

NAME OF THE MEDICINE

PULMOZYME[®]

(*dornase alfa*)

C₁₃₂₁H₁₉₉₅N₃₃₉O₃₉₆S₉

CAS registry number: 143831-71-4

DESCRIPTION

PULMOZYME (*dornase alfa*) is an enzyme that cleaves extracellular DNA and reduces the viscosity of purulent lung secretions. The active ingredient is produced by genetically engineered Chinese hamster ovary (CHO) cells containing DNA that encodes for the human protein, deoxyribonuclease I (DNase). Purification of the product is achieved by conventional tangential flow filtration and column chromatography technology. The purified glycoprotein contains 260 amino acids with a relative molecular weight of approximately 37,000 daltons. The primary amino acid structure of rhDNase is the same as the native human enzyme (DNase).

PULMOZYME is administered by oral inhalation with the aid of a compressed air-driven nebuliser. Each PULMOZYME single-use ampoule will deliver 2.5 mL of a sterile, clear, colourless to slightly yellowish, aqueous solution to the nebuliser bowl. The solution contains 1.0 mg/mL *dornase alfa* with 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.

PHARMACOLOGY

Pharmacodynamics

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. Infected sputum of cystic fibrosis (CF) patients contains an abundant amount of mucus glycoproteins and extracellular DNA (approximately 6 mg/mL) derived primarily from degenerating neutrophils that accumulate in the airways in response to infection. DNA is believed to be the major factor responsible for the abnormal viscoelastic properties of infected sputum. In *in vitro* studies, rhDNase cleaves extracellular DNA in purulent sputum and greatly alters the viscoelastic properties of sputum rich in DNA.

Pharmacokinetics

Absorption and Bioavailability

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 rhDNase 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 6 days did not result in a significant elevation of serum DNase concentrations above normal, suggesting negligible systemic exposure. No increase in serum DNase concentration greater than 10 ng/mL was observed. After administration of dornase alfa 2.5 mg bd for 24 weeks, serum concentrations of DNase were not different from the pre-treatment baseline value of 3.5 ± 0.1 ng/mL; suggesting low systemic absorption or accumulation.

Distribution

Studies in rats and monkeys have shown that, following intravenous administration, rhDNase 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 µg/mL within 15 minutes in CF 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 rhDNase 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.

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

CLINICAL TRIALS

PULMOZYME has been evaluated in CF 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 Forced Vital Capacity (FVC) Over 40% Predicted

A parallel-design, randomised, placebo-controlled, three-armed, double-blind, multicentre study was undertaken to determine the safety and effectiveness of once or twice daily therapy using PULMOZYME in cystic fibrosis outpatients treated for 24 weeks. A total of 968 cystic fibrosis patients equal to or greater than 5 years of age were enrolled if clinically stable and if their forced vital capacity (FVC) was equal to or greater than 40% of predicted.

Respiratory Tract Infection

Patients were treated with placebo or PULMOZYME 2.5 mg once daily or 2.5 mg twice daily.

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 1). The data suggest that the effects of PULMOZYME 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 forced expiratory volume in one second (FEV₁) during the initial two weeks of therapy.

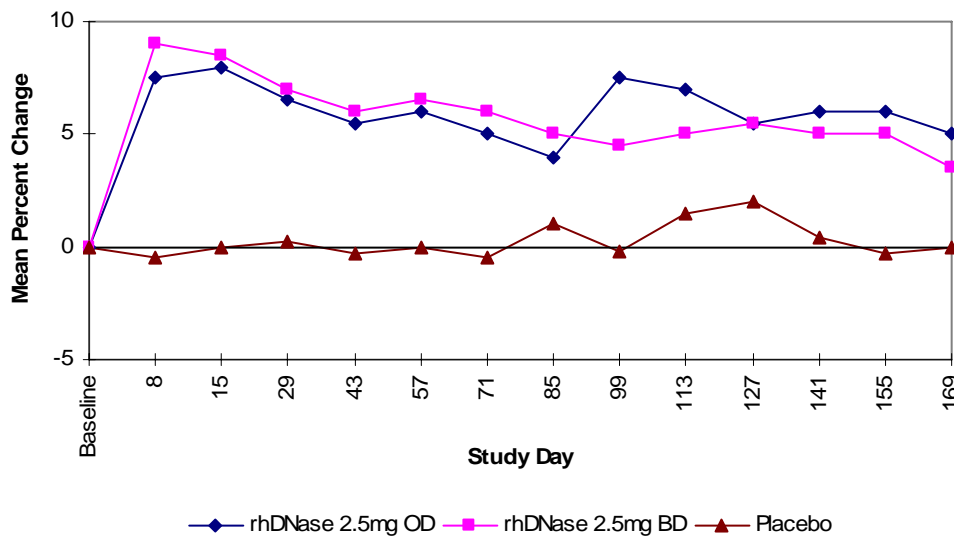
Table 1 Incidence of First Respiratory Tract Infection Requiring Parenteral Antibiotics in a Controlled Trial

