

# Data Sheet

## Pulmozyme<sup>®</sup>

*Dornase alfa solution for inhalation 1.0 mg/mL*

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### Pharmaceutical Form

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Pulmozyme inhalation solution contains 2,500 U (2.5 mg) dornase alfa in 2.5 mL solution.

Class: Respiratory system (mucolytics). ATC Code: R05CB13.

Sterile.

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### Qualitative and Quantitative Composition

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Pulmozyme is supplied in a single-use ampoule. Each ampoule delivers 2.5 mL of a sterile, clear, colourless to slightly yellowish, 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.

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### Clinical Particulars

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#### ***Therapeutic Indications***

Management of cystic fibrosis (CF) patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function.

#### ***Dosage and Administration***

The recommended dose is 2.5 mg dornase alfa by inhalation once daily. Inhale the contents of one ampoule (2.5 mL of solution) undiluted using a recommended jet nebuliser/compressor system (see Instructions for use/handling).

Some patients over the age of 21 years may benefit from twice daily dosage.

Most patients gain optimal benefit from regular daily use of Pulmozyme. In studies in which Pulmozyme was given in an intermittent regimen, improvement in pulmonary function was lost on cessation of therapy. Patients should therefore be advised to take their medication every day without a break.



Patients should continue their regular medical care, including their standard regimen of chest physiotherapy.

Administration can be safely continued in patients who experience exacerbation of respiratory tract infection.

### **Special dosage instructions**

None

### ***Contraindications***

Pulmozyme should not be administered to patients with known hypersensitivity to the active ingredient or its excipients.

### ***Warnings and Precautions***

#### **General**

None

#### **Drug abuse and dependence**

No effects are known

#### **Ability to drive and use machines**

No effects on the patient's ability to drive and use machines have been reported.

#### **Interactions with other medicinal products and other forms of interaction**

Pulmozyme can be effectively and safely used in conjunction with standard cystic fibrosis (CF) therapies such as antibiotics, bronchodilators, pancreatic enzymes, vitamins, inhaled and systemic corticosteroids and analgesics.

### ***Use in Special Populations***

#### **Pregnancy**

Pregnancy Category: B1

The safety of dornase alfa has not been established in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, or embryofetal development (see Preclinical Safety). Caution should be exercised when prescribing dornase alfa to pregnant women.

#### **Nursing mothers**

When dornase alfa is administered to humans according to the dosage recommendation, there is minimal systemic absorption; therefore no measurable concentrations of dornase alfa would be expected in human milk. Nevertheless, caution should be exercised when dornase alfa is administered to a breast-feeding woman (see Absorption and Preclinical Safety).

#### **Paediatric use**

There is limited experience in the use of Pulmozyme in patients under the age of 5 years (see Special Instructions for Use, Handling and Disposal).



## Other

Safety and efficacy have not yet been demonstrated in patients with forced vital capacity less than 40% of predicted.

## Undesirable Effects

### Clinical trials

Adverse reactions attributed to Pulmozyme are rare (< 1/1,000). In most cases, the adverse reactions are mild and transient in nature and do not require alterations in Pulmozyme dosing.

<i>Eye disorders:</i>	Conjunctivitis
<i>Respiratory, Thoracic and Mediastinal disorders:</i>	Dysphonia, dyspnoea, pharyngitis, laryngitis, rhinitis (all non-infectious)
<i>Investigations:</i>	Pulmonary function tests decreased
<i>Gastrointestinal disorders:</i>	Dyspepsia
<i>Skin and appendages disorders:</i>	Rash, urticaria
<i>General disorders:</i>	Chest pain (pleuritic / non-cardiac), pyrexia

Patients who experience adverse events common to cystic fibrosis can, in general, safely continue administration of Pulmozyme as evidenced by the high percentage of patients completing clinical trials with Pulmozyme.

In clinical trials, few patients experienced adverse events resulting in permanent discontinuation from dornase alfa, and the discontinuation rate was observed to be similar between placebo (2%) and dornase alfa (3%).

Upon initiation of dornase alfa therapy, as with any aerosol, pulmonary function may decline and expectoration of sputum may increase.

Less than 5% of patients treated with dornase alfa have developed antibodies to dornase alfa and none of these patients have developed IgE antibodies to dornase alfa. Improvement in pulmonary function tests has still occurred even after the development of antibodies to dornase alfa.

