Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmozyme 2500 U/ 2.5ml, nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 2500 U (corresponding to 2.5mg) of dornase alfa* per 2.5ml corresponding to 1000 U/ml or 1mg/ml**.

*phosphorylated glycosylated protein human deoxyribonuclease 1 produced in in Chinese Hamster Ovary Cell Line CHO A14.16-1 MSB #757 by recombinant DNA technology

**1 Genentech unit/ml = 1 microg/ml)

For a full list of excipients, seesection 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution
Clear, colourless to slightly yellowish solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted and over 5 years of age to improve pulmonary function.

4.2 Posology and method of administration

Posology

2.5 mg (corresponding to 2500 U) deoxyribonuclease I by inhalation once daily.
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.

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

Paediatric population
Safety and efficacy have not yet been established in patients under the age of 5 years.

Method of administration
Inhale the content of one ampoule (2.5 ml of solution) undiluted using a recommended nebuliser system (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability of PULMOZYME: In order to improve the traceability of Pulmozyme the trade name of the administered dornase alfa and the batch number should be clearly recorded in the patient file.

4.5 Interaction with other medicinal products and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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 embryofoetal development (see section 5.3). Caution should be exercised when prescribing dornase alfa to pregnant women.

Breastfeeding
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 section 5.3).

4.7 Effects on ability to drive and use machines

Pulmozyme has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse event data reflect the clinical trial and post-marketing experience of using Pulmozyme 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 Pulmozyme dosing.

Eye disorders:
Conjunctivitis.

Respiratory, thoracic and mediastinal disorders:
Dysphonia, dyspnea, pharyngitis, laryngitis, rhinitis (all non-infectious).

Gastrointestinal disorders:
Dyspepsia.

Skin and subcutaneous tissue disorders:
Rash, urticaria.

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

Investigations:
Pulmonary function tests decreased.

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 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: : www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

The effect of Pulmozyme overdosage has not been established.

In clinical studies, 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 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 section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: respiratory system, ATC code: R 05 C B13.

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 and safety
Efficacy and safety was established in double-blind, placebo-controlled studies (Z0342/Z0343) in which patients over 5 years of age and with FVC over 40% predicted received 2.5 mg Pulmozyme once or twice daily over a 24-week period. Overall, 968 patients (mean age of 19 years) with a mean baseline FVC of 78% were randomised in these trials.
Another placebo-controlled double-blind study (Z0713) evaluated the effect of Pulmozyme (2.5 mg once daily for 2 years) on pulmonary function in young patients (aged 6-11 years) with minimum evidence of lung disease as defined by FVC of ≥ 85% predicted. Overall, 474 patients (mean age of 8.4 years) with a mean baseline FVC of 102.3% were randomised in this trial.

Results of the main endpoints are shown in the following tables. A significant increase in FEV_1 was observed in the beginning of treatment with Pulmozyme and subsided over time, especially after the first year of treatment; however, the difference with placebo remained statistically significant. Pulmozyme reduced the relative risk of respiratory tract exacerbations requiring parenteral antibiotics by about 30%; this reduction did not correlate with the improvement in FEV_1 measured during the first weeks of therapy.

Studies Z0342/Z0343

FEV_1 (% predicted)
Day 8
Week 24
Overall

% patients with exacerbations
Relative risk (95% CI)

	Placebo N = 325	**2.5mg QD** N = 322	**2.5mg BID** N = 321
Mean % change from baseline			
- 0.5%	7.9%	9.0%	
0.1%	5.1%	3.6%	
0.0%	5.8%	5.6%	
	p < 0.001	p < 0.001	
over 24 weeks	43%	34%	33%
	0.73 (0.57 - 0.94)	0.71 (0.55 - 0.91)	
	p = 0.015	p = 0.007	

Study Z0713

Spirometry
FEV_1 (% predicted)

FVC (% predicted)

FEF_{25-75} (% predicted)

% patients with exacerbations
Relative risk (95% CI)

	Placebo N = 235	**2.5mg QD** N = 237
Mean change from baseline (at Week 96)		
	- 3.10	0.03
		p = 0.008
	- 2.88	- 2.23
		p = 0.54
	- 4.05	3.83
		p = 0.0008
over 96 weeks	24%	17%
	0.66 (0.44 - 0.996)	
	p = 0.048	

Post-hoc 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. The percentage of older patients developing exacerbations over 24 weeks was 44% on placebo, 48% and 39% on Pulmozyme 2.5 mg daily and twice daily, respectively.

