CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103532Orig1s5194

Trade Name:	PULMOZYME
Generic or Proper Name:	dornase alfa
Sponsor:	Genentech, Inc.
Approval Date:	February 9, 2024
Indication:	PULMOZYME is a recombinant DNase enzyme indicated in conjunction with standard therapies for the management of cystic fibrosis (CF) patients to improve pulmonary function.

CENTER FOR DRUG EVALUATION AND RESEARCH

103532Orig1s5194

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 103532/S-5194

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Rey Tirughana
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Rey Tirughana:

Please refer to your supplemental biologics license application (sBLA), dated May 11, 2023, received May 11, 2023, and your amendments submitted under section 351(a) of the Public Health Service Act for Pulmozyme (dornase alfa) inhalation solution.

This Prior Approval supplemental biologics application provides for the addition of four 510(k) cleared vibrating mesh nebulizers to the Dosage and Administration section of the Prescribing Information and to the Instructions for Use.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, and Instructions for Use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on September 25, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 103532/S-5194**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Brandi Wheeler, Regulatory Project Manager, at (301)796-4495.

Sincerely,

{See appended electronic signature page}

Banu Karimi Shah, MD
Deputy Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BANU A KARIMI SHAH
02/09/2024 01:14:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103532Orig1s5194

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PULMOZYME safely and effectively. See full prescribing information for PULMOZYME.

PULMOZYME® (dornase alfa) inhalation solution, for inhalation use
Initial U.S. Approval: 1993

---------- RECENT MAJOR CHANGES ----------
Dosage and Administration. (2.1, 2.2) 02/2024

---------- INDICATIONS AND USAGE ----------
PULMOZYME is a recombinant DNase enzyme indicated in conjunction with standard therapies for the management of cystic fibrosis (CF) patients to improve pulmonary function. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- The recommended dosage is 2.5 mg (one single-dose ampule) inhaled once daily using a recommended nebulizer. (2.1)
- Some patients may benefit from twice daily administration. (2.1)
- See full prescribing information for the recommended nebulizers for use with PULMOZYME. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Inhalation solution: 2.5 mg/2.5 mL (1 mg/mL) clear, colorless solution in single-dose ampules (3)

---------- CONTRAINDICATIONS ----------
PULMOZYME is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product. (4)

---------- WARNINGS AND PRECAUTIONS ----------
None. (5)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (occurring in ≥3% of patients treated with PULMOZYME over placebo) seen in clinical trials in CF patients were: voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥10%, fever, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PULMOZYME® is indicated, in conjunction with standard therapies, for the management of pediatric and adult patients with cystic fibrosis (CF) to improve pulmonary function.

In CF patients with an FVC ≥ 40% of predicted, daily administration of PULMOZYME has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage, in most cystic fibrosis patients, is 2.5 mg (one single-dose ampule) inhaled once daily using a recommended jet nebulizer connected to an air compressor system or via a vibrating mesh nebulizer *[see Dosage and Administration (2.2)]*.

Some patients may benefit from twice daily administration *[see Clinical Studies (14)]*.

2.2 Administration Instructions

Nebulizer Information

- Administer PULMOZYME via a jet nebulizer connected to an air compressor with an adequate air flow and equipped with a mouthpiece or suitable face mask, or via a vibrating mesh nebulizer. Refer to Table 1 for the recommended Jet Nebulizers or Vibrating Mesh Nebulizers for use with PULMOZYME. No data are currently available to support the administration of PULMOZYME with other nebulizer systems.
- The eRapid Nebulizer System should only be used by adults and pediatric patients who can use a mouthpiece, and not by younger patients who need a mask to inhale PULMOZYME.
- Use the selected nebulizer in accordance with the manufacturer’s instruction manual.
- Refer to the manufacturer's instruction manual on the use, maintenance, and replacement of the equipment, including cleaning and disinfection procedures for the selected nebulizer.
- For additional information, refer to the selected nebulizer manufacturer’s instruction manual.

Table 1. Recommended Jet Nebulizers or Vibrating Mesh Nebulizers for Use with PULMOZYME

Jet Nebulizer[1]	Compressor
Hudson T Up-draft II®	Pulmo-Aide® or legally marketed compressor of identical pressure and flow rate (maximum 30 psi, 12 LPM).
Marquest Acorn II®	
PARI LC® Plus	PARI PRONEB® or legally marketed compressor of identical pressure and flow rate (maximum 24 psi, 9 LPM).
PARI BABY™**	
Durable Sidestream®	MOBILAIRE™, Porta-NEB® or legally marketed compressor of identical pressure and flow rate (maximum 45 psi, 7 LPM).
Vibrating Mesh Nebulizers[1]	
eRapid® Nebulizer System*	
Innospire Go	
Pulmogine Vibrating Mesh Nebulizer	
AireHealth Nebulizer™	
Intelligent Mesh Nebulizer	

[1]Follow the selected nebulizer manufacturer's instruction manual.

*Consisting of the eRapid® Nebulizer Handset with eBase™ Controller. Avoid use in patients who need a mask to inhale PULMOZYME.

**Patients who are unable to inhale or exhale orally throughout the entire nebulization period may use the PARI BABY™ nebulizer.

PULMOZYME Information

- Each PULMOZYME ampule should be squeezed prior to use in order to check for leaks. Discard ampules if the solution is cloudy or discolored. Once opened, the entire contents of the ampule must be used or discarded.
- Do not dilute or mix PULMOZYME 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.

3 DOSAGE FORMS AND STRENGTHS

Inhalation solution: 2.5 mg/2.5 mL (1 mg/mL) clear, colorless solution in single-dose ampules.

4 CONTRAINDICATIONS

PULMOZYME is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.

5 WARNINGS AND PRECAUTIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to PULMOZYME in 902 patients, with exposures ranging from 2 weeks of daily administration up to once or twice daily administration for six months. PULMOZYME was studied in both placebo-controlled (n=804) and uncontrolled trials (n=98). The population of patients in placebo-controlled trials was with FVC ≥ 40% of predicted (n=643) or with more advanced pulmonary disease, FVC < 40% of predicted (n=161). The population in the uncontrolled trial included 98 pediatric patients with CF ranging from 3 months to 10 years of age. More than half of the patients received PULMOZYME 2.5 mg by inhalation once a day (n=581), while the rest of patients (n=321) received PULMOZYME 2.5 mg by inhalation twice a day.

