**

None.

## **PRECAUTIONS**

### **General**

Pulmozyme should be used in conjunction with standard therapies for CF.

### **Information for Patients**

Pulmozyme must be stored in the refrigerator at 2–8°C (36–46°F) and protected from strong light. It should be kept refrigerated during transport and should not be exposed to room temperatures for a total time of 24 hours. The solution should be discarded if it is cloudy or discolored. Pulmozyme contains no preservative and, once opened, the entire contents of the ampule must be used or discarded. Patients should be instructed in the proper use and maintenance of the nebulizer and compressor system used in its delivery.

Pulmozyme should not be diluted or mixed with other drugs in the nebulizer. Mixing of Pulmozyme with other drugs could lead to adverse physicochemical and/or functional changes in Pulmozyme or the admixed compound.

### **Drug Interactions**

Clinical trials have indicated that Pulmozyme can be effectively and safely used in conjunction with standard cystic fibrosis therapies including oral, inhaled and/or parenteral antibiotics, bronchodilators, enzyme supplements, vitamins, oral or inhaled corticosteroids, and analgesics. No formal drug interaction studies have been performed.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** Lifetime studies in Sprague Dawley rats showed no carcinogenic effect when Pulmozyme was administered at doses up to 246 µg/kg body weight per day. Pulmozyme was administered to rats as an aerosol for up to 30 minutes per day, daily for two years, with resulting lower respiratory tract doses of up to 246 µg/kg per day, which represents up to a 28.8-fold multiple of the clinical dose. There was no increase in the development of benign or malignant neoplasms and no occurrence of unusual tumor types in rats after lifetime exposure.

**Mutagenesis:** Ames tests using six different tester strains of bacteria (4 of *S. typhimurium* and 2 of *E. coli*) at concentrations up to 5000 µg/plate, a cytogenetic assay using human peripheral blood lymphocytes at concentrations up to 2000 µg/plate, and a mouse lymphoma assay at concentrations up to 1000 µg/plate, with and without metabolic activation, revealed no evidence of mutagenesis potential. Pulmozyme was tested in a micronucleus (in vivo) assay for its potential to produce chromosome damage in bone marrow cells of mice following a bolus intravenous dose of 10 mg/kg on two consecutive days. No evidence of chromosomal damage was noted.

**Impairment of Fertility:** In studies with rats receiving up to 10 mg/kg/day, a dose representing systemic exposures greater than 600 times that expected following the recommended human dose, fertility and reproductive performance of both males and females was not affected.

### **Pregnancy (Category B)**

Reproduction studies have been performed in rats and rabbits with intravenous doses up to 10 mg/kg/day, representing systemic exposures greater than 600 times that expected following the recommended human dose. These studies have revealed no evidence of impaired fertility, harm to the fetus, or effects on development due to Pulmozyme. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of

the human response, this drug should be used during pregnancy only if clearly needed.

### Nursing Mothers

It is not known whether Pulmozyme is excreted in human milk. Small amounts of dornase alfa were detected in maternal milk of cynomolgus monkeys when administered a bolus dose (100 µg/kg) of dornase alfa followed by a six hour intravenous infusion (80 µg/kg/hr). Little or no measurable dornase alfa would be expected in human milk after chronic aerosol administration of recommended doses. Because many drugs are excreted in human milk, caution should still be exercised when Pulmozyme is administered to a nursing woman.

### Pediatric Use

Because of the limited experience with the administration of Pulmozyme to patients younger than 5 years of age, its use should be considered only for those patients in whom there is a potential for benefit in pulmonary function or in risk of respiratory tract infection.

### Geriatric Use

Cystic fibrosis is primarily a disease of pediatrics and young adults. Clinical studies of Pulmozyme did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

## ADVERSE REACTIONS

Patients have been exposed to Pulmozyme for up to 12 months in clinical trials.

In a randomized, placebo-controlled clinical trial in patients with FVC ≥40% of predicted, over 600 patients received Pulmozyme once or twice daily for six months; most adverse events were not more common on Pulmozyme than on placebo and probably reflected the sequelae of the underlying lung disease. In most cases events that were increased were mild, transient in nature, and did not require alterations in dosing. Few patients experienced adverse events resulting in permanent discontinuation from Pulmozyme, and the discontinuation rate was similar for placebo (2%) and Pulmozyme (3%). Events that were more frequent (greater than 3%) in Pulmozyme treated patients than in placebo-treated patients are listed in Table 2.

