Pulmozyme®

Dornase alfa

COMPOSITION

Active substance: Dornase alfa.

Recombinant human deoxyribonuclease I (rhDNase), produced by genetic engineering in Chinese hamster ovary cells, consisting of an active mixture of DNase and deamido-DNase (specification: 65±17% deamido-DNase).

Excipients: calcium chloride dihydrate, sodium chloride, excipients for solution.

GALENICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Each plastic ampoule contains 2.5 ml of a sterile, clear, colourless to slightly yellowish, aqueous nebuliser solution containing 1.0 mg/ml dornase alfa, 0.15 mg/ml calcium chloride dihydrate and 8.77 mg/ml sodium chloride.

INDICATIONS AND POTENTIAL USES

For symptomatic treatment in combination with standard cystic fibrosis (mucoviscidosis) therapies in patients with a forced vital capacity (FVC) of more than 40% of normal.

Currently, clinical data are available in patients over 5 years of age treated for up to 2 years.

Long-term Pulmozyme use is indicated for the prevention of respiratory complications caused by the build-up of DNA in the infected mucus that accumulates in the respiratory tract in cystic fibrosis (mucoviscidosis). Such long-term therapy has the following effects:

- reduction in the frequency of recurrent symptomatic infections requiring parenteral antibiotic treatment and hospitalisation;
- improvement in respiratory function, with alleviation of symptoms such as shortness of breath, cough and mucus accumulation;
- improvement in the patient's general well-being.

DOSAGE AND ADMINISTRATION

Standard dosage

For cystic fibrosis patients, long-term treatment is recommended with dornase alfa 2.5 mg daily, i.e. inhalation with the undiluted contents of one 2.5 ml ampoule of solution daily (see "Instructions for use and handling").

Some patients over 21 years of age may benefit from twice-daily administration of a daily dose.

Use

Most patients gain optimal benefit from regular daily use of Pulmozyme. Studies in which Pulmozyme was administered intermittently have shown that improvement in pulmonary function regresses within a few days after discontinuation of treatment. Clinical trials have shown that only daily and continued administration reduces the frequency of exacerbations of respiratory infections. Patients should therefore be instructed to use the preparation daily.

During Pulmozyme therapy, patients should continue their regular medical care, including the standard regimen of physiotherapy to improve respiratory function.

Patients who experience exacerbation of respiratory tract infection during treatment with Pulmozyme may safely continue to use Pulmozyme. They should continue physiotherapy to improve respiratory function.

Only limited experience is available on use in patients younger than 5 years of age. Pharmacokinetic and prospective observational postmarketing studies indicate that Pulmozyme can be safely administered to children under 5 years of age at the same dose as for older children using a face mask. However, such use should be considered only if there is potential benefit in terms of lung function and respiratory infection risk (see "Undesirable effects").

Efficacy and long-term safety have not been established in this age group.

The safety and efficacy of Pulmozyme use in patients with forced vital capacity less than 40% of predicted have not yet been demonstrated in clinical studies.

Special dosage instructions

There is no evidence that particular patient groups require special dosage instructions.

CONTRAINDICATIONS

Pulmozyme must not be given to patients with known hypersensitivity to the active ingredient or other components of the product.

WARNINGS AND PRECAUTIONS

There are no special precautions.

INTERACTIONS

Pulmozyme can be safely used in conjunction with standard cystic fibrosis therapies such as antibiotics, bronchodilators, pancreatic enzyme preparations, vitamins, inhaled and systemic corticosteroids and analgesics. However, Pulmozyme should not be mixed with such preparations in the nebuliser (see "Additional information – Incompatibilities").

PREGNANCY AND LACTATION

Pregnancy

The safety of dornase alfa use during pregnancy has not been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, or embryofetal development (see "Preclinical data"); however, there are no controlled studies in pregnant women. Caution is therefore required during use in pregnancy.

Lactation

When dornase alfa is administered to patients 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 is required when dornase alfa is administered to breast-feeding women (see "Absorption" and "Preclinical data").