Placebo-Controlled Trials

Trial 1: Trial 1 was a randomized, placebo-controlled clinical trial in patients with FVC ≥ 40% of predicted. In this trial, over 600 patients received PULMOZYME once or twice daily for six months. The most common adverse reaction (risk difference ≥5%) was voice alteration. The proportion of most adverse events was similar for patients on PULMOZYME and on placebo, probably reflecting the sequelae of the underlying lung disease. In most cases reactions that were increased were mild, transient in nature, and did not require alterations in dosing. Few patients experienced adverse reactions resulting in permanent discontinuation from PULMOZYME, and the proportion of discontinuations were similar for placebo (2%) and PULMOZYME (3%). Adverse reactions occurring in a higher proportion (greater than 3%) of PULMOZYME treated patients than in placebo-treated patients are listed in Table 2.

Trial 2: Trial 2 was a randomized, placebo-controlled trial in patients with more advanced pulmonary disease (FVC < 40% of predicted) who were treated for 12 weeks. In this trial, the safety profile of PULMOZYME was similar to that reported in patients with less advanced pulmonary disease (FVC ≥ 40% of predicted). Adverse reactions that were reported in this trial with a higher proportion (greater than 3%) in the PULMOZYME treated patients are listed in Table 2.

Table 2. Adverse Reactions Increased 3% or More in PULMOZYME Treated Patients Over Placebo in CF Clinical Trials

Adverse Reactions (of any severity or seriousness)	**Trial 1** CF Patients with FVC ≥ 40% of predicted treated for 24 weeks			**Trial 2** CF Patients with FVC <40% of predicted treated for 12 weeks	
	Placebo n=325	Pulmozyme QD n=322	Pulmozyme BID n=321	Placebo n=159	Pulmozyme QD n=161
Voice alteration	7%	12%	16%	6%	18%
Pharyngitis	33%	36%	40%	28%	32%
Rash	7%	10%	12%	1%	3%
Laryngitis	1%	3%	4%	1%	3%
Chest Pain	16%	18%	21%	23%	25%
Conjunctivitis	2%	4%	5%	0%	1%
Rhinitis	Differences were less than 3%			24%	30%
FVC decrease of ≥10% of predicted°				17%	22%
Fever				28%	32%
Dyspepsia				0%	3%
Dyspnea (when reported as serious)	Differences were less than 3%			12%†	17%†

° Single measurement only, does not reflect overall FVC changes.

† Total reports of dyspnea (regardless of severity or seriousness) had a difference of less than 3% in Trial 2.

Mortality rates observed in controlled trials were similar for the placebo and PULMOZYME treated patients. 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.

Uncontrolled Trial

Trial 3: The safety of PULMOZYME, 2.5 mg by inhalation, was studied with 2 weeks of daily administration in 98 pediatric patients with cystic fibrosis 3 months to 10 years of age (65 aged 3 months to < 5 years, 33 aged 5 to ≤ 10 years). 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). Overall, the nature of adverse reactions was similar to that seen in the placebo-controlled trials. 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%). 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).

Allergic Reactions

There have been no reports of anaphylaxis attributed to the administration of PULMOZYME. Urticaria, mild to moderate, and mild skin rash have been observed and have been transient. Within all of the studies, a small percentage (average of 2-4%) of patients treated with PULMOZYME developed serum antibodies to PULMOZYME. None of these patients developed anaphylaxis, and the clinical significance of serum antibodies to PULMOZYME is unknown.

7 DRUG INTERACTIONS

Available data indicate there are no clinically important drug-drug interactions with PULMOZYME.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with PULMOZYME in pregnant women. However, animal reproduction studies have been conducted with dornase alfa. In these studies, no evidence of fetal harm was observed in rats and rabbits at doses of dornase alfa up to approximately 600 times the maximum recommended human dose (MRHD).

The background risk of major birth defects and miscarriage for the cystic fibrosis population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

Reproductive studies have been performed in rats and rabbits at intravenous doses of dornase alfa up to 10 mg/kg/day (approximately 600 times the MRHD in adults). In a combined embryo-fetal development and pre- and post-natal development study, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when dornase alfa was administered to dams throughout organogenesis (Gestation days 6 to 17). Dornase alfa did not elicit adverse effects on fetal or neonatal growth when administered to dams throughout most of gestation and delivery (Gestation days 6 to 25) and nursing (Post-partum days 6 to 21).

A pharmacokinetic study in Cynomolgus monkeys found no detectable levels of dornase alfa in fetal blood or amniotic fluid on gestation day 150 (end of gestation) from mothers that were administered an intravenous bolus dose (0.1 mg/kg) followed by an intravenous infusion dose (0.080 mg/kg) over a 6-hour period during pregnancy.

8.2 Lactation

Risk Summary

It is not known whether PULMOZYME is present in human milk. In a pharmacokinetic study in Cynomolgus monkeys, levels of dornase alfa detected in milk were less than 0.1% of the maternal serum concentration at 24 hours after dosing [intravenous bolus dose (0.1 mg/kg) of dornase alfa followed by an intravenous infusion (0.080 mg/kg/hr) over a 6-hour period] on post-partum day 14. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for

PULMOZYME and any potential adverse effects on the breastfed child from PULMOZYME or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of PULMOZYME in conjunction with standard therapies for cystic fibrosis have been established in pediatric patients. Use of PULMOZYME in pediatric patients is supported by evidence in the following age groups:

- Patients 5 to 17 years of age: Use of PULMOZYME in patients 5 to 17 years of age is supported by evidence from a randomized, placebo-controlled trial of 303 of clinically stable cystic fibrosis patients 5 to 17 years of age who received PULMOZYME *[see Clinical Studies (14)]*.

- Patients less than 5 years: Use of PULMOZYME in patients less than 5 years of age is supported by extrapolation of efficacy data in patients 5 years of age and older with additional safety data in 65 pediatric patients aged 3 months to less than 5 years who received PULMOZYME 2.5 mg daily by inhalation for 2 weeks *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

8.5 Geriatric Use

Cystic fibrosis is primarily a disease of children and young adults. Clinical studies of PULMOZYME did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Dornase alfa is a 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 column chromatography and tangential flow filtration. The purified glycoprotein contains 260 amino acids with an approximate molecular weight of 37,000 daltons. The primary amino acid sequence is identical to that of the native human enzyme.

PULMOZYME (dornase alfa) inhalation solution is administered by inhalation of an aerosol mist produced by a compressed air driven nebulizer or a recommended nebulizer system *[see Clinical Studies (14) and Dosage and Administration (2.2)]*. PULMOZYME is a sterile, clear, colorless, highly purified solution in single-dose ampules. Each ampule delivers 2.5 mL of the solution to the nebulizer bowl. Each mL of aqueous solution contains 1 mg dornase alfa, calcium chloride dihydrate (0.15 mg) and sodium chloride (8.77 mg). The solution contains no preservative. The nominal pH of the solution is 6.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PULMOZYME is recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. In preclinical *in vitro* studies, PULMOZYME hydrolyzes the DNA in sputum of CF patients and reduces sputum viscoelasticity. In CF patients, retention of viscous purulent secretions in the airways contributes both to reduced pulmonary function and to exacerbations of infection. Purulent pulmonary secretions contain very high concentrations of extracellular DNA released by degenerating leukocytes that accumulate in response to infection.