5.2 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 10ng/ml was observed. Following administration of 2500 U (2.5 mg) of dornase alfa twice daily for 24 weeks, mean serum DNase concentrations were no different from the mean 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, dornase alfa was cleared rapidly from the serum. The initial volume of distribution was similar to serum volume in these studies.

Inhalation of 2500 U (2.5 mg) dornase alfa results in a mean 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 expected to be metabolised by proteases present in biological fluids.

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

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.

Paediatric population
Pulmozyme, 2.5 mg by inhalation, was administered daily for 2 weeks to 98 patients aged 3 months to 9 years (65 aged 3 months to <5 years, 33 aged 5 to 9 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 µg/ml. Over an average of 14 days of exposure, serum DNase concentrations (mean ± 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 9 year age group. The incidence of fever was more frequent in the younger than older age group (41% vs. 24%, respectively); fever is a known complication of bronchoscopy.

5.3 Preclinical safety data

Non-clinical data based on standard studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction do not indicate a specific safety risk to humans.

In a study performed in lactating cynomolgus monkeys, receiving high doses of dornase alfa by the intravenous route (100 µg/kg bolus followed by 80 µg/kg/hour for 6 hours), low concentrations (< 0.1% of the concentrations seen in the maternal serum of cynomolgus monkeys), 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 µg/kg/day. Dornase alfa was well tolerated, and no lesions were found in the respiratory tract.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Calcium Chloride Dihydrate
Water for Injections

6.2 Incompatibilities

Pulmozyme is an unbuffered aqueous solution and should not be diluted or mixed with other drugs 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.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Keep the ampoule in the outer carton in order to protect 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.

6.5 Nature and contents of container

2.5 ml of nebuliser solution in an ampoule (low density polyethylene plastic).
Pack sizes of 6 and 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The contents of one 2.5 mg (2500 U) single-use ampoule of Pulmozyme sterile solution for inhalation should be inhaled once a day using a recommended nebuliser.

Pulmozyme should not be mixed with other drugs or solutions in the nebuliser (see section 6.2).

- Pulmozyme may be used in conjunction with 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 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.

- The Pari eFlow Rapid nebuliser, a general purpose electronic vibrating membrane nebuliser may be used. Parity between the eFlow Rapid electronic nebuliser and the LC Plus jet nebuliser has been demonstrated *in vitro* and *in vivo*. The average droplet size distribution of the aerosol generated by the eFlow Rapid nebuliser compared with the LC Plus jet nebuliser is shown below, using an adult breath simulator profile. The mass median aerodynamic

diameter (MMAD) was 4.8 ± 0.4 µm (n=16) for e Flow Rapid and 4.6 ± 0.4 µm (n=12) for LC Plus. The geometric standard deviation (GSD) was 1.80 ± 0.11 for eFlow Rapid and 2.14 ± 0.04 for LC Plus. The drug delivery rate was 380 ± 60 µg/min (n=88) for eFlow Rapid and 93 ± 16 µg/min (n=40) for LC Plus. The total drug delivered was 567 ± 62 µg for eFlow Rapid and 570 ± 80 µg for LC Plus. The Pari eFlow Rapid nebuliser should be used with the Pari EasyCare cleaning accessory and cleaning should be performed every seventh nebulisation cycle (a cycle being defined as a nebulisation of a single ampoule of Pulmozyme followed by cleaning and disinfecting in accordance with the PARI eFlow Rapid nebuliser system instruction for use). Using the eFlow Rapid nebuliser without EasyCare cleaning accessory may lead to lower and more variable dose delivery.

- 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. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Roche Products (Ireland) Ltd
3004 Lake Drive
Citywest
Naas Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2307/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 March 1994
Date of last renewal: 11 March 2009

10 DATE OF REVISION OF THE TEXT

August 2018