

PRODUCT MONOGRAPH

PrPULMOZYME®

(dornase alfa)
recombinant

For inhalation, 1 mg/mL, 2.5 mg/ampoule

Professed Standard

An enzyme that cleaves DNA
(Mucolytic)

Distributed by:
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PrPULMOZYME®

dornase alfa

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Inhalation (using a nebulizer)	Solution / 1 mg/mL	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Daily administration of PULMOZYME (dornase alfa) for inhalation in conjunction with standard therapies is indicated in the management of cystic fibrosis patients to reduce the frequency of respiratory infections requiring parenteral antibiotics and to improve pulmonary function. Safety and efficacy of daily administration have not been demonstrated in patients with FVC<40% of predicted, or for longer than twelve months.

CONTRAINDICATIONS

PULMOZYME (dornase alfa) is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products or any component of the product. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

PULMOZYME (dornase alfa) should be used in conjunction with standard therapies for cystic fibrosis (CF).

Patients should be instructed in the proper use and maintenance of the nebulizer and compressor system used in its delivery.

Carcinogenesis and Mutagenesis

There is no evidence of oncogenic or mutagenic potential (see TOXICOLOGY: Carcinogenesis, Mutagenesis for discussion on animal data).

Sexual Function/Reproduction

Fertility and reproductive performance were not affected in animal studies (see TOXICOLOGY: Reproduction/Development Studies).

Special Populations

Pregnant Women: The safety of PULMOZYME 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 TOXICOLOGY: Reproduction/Developmental Studies). Caution should be exercised when prescribing PULMOZYME to pregnant women.

Nursing Women: As it is not known whether dornase alfa is excreted in human milk, caution should be exercised when PULMOZYME is administered to a nursing woman (see DETAILED PHARMACOLOGY: Pharmacokinetics).

Pediatrics (<5 years of age): There is limited experience in the use of PULMOZYME in patients under the age of 5 years. The clinical efficacy in patients under the age of 5 years is not established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse event data reflect the clinical trial and post-marketing experience of using PULMOZYME (dornase alfa) at the recommended dose regimen.

Adverse reactions attributed to PULMOZYME are rare (<1/1000). In most cases, the adverse reactions are mild and transient in nature and do not require alterations in the dosing of PULMOZYME.

Body as a Whole:	Chest pain (pleuritic/non-cardiac), fever
Gastrointestinal System:	Dyspepsia
Respiratory System:	Voice alteration (hoarseness), pharyngitis (inflammation of the throat), dyspnea, laryngitis, rhinitis, decreased lung function
Skin and Appendages:	Rash, urticaria
Special Senses:	Conjunctivitis

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.

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Mortality rates observed in a controlled trial were similar for the placebo (1%) and PULMOZYME (1%). 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 ≤10 years) all of whom received bronchoalveolar lavage on the first day of therapy (Z0644g).¹⁰ 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). Adverse events were common in this

study and some were considered to be due to bronchoalveolar lavage. The nature of adverse drug reactions was similar to that seen in the larger trials of PULMOZYME.

In this phase II uncontrolled study (Z0644g), 98 patients aged 3 months to 9 years were treated with PULMOZYME by inhalation daily at a dose of 2.5 mg (the recommended dose). Data presented in Table 1 are based on adverse drug reactions reported in Study Z0644g.

Table 1 Adverse Drug Reactions Occurring in $\geq 1\%$ of Patients and Occurring in >1 Patient in Study Z0644g

Adverse Event System Organ Class (MedDRA)	Number	Percentage (n=98)
Infections And Infestations		
Rhinitis	12	12.2
Pharyngitis	7	7.1
Psychiatric Disorders		
Nervousness	4	4.1
Nervous System Disorders		
Headache	4	4.1
Hyperkinesias	2	2.0
Eye Disorders		
Conjunctivitis	2	2.0
Respiratory, Thoracic And Mediastinal Disorders		
Cough increased	35	35.7
Lung disorder	3	3.1
Hyperventilation	2	2.0
Voice alteration	14	14.3
Gastrointestinal Disorders		
Abdominal pain	2	2.0
Nausea	2	2.0
Vomiting	7	7.1
Skin And Subcutaneous Tissue Disorders		
Rash	2	2.0
General Disorders And Administration Site Conditions		
Pyrexia	7	7.1
Unevaluable reaction	5	5.1
Investigations		
Sputum increased	6	6.1

Allergic Reactions

There have been no reports of anaphylaxis attributed to the administration of PULMOZYME to date. Skin rash and urticaria have been observed, and were mild and transient in nature. Less than 5% of patients treated with PULMOZYME have developed antibodies to the drug and none

of these patients have developed IgE antibodies to PULMOZYME. Improvement in pulmonary function tests has still occurred even after the development of antibodies to PULMOZYME.