The safety of 2 weeks' daily inhalation of Pulmozyme was compared in 65 patients aged 3 months to <5 years and 33 patients aged 5 to 10 years (see Pharmacokinetics in special populations). The number of patients reporting cough as an adverse event was higher in the younger than 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 adverse events tended to be of mild to moderate severity. The number of patients reporting rhinitis was also higher in the younger 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.

### Post-marketing

Post marketing spontaneous reports and prospectively collected safety data from observational studies confirm the safety profile to be as described in clinical trials.



## Overdosage

The effect of Pulmozyme overdosage has not been established. Cystic fibrosis patients have inhaled up to 20 mg Pulmozyme twice daily (16 times the recommended daily dose) for up to 6 days and 10 mg twice daily (8 times the recommended dose) intermittently (2 weeks on / 2 weeks off Pulmozyme) for 168 days. Six adult non-cystic fibrosis patients received a single intravenous dose of 125 mcg/kg of Pulmozyme, followed 7 days later by 125 mcg/kg subcutaneously for two consecutive 5-day periods, without either neutralising antibodies to DNase or any change in serum antibodies against double-stranded DNA being detected. All of these doses were well tolerated.

Systemic toxicity of Pulmozyme has not been observed and is not expected due to the poor absorption and short serum half-life of dornase alfa. Systemic treatment of overdose is therefore unlikely to be necessary (see Pharmacokinetic Properties).

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## Pharmacological Properties and Effects

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### *Pharmacodynamic Properties*

#### **Mechanism of action**

Recombinant human DNase is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular DNA.

Retention of viscous purulent secretions in the airways contributes both to reduced pulmonary function and to exacerbations of infection. Purulent secretions contain very high concentrations of extracellular DNA, a viscous polyanion released by degenerating leukocytes, which accumulate in response to infection. In vitro, dornase alfa hydrolyses DNA in sputum and greatly reduces the viscoelasticity of cystic fibrosis sputum.

#### **Clinical / efficacy studies**

Pulmozyme has been evaluated in cystic fibrosis patients of various ages and with differing severities of lung disease. Most studies were double-blind and placebo-controlled, and all patients received concomitant therapies as deemed necessary by their physician.

#### ***Patients over 5 years of age with FVC over 40% predicted***

Pulmozyme 2.5 mg once or twice daily, administered via a Hudson T Up-draft II nebuliser with a Pulmo-Aide compressor, decreased the incidence of first respiratory tract exacerbation (infection requiring parenteral antibiotics) and improved mean FEV<sub>1</sub> compared to placebo, regardless of age or baseline FVC.

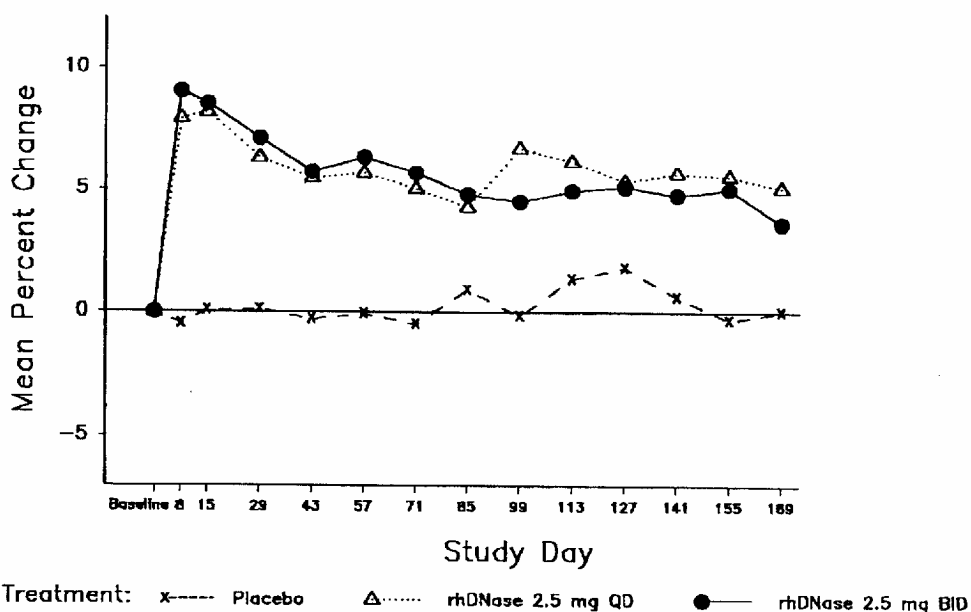
Pulmozyme reduced the relative risk of respiratory tract exacerbation by 27% and 29% at the once and twice daily doses, respectively (see Table 1). Sub-analysis of the data suggests that the effects of Pulmozyme on respiratory tract exacerbations in older patients (>21 years) may be smaller than in younger patients, and that twice daily dosing may be required in the older patients. Patients with baseline FVC >85% may also benefit from twice daily dosing (see Table 1). The reduced risk of respiratory exacerbation observed in patients treated with Pulmozyme persisted throughout the 6-month study period and did not correlate with improvement in FEV<sub>1</sub> during the initial two weeks of therapy.