In a study in which high doses of dornase alfa were administered intravenously to lactating cynomolgus monkeys, only low concentrations (<0.1% of the concentrations measured in the serum of pregnant cynomolgus monkeys) were measured in the milk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no reports of effects on driving ability or the ability to operate machinery.

UNDESIRABLE EFFECTS

Relevant undesirable effects causally related to Pulmozyme are rare (<1/1000). In most cases the undesirable effects are mild and transient and do not require dose adjustment.

Eyes: Conjunctivitis.

Respiratory tract: Dysphonia, dyspnea, pharyngitis, laryngitis, rhinitis (all non-infectious).

Gastrointestinal disorders: Dyspepsia.

Skin: Rash, urticaria.

General disorders: Chest pain (pleuritic, non-cardiac), pyrexia.

Investigations: Pulmonary function tests decreased.

Undesirable effects	Placebo (n=325)	2.5 mg once daily (n=322)	2.5 mg twice daily (n=321)

Eyes			
Conjunctivitis	2%	4%	5%
Respiratory organs			
Pharyngitis	33%	36%	40%
Voice changes	7%	12%	16%
Laryngitis	1%	3%	4%
Skin			
Skin rash	7%	10%	12%
Body as a whole			
Chest pain	16%	18%	21%

Patients who experience adverse events common to cystic fibrosis can, in general, safely continue to use 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 of 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 have developed antibodies to dornase alpha, 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.

Children under 5 years of age:

In a pharmacokinetic study in which 65 children under 5 years of age and 33 children aged 5–9 years received Pulmozyme 2.5 mg once daily for 14 days, no clinically relevant difference in Pulmozyme side effect profile was observed between the two age groups (see "Pharmacokinetics in special patient groups"). Prospective observation of children under 5 years of age, which was conducted both after treatment with Pulmozyme and during the treatment-free interval, showed no increase in the incidence of serious adverse events during Pulmozyme administration.

Pulmozyme should be administered to patients under 5 years of age only if there is potential benefit in terms of lung function or respiratory infection risk.

Undesirable effects, postmarketing data

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

OVERDOSAGE

Overdosage with Pulmozyme is unknown. 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 daily dose) intermittently (2 weeks on/2 weeks off treatment) for 168 days.

Systemic toxicity of Pulmozyme has not been observed and is unlikely, given the poor absorption and short serum half-life of dornase alfa.

PROPERTIES/EFFECTS

ATC code: R05CB13

Mechanism of action and pharmacodynamics

Recombinant human DNase (rhDNase) is the genetically engineered form of an enzyme that occurs naturally in man and cleaves extracellular DNA.

Accumulation of viscous purulent secretions in the airways contributes 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 viscosity of sputum from cystic fibrosis patients.

In-vivo inhalation of dornase alfa improves lung function and decreases the frequency of acute exacerbations in cystic fibrosis by facilitating improved airway clearance of secretions and mucus.

Clinical efficacy studies

Pulmozyme has been evaluated in cystic fibrosis patients over 5 years of age with differing severities of lung disease. Most studies were double-blind and placebo-controlled. All patients received additional therapies as deemed necessary by their physicians.

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 a first respiratory tract infection (infection requiring parenteral antibiotics) and improved mean FEV_1 (forced expiratory volume in one second) compared to placebo.