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 parenteral antibiotics, bronchodilators, enzyme supplements, vitamins, oral and inhaled corticosteroids, and analgesics. No formal drug interaction studies have been performed.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose for use in most cystic fibrosis patients is one 2.5 mg single use ampoule inhaled once daily using a recommended nebulizer (see Administration). Some patients may benefit from twice daily administration (see CLINICAL TRIALS: Phase III Studies, Table 2).

Missed Dose

The missed dose should be taken as soon as remembered, then the regular dosing schedule should be continued. Two doses of PULMOZYME should not be taken at the same time.

Administration

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 ampoule prior to use in order to check for leaks.

Clinical trials have been performed with the following nebulizers and compressors:

- the disposable jet nebulizer Hudson T Up draft II,
- the disposable jet nebulizer Marquest Acorn II in conjunction with a Pulmo Aide compressor,
- the PARI LC Plus Reusable Nebulizer in conjunction with the PARI PRONEB compressor, and
- eRapid Nebulizer System consisting of the eRapid Nebulizer Handset with eBase Controller.

Patients who are unable to inhale or exhale orally throughout the entire nebulization period may use the reusable PARI BABY nebulizer with a tight fitting face mask. It is recommended that patients <5 years of age use the PARI BABY nebulizer. Safety and efficacy have been demonstrated only with these recommended nebulizer systems.

No clinical data are currently available that support the safety and efficacy of administration of

PULMOZYME (dornase alfa) with other nebulizer systems. The patient should follow the manufacturer's instructions on the use and maintenance of the equipment.

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 (dornase alfa) in doses up to 200 mg/kg are also well tolerated by rats.

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

No data are available specifically for patients <5 years of age.

For management of a suspected drug overdose contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PULMOZYME (dornase alfa) for inhalation is a sterile, clear, colourless, 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). The product is purified by tangential flow filtration and column chromatography.

PULMOZYME is administered by inhalation of an aerosol mist produced by a compressed air driven nebulizer system (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION). PULMOZYME may also be aerosolized and administered via micro-perforated vibrating membrane nebulizer technology. Each single use ampoule will deliver 2.5 mL of the solution to the nebulizer bowl.

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 dornase alfa 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 three times daily of dornase alfa 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 dornase alfa twice daily for six months to 321 CF patients, no accumulation of serum DNase was noted.

For pharmacokinetic data obtained in patients < 5 years old, please see CLINICAL TRIALS: Phase II Studies.

STORAGE AND STABILITY

PULMOZYME must be stored in the refrigerator at 2-8°C (36-46°F) and protected from 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 discoloured. PULMOZYME contains no preservative and, once opened, the entire ampoule must be used or discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Each 2.5 mL PULMOZYME (dornase alfa) single-use ampoule contains 1.0 mg/mL (2.5 mg) of dornase alfa formulated in calcium chloride dihydrate, sodium chloride and Sterile Water for Injection. The solution contains no preservative. The nominal pH of the solution is 6.3.

Availability

PULMOZYME (dornase alfa) is available in:

- **30 ampoule cartons:** Each carton contains 5 foil pouches each containing 6 sterile, single-use ampoules of dornase alfa, PULMOZYME

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: dornase alfa

Chemical name: recombinant human deoxyribonuclease 1 (rhDNase)

Molecular formula and molecular mass: 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.

Structural Formula: Not available

Physicochemical properties: PULMOZYME for inhalation is a sterile, clear, colourless, highly purified solution of recombinant human deoxyribonuclease I (rhDNase). The nominal pH of the solution is 6.3.

CLINICAL TRIALS

Phase II Studies:

PULMOZYME has been evaluated in an open-label 2-week study in cystic fibrosis patients aged 3 months to 9 years of age (Z0644g).¹⁰ 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 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). BAL DNase concentrations were detectable in all patients but showed a broad range, from 0.007 to 1.8 $\mu\text{g/mL}$. Over an average of 14 days of exposure, serum DNase concentrations (mean \pm s.d.) increased by 1.1 ± 1.6 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.