12.3 Pharmacokinetics

When 2.5 mg PULMOZYME 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 TID of PULMOZYME by 4 CF patients for six consecutive days, did not result in a significant elevation of serum concentrations of DNase above normal endogenous levels. After administration of up to 2.5 mg of PULMOZYME twice daily for six months to 321 CF patients, no accumulation of serum DNase was noted. Dornase alfa is expected to be metabolized by proteases present in biological fluids. A human intravenous dose study suggested an elimination half-life of 3-4 hours for dornase alfa.

PULMOZYME, 2.5 mg by inhalation, was administered daily to 98 patients aged 3 months to ≤ 10 years, and bronchoalveolar 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. 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 ≤ 10 year age group. The relationship between BAL or serum DNase concentration and adverse experiences and clinical outcomes is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PULMOZYME produced no treatment-related increases in the incidence of tumors in a lifetime study in Sprague Dawley rats that were administered inhaled doses up to 0.246 mg/kg/day (approximately 30 times the MRHD in adults). There was no increase in the development of benign or malignant neoplasms and no occurrence of unusual tumor types in rats after lifetime exposure.

PULMOZYME tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* mouse bone marrow micronucleus assay. No evidence of impairment of fertility was observed in male and female rats that received intravenous doses up to 10 mg/kg/day (approximately 600 times the MRHD in adults).

14 CLINICAL STUDIES

Trial in CF Patients with FVC >40% of Predicted

PULMOZYME has been evaluated in a 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. 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 in the number of patients experiencing respiratory tract infections requiring use of parenteral antibiotics compared with the placebo group. 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 3). 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 3). The reduced

risk of respiratory infection observed in PULMOZYME treated patients did not directly correlate with improvement in FEV_1 during the initial two weeks of therapy.

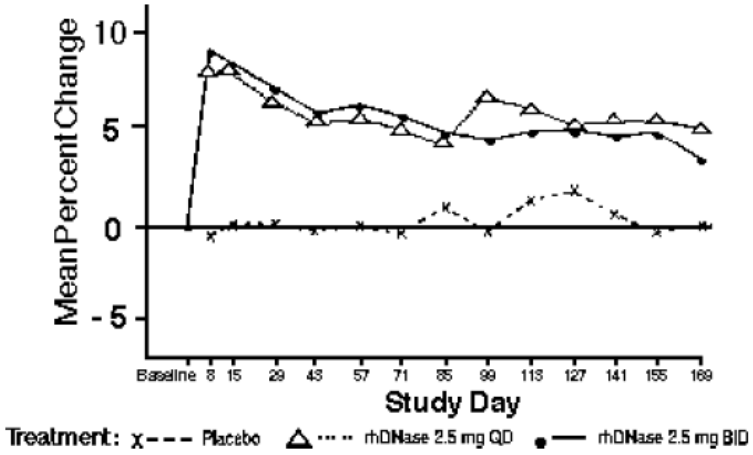
Within 8 days of the start of treatment with PULMOZYME, mean FEV_1 increased 7.9% in those treated once a day and 9.0% in those treated twice a day compared to the baseline values. The overall mean FEV_1 during long-term therapy increased 5.8% from baseline at the 2.5 mg daily dose level and 5.6% from 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 FEV_1, regardless of age or baseline FVC.

Table 3. Incidence of First Respiratory Tract Infection Requiring Parenteral Antibiotics in Patients with FVC ≥40% of Predicted

	Placebo N=325	**2.5 mg QD N=322**	**2.5 mg BID 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 QD % (N)	2.5 mg BID % (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 FEV_1 in Patients with FVC ≥40% of Predicted



Trial in CF Patients with FVC <40% of Predicted

PULMOZYME has also been evaluated in a second randomized, placebo-controlled trial in clinically stable patients with baseline FVC < 40% of predicted. Patients were enrolled and treated with placebo (162 patients) or PULMOZYME 2.5 mg QD (158 patients) for twelve weeks. In patients who received PULMOZYME, there was an increase in mean change (as percent of baseline) compared to placebo in FEV_1 (9.4% vs. 2.1%, $p < 0.001$) and in FVC (12.4% vs. 7.3%, $p < 0.01$). PULMOZYME did not significantly reduce the risk of developing a respiratory tract infection requiring parenteral antibiotics (54% of PULMOZYME patients vs. 55% of placebo patients had experienced a respiratory tract infection by 12 weeks, relative risk = .93, $p = 0.62$).

The effect of PULMOZYME on exercise tolerance has not been established in adult and pediatric patients.

Other Studies

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

Short-term dose ranging studies demonstrated that doses in excess of 2.5 mg BID did not provide further improvement in FEV_1. Patients who have received drug on a cyclical regimen (i.e., administration of PULMOZYME 10 mg BID for 14 days, followed by a 14 day wash out period) showed rapid improvement in FEV_1 with the initiation of each cycle and a return to baseline with each PULMOZYME withdrawal.

16 HOW SUPPLIED/STORAGE AND HANDLING

PULMOZYME (dornase alfa) inhalation solution is a sterile, clear, colorless solution supplied in:

- 30 unit cartons containing 5 foil pouches of 6 single-dose ampules. Each 2.5 mL ampule contains 2.5 mg of dornase alfa (1 mg/mL): NDC 50242-100-40.

Storage and Handling

Store PULMOZYME ampules at a refrigerated temperature between 2°C to 8°C (36°F to 46°F) in their protective foil to protect from light and heat. Once the protective foil pouch is opened, the unused ampules must be kept refrigerated in the protective foil pouch to protect from light and heat. Do not use beyond the

expiration date stamped on the ampule. During transport, keep the ampules refrigerated in their protective foil pouch to protect from light and heat. Do not use if the ampules are exposed to room temperature (22°C to 28°C [72°F to 82°F]) for more than a total of 60 hours. Avoid excessive heat and light.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Instructions for Use).

Preparation

Advise patients to squeeze each ampule prior to use in order to check for leaks. The solution should be discarded if it is cloudy or discolored. Once opened, the entire contents of the ampule must be used or discarded *[see Dosage and Administration (2.2)]*.

Drug Incompatibilities

Instruct patients not to dilute or mix PULMOZYME 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 *[see Dosage and Administration (2.2)]*.