**Table 1 Incidence of Occurrence of First Respiratory Tract Infection Requiring Parenteral Antibiotics in a Controlled Trial**

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

Within 8 days of the start of Pulmozyme, mean FEV<sub>1</sub> increased from baseline by 7.9% and 9.0% in those treated once and twice daily, respectively. The overall mean FEV<sub>1</sub> observed during 6 months' therapy increased 5.8% and 5.6% from baseline at the once and twice daily dose levels. Placebo recipients did not show significant mean changes in pulmonary function testing (see Figure 1).

**Figure 1 Mean Percent Change from Baseline FEV<sub>1</sub> in Patients aged >5 Years and with FVC >40% Predicted**

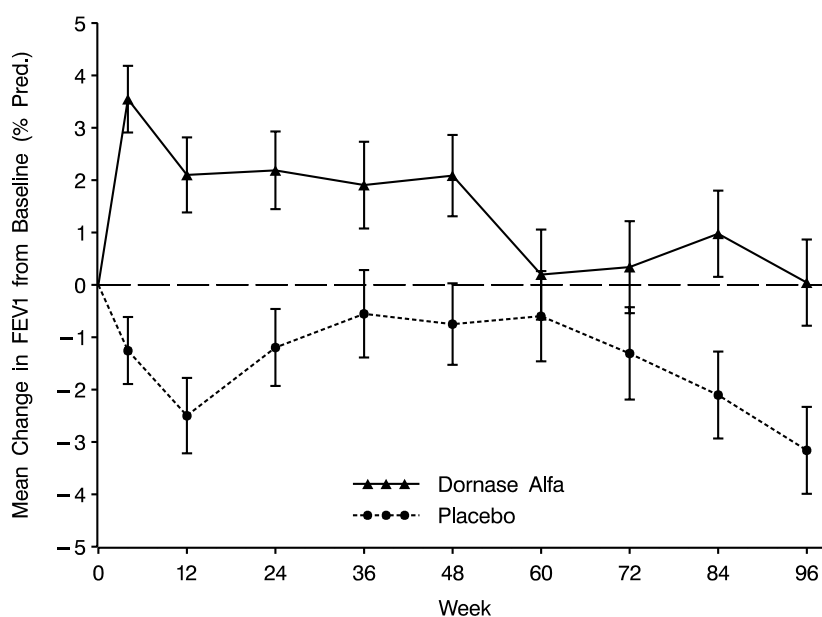


Pulmozyme also improved quality of life as assessed by change in cystic fibrosis-related symptom score, days in hospital, dyspnoea score (once daily), change in well-being score (once daily) and days at home due to illness (once daily).

### **Patients aged 6-10 years with FVC over 85% predicted**

After 2 years of treatment with Pulmozyme 2.5 mg once daily, administered via a Durable SideStream nebuliser with a PortaNeb compressor, the treatment benefit observed for FEV<sub>1</sub> in patients treated with Pulmozyme compared with placebo was 3.2 ± 1.2 % predicted (p=0.006). An increase in FEV<sub>1</sub> was observed up to 48 weeks of treatment; at 2 years, patients treated with Pulmozyme maintained FEV<sub>1</sub> at their baseline value, while patients in the control group experienced a mean decrease from baseline (see Figure 2).

**Figure 2 Mean Absolute Change from Baseline FEV<sub>1</sub> in Patients aged 6-10 Years with FVC>85% Predicted**



In this population, a larger benefit in FEF<sub>25-75</sub> (7.9 ± 2.3, p=0.008) was reported in patients treated with Pulmozyme versus placebo, while the difference in FVC values (0.7 ± 1.0, p=0.51) was not significant.