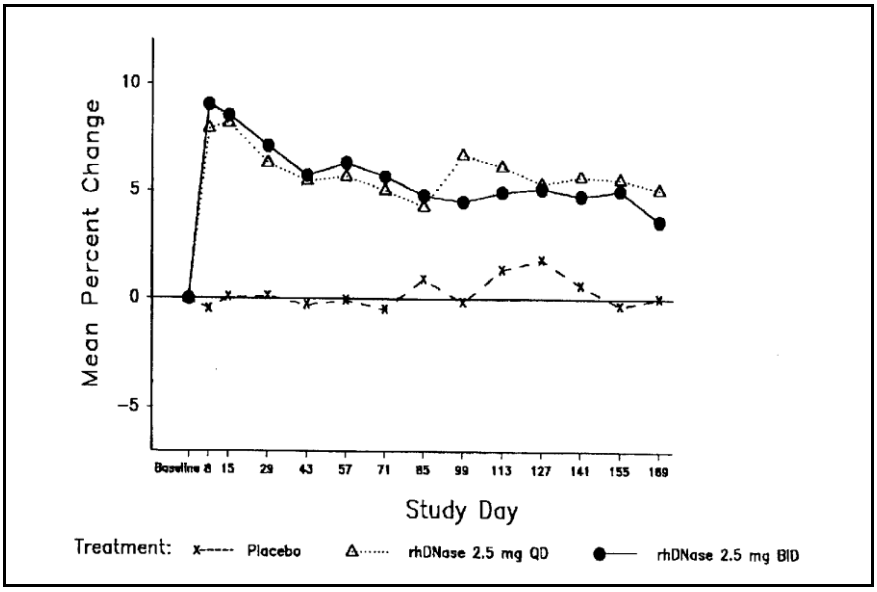
Pulmozyme reduced the relative risk of exacerbation of respiratory tract infection by 27% and 29% on once- and twice-daily dosing, respectively (see Table 1). Subanalysis of the data suggests that the effect of Pulmozyme on infective exacerbations may be smaller in older patients (over 21 years), and that twice-daily dosing may be required in these patients. Patients with baseline FVC >85% may also benefit from twice-daily dosing (see Table 1). The reduced risk of infective exacerbation in patients treated with Pulmozyme persisted throughout the 6-month study period and did not correlate directly with improvement in FEV_1 during the initial two weeks of therapy.

Table 1 Incidence 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
Subgroups 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)

Within 8 days of the start of treatment with Pulmozyme once and twice daily, mean FEV_1 improved by 7.9% and 9.0%, respectively, compared to baseline. After 6 months of treatment the improvement in FEV_1 compared to baseline was 5.8% and 5.6%, respectively, on once- and twice-daily dosing. Patients receiving placebo showed no significant changes in pulmonary function tests throughout the duration of the study (see Figure 1).

Figure 1 Mean percent change from baseline FEV_1 in patients aged >5 years with FVC >40% predicted



Patients aged under 5 years

Pharmacokinetic data from a study in 65 children aged 3 months to 5 years and 33 children aged 5–10 years indicate that administration of 2.5 mg Pulmozyme with the Pari Baby nebuliser and Proneb (= PariBoy) compressor produces concentrations of DNase in the lungs of patients under 5 years old similar to those achieved with the Pari LC Plus nebuliser and the same compressor in the lungs of older children who have responded to Pulmozyme (see "Pharmacokinetics in special patient groups").

Regarding safety in this patient population, see "Undesirable effects".

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

PHARMACOKINETICS

Results from preclinical studies

Absorption

Inhalation studies in rats and non-human primates have indicated that only a small proportion of dornase alfa is absorbed systemically (<15% in rats and <2% in monkeys). Consistent with the results of these animal studies, dornase alfa is found to undergo only slight systemic absorption when administered to patients in the form of an aerosol for inhalation.

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

Distribution and elimination

Studies in rats and monkeys have shown that Pulmozyme is rapidly cleared from serum after intravenous administration. In these studies the initial volume of distribution was similar to the serum volume.

Studies in rats indicate that, after aerosol administration, dornase alfa is eliminated from the lungs with a half-life of 11 hours.

No pharmacokinetic data are currently available in very young or old animals.

Results from clinical studies

Absorption

DNase is normally present in human serum. Inhalation of up to 40 mg dornase alfa for up to 6 days did not result in significant elevation of dornase alfa serum concentrations above normal endogenous levels. No increase in serum DNase concentration greater than 10 ng/ml was observed. After administration of 2.5 mg dornase alfa twice daily for 24 weeks, mean serum DNase concentrations were unchanged from mean baseline (pretreatment) levels (3.5±0.1 ng/ml). This suggests low systemic absorption or accumulation (see "Preclinical data").

Distribution

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

Metabolism

Dornase alfa is assumed to be metabolised by proteases present in body 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 DNase is rapidly cleared from serum following intravenous administration.

After aerosol administration to rats, dornase alfa was eliminated from the lungs with a half-life of 11 hours.