Storage

Instruct patients on the proper techniques to store and handle PULMOZYME *[see How Supplied/Storage and Handling (16)]*.

Manufacturer's Instruction Manual

Instruct patients to read and follow the manufacturer's instruction manual for the proper use and maintenance of the jet nebulizer/compressor system, or the vibrating mesh nebulizer used in PULMOZYME delivery.

Pulmozyme® (dornase alfa)

Inhalation Solution

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

US License No. 1048

INSTRUCTIONS FOR USE

PULMOZYME® (PULL-muh-zyme)

(dornase alfa)

Inhalation Solution

This Instructions for Use contains information on how to use PULMOZYME with Jet Nebulizers and Compressors

See the other side of this Instructions for Use for information on use of Pulmozyme with the recommended vibrating mesh nebulizers

Read and understand this Instructions for Use and the nebulizer manufacturer's instruction manual before you start taking Pulmozyme and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

A nebulizer and a compressor are used together to give a dose of Pulmozyme. A nebulizer changes the Pulmozyme liquid medicine into a fine mist you inhale by breathing through a mouthpiece. A compressor gives the nebulizer power and makes the nebulizer work.

Pulmozyme should only be used with the approved nebulizers and appropriate compressors as **recommended below, or with the recommended vibrating mesh nebulizers (see other side of this Instructions for Use). Read and follow the manufacturer's instruction manual.**

Do not use any other inhaled medicines in the nebulizer at the same time. Keep all other inhaled medicine systems completely separate from Pulmozyme.

Use the mouthpiece or face mask provided with the nebulizer kit.

If your child cannot breathe in or breathe out by mouth, you may use the PARI BABY reusable nebulizer, but you should discuss it with your doctor first. The PARI BABY nebulizer is the same as the PARI LC Plus Jet system, except the mouthpiece is replaced by a tight-fitting face mask connected to an elbow piece.

Follow the steps on this side of the Instructions for Use to give Pulmozyme using the following jet nebulizer systems

Jet Nebulizer	Compressor
Hudson T Up-draft II	A compressor with the following specifications is recommended: ▪ Approximate air flow of 3.5 L/min to 12 L/min at approximately 20 psi to 45 psi pressure
Marquest Acorn II	
PARI LC Plus	
PARI BABY	
Durable Sidestream	

For additional information on an appropriate compressor to use with Pulmozyme, read the manufacturer's instruction manual for the recommended nebulizer.

Important Information You Need to Know Before Using PULMOZYME

Read and follow the nebulizer manufacturer's instruction manual for correct use and maintenance:
- to clean the nebulizer before first use and after each use as recommended.
- to disinfect the nebulizer parts by using the disinfecting method recommended.
- to replace nebulizer parts as recommended.

Supplies you will need to give a dose of Pulmozyme (See Figure A):

- 1 Pulmozyme ampule
- Compressor
- Nebulizer cup and cap (screw-on or snap-on)
- Plastic T (not needed for Sidestream nebulizer or PARI BABY)
- Flexible aerosol tube (not needed for Sidestream nebulizer or PARI BABY)
- Mouthpiece (clean) or PARI BABY facemask
- Long connecting tube
- Nose clip (optional, not needed for PARI BABY)

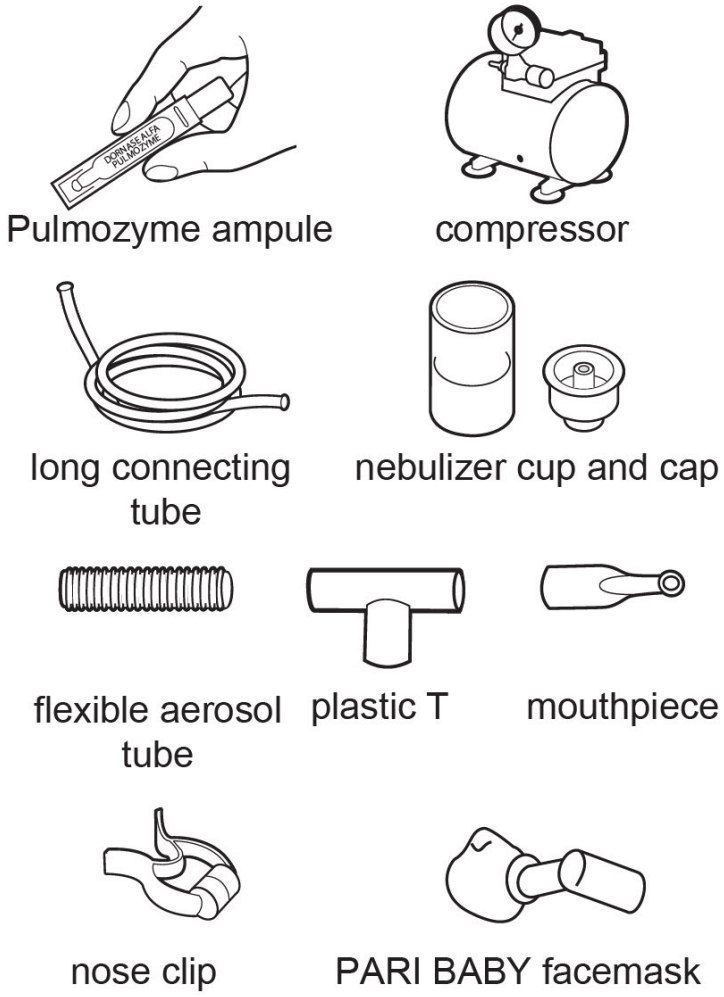


Figure A

Preparing the jet nebulizer and compressor:

Step 1. Clean a flat table surface and wash your hands.

- Clean a flat table surface.
- Wash your hands well with soap and water before using the Pulmozyme ampule and nebulizer. This helps prevent infection **(See Figure B)**.

Figure B

Step 2. Gather the nebulizer and test the compressor.

- Place the nebulizer parts on a clean, flat table surface within reach.
- Test the compressor by turning it on and putting your finger in front of the "air out" or "air" port to feel air flowing. Turn off the compressor **(See Figure C)**.

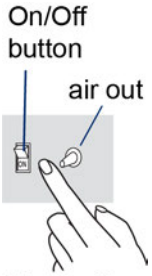


Figure C

Step 3. Gather the Pulmozyme ampule and check the expiration date.

- Remove **1** foil pouch of Pulmozyme from the refrigerator. Open the foil pouch and remove **1** ampule of Pulmozyme. Put the remaining ampules back in the foil pouch and return them to the refrigerator.
- Check the expiration (exp.) date printed on the ampule **(See Figure D)**.
- **Do not** use the Pulmozyme ampule if the expiration date has passed.