Phase III Studies:

PULMOZYME has been evaluated in a large, 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 nebulizer with a Pulmo-Aide compressor.

Both doses of PULMOZYME resulted in significant reductions 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 2). 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 2). The reduced risk of respiratory infection observed in patients treated with PULMOZYME did not directly correlate with improvement in forced expiratory volume in 1 second (FEV₁) during the initial two weeks of therapy.

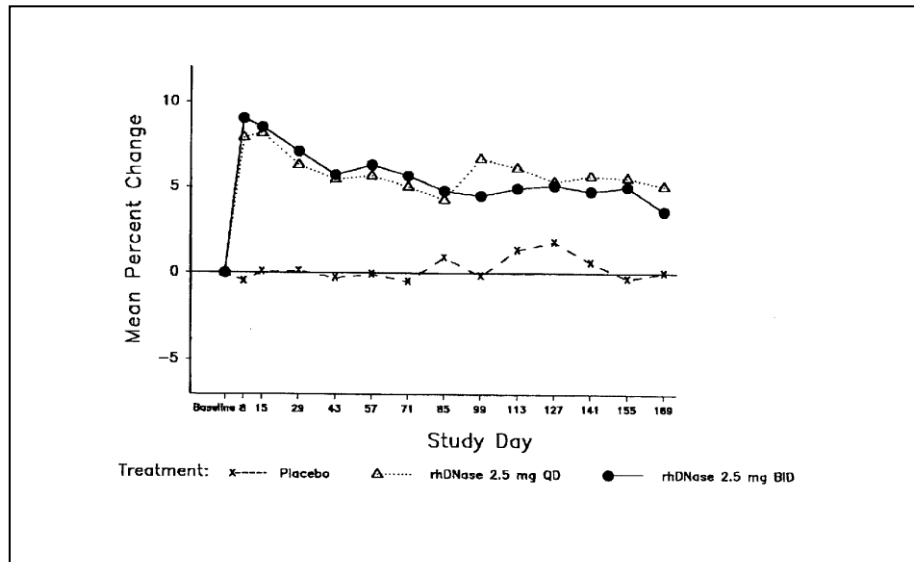
Within 8 days of the start of treatment with PULMOZYME mean FEV₁ increased 7.9% in those treated once a day and 9.0% in those treated twice a day compared to the baseline values. The overall mean FEV₁ observed during long-term therapy increased 5.8% from baseline at the 2.5 mg daily dose level and 5.6% 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 FEV₁ regardless of age or baseline FVC.

Table 2 Incidence of Occurrence of First Respiratory Tract Infection Requiring Parenteral Antibiotics in a Controlled Trial

	Placebo n=325	2.5 mg Once Daily n=322	2.5 mg Twice Daily 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
Subgroup by Age and Baseline FVC	Placebo (n)	2.5 mg Once Daily (n)	2.5 mg Twice Daily (n)
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)

Figure 1: Mean Percent Change from Baseline FEV₁ in a Controlled Trial



Other Studies:

The PULMOZYME Early Intervention trial was a 2 year randomized, double-blind, placebo-controlled trial that determined whether long-term treatment of young patients with CF (ages 6 to 10) with PULMOZYME maintains lung function and reduces respiratory tract exacerbations.¹¹ A total of 474 patients were randomized into the trial (239 to the PULMOZYME group and 235 to the placebo group). At baseline, mean FEV₁ was 95% predicted, mean forced expiratory flow, midexpiratory phase (FEF₂₅₋₇₅) was 85% predicted and FVC was 102% predicted. At 2 years, the treatment benefit observed for FEV₁ in patients treated with PULMOZYME compared with placebo in percent predicted was 3.2±1.2 (p=0.006). An increase in FEV₁ was observed up to 48 weeks of treatment; at 2 years, patients treated with PULMOZYME maintained FEV₁ at their baseline value, while patients in the control group had a mean decrease from baseline. Corresponding improvements in FEF₂₅₋₇₅ (7.9 ± 2.3, p=0.008) and FVC (0.7 ± 1.0, p=0.51) were reported in patients treated with PULMOZYME versus placebo. The risk of respiratory tract exacerbations was reduced by 34% in patients treated with Pulmozyme versus placebo (RR=0.33, p=0.048).

PULMOZYME did not produce a pulmonary function benefit in short-term usage in patients with FVC less than 40% of predicted. Studies are in progress to assess the impact of chronic use on pulmonary function and infection risk in this population.