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

Pulmonary Function

After treatment for 1 week, administration of PULMOZYME once daily improved FEV₁ by 7.9%, and administration of PULMOZYME twice daily improved FEV₁ by 9.0% compared to pre-treatment baseline values. Administration of PULMOZYME once daily improved the average FEV₁ during the 24 week double-blind period by 5.8% (*p* < 0.001). Administration of PULMOZYME twice daily improved the average FEV₁ during the 24-week double-blind period by 5.6% (*p* < 0.001). Placebo had no demonstrable effect on FEV₁ over these periods of observation (Figure 1).

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

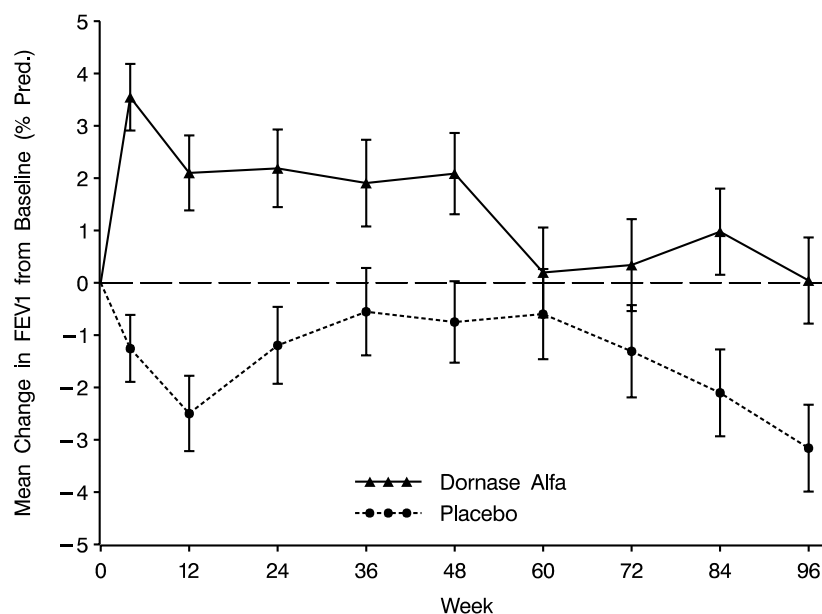


PULMOZYME also improved quality of life as assessed by change in CF-related symptom score, days in hospital, dyspnoea score (once daily), change in well-being score (once daily) and days at home due to illness (once daily).

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 FEV₁ in patients treated with PULMOZYME compared with placebo was $3.2 \pm 1.2\%$ predicted ($p = 0.006$) (treatment group, $n = 237$; placebo group, $n = 234$). 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 experienced a mean decrease from baseline (Figure 2).

Figure 2 Mean Absolute Change from Baseline FEV₁ in Patients aged 6 - 10 Years with FVC > 85% Predicted



In this population, a larger benefit in forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅) (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 FEV₁ at 4 weeks (< 3% predicted group, $n = 118$; $\geq 3\%$ predicted group, $n = 115$).

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 FEV₁ and FVC in this patient population. Relative increases from baseline FEV₁ and FVC were 9.4% and 12.4% in the PULMOZYME group versus 2.1% and 7.3% in the placebo group, respectively ($p < 0.01$) (treatment group, $n = 156$; placebo group, $n = 162$). A second study found no difference between treatments during a 14-day double-blind, placebo-controlled trial (2.5 mg PULMOZYME twice daily, $n = 31$; placebo twice daily, $n = 34$) but found continued improvements in FEV₁ and FVC over a 6-month open extension period when all patients received PULMOZYME 2.5 mg twice daily ($n = 38$).