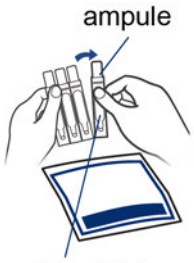


Figure D

Step 4. Check the Pulmozyme ampule.

- Check the ampule for leaks by turning it upside down and gently squeezing **(See Figure E)**.
  Do not use the ampule if it is leaking. Throw it away and get a new one.
- Check the Pulmozyme liquid in the ampule and make sure it is clear and free of particles.
- **Do not** use Pulmozyme if the liquid is cloudy or discolored. Take the Pulmozyme back to the pharmacy, hospital, or clinic that gave you the medicine.

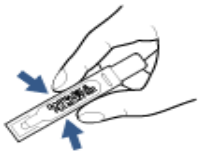


Figure E

Step 5. Attach the long connecting tube to the compressor.

- Attach the long connecting tube to the "air out" or "air" port on the compressor **(See Figure F)**.

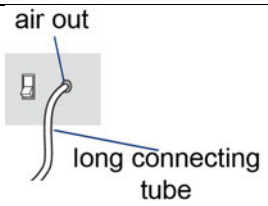


Figure F

Step 6. Attach the mouthpiece.

- **Skip to Step 7 if you use the Sidestream nebulizer or the PARI BABY nebulizer.**
- Push the mouthpiece into the wider end of the plastic T. Attach the flexible aerosol tube to the other end of the T **(See Figure G)**.

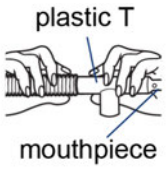


Figure G

Step 7. Remove the cap from the cup.

- Unscrew or unsnap the cap from the nebulizer cup **(See Figure H)**.

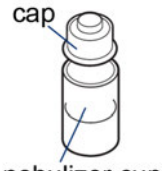


Figure H

- Put the nebulizer cup on the table face up and place the cap upside down on a clean surface **(See Figure I)**.

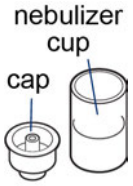


Figure I

Step 8. Open the Pulmozyme ampule.

- Hold the tab at the bottom of the Pulmozyme ampule firmly. Twist off the top. **Do not** squeeze the body of the ampule **(See Figure J)**.

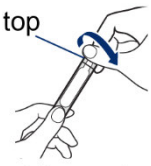


Figure J

Step 9. Pour the full Pulmozyme dose into the nebulizer cup.

- Turn the ampule upside down and squeeze gently to empty the medicine into the nebulizer cup. Keep squeezing until the ampule is empty. It is very important you squeeze all of the medicine out of the ampule **(See Figure K)**.

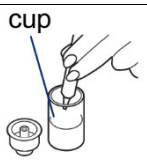


Figure K

- Screw or snap the cap onto the nebulizer cup **(See Figure L)**.

Figure L

Step 10. Connect the plastic T.

- Connect the plastic T to the nebulizer cap **(See Figure M)**.

Figure M

- **If you are using the Sidestream nebulizer, attach the mouthpiece to the top of the nebulizer (See Figure N).**

Figure N

- **If you are using the PARI BABY nebulizer, connect the elbow piece and mask to the nebulizer outlet (See Figure O).**

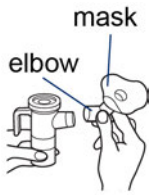


Figure O

Step 11. Attach the long connecting tube to the cup.

- Connect the open end of the long connecting tube to the port on the bottom of the nebulizer cup by pushing up firmly **(See Figure P)**.

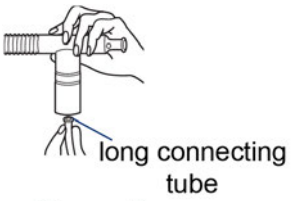


Figure P

Step 12. Turn on the compressor.

- Turn on the compressor and check to see that mist is coming out of the nebulizer **(See Figure Q)**.

Figure Q

Taking your dose of Pulmozyme with a nebulizer:

Step 13. Breathe through the mouthpiece.

- **Skip to Step 14 if you are using the PARI BABY to give Pulmozyme to your child.**
- Place the mouthpiece between your teeth and on top of your tongue **(See Figure R)**.
- Breathe slowly in and out through your mouth. **Do not** block the airflow with your tongue.
- **Do not** breathe through your nose. If you have problems breathing only through your mouth, use a nose clip **(See Figure S)**.

Figure R

- **Do not** be concerned if liquid droplets form 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 making mist **(See Figure T)**.
- If you need to stop treatment before you are finished, or you begin coughing, turn off the compressor and do not spill any of the medicine.
- To start treatment again, turn on the compressor and continue breathing slowly in and out through your mouth.
- The complete treatment usually takes from **10 to 15** minutes for most nebulizers.
- If you are using the Sidestream nebulizer, treatment usually takes from **2 to 6** minutes.
- It is important to inhale the full dose of Pulmozyme. If you find a leak or feel any moisture coming from the nebulizer during treatment, turn off the compressor and check to make sure the nebulizer cap is sealed correctly before continuing **(See Figure U)**.

Figure S

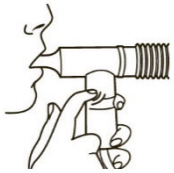


Figure T

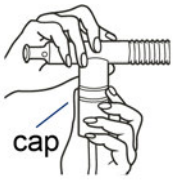


Figure U

If you are using the PARI BABY nebulizer to give Pulmozyme to your child, follow the instructions below in Step 14. If not, go to Step 15

Step 14. Breathing through the facemask.

- During the treatment your child may sit, lie down or stand.
- Place the facemask gently but firmly over your child's nose and mouth **(See Figure V)**.
- **Make sure there are no air gaps between the mask and your child's face. This will help make sure that your child will get the full dose of Pulmozyme.**
- It is important that you try to keep the body of the nebulizer upright during the entire treatment **(See Figure V)**. The elbow piece will allow you to move the mask for a good fit while keeping the nebulizer body upright.
- When the nebulizer begins "spitting," gently tap the nebulizer cup and continue treatment until the nebulizer is empty or stops making a mist **(See Figure W)**.

Figure V

- **If you need to stop the treatment or your child begins to cough during treatment, turn the compressor off. Do not spill any Pulmozyme.**
- If you have not removed the mask and you want to begin the treatment again, turn on the compressor.
- If you have removed the mask, repeat the steps above to replace the mask on your child's face and restart the compressor.
- The complete treatment usually takes from **10 to 15** minutes.


Figure W

It is important that your child inhale the full dose of Pulmozyme. If you find a leak or feel moisture coming from the nebulizer during the treatment, turn off the compressor and make sure the nebulizer cap is sealed correctly before starting the compressor again **(See Figure X)**.