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

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

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

Study ML28249 (IMPART) was a multicenter, randomized, open-label, two-period crossover Phase IV trial designed to compare the efficacy and safety of PULMOZYME in 85 patients with cystic fibrosis when delivered by two different nebulizer systems: the PARI eRapid and the PARI LC Plus Reusable Nebulizer. Study ML28249 met its primary efficacy endpoint of equivalence between the PARI eRapid (test) and the PARI LC Plus Reusable Nebulizer (reference) nebulizer with respect to lung function assessed by percent predicted FEV₁ [95% Confidence Interval (CI) of the ratio (test/reference): 99.2%, 102.5%]. The incidence, severity, and nature of reported adverse events were similar between treatments administered using the two nebulizer systems. Patients reported mean PULMOZYME administration times of 2.7 minutes using the eRapid nebulizer compared with 10.2 minutes using the PARI LC Plus Reusable Nebulizer.

DETAILED PHARMACOLOGY

In vitro, rhDNase significantly reduces the viscoelasticity of infected cystic fibrosis sputum, as measured by quantitative viscometry. The reduction in viscoelasticity was concentration-dependent, at a range of concentrations of 1-20 µg rhDNase/mL sputum. Greater than 50% reduction in viscoelasticity was observed at concentrations of 2-4 µg/mL.¹ Similar DNase concentrations are found in the sputum of cystic fibrosis patients 15 minutes following a 2.5 mg dornase alfa dose.

Safety Pharmacology/Acute Toxicity

Rats were evaluated for pharmacological effects of dornase alfa on the renal, gastrointestinal, and central nervous systems following administration of a single intravenous bolus injection. Doses of up to 10.0 mg/kg had no apparent effect on any of the pharmacological parameters evaluated.

Single, intravenous bolus doses of dornase alfa up to 10.0 mg/kg had no apparent effect when administered to Cynomolgus monkeys.

When a single dose (0.1 mL, 5 mg/mL) of dornase alfa was instilled into the conjunctival sac of rabbits to assess the potential for eye irritation, there was no ocular irritation up to 72 hours after application.

Pharmacokinetics

Following inhalation exposure pulmonary bioavailability of dornase alfa was <15% in rats and <2% in monkeys. Following i.v. administration in rats and primates, dornase alfa was rapidly removed from the systemic circulation and no evidence of accumulation was observed.

In a study performed in lactating Cynomolgus monkeys, receiving high doses of dornase alfa by the intravenous route, low concentrations (< 0.1% of the concentrations seen in the serum of pregnant Cynomolgus monkeys), were detectable in the maternal milk. When administered to

humans according to the dosage recommendation, there is minimal systemic absorption of dornase alfa; therefore no measurable concentrations of dornase alfa would be expected in human milk (see WARNINGS AND PRECAUTIONS: Nursing Women).

TOXICOLOGY

The safety of dornase alfa was evaluated by conducting acute and subacute toxicity studies in rats, monkeys and mice. Subchronic inhalation studies were performed in rats and monkeys. A carcinogenicity study in rats was completed. Mutagenic, reproduction and teratologic studies were conducted using rats and rabbits.

SHORT-TERM MULTIDOSE STUDIES			
SPECIES/ ROUTE	INHALED DOSE/ DURATION	DOSE TO LRT*	COMMENTS
Rat/ Inhalation	0, 0.21, 0.75, 2.18 mg/kg 4-week and 4-week recovery	0, 0.02, 0.06, 0.24 mg/kg	Well tolerated at all doses. There were no significant antemortem findings, other than a dose-dependent increase in incidence of serum antibody titers at Week 4 (5, 10, and 32%, in low-, mid- and high-dose groups, respectively). Microscopic evidence of alveolitis in the high-dose rats was noted. This change fully regressed by the end of the treatment-free period.
Monkey/ Inhalation	0, 0.25, 0.53, 2.15 mg/kg 4-week and 4-week recovery	0, 0.14, 0.29, 1.18 mg/kg	Well tolerated at all doses. There were no significant antemortem findings. A dose-dependent increase in incidence of serum antibody titers (Week 4) was apparent (50, 75, and 92%, at the low-, mid- and high-dose levels, respectively). Titers in high-dose recovery monkeys were unchanged at Week 8. Microscopic evidence of bronchiolitis was noted in one high-dose animal at Week 4.