Phase II Study in Infants and Children

PULMOZYME has been evaluated in an open-label 2 week study in 98 patients with cystic fibrosis aged 3 months to 9 years of age. PULMOZYME, 2.5 mg by inhalation, was administered daily (65 infants 3 months to < 5 years – of which 37/65 were aged ≤ 2 years; 33 children aged 5 to 9 years); a tight fitting facemask was used 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). Broncheolar 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. Median concentrations in children aged less than 5 years were comparable to those obtained in the 5 - 9 years age group. The study therefore demonstrated that adequate lung deposition can be obtained in patients under the age of 5 years. Over an average of 14 days of exposure, serum DNase concentrations (mean ± sd) increased by 1.1 ± 1.6 ng/mL for the younger age group and by 0.8 ± 1.2 ng/mL for the older age group. Safety in this population is addressed in the **ADVERSE EFFECTS** section.

INDICATIONS

Chronic administration of PULMOZYME is indicated for the management of demonstrated respiratory complications in cystic fibrosis. Continued use should depend on demonstrating a sustained benefit based on clinical response and, if able to be performed, pulmonary function tests.

CONTRAINDICATIONS

PULMOZYME is contraindicated in patients who develop or have known hypersensitivity to dornase alfa, Chinese hamster ovary cell products or any component of the product.

PRECAUTIONS

Patients should continue to receive regular medical care for their cystic fibrosis when being treated with PULMOZYME.

Effects on Fertility

In studies with rats given intravenous doses up to 10 mg/kg/day, fertility and reproductive performance of either males or females were not affected.

Use in Pregnancy - Category B1

Reproduction studies have been performed in rats and rabbits with intravenous doses of 10 mg/kg/day. These studies have revealed no evidence of impaired fertility or harm to the foetus in rats and rabbits, and no effects on peri- and post-natal development in rats due to dornase alfa. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this medicine should be used in pregnancy only if clearly needed.

Use in Lactation

When dornase alfa is administered to humans according to the dosage recommendations, 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 **PHARMACOLOGY, Pharmacokinetics**).

In a study performed in lactating cynomolgus monkeys, in which high doses of dornase alfa were given by the intravenous route (100 µg/kg bolus followed by 80 µg/kg/hour for 6 hours), low concentrations of the drug (< 0.1% of the concentrations seen in the serum of pregnant cynomolgus monkeys given the same dose) were measurable in milk. Thus, concentrations of dornase alfa in

human milk would be expected to be negligible. Any dornase alfa excreted in milk and ingested by the nursing infant would be expected to be rapidly degraded in the infant's gastrointestinal tract.

Paediatric Use

There is limited experience in the use of PULMOZYME in patients under the age of 5 years (see **CLINICAL TRIALS – Phase II Study in Infants and Children**).

Treatment of young adult animals with a dose that gave a concentration of drug at the alveoli calculated to be similar to that in children given the recommended dose caused alveolitis sometimes with bronchiolitis.

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

Interactions with Other Medicines

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

PULMOZYME can be effectively and safely used in conjunction with standard cystic fibrosis therapies such as antibiotics, bronchodilators, digestives, vitamins, inhaled and systemic corticosteroids and analgesics.

Carcinogenicity

Groups of 60 rats per sex received dornase alfa at 51, 101 or 246 µg/kg/day to the 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. The maximum dose tested was approximately 11 – 16 times (depending on age) the maximum recommended dose in humans.

Genotoxicity

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 or in the mouse micronucleus test.

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.

ADVERSE EFFECTS

Clinical Trials

PULMOZYME is well tolerated. In double-blind clinical trials in over 600 patients receiving PULMOZYME 2.5 mg once or twice a day for six months, most adverse events were the sequelae of the underlying lung disease.

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 PULMOZYME dosing.

Events that increased in incidence in the double-blind, placebo-controlled trials increased with higher dose.

Eye Disorder:

Conjunctivitis.

Respiratory, Thoracic and Mediastinal Disorders:

Dysphonia, dyspnoea, pharyngitis, laryngitis, rhinitis (all non-infectious).