Figure X

After your treatment with Pulmozyme:

Step 15. Prepare the nebulizer for cleaning and storage.

- Turn off the compressor and take apart the nebulizer system. Set aside the flexible aerosol tube and the long connecting tube.

Note: The Sidestream nebulizer does not use a flexible aerosol tube.

- Throw away the Pulmozyme ampule in your household trash.
- Follow the manufacturer's recommendations for care of your nebulizer and compressor.

How should I store Pulmozyme?

- **Store Pulmozyme ampules at a refrigerated temperature between 36°F to 46°F (2°C to 8°C) in their protective foil pouch to protect from light and heat** until you are ready to use them. When the protective foil pouch is opened, the unused ampules must be kept refrigerated in the protective foil pouch to protect from light and heat.
- When traveling, Pulmozyme ampules should be kept refrigerated in their protective foil pouch to protect from light and heat.
- Protect Pulmozyme from excessive heat and light.
- Do not use Pulmozyme if the ampules have been exposed to room temperature 72°F to 82°F (22°C to 28°C) for more than a total of 60 hours or if the solution has turned cloudy or discolored.
- **Do not** use Pulmozyme past the expiration date printed on the ampule.

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US License No. 1048

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 02/2024

INSTRUCTIONS FOR USE

PULMOZYME® (PULL-muh-zyme)

(dornase alfa)

Inhalation Solution

This Instructions for Use contains information on how to use PULMOZYME with the following recommended vibrating mesh nebulizers:

Recommended Vibrating Mesh Nebulizers
eRapid® Nebulizer System
Innospire Go
Pulmogine Vibrating Mesh Nebulizer
AireHealth Nebulizer™
Intelligent Mesh Nebulizer

See the other side of this Instructions for Use for information on use with Jet Nebulizers and Compressors

Read and understand this Instructions for Use and the nebulizer manufacturer's instruction manual before you start taking Pulmozyme and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This information does not take the place of the manufacturer's instruction manual for the vibrating mesh nebulizer.

The vibrating mesh nebulizer changes the Pulmozyme liquid medicine into a fine mist you inhale by breathing through a mouthpiece.

Do not use any other inhaled medicines in the nebulizer at the same time. Keep all other inhaled medication systems completely separate from Pulmozyme.

The eRapid Nebulizer System should only be used by adults and children who can use a mouthpiece, and not by younger children who need a mask to take Pulmozyme.

Follow the instructions on this side of the Instructions for Use to give Pulmozyme using a vibrating mesh nebulizer.

Important Information You Need to Know Before Using PULMOZYME

Read and follow the nebulizer manufacturer's instruction manual for correct use and maintenance:

- to clean the nebulizer before first use and after each use as recommended
- to disinfect the nebulizer parts by using the disinfecting method recommended
- to replace nebulizer parts as recommended

Supplies you will need to give a dose of PULMOZYME:

- **1** Pulmozyme ampule **(See Figure A)**
- Vibrating mesh nebulizer and its parts
- Manufacturer's instruction manual for the vibrating mesh nebulizer
- **Nose clip (optional) (See Figure B)**

Pulmozyme ampule
Figure A

Figure B

Prepare the vibrating mesh nebulizer:

Step 1. Clean a flat table surface and wash your hands.

- Clean a flat table surface.
- Wash your hands well with soap and water before using the Pulmozyme ampule and nebulizer. This helps prevent infection **(See Figure C)**.

Figure C

Step 2. Gather the nebulizer. Make sure you have all parts and make sure they are clean and not damaged. Prepare and test it as recommended in the manufacturer's instruction manual.

- Place the vibrating mesh nebulizer on a clean, flat table surface within reach. Make sure you have followed the manufacturer's instruction manual to make sure that the nebulizer is charged and ready for use.

Step 3. Gather the Pulmozyme ampule and check the expiration date.

- Remove **1** foil pouch of Pulmozyme from the refrigerator. Open the foil pouch and remove **1** ampule of Pulmozyme. Put the remaining ampules back in the foil pouch and return them to the refrigerator.
- Check the expiration (exp.) date printed on the ampule **(See Figure D)**.

  Do not use the Pulmozyme ampule if the expiration date has passed.

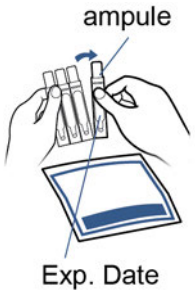

Figure D

Step 4. Check the Pulmozyme ampule.

- Check the ampule for leaks by turning it upside down and gently squeezing **(See Figure E)**.
  Do not use the ampule if it is leaking. Throw it away and get a new one.
- Check the Pulmozyme liquid in the ampule and make sure it is clear and free of particles.

  Do not use Pulmozyme if the liquid is cloudy or discolored. Take the Pulmozyme back to the pharmacy, hospital, or clinic that gave you the medicine.

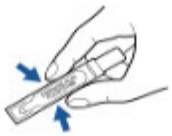

Figure E

Step 5. Put the vibrating mesh nebulizer together.

- Put the nebulizer together according to the step-by-step manufacturer's **instruction manual.**

Step 6. Prepare to take the Pulmozyme treatment.

- Follow the manufacturer's instruction manual on how to add the Pulmozyme medicine to the nebulizer.
- Open the Pulmozyme ampule.
- Hold the tab at the bottom of the Pulmozyme ampule firmly. Twist off the top. **Do not** squeeze the body of the ampule **(See Figure F)**.
- Turn the ampule upside down and squeeze gently to empty the medicine into the medicine cup. Keep squeezing until the ampule is empty. It is very important that you squeeze out all the medicine in the ampule.

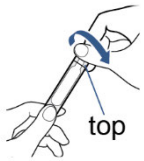

Figure F

Taking your dose of Pulmozyme with a nebulizer:

- Read the manufacturer's instruction manual on how to turn the nebulizer on and off and follow the steps for how to:
  - take your nebulized treatment,
  - breathe through the mouthpiece or facemask,
  - restart treatment if you need to stop before you are finished, and
  - confirm that your treatment is complete.

Step 7. Breathing through the mouthpiece.

- **Skip to Step 8 if you are using a facemask to take your dose of Pulmozyme.**
- Place the mouthpiece between your teeth and on top of your tongue.
  - Breathe slowly in and out through your mouth when using a mouthpiece**. Do not** block medicine flow with your tongue.
  - **Do not** breathe through your nose when using a mouthpiece. If you have problems breathing only through your mouth, use a nose clip **(See Figure B)**.

Step 8. Breathing through the facemask.