- Doses in inhalation studies are estimations of inhaled doses. Doses to the lower respiratory tract (LRT) are lower based upon minute ventilation and fractional deposition to the LRT.

LONG-TERM MULTIDOSE STUDIES			
SPECIES / ROUTE	INHALED DOSE/ DURATION	DOSE TO LRT*	COMMENTS
Rat/ Inhalation	0, 0.44, 0.87, 2.23 mg/kg 26-week and 4- week recovery	0, 0.05, 0.10, 0.25 mg/kg	Well tolerated at all doses. No treatment-related mortalities or clinical or gross pathologic changes were apparent. Nondose-related incidence of positive antibody titers at Week 27 was evident at all doses. Serum concentrations of dornase alfa evident at mid- and high-dose levels. Microscopically, an increased incidence of animals with germinal centres in the bronchus associated lymphoid tissue (all doses), increased incidence of females with germinal centres in bronchial lymph nodes (all doses), and minimal to mild focal alveolitis (mid- and high-dose) were apparent. With the exception of alveolitis at the mid-dose level, all changes were reversible.
Monkey/ Inhalation	0, 0.38, 1.00, 1.76, 2.00 mg/kg† 26-week and 4- week recovery † Intermittent exposure regimen (Weeks 1-13, 22-26)	0, 0.21, 0.55, 0.98 and 1.11 mg/kg	Well tolerated at all doses. No treatment-related clinical or gross pathologic findings were evident. Positive antibody titers were initially noted at Week 4 and persisted throughout the treatment and recovery periods (all doses). Serum concentrations of dornase alfa indicated that no significant systemic accumulation occurred. Microscopic evidence of perivascular cuffing, peribronchial lymphoid hyperplasia, terminal airway-related bronchiolitis/alveolitis and siderophages in lung tissue was noted at all doses. There was a general trend toward an increase in the incidence or severity of pulmonary lesion in animals with elevated antibody titers. Overall, the histopathologic lung changes were indicated to be regressing at the end of the recovery period. Intermittent exposure (two months) at the high-dose level did not influence the safety profile of dornase alfa relative to continuous treatment.

* Doses in inhalation studies are estimations of inhaled doses. Doses to the lower respiratory tract (LRT) are lower based upon minute ventilation and fractional deposition to the LRT.

In addition, two week repeat dose intravenous studies were conducted at doses up to 1.2 mg/kg/day in rats and primates. No evidence of any systemic toxicity was observed.

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. Dornase alfa 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 up to 10 mg/kg on two consecutive days. No evidence of chromosomal damage was noted.

Reproduction/Developmental Studies

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 maximum recommended human dose. These studies have revealed no evidence of impaired fertility, harm to the fetus, or effects on development due to dornase alfa (see WARNINGS AND PRECAUTIONS: Pregnant Women).

Carcinogenesis

Lifetime studies in Sprague Dawley rats showed no carcinogenic effect when dornase alfa was administered as doses up to 246 µg/kg body weight per day. Dornase alfa 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.

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PART III: CONSUMER INFORMATION

PrPULMOZYME®
dornase alfa

This leaflet is part III of a three-part "Product Monograph" published when PULMOZYME was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PULMOZYME. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

PULMOZYME is used to treat patients with cystic fibrosis. It helps to break down the thick mucous in the airways, which improves lung function and reduces the risk of respiratory tract infections.

What it does:

PULMOZYME contains the active ingredient dornase alfa (also called recombinant human deoxyribonuclease I or rhDNase) which is a man-made protein similar to a natural protein in your body called DNase. PULMOZYME works by helping to break down the thick mucous produced in the lungs of patients with cystic fibrosis.

When it should not be used:

If you are allergic to PULMOZYME or any of the ingredients it contains.

What the medicinal ingredient is:

dornase alfa

What the non-medicinal ingredients are:

calcium chloride, sodium chloride and water

What dosage forms it comes in:

Ampoule 2.5 mg

WARNINGS AND PRECAUTIONS**BEFORE using PULMOZYME talk to your doctor or pharmacist if:**

- you are allergic to other medicines, including those not prescribed by your doctor
- you are taking any other medicines, including those not prescribed by your doctor
- you are pregnant, plan to become pregnant, or are breastfeeding

This information will help your doctor and you decide whether you should use PULMOZYME and what extra care may need to be taken while you are on the medicine.