In a randomized, placebo-controlled trial of patients with advanced disease (FVC <40% of predicted) the safety profile for most adverse events was similar to that reported for the trial in patients with mild to moderate disease. For this study, adverse events that were reported with a higher frequency (greater than 3%) in the Pulmozyme treated patients, are also listed in Table 2.

**Table 2: Adverse Events Increased 3% or More in Pulmozyme Treated Patients Over Placebo in CF Clinical Trials**

Adverse Event (of any severity or seriousness)	Trial in Mild to Moderate CF Patients (FVC ≥ 40% of predicted) treated for 24 weeks			Trial in Advanced CF Patients (FVC < 40% of predicted) treated for 12 weeks	
	Placebo n=325	Pulmozyme QD n=322	Pulmozyme BID n=321	Placebo n=159	Pulmozyme QD n=161
Voice alteration	7%	12%	16%	6%	18%
Pharyngitis	33%	36%	40%	28%	32%
Rash	7%	10%	12%	1%	3%
Laryngitis	1%	3%	4%	1%	3%
Chest Pain	16%	18%	21%	23%	25%
Conjunctivitis	2%	4%	5%	0%	1%

Rhinitis	Differences were less than 3% for these adverse events in the Trial in mild to moderate CF patients	24%	30%
FVC decrease of $\geq 10\%$ of predicted*		17%	22%
Fever		28%	32%
Dyspepsia		0%	3%
Dyspnea (when reported as serious)	Differences were less than 3% for this adverse event in the Trial in mild to moderate CF patients	12% <sup>†</sup>	17% <sup>†</sup>

\* Single measurement only, does not reflect overall FVC changes.

<sup>†</sup> Total reports of dyspnea (regardless of severity or seriousness) had a difference of less than 3% for the Trial in advanced CF patients.

### Events Observed at Similar Rates in Pulmozyme<sup>®</sup> (dornase alfa) Inhalation Solution and Placebo Treated Patients with FVC $\geq 40\%$ of Predicted

<b>Body as a Whole</b>	Abdominal pain, Asthenia, Fever, Flu syndrome, Malaise, Sepsis
<b>Digestive System</b>	Intestinal Obstruction, Gall Bladder disease, Liver disease, Pancreatic disease
<b>Metabolic Nutritional System</b>	Diabetes Mellitus, Hypoxia, Weight Loss
<b>Respiratory System</b>	Apnea, Bronchiectasis, Bronchitis, Change in Sputum, Cough Increase, Dyspnea, Hemoptysis, Lung Function Decrease, Nasal Polyps, Pneumonia, Pneumothorax, Rhinitis, Sinusitis, Sputum Increase, Wheeze

Mortality rates observed in controlled trials were similar for the placebo and Pulmozyme treated patients. Causes of death were consistent with progression of cystic fibrosis and included apnea, cardiac arrest, cardiopulmonary arrest, cor pulmonale, heart failure, massive hemoptysis, pneumonia, pneumothorax, and respiratory failure.

The safety of Pulmozyme, 2.5 mg by inhalation, was studied with 2 weeks of daily administration in 98 patients with cystic fibrosis (65 aged 3 months to <5 years, 33 aged 5 to  $\leq 10$  years). The PARI BABY<sup>™</sup> reusable nebulizer (which uses a facemask instead of a mouthpiece) was utilized in patients unable to demonstrate the ability to inhale or exhale orally throughout the entire treatment period (54/65, 83% of the younger and 2/33, 6% of the older patients). The number of patients reporting cough was higher in the younger age group as compared to the older age group (29/65, 45% compared to 10/33, 30%) as was the number reporting moderate to severe cough (24/65, 37% as compared to 6/33, 18%). Other events tended to be of mild to moderate severity. The number of patients reporting rhinitis was higher in the younger age group as compared to the older age group (23/65, 35% compared to 9/33, 27%) as was the number reporting rash (4/65, 6% as compared to 0/33). The nature of adverse events was similar to that seen in the larger trials of Pulmozyme.

### Allergic Reactions

There have been no reports of anaphylaxis attributed to the administration of Pulmozyme to date. Urticaria, mild to moderate, and mild skin rash have been observed and have been transient. Within all of the studies, a small percentage (average of 2–4%) of patients treated with Pulmozyme developed serum antibodies to Pulmozyme. None of these patients developed anaphylaxis, and the clinical significance of serum antibodies to Pulmozyme is unknown.