- Place the facemask gently but firmly over the nose and mouth.
- Make sure there are no air gaps between the mask and the face. This will help make sure that you will get the full dose of Pulmozyme.

After Your Treatment with Pulmozyme:

Step 9. Clean the nebulizer

- Throw away the empty Pulmozyme ampule in your household trash.
- Clean the nebulizer thoroughly after each use. Follow the **manufacturer's instruction manual** for cleaning the nebulizer.
- All nebulizer parts **must** be cleaned after each use and disinfected after each day of use as recommended in the manufacturer's instruction manual.
- Replace the handset as recommended in the manufacturer's instruction manual.

How should I store Pulmozyme?

- **Store Pulmozyme ampules at a refrigerated temperature between 36°F to 46°F (2°C to 8°C) in their protective foil pouch to protect from light and heat** until you are ready to use them. When the protective foil pouch is opened, the unused ampules must be kept refrigerated in the protective foil pouch to protect from light and heat.
- When traveling, Pulmozyme ampules should be kept refrigerated in their protective foil pouch to protect from light and heat.
- Protect Pulmozyme from excessive heat and light.
- **Do not** use Pulmozyme if the ampules have been exposed to room temperature at 72°F to 82°F (22°C to 28°C) for more than a total of **60** hours or if the solution has turned cloudy or discolored.
- **Do not** use Pulmozyme past the expiration date printed on the ampule.

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Revised: 02/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103532Orig1s5194

CLINICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonology, Allergy and Critical Care

APPLICATION #:	BLA 103532
PRODUCT:	Dornase Alfa (Pulmozyme)
INDICATION:	Cystic fibrosis
SPONSOR:	Genentech
MEDICAL OFFICER:	Lydia Kim, MD
TEAM LEADER:	Elisabeth Boulos, MD
DATE OF REVIEW:	11/3/2023

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document	Sequence Number	Submission Date
Prior Approval Supplement (S-5194)		5/11/2023

REVIEW SUMMARY:

The Applicant submitted a labeling supplement to support the addition of four 510(k) cleared vibrating mesh nebulizers to the Prescribing Information and Instructions for Use. Pulmozyme is approved in conjunction with standard therapies for the management of cystic fibrosis patients to improve pulmonary function. Pulmozyme is approved to be used via either a jet nebulizer connected to an air compressor system or the eRapid Nebulizer System. (b) (4) (b) (4) (b) (4) In this PAS, the Applicant proposes to add four 510(k)-cleared vibrating mesh nebulizers to the Pulmozyme labeling: InnoSpire Go, Pulmogine Vibrating Mesh Nebulizer, AireHealth Nebulizer, and Intelligent Mesh Nebulizer.

The Applicant proposed changes to the following sections of the USPI:

- Dosage and Administration: Sections 2.1, 2.2
- Patient Counseling Information: Section 17
- Instructions for Use

The Division noted that two of the vibrating mesh nebulizers ((b) (4) InnoSpire Go and (b) (4) Pulmogine) have average delivered doses of (b) (4)% and (b) (4)%, respectively, which are outside of the (b) (4)% accepted range. The Division asked the Applicant to provide justification for the safety and acceptability of the higher doses delivered by these two nebulizers. In response, the Applicant provided references to previous clinical trials that established safe and effective dose limits for Pulmozyme.

DMEPA was consulted and provided recommendations to the Applicant to minimize risk for medication error in Section 4. The Applicant submitted a revised container label and carton labeling, which were viewed to be acceptable by DMEPA. CDRH was consulted and determined that the aerosol characterization testing results for the four nebulizers are acceptable from a device perspective. OBP provided minor edits to the USPI.

The Division reviewed the Applicant's submission, including the USPI and IFU. The Applicant provided adequate clinical rationale and justification to support the addition of the four proposed vibrating mesh nebulizers. Recommendations and revisions to the Applicant's proposed labeling changes were conveyed to the Applicant on December 8, 2023. Final labeling was agreed upon on January 11, 2024.

RECOMMENDED REGULATORY ACTION: Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LYDIA Y KIM
01/25/2024 10:30:24 AM

ELISABETH S BOULOS
01/25/2024 03:15:28 PM

BANU A KARIMI SHAH
01/25/2024 03:46:32 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103532Orig1s5194

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 20, 2023
To:	Brandi Wheeler Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFUs)
Drug Name (established name):	PULMOZYME (dornase alpha)
Dosage Form and Route:	inhalation solution, for inhalation use
Application Type/Number:	BLA 103532
Supplement Number:	(b) (4) and S-5194
Applicant:	Genentech, Inc.

1 INTRODUCTION

(b) (4)

In addition, on May 31, 2023, Genentech, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS) for approved Biologics License Application (BLA)#103532/S-5194 to support the addition of four 501(k) cleared vibrating mesh nebulizers.

2 This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonology, Allergy, and Critical Care (DPACC) on June 2, 2023, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFUs) for PULMOZYME (dornase alpha) inhalation solution, for inhalation use.

3 MATERIAL REVIEWED

- Draft PULMOZYME (dornase alpha) IFUs received on May 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on November 13, 2023, and OPDP on November 14, 2023.
- Draft PULMOZYME (dornase alpha) Prescribing Information (PI) received on May 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on November 13, 2023, and OPDP on November 15, 2023.
- Approved PULMOZYME (dornase alpha) labeling dated July 30, 2021.

4 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU documents using the Arial font, size 10.

In our collaborative review of the IFUs we:

- simplified wording and clarified concepts where possible

- ensured that the IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFUs are consistent with the approved labeling where applicable.

5 CONCLUSIONS

The IFUs are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFUs.

Please let us know if you have any questions.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARIA T NGUYEN
11/20/2023 11:52:19 AM
DMPP-OPDP review of (PULMOZYME) dornase alfa BLA 103532/S-5190 & 5194 IFUs

QUYNH-NHU D CAPASSO
11/20/2023 12:23:18 PM

MARCIA B WILLIAMS
11/20/2023 12:28:17 PM

LASHAWN M GRIFFITHS
11/20/2023 12:30:50 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 17, 2023

To: Brandi Wheeler, Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for PULMOZYME® (dornase alfa) inhalation solution, for inhalation use

BLA: 103532, S-5194 and (b) (4)

Background:
In response to DPACC's consult request dated November 15, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Instructions for Use (IFUs) for supplements 5194 and (b) (4) for PULMOZYME® (dornase alfa) inhalation solution, for inhalation use. This supplement proposes the addition of four vibrating mesh nebulizers to the PI and IFU.