INTERACTIONS WITH THIS MEDICATION

You should continue to take your standard cystic fibrosis treatment while you are on PULMOZYME (for example, antibiotics, bronchodilators, enzyme supplements, vitamins, corticosteroids and pain killers).

PROPER USE OF THIS MEDICATION**Usual dose:**

The usual dose is the contents of one ampoule to be inhaled each day. Some patients may benefit from taking PULMOZYME twice a day. Your doctor will decide the best dose for you.

DO NOT INHALE PULMOZYME UNTIL YOUR DOCTOR HAS THOROUGHLY TRAINED YOU IN THE PROPER TECHNIQUE.

PULMOZYME should be administered only using the nebulizers and compressors listed in the following tables:

Recommended Jet Nebulizer and Compressor Systems

Jet Nebulizer	Compressor
Hudson T Up-draft II with	Pulmo-Aide
Marquest Acorn II with	Pulmo-Aide
PARI LC Plus Reusable Nebulizer with	PARI PRONEB
PARI BABY with	PARI PRONEB

Recommended Nebulizer System

eRapid Nebulizer System (Consisting of the eRapid Nebulizer Handset with eBase Controller)

Keep all other inhaled medication systems completely separate from PULMOZYME. Do not use any other inhaled medications in the nebulizer at the same time. Do not use a mask. Use the mouthpiece provided with each nebulizer kit.

If you are unable to breathe through your mouth for the entire nebulization period, you may use the reusable PARI BABY nebulizer. It is recommended that patients under 5 years of age use the PARI BABY nebulizer. Please talk to your doctor about using the PARI BABY nebulizer before you do this. The PARI BABY nebulizer is identical to the PARI LC Plus Reusable Nebulizer except that the mouthpiece is replaced by a tight-fitting facemask connected to an elbow piece.

The eRapid Nebulizer System directions for assembly and use are different from the other Jet Nebulizer and Compressor systems.

- If you are using **Jet Nebulizer and Compressor systems**, refer to **Section A**.
- If you are using the **eRapid Nebulizer System**, refer to **Section B**.

This information does not take the place of talking to your doctor about your medical condition or your treatment. In addition, this information does not take the place of the Manufacturer’s Instruction Booklet which is necessary for proper use of each device.

SECTION A) - JET NEBULIZER AND COMPRESSOR SYSTEMS

- Hudson T Up-draft II with Pulmo-Aide,
- Marquest Acorn II with Pulmo-Aide,
- PARI LC Plus Reusable Nebulizer with PARI PRONEB and
- PARI BABY with PARI PRONEB

IF YOU ARE USING THE eRAPID NEBULIZER SYSTEM, REFER TO SECTION B.

Items needed for administration

- 1 ampoule of PULMOZYME
- Compressor
- Nebulizer cup and screw-on or snap-on cap
- Plastic T connector (not needed for PARI BABY)
- Flexible aerosol tube (not needed for PARI BABY)
- Clean mouthpiece or PARI BABY facemask
- Long connecting tube
- Nose clip (optional, not needed for PARI BABY)
- Manufacturer’s Nebulizer System Instruction Booklet

THE FOLLOWING INSTRUCTIONS ARE A GUIDE FOR ASSEMBLY AND USE OF THE RECOMMENDED NEBULIZER SYSTEMS :

Preparing the Treatment

1. Wash your hands thoroughly with soap and water before preparing the medication. This helps prevent infection.
2. Clean a table surface and lay out the nebulizer components. Place the compressor on the table within reach. Test the compressor by turning it on and putting your finger in front of the “air out” port to feel air flowing. Turn off the compressor.
3. Remove one ampoule of PULMOZYME from its pouch stored in the refrigerator and make sure the expiration date has not passed. Do not use PULMOZYME ampule if expiration date has passed. Test the ampoule for leaks by turning it upside down and gently squeezing. If there appears to be a leak, do not use that ampoule of PULMOZYME. Next, check the PULMOZYME solution. It should be clear and free of particles. Do not use the PULMOZYME solution if it is cloudy or discoloured, but return it to your doctor or pharmacist.
4. Attach the long connecting tube to the “air out” port on the compressor.
5. Push the mouthpiece into the wider end of the plastic T. Attach the flex tube to the other end of the T. (For the PARI BABY, skip this step.)
6. Unscrew or unsnap the cap from the nebulizer cup. Put the cup on the table face up.
7. Hold the tab at the base of the ampoule of PULMOZYME firmly, taking care not to squeeze the body of the ampoule, and twist off the top.
8. Turn the ampoule upside-down and squeeze gently to empty contents into the nebulizer cup. Continue squeezing until the ampoule is empty. **It is very important that you use the full dose of the drug.** Screw or snap the cap onto the nebulizer cup.
9. Connect the plastic T to the nebulizer cap. (For the PARI BABY, connect the elbow piece and mask to the nebulizer outlet.)
10. Connect the open end of the long tube to the port on the bottom of the nebulizer cup by pushing up firmly.
11. Turn on the compressor and check to see that mist is coming out of the nebulizer.

