

1 **1.14.1.3**

2 **Pulmozyme®**
3 **(dornase alfa)**
4 **Inhalation Solution**

5 **DESCRIPTION**

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

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

21 **CLINICAL PHARMACOLOGY**

22 **General**

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

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

29 **Pharmacokinetics**

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

37 Pulmozyme, 2.5 mg by inhalation, was administered daily to 98 patients aged 3 months to
38 ≤ 10 years, and bronchoalveolar lavage (BAL) fluid was obtained within 90 minutes of the
39 first dose. BAL DNase concentrations were detectable in all patients but showed a broad
40 range, from 0.007 to 1.8 µg/mL. Over an average of 14 days of exposure, serum DNase
41 concentrations (mean ± s.d.) increased by 1.3 ± 1.3 ng/mL for the 3 months to < 5 year age
42 group and by 0.8 ± 1.2 ng/mL for the 5 to ≤ 10 year age group. The relationship between
43 BAL or serum DNase concentration and adverse experiences and clinical outcomes is
44 unknown.

45 **Clinical Experience**

46 Pulmozyme has been evaluated in a randomized, placebo-controlled trial of clinically stable
47 cystic fibrosis patients, 5 years of age and older, with baseline forced vital capacity (FVC)
48 greater than or equal to 40% of predicted and receiving standard therapies for cystic fibrosis
49 (7). Patients were treated with placebo (325 patients), 2.5 mg of Pulmozyme once a day
50 (322 patients), or 2.5 mg of Pulmozyme twice a day (321 patients) for six months
51 administered via a Hudson T Up-draft II® nebulizer with a Pulmo-Aide® compressor.

52 Both doses of Pulmozyme resulted in significant reductions when compared with the placebo
53 group in the number of patients experiencing respiratory tract infections requiring use of
54 parenteral antibiotics. Administration of Pulmozyme reduced the relative risk of developing
55 a respiratory tract infection by 27% and 29% for the 2.5 mg daily dose and the 2.5 mg twice
56 daily dose, respectively (see Table 1). The data suggest that the effects of Pulmozyme on
57 respiratory tract infections in older patients (>21 years) may be smaller than in younger
58 patients, and that twice daily dosing may be required in the older patients. Patients with
59 baseline FVC >85% may also benefit from twice a day dosing (see Table 1). The reduced

60 risk of respiratory infection observed in Pulmozyme treated patients did not directly correlate
61 with improvement in FEV₁ during the initial two weeks of therapy.

62 Within 8 days of the start of treatment with Pulmozyme, mean FEV₁ increased 7.9% in those
63 treated once a day and 9.0% in those treated twice a day compared to the baseline values.
64 The overall mean FEV₁ during long-term therapy increased 5.8% from baseline at the 2.5 mg
65 daily dose level and 5.6% from baseline at the 2.5 mg twice daily dose level. Placebo
66 recipients did not show significant mean changes in pulmonary function testing (see
67 Figure 1).

68 For patients 5 years of age or older, with baseline FVC greater than or equal to 40%,
69 administration of Pulmozyme decreased the incidence of occurrence of first respiratory tract
70 infection requiring parenteral antibiotics, and improved mean FEV₁, regardless of age or
71 baseline FVC.

Table 1
Incidence of First Respiratory Tract Infection
Requiring Parenteral Antibiotics in Patients with FVC \geq 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)

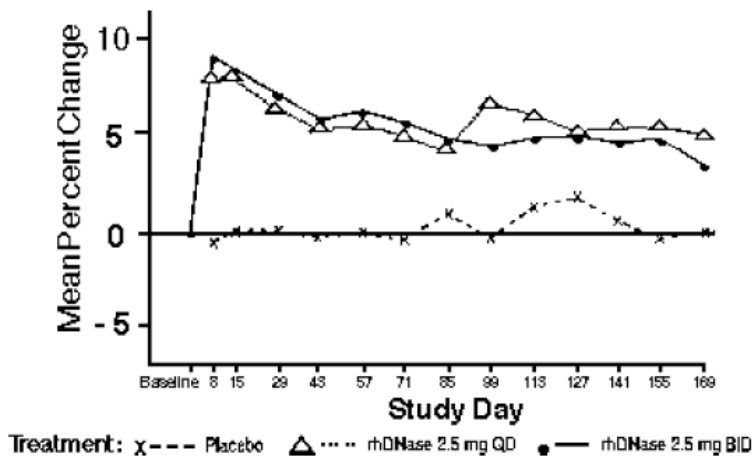
72

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Figure 1:

74

Mean Percent Change from Baseline FEV₁ in Patients with FVC ≥40% of Predicted



75

76

77 Pulmozyme has also been evaluated in a second randomized, placebo-controlled study in
78 clinically stable patients with baseline FVC <40% of predicted (8). Patients were enrolled
79 and treated with placebo (162 patients) or Pulmozyme 2.5 mg QD (158 patients) for
80 twelve weeks. In patients who received Pulmozyme, there was an increase in mean change
81 (as percent of baseline) compared to placebo in FEV₁ (9.4% vs. 2.1%, p<0.001) and in FVC
82 (12.4% vs. 7.3%, p<0.01). Pulmozyme did not significantly reduce the risk of developing a
83 respiratory tract infection requiring parenteral antibiotics (54% of Pulmozyme patients vs.
84 55% of placebo patients had experienced a respiratory tract infection by 12 weeks, relative
85 risk = .93, p=0.62).