The risk of respiratory tract exacerbations was reduced by 34% in patients treated with Pulmozyme (p=0.048). Sub-analysis did not detect any correlation between this response and change in FEV<sub>1</sub> at 4 weeks.

### **Patients with FVC less than 40% predicted**

A double-blind placebo-controlled trial showed that 12 weeks' treatment with Pulmozyme 2.5 mg once daily significantly improved FEV<sub>1</sub> and FVC in this patient population. Relative increases from baseline FEV<sub>1</sub> and FVC were 9.4% and 12.4% in the Pulmozyme group versus 2.1% and 7.3% in the placebo group, respectively (p<0.01). A second study found no difference between treatments during a 14-day double-blind, placebo-controlled trial but found continued improvements in FEV<sub>1</sub> and FVC over a 6-month open extension period when all patients received Pulmozyme 2.5 mg twice daily.



No change was detected in risk of pulmonary exacerbations in this population, and the power of the 12-week double-blind study to detect any difference in this parameter was retrospectively estimated at only 40%.

### ***Patients aged under 5 years***

Pharmacokinetic data indicate that administration of 2.5 mg Pulmozyme via the Pari Baby reusable nebuliser with the Proneb (= PariBoy) compressor delivers similar concentrations of DNase to the lungs of patients younger than 5 years old as the Pari LC Plus nebuliser with the same compressor does to the lungs of older children who have been shown to respond to Pulmozyme (see Pharmacokinetics in special populations).

Safety in this population is addressed in the Undesirable Effects section.

Clinical efficacy studies have not been performed in patients younger than 5 years.

## ***Pharmacokinetic Properties***

### **Absorption**

Inhalation studies conducted in rats and non-human primates show a low percentage of dornase alfa systemic absorption (<15% for rats and <2% for monkeys). Consistent with the results of these animal studies, dornase alfa administered to patients as an inhaled aerosol shows low systemic exposure.

Absorption of dornase alfa from the gastrointestinal tract following oral administration to rats is negligible.

DNase is normally present in human serum. Inhalation of up to 40 mg of dornase alfa for up to 6 days did not result in a significant elevation of serum DNase concentration above normal endogenous levels. No increase in serum DNase concentration greater than 10 ng/mL was observed. Following administration of 2.5 mg of dornase alfa twice daily for 24 weeks, mean serum DNase concentrations were no different from the mean pretreatment baseline value of  $3.5 \pm 0.1$  ng/mL; suggesting low systemic absorption or accumulation.

### **Distribution**

Studies in rats and monkeys have shown that, following intravenous administration, dornase alfa was cleared rapidly from the serum. The initial volume of distribution was similar to serum volume in these studies.

Inhalation of 2.5 mg dornase alfa results in a mean sputum concentration of dornase alfa of approximately 3 mcg/mL within 15 minutes in cystic fibrosis patients. Concentrations of dornase alfa in sputum rapidly decline following inhalation.

### **Metabolism**

Dornase alfa is expected to be metabolised by proteases present in biological fluids.

### **Elimination**

Human intravenous studies suggest an elimination half-life from serum of 3-4 hours. Studies in rats and monkeys have also shown that, following intravenous administration, DNase is cleared rapidly from the serum.



Studies in rats indicate that, following aerosol administration, the disappearance half-life of dornase alfa from the lungs is 11 hours. In humans, sputum DNase levels declined below half of those detected immediately post-administration within 2 hours but effects on sputum rheology persisted beyond 12 hours.

### **Pharmacokinetics in special populations**

Pulmozyme has been evaluated in an open-label 2-week study in cystic fibrosis patients 3 months to 9 years of age. Pulmozyme, 2.5 mg by inhalation, was administered daily to 98 patients aged 3 months to <10 years (65 aged 3 months to <5 years, 33 aged 5 to <10 years), and bronchoalveolar lavage (BAL) fluid was obtained within 90 minutes of the first dose. The Pari Baby reusable nebuliser (which uses a facemask instead of a mouthpiece) was utilised 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). BAL DNase concentrations were detectable in all patients but showed a broad range, from 0.007 to 1.8 mcg/mL. Over an average of 14 days of exposure, serum DNase concentrations (mean  $\pm$  s.d.) increased by  $1.3 \pm 1.3$  ng/mL for the 3 months to <5 year age group and by  $0.8 \pm 1.2$  ng/mL for the 5 to <10 year age group. The relationship between BAL or serum DNase concentration and adverse experiences or clinical outcomes is unknown.