Investigations:

Pulmonary function tests decreased.

Gastrointestinal Disorders:

Dyspepsia.

Skin and Appendages Disorders:

Rash, urticaria.

General Disorders:

Chest pain (pleuritic/non-cardiac), pyrexia.

In a phase III clinical trial, 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%).

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

Allergic Reactions

Rhinitis, wheeze and haemoptysis do not appear to be related to PULMOZYME administration when compared to placebo in controlled trials. However, an increased incidence of these events was noted in patients treated with 10 mg PULMOZYME on an intermittent schedule.

There have been no reports of serious allergic reactions or anaphylaxis associated with administration of dornase alfa. Skin rashes have been observed and have been mild and transient in nature. 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 have 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 **CLINICAL TRIALS – Phase II Study in Infants and Children**). 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 Experience

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

DOSAGE AND ADMINISTRATION

The recommended dose for use in most patients is one 2.5 mg single-use ampoule inhaled once per day using the recommended nebuliser (see below).

Patients over the age of 21 may benefit from twice daily dosing.

Most patients gain optimal benefit from continued daily use of PULMOZYME. The optimal timing for the use of PULMOZYME in relation to the use of standard treatments such as physiotherapy and antibiotics has not been established.

The recommended dose should not be exceeded because of the dose-dependent occurrence of "irritant" side-effects with no additional efficacy.

Cystic fibrosis patients have received up to 10 mg bd for up to 2 out of 4 weeks intermittently over a 6-month period and these doses are well tolerated, and improved pulmonary function. The results of this study indicate that improvement in pulmonary function subsides within several days of cessation of therapy. Studies demonstrating the reduction in the rate of respiratory tract infectious exacerbations involved chronic, daily administration of dornase alfa. Therefore, patients should be instructed to take their medication every day.

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 the clinical trials.

PULMOZYME is provided as a solution for inhalation in single-use ampoules. The complete contents of a single ampoule should be placed in the bowl of a jet nebuliser and used in conjunction with a source of compressed air (nominal flow rate 6 - 8 L/minute). PULMOZYME should not be diluted or mixed with any other medicines or solutions in the nebuliser bowl.

The patient should continue his/her standard regimen of chest physiotherapy. At present, no recommendation can be made as to the optimal time of day for the administration of PULMOZYME.

Patients should be instructed on proper use, maintenance and care of the nebuliser and compressor used to deliver PULMOZYME. Only nebulisers and compressors registered as devices in Australia and trialled for administration with PULMOZYME should be used (see Consumer Medicine Information for a list of recommended nebulisers and compressors). Ultrasonic nebulisers may be unsuitable for delivery of PULMOZYME because they may inactivate PULMOZYME or have unacceptable aerosol delivery characteristics. In children under the age of 5 years, it is

recommended that PULMOZYME be administered with a tight fitting mask. This was the method used for most patients in this age group, in the clinical study which demonstrated adequate lung deposition.

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 dose) for up to 6 days and 10 mg twice daily (8 times the recommended dose) intermittently (2 weeks on/2 weeks off drug) for 168 days. Six adult non-cystic fibrosis patients received a single intravenous dose of 125 µg/kg of dornase alfa, followed 7 days later by 125 µg/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 **PHARMACOLOGY, Pharmacokinetics**).

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

PULMOZYME is supplied in a single-use, low-density polyethylene plastic ampoule. Each ampoule delivers 2.5 mL of PULMOZYME to the nebuliser chamber.

Each pack of 30 ampoules consists of five foil pouches, each containing six ampoules.

PULMOZYME does not contain any preservative. Once opened, the entire ampoule must be used at one time. The product must be stored in the refrigerator at 2 – 8 °C and protected from light. A single brief exposure to elevated temperatures (less than or equal to 24 hours at up to 30 °C) does not affect product stability. The solution should not be used if it is cloudy or discoloured.

PROTECT AMPOULES FROM LIGHT.

Do not use beyond the expiration date stamped on the pack. Store unused ampoules in their protective foil pouch in the outer carton under refrigeration.

POISON SCHEDULE OF THE MEDICINE

S4. Prescription only medicine.



NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
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Dee Why, NSW, 2099

DATE OF APPROVAL

TGA Approval Date: 27 July 2009