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

88 **Other Studies**

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

91 Short-term dose ranging studies demonstrated that doses in excess of 2.5 mg BID did not
92 provide further improvement in FEV₁. Patients who have received drug on a cyclical
93 regimen (i.e., administration of Pulmozyme 10 mg BID for 14 days, followed by a 14 day

94 wash out period) showed rapid improvement in FEV₁ with the initiation of each cycle and a
95 return to baseline with each Pulmozyme withdrawal.

96 **INDICATIONS AND USAGE**

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

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

104 **CONTRAINDICATIONS**

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

107 **WARNINGS**

108 None.

109 **PRECAUTIONS**

110 **General**

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

112 **Information for Patients**

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

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

122 **Drug Interactions**

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

127 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

147 **Pregnancy (Category B)**

148 Reproduction studies have been performed in rats and rabbits with intravenous doses up to
149 10 mg/kg/day, representing systemic exposures greater than 600 times that expected
150 following the recommended human dose. These studies have revealed no evidence of
151 impaired fertility, harm to the fetus, or effects on development due to Pulmozyme. There
152 are, however, no adequate and well-controlled studies in pregnant women. Because animal

153 reproductive studies are not always predictive of the human response, this drug should be
154 used during pregnancy only if clearly needed.

155 **Nursing Mothers**

156 It is not known whether Pulmozyme is excreted in human milk. Small amounts of dornase
157 alfa were detected in maternal milk of cynomolgus monkeys when administered a bolus dose
158 (100 µg/kg) of dornase alfa followed by a six hour intravenous infusion (80 µg/kg/hr). Little
159 or no measurable dornase alfa would be expected in human milk after chronic aerosol
160 administration of recommended doses. Because many drugs are excreted in human milk,
161 caution should still be exercised when Pulmozyme is administered to a nursing woman.

162 **Pediatric Use**

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

166 **Geriatric Use**

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

170 **ADVERSE REACTIONS**

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

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

181 In a randomized, placebo-controlled trial of patients with advanced disease (FVC <40% of
 182 predicted) the safety profile for most adverse events was similar to that reported for the trial
 183 in patients with mild to moderate disease. For this study, adverse events that were reported
 184 with a higher frequency (greater than 3%) in the Pulmozyme treated patients, are also listed
 185 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 ≥10% of predicted ^o				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%†	17%†

^o Single measurement only, does not reflect overall FVC changes.

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

186

187 **Events Observed at Similar Rates in Pulmozyme[®] (dornase alfa) Inhalation**
 188 **Solution and Placebo Treated Patients with FVC ≥ 40% of Predicted**

189 **Body as a Whole** Abdominal pain, Asthenia, Fever, Flu syndrome,
 190 Malaise, Sepsis

191 **Digestive System** Intestinal Obstruction, Gall Bladder disease, Liver
 192 disease, Pancreatic disease

193	Metabolic Nutritional System	Diabetes Mellitus, Hypoxia, Weight Loss
194	Respiratory System	Apnea, Bronchiectasis, Bronchitis, Change in Sputum,
195		Cough Increase, Dyspnea, Hemoptysis, Lung Function
196		Decrease, Nasal Polyps, Pneumonia, Pneumothorax,
197		Rhinitis, Sinusitis, Sputum Increase, Wheeze

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

202 The safety of Pulmozyme, 2.5 mg by inhalation, was studied with 2 weeks of daily
 203 administration in 98 patients with cystic fibrosis (65 aged 3 months to <5 years, 33 aged 5 to
 204 ≤10 years). The PARI BABY™ reusable nebulizer (which uses a facemask instead of a
 205 mouthpiece) was utilized in patients unable to demonstrate the ability to inhale or exhale
 206 orally throughout the entire treatment period (54/65, 83% of the younger and 2/33, 6% of the
 207 older patients). The number of patients reporting cough was higher in the younger age group
 208 as compared to the older age group (29/65, 45% compared to 10/33, 30%) as was the number
 209 reporting moderate to severe cough (24/65, 37% as compared to 6/33, 18%). Other events
 210 tended to be of mild to moderate severity. The number of patients reporting rhinitis was
 211 higher in the younger age group as compared to the older age group (23/65, 35% compared
 212 to 9/33, 27%) as was the number reporting rash (4/65, 6% as compared to 0/33). The nature
 213 of adverse events was similar to that seen in the larger trials of Pulmozyme.

214 **Allergic Reactions**

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

221 **OVERDOSAGE**

222 Single-dose inhalation studies in rats and monkeys at doses up to 180-times higher than doses
223 routinely used in clinical studies are well tolerated. Single dose oral administration of
224 Pulmozyme in doses up to 200 mg/kg are also well tolerated by rats.

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

227 **DOSAGE AND ADMINISTRATION**

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

Table 3
Recommended Nebulizer/Compressor Systems

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

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

233

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

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

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

245 **HOW SUPPLIED**

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

250 Pulmozyme is supplied in:

- 251 • 30 unit cartons containing 5 foil pouches of 6 single-use ampules: NDC 50242-100-40.

252 **Storage**

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

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- 278

Pulmozyme[®]
(dornase alfa)
Inhalation Solution

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