No pharmacokinetic data are available in very young or geriatric animals.

## ***Preclinical Safety***

### **Carcinogenicity**

Groups of 60 rats per sex received dornase alfa at 51, 101 or 246 mcg/kg/day to the lower respiratory tract (LRT) for up to two years. Two control groups of the same size received air and vehicle, respectively. Dornase alfa was well tolerated, and there were no unusual tumour types or increased incidence of tumours attributable to test article oncogenicity in the respiratory tract or other organs or tissues in the rat.

### **Mutagenicity**

No evidence of genotoxic potential was found in the Ames Test, the mouse lymphoma test, a chromosomal aberration test in cultured human peripheral blood lymphocytes and in the mouse micronucleus test.

### **Impairment of fertility**

Studies of dornase alfa in rats show no evidence of impaired fertility.

### **Teratogenicity**

Studies of dornase alfa in rabbits and rodents show no evidence of teratogenicity.

### **Other**

In a study performed in lactating cynomolgus monkeys, receiving high doses of dornase alfa by the intravenous route (100 mcg/kg bolus followed by 80 mcg/kg/hour for six hours), low concentrations (< 0.1% of the concentrations seen in serum), were detectable in the maternal milk.

A four-week inhalation toxicity study in juvenile rats commenced dosing 22 days after parturition at doses to the LRT of 0, 51, 102 and 260 mcg/kg/day. Dornase alfa was well tolerated, and no lesions were found in the respiratory tract.

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## Pharmaceutical Particulars

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### **Storage**

Pulmozyme should not be used after the expiry date shown on the pack.

Pulmozyme should be stored in a refrigerator at 2–8°C. The ampoules should be stored in the foil pouch in the outer carton and protected from strong light. Avoid exposure to excessive heat.

A single brief exposure to elevated temperatures (less than or equal to 24 hours at up to 30°C) does not affect product stability.

Shelf-life: 24 months.

### **Special Instructions for Use, Handling and Disposal**

Pulmozyme is supplied in a single-use, low-density polyethylene plastic ampoule. The volume in each ampoule is 2.6 ± 0.1 mL. Each ampoule will deliver 2.5 mL of Pulmozyme to the nebuliser chamber.

The contents of one 2.5 mg single-use ampoule of Pulmozyme sterile solution for inhalation should be inhaled once a day using a recommended jet nebuliser.

- Pulmozyme should not be mixed with other medicines or solutions in the nebuliser (see Incompatibilities).
- The complete contents of a single ampoule should be placed in the bowl of a jet nebuliser/compressor system, such as the Hudson T Up-draft II/Pulmo-Aide, Airlife Misty/Pulmo-Aide, customised Respigard/Pulmo-Aide, or AcornII/Pulmo-Aide.
- Pulmozyme may also be used in conjunction with a reusable jet nebuliser/compressor system, such as the Pari LL/Inhalierboy, Pari LC/Inhalierboy or Master, Aiolos/2 Aiolos, Side Stream/CR50 or MobilAire or Porta-Neb.
- Patients who are unable to inhale or exhale orally throughout the entire nebulisation period may use the Pari Baby nebuliser with a tight fitting face mask.
- Ultrasonic nebulisers may be unsuitable for delivery of Pulmozyme because they may inactivate Pulmozyme or have unacceptable aerosol delivery characteristics.
- The manufacturers' instructions on the use and maintenance of the nebuliser and compressor should be followed.
- Containment of the aerosol is not necessary.
- Pulmozyme ampoules are for single administration only.



## **Incompatibilities**

Pulmozyme is an unbuffered aqueous solution and should not be diluted or mixed with other medicines or solutions in the nebuliser bowl. Mixing of this solution could lead to adverse structural and/or functional changes in Pulmozyme or the admixed compound.

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## **Medicine Classification**

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Prescription Medicine

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## **Package Quantities**

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Pulmozyme 1.0 mg/mL solution is supplied in packs consisting of a carton with a foil pouch containing 6 x 2.5 mL unit-dose ampoules.

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## **Name and Address**

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## **Date of Preparation**

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14 April 2008

Reference: Pulmozyme International Core Data Sheet Version 1.0, 11 February 2008.