### OVERDOSAGE

Single-dose inhalation studies in rats and monkeys at doses up to 180-times higher than doses routinely used in clinical studies are well tolerated. Single dose oral administration of Pulmozyme in doses up to

200 mg/kg are also well tolerated by rats.

Cystic fibrosis patients have received up to 20 mg BID for up to 6 days and 10 mg BID intermittently (2 weeks on/2 weeks off drug) for 168 days. These doses were well tolerated.

## DOSAGE AND ADMINISTRATION

The recommended dose for use in most cystic fibrosis patients is one 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients may benefit from twice daily administration (see Clinical Experience, Table 1). Clinical trial results and laboratory information are only available to support use of the following nebulizer/compressor systems (see Table 3).

**Table 3: Recommended Nebulizer/Compressor Systems**

Jet Nebulizer	Compressor
Hudson T Up-draft II <sup>®</sup> with	Pulmo-Aide <sup>®</sup>
Marquest Acorn II <sup>®</sup> with	Pulmo-Aide <sup>®</sup>
PARI LC Jet+ with	PARI PRONEB <sup>®</sup>
*PARI BABY <sup>™</sup> with	PARI PRONEB <sup>®</sup>
Durable Sidestream <sup>®</sup> with	MOBILAIRE <sup>™</sup>
Durable Sidestream <sup>®</sup> with	Porta-Neb <sup>®</sup>

\* Patients who are unable to inhale or exhale orally throughout the entire nebulization period may use the PARI BABY<sup>™</sup> nebulizer.

Patients who use the Sidestream<sup>®</sup> Nebulizer with the MOBILAIRE<sup>™</sup> compressor should turn the compressor control knob fully to the right and then turn on the compressor. At this setting, the needle on the pressure gauge should vibrate between 35 and 45 pounds per square inch (highest pressure output).

No data are currently available that support the administration of Pulmozyme with other nebulizer systems. The patient should follow the manufacturer's instructions on the use and maintenance of the equipment.

Pulmozyme should not be diluted or mixed with other drugs in the nebulizer. Mixing of Pulmozyme with other drugs could lead to adverse physicochemical and/or functional changes in Pulmozyme or the admixed compound. Patients should be advised to squeeze each ampule prior to use in order to check for leaks.

## HOW SUPPLIED

Pulmozyme is supplied in single-use ampules. Each ampule delivers 2.5 mL of a sterile, clear, colorless, aqueous solution containing 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride with no preservative. The nominal pH of the solution is 6.3.

Pulmozyme is supplied in:

- 30 unit cartons containing 5 foil pouches of 6 single-use ampules: NDC 50242-100-40.

## Storage

Pulmozyme should be stored under refrigeration (2–8°C/36–46°F). Ampules should be protected from strong light. Do not use beyond the expiration date stamped on the ampule. Unused ampules should be stored in their protective foil pouch under refrigeration.

## REFERENCES

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- viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 1990;87:9188–92.
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**Pulmozyme®**  
**(dornase alfa)**  
**Inhalation Solution**

Manufactured by  
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(4824302)

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FDA Approval Date: January 2001  
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**PRINCIPAL DISPLAY PANEL - Pulmozyme® 2.5 mg Ampule, 30 Ampules per Carton**

NDC 50242-100-40  
List No. 10040

# DORNASE ALFA

## PULMOZYME<sup>®</sup>

INHALATION SOLUTION



**KEEP REFRIGERATED**

**Genentech, Inc.**

A Member of the Roche Group  
1 DNA Way, South San Francisco, CA 94080-4990  
US License No.: 1048

## PULMOZYME

dornase alfa solution

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:50 242-100
Route of Administration	RESPIRATORY (INHALATION)	DEA Schedule	

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DORNASE ALFA (DORNASE ALFA)	DORNASE ALFA	1 mg in 1 mL

### Inactive Ingredients

Ingredient Name	Strength
CALCIUM CHLORIDE	0.15 mg in 1 mL
SODIUM CHLORIDE	8.77 mg in 1 mL

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50 242-100-40	5 in 1 CARTON		
1		6 in 1 POUCH		

1	2.5 mL in 1 AMPULE		
<b>Marketing Information</b>			
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
BLA	BLA103532	12/30/1993	

**Labeler** - Genentech, Inc. (080129000)

**Registrant** - Genentech, Inc. (080129000)

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Genentech, Inc. (SSF)		080129000	API MANUFACTURE, ANALYSIS

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Catalent Pharma Solutions, LLC		043911403	MANUFACTURE

Revised: 10/2010

Genentech, Inc.