In humans, sputum DNase levels decline below half of those measured immediately post-dose within 2 hours, but effects on sputum rheology persist beyond 12 hours.

Pharmacokinetics in special patient groups

Pulmozyme has been evaluated in an open-label 2-week study in cystic fibrosis patients 3 months to 9 years of age. Pulmozyme was administered by inhalation at a dose of 2.5 mg daily to 98 patients (65 aged 3 months to <5 years and 33 aged 5 to <10 years). Bronchoalveolar lavage (BAL) was performed within 90 minutes of the first dose. A Pari Baby nebuliser (which uses a face mask instead of a mouthpiece) was utilised in patients unable to inhale and exhale orally throughout the treatment period (54/65 [83%] of the younger and 2/33 [6%] of the older patients). However, the DNase concentrations detected in the BAL fluid of all patients showed a broad range (0.007 to 1.8 µg/ml). Over the average 14-day treatment, serum DNase concentrations (mean±SD) increased by 1.3±1.3 ng/ml in the 3 months to <5 years age group and by 0.8±1.2 ng/ml in the 5 to <10 years age group.

PRECLINICAL DATA

Carcinogenicity

A 2-year study in rats produced no evidence of oncogenic potential for administration by inhalation.

Groups of 60 rats per sex received dornase alfa at 51, 101 or 246 µg/kg/day to the lower respiratory tract for up to two years. Two control groups of the same size received air and vehicle, respectively. Dornase alfa was well tolerated. There were no unusual tumours or increased incidence of tumours attributable to dornase alfa 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 lymphocytes or in the mouse micronucleus test.

Impaired fertility

Studies of dornase alfa in rats showed no evidence of impaired fertility, teratogenicity or effects on development.

Teratogenicity

Studies of dornase alfa in rabbits and rodents showed no evidence of impaired fertility or teratogenicity.

Other studies

A study in lactating cynomolgus monkeys receiving high intravenous doses of dornase alfa (100 µg/kg bolus followed by 80 µg/kg/hour for 6 hours) showed low concentrations (<0.1% of serum concentration) in the milk.

A four-week inhalation toxicity study in juvenile rats began 22 days after parturition with doses of 0, 51, 102 and 260 µg/kg/day. Dornase alfa was well tolerated. No lesions were found in the respiratory tract.

SPECIAL REMARKS

Incompatibilities

Pulmozyme is an unbuffered aqueous solution. It must not be diluted or mixed with other drugs for inhalation. Mixing of the solution with other drugs could lead to adverse structural or functional changes in Pulmozyme or the admixed compound.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the container.

Special precautions for storage

Store in a refrigerator (2–8°C), keeping the product in the original pack to protect the contents from light.

Avoid exposure to excessive heat. A single, brief exposure of the unopened ampoules to elevated temperatures (not more than 24 hours at up to 30°C) does not impair product stability; do not use if cloudy or discoloured.

Pulmozyme contains no preservative. Once opened, the entire contents of the ampoule must be used at once. Unused solution should be destroyed.

Instructions for use and handling

The contents (2.5 mg) of the Pulmozyme single-use plastic ampoule of sterile nebuliser solution should be inhaled once daily using a recommended nebuliser.

The contents of an ampoule of Pulmozyme is 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 Respirgard/Pulmo-Aide or AcornII/Pulmo-Aide.

Pulmozyme may also be used in conjunction with an inhaler, such as the Pari LL/Inhalierboy, Pari LC/Inhalierboy or Master, Aiolos/2 Aiolos, Side Stream/CR50, MobilAire or Porta-Neb.

Patients unable to inhale or exhale orally throughout the nebulisation period may use the Pari Baby nebuliser with a face mask.

Ultrasonic nebulisers may not be suitable for delivery of Pulmozyme because Pulmozyme may be inactivated or the aerosols produced by these devices may have unacceptable characteristics.

The manufacturers' instructions on the use and maintenance of the nebulisers and compressors should be followed.

Measures to prevent the release of aerosol from the inhaler into the environment are not necessary.

Pulmozyme ampoules are for single administration only.

Pulmozyme is not suitable for injection or oral administration.

PACKS

Ampoules of 2.5 mg/2.5 ml	30

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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