Taking the Treatment

IF YOU ARE USING A NEBULIZER OTHER THAN PARI BABY USE THE FOLLOWING INSTRUCTIONS:

1. Place the mouthpiece between your teeth and on top of your tongue. Be sure that you do not block the airflow with your tongue. Breathe normally by inhaling and exhaling through your mouth. **Do not breathe through your nose.** If you have difficulty breathing only through your mouth, use a nose clip.
2. Do not be concerned if condensation collects in the long connecting tube during treatment. When the nebulizer begins “spitting”, gently tap the nebulizer cup and continue breathing until the nebulizer cup is empty, or stops producing mist.

If you are interrupted or begin coughing during treatment, turn off the compressor taking care not to spill any of the drug. To resume treatment, turn on the compressor and continue. The complete treatment usually takes from 10 to 15 minutes.

It is important to inhale the full dose of PULMOZYME. If you detect a leak or feel any moisture coming from the nebulizer during treatment, turn off the compressor and check to be sure the nebulizer cap is sealed correctly before continuing.

IF YOU ARE USING THE PARI BABY NEBULIZER TO GIVE PULMOZYME TO YOUR CHILD YOU SHOULD USE THE FOLLOWING INSTRUCTIONS:

1. Place the facemask gently but firmly over the nose and mouth of your child. Make sure there are no air gaps between the mask and your child’s face. This will help ensure that your child will get the full dose of PULMOZYME. During the treatment your child may sit, lie down or stand. It is important that you try to keep the body of the nebulizer upright during the entire treatment period. The elbow piece will allow you to adjust the position of the mask while keeping the nebulizer body upright.

2. When the nebulizer begins “spitting”, gently tap the nebulizer cup and continue treatment until the nebulizer is empty or stops producing a mist.
 - If you are interrupted or your child begins to cough during treatment, turn the compressor off, taking care not to spill any PULMOZYME.
 - If you have not removed the mask and you wish to begin treatment again, simply turn on the compressor.
 - If you have removed the mask repeat Step 1. A complete treatment usually takes about 10 to 15 minutes.
3. It is important that you child inhale the full dose of PULMOZYME. If you detect a leak or feel moisture coming from the nebulizer during treatment, turn off the compressor and make sure the nebulizer cap is sealed correctly before starting the compressor again.

After the Treatment

Turn off the compressor and disassemble the nebulizer system, setting aside the flex tube and the long connecting tube.

FOLLOW MANUFACTURER’S RECOMMENDATIONS FOR CARE OF YOUR NEBULIZER AND COMPRESSOR.

SECTION B) - eRAPID NEBULIZER SYSTEM

- eRapid Nebulizer consisting of the eRapid Nebulizer Handset with eBase Controller

IF YOU ARE USING JET NEBULIZER AND COMPRESSOR SYSTEMS, REFER TO SECTION A.

Items needed for administration

- 1 ampoule of PULMOZYME
- eRapid Nebulizer System, consisting of:
 - eRapid Nebulizer Handset (handset)
 - eBase Controller (controller)
- Power source consisting of:
 - Controller can be used with 4 “AA” batteries (disposable or rechargeable)
 - Controller can also be used with AC Power Supply plugged into a typical wall outlet (110 volt power outlet)
- Nose clip (optional)
- Manufacturer’s eRapid Nebulizer System Instruction Booklet

THE FOLLOWING INSTRUCTIONS ARE A GUIDE FOR ASSEMBLY AND USE OF THE eRapid NEBULIZER SYSTEM:

Preparing the Treatment

1. Wash your hands thoroughly with soap and water before preparing the medication. This helps prevent infection.
2. Clean a table surface and lay out the nebulizer components. Make sure the controller batteries are charged or that the unit is plugged into a power outlet. Press and hold the ON/OFF button on the controller for a few seconds to test if the controller will turn on. When controller is turned on, press and hold the ON/OFF button to turn the controller off.
3. Remove one ampoule of PULMOZYME from its pouch stored in the refrigerator and make sure the expiration date has not passed. Do not use PULMOZYME ampule if expiration date has passed. Test the ampoule for leaks by turning it upside down and gently squeezing. If there appears to be a leak, do not use that ampoule of PULMOZYME. Next, check the PULMOZYME solution. It should be clear and free of particles. Do not use the PULMOZYME solution if it is cloudy or discoloured, but return it to your doctor or pharmacist.
4. To assemble the eRapid Nebulizer System, follow the Manufacturer’s eRapid Nebulizer System Instruction Booklet for cleaning instructions and step-by-step assembly instructions, such as: Components must be cleaned and disinfected at least once before first use. The eRapid Nebulizer System has several small parts that must be put together the right way to give your dose of PULMOZYME.
5. After you put together the eRapid Nebulizer System, prepare the PULMOZYME ampule. Hold the tab at the base of the ampoule of PULMOZYME firmly, taking care not to squeeze the body of the ampoule, and twist off the top.

- Turn the ampoule upside-down and squeeze gently to empty contents into the medicine reservoir. Continue squeezing until the ampoule is empty. **It is very important that you use the full dose of the drug.** Line up the tabs on medicine cap with the slots on medicine reservoir. Turn medicine cap clockwise until it stops and the nebulizer handset is now almost ready for use.
- Press and hold ON/OFF button on the controller for a few seconds. The controller will beep and the light will turn green. The nebulizer will start making mist.

Taking the Treatment

- Keep the eRapid Nebulizer handset level when in use. If the handset is tilted, the dosage may not be accurate.
- Place the mouthpiece between your teeth and on top of your tongue. Be sure that you do not block the airflow with your tongue. Breathe normally by inhaling and exhaling through your mouth. **Do not breathe through your nose.** If you have difficulty breathing only through your mouth, use a nose clip.
- If you are interrupted or begin coughing during treatment, turn off the nebulizer controller by pressing and holding the ON/OFF button on the controller for 1 second. To resume treatment, press and hold the ON/OFF button for 1 second and continue the treatment until the controller beeps twice. The nebulizer will shut off by itself when your dose is complete. The complete treatment usually takes from 1 to 5 minutes.

After the Treatment

- It is important to inhale the full dose of PULMOZYME.** After your treatment, about 1/5 teaspoon (1 mL) of medicine should be left in the medicine reservoir. Open the medicine cap and check the medicine reservoir. If more than 1/5 teaspoon (1 mL) is left in the medicine reservoir, put the medicine cap back on and continue treatment. When treatment is complete, throw away the 1/5 teaspoon (1 mL) of medicine that is left in the medicine reservoir.
- If the nebulizer controller is on, turn off the controller by pressing and holding the ON/OFF button.
- Take apart the nebulizer system. Throw away the empty PULMOZYME ampule in your household trash. See the **Manufacturer's eRapid Nebulizer System Instruction Booklet** for cleaning instructions. Specifically, when the eRapid Nebulizer is used for PULMOZYME medicine delivery, the use of the EasyCare cleaning aid is recommended for cleaning the aerosol head once a week. As per the EasyCare cleaning aid Instructions For Use, aerosol head should not be cleaned more than 25 times with the EasyCare cleaning aid.

FOLLOW MANUFACTURER'S RECOMMENDATIONS FOR CARE OF YOUR NEBULIZER SYSTEM.

Overdose:

If you take more than the prescribed amount of PULMOZYME, contact your doctor right away.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of PULMOZYME is missed, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects are voice alteration, sore throat, laryngitis, cough, rash, chest pain, and conjunctivitis. These effects are generally mild and they usually go away within a few weeks after starting therapy.

This is not a complete list of side effects. For any unexpected effects while taking PULMOZYME, contact your doctor or pharmacist.

HOW TO STORE IT

- Refrigerate in its foil pouch at 2-8°C.
- Store away from heat and direct light. Do not use the medicine if it has been exposed to room temperature for more than 24 hours.
- Do not use this medicine if it becomes cloudy or discoloured.
- Do not use this medicine after the expiry date on the package.
- Keep out of reach of young children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program**
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.rochecanada.com
or by contacting the sponsor, Hoffmann-La Roche Limited, at 1-888-762-4388.

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