PI/IFUs:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 15, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed IFUs, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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/s/

QUYNH-NHU D CAPASSO
11/17/2023 04:00:09 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 27, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 103532/S-5194
Product Name, Dosage Form, and Strength:	Pulmozyme (dornase alfa) Inhalation Solution, 2.5 mg/2.5 mL (1 mg/mL)
Applicant/Sponsor Name:	Genentech, Inc
TTT ID #:	2023-4992-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on September 25, 2023 for Pulmozyme. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Pulmozyme (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Owens, L. Label and Labeling Review for Pulmozyme (BLA 103532/S-5194). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 SEP 11. TTT ID No.: 2023-4992.

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/s/

LISSA C PRINGLE-OWENS
09/27/2023 03:57:47 PM

IDALIA E RYCHLIK
09/27/2023 04:04:02 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 11, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 103532/S-5194
Product Name, Dosage Form, and Strength:	Pulmozyme (dornase alfa) Inhalation Solution, 2.5 mg/2.5 mL (1 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc
FDA Received Date:	May 11, 2023
TTT ID #:	2023-4992
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Genentech, Inc submitted a Labeling Supplement for Pulmozyme (dornase alfa) Inhalation Solution to support the addition of four 510(k) cleared vibrating mesh nebulizers to the Pulmozyme (dornase alfa) United States Prescribing Information (USPI) and the Pulmozyme Instructions for Use (IFU). Subsequently, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Pulmozyme prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Genentech, Inc.

4 RECOMMENDATIONS FOR GENENTECH, INC

Table 2. Identified Issues and Recommendations for Genentech, Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Pulmozyme that Genentech, Inc submitted on May 11, 2023.

Table 3. Relevant Product Information for Pulmozyme	
Initial Approval Date	December 30, 1993
Active Ingredient	Dornase alfa
Indication	indicated in conjunction with standard therapies for the management of cystic fibrosis (CF) patients to improve pulmonary function
Route of Administration	Oral inhalation
Dosage Form	Inhalation solution
Strength	2.5 mg/2.5 mL (1 mg/mL)
Dose and Frequency	One 2.5 mg single-dose ampule inhaled once daily
How Supplied	30-unit cartons containing 5 foil pouches of 6 single-dose ampules
Storage	Refrigerated temperature between (2°C to 8°C /(36°F to 46°F) in their protective foil to protect from light and heat

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 7, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Pulmozyme. Our search identified 1 previous review since the date of our last search on May 5, 2014[a], and we confirmed that our previous recommendations were implemented.

[a] Owens, L. Label and Labeling Review for Pulmozyme (BLA 103532/S-5175). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAY 21. OSE RCM No.: 2014-909.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error experiences with similar products, we reviewed the following Pulmozyme labels and labeling submitted by Genentech, Inc.

- Container label(s) received on May 11, 2023
- Carton labeling received on May 11, 2023
- Instructions for Use received on May 11, 2023, available from \\CDSESUB1\EVSPROD\bla103532\0433\m1\us\ifu-redlined.pdf
- Prescribing Information (Image not shown) received on May 11, 2023, available from \\CDSESUB1\EVSPROD\bla103532\0433\m1\us\redlined-label-text.pdf

F.2 Label and Labeling Images

Container label(s)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LISSA C PRINGLE-OWENS
09/11/2023 03:53:06 PM

IDALIA E RYCHLIK
09/11/2023 04:58:09 PM

Division of Pulmonology, Allergy, and Critical Care

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 103532 S-5194, Labeling supplement

Name of Drug: Pulmozyme (dornase alfa) inhalation solution

Applicant: Genentech, Inc.

Labeling Reviewed

Submission Date: May 11, 2023, amended September 25, and December 15, 2023

Receipt Date: May 11, 2023, September 25, and December 15, 2023

Background and Summary Description: Genentech submitted a prior approval supplement to provide the addition of four 510(k)-cleared vibrating mesh nebulizers for use with the Pulmozyme to the labeling.

Review

FDA issued labeling comments on September 15 and December 8, 2023. Genetech submitted revised labeling on September 25, and December 15, 2023.

The applicant's proposed labeling for Pulmozyme, submitted December 15, 2023, was compared side by side to the last approved label, dated July 30, 2021. The comparison of the documents indicates the proposed changes with minor revisions to spelling, hyphenations, and punctuation.

Refer to the following reviews:
CDRH dated August 8, 2023
DMEPA dated September 11 and 27, 2023
OBP dated November 3, 2023
OPDP dated November 17, 2023
Patient Labeling Team dated November 20, 2023
OBP labeling dated December 18, 2023

Recommendations

Pending completion of the clinical review, I recommend approval.

Brandi Wheeler	01/04/23
Regulatory Project Manager	Date
Ladan Jafari	01/04/23
Chief, Project Management Staff	Date

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/s/

BRANDI E WHEELER
01/04/2024 03:05:57 PM

LADAN JAFARI
01/04/2024 03:10:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103532Orig1s5194

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ADVICE / INFORMATION REQUEST

DATE: December 8, 2023

To: Sheila Ehrenberg Regulatory Program Management	**From:** Brandi Wheeler, PharmD, RAC Regulatory Project Manager
Company: Genentech, Inc.	Division of Pulmonology, Allergy, and Critical Care
Email: sheila.ehrenberg@contractors.roche.com	**Email:** Brandi.Wheeler@fda.hhs.gov
Subject: BLA 103532 S-5194 Labeling Comments	

Comments:

We are currently reviewing your submission dated May 11, 2023, and have the following requests for information:

We are providing our labeling comments and recommendations in the attached marked-up Prescribing Information and Instructions for Use. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text.

Please note these are not our final labeling recommendations and that additional comments or requests may be forthcoming as we continue to review this application

Submit your response to the BLA by December 15, 2023.

If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at Brandi.Wheeler@fda.hhs.gov.

Drafted by: L Kim / E Boulos / J Lee 12/6/23
Initialed by: L Jafari 12/8/23
Finalized by: B Wheeler 12/8/23

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BRANDI E WHEELER
12/08/2023 10:37:34 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Brandi Wheeler, RPM, DPACC, 6-4495

REQUEST DATE:	IND NO.	BLA NO.	TYPE OF DOCUMENTS
11/15/23		103532 S – 5194 (b) (4)	(PLEASE CHECK OFF BELOW)

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Pulmozyme	Standard	DNase enzyme	ASAP

NAME OF FIRM:	
Genentech	PDUFA Date: 11/11/23

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PRESCRIBING INFORMATION (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission: \\CDSESUB1\evsprod\BLA103532\0433

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
Genentech submitted a supplement in order to support the addition of four 510(k) cleared vibrating mesh nebulizers to the USPI and the IFU.

(b) (4)

SIGNATURE OF REQUESTER
Brandi Wheeler

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)

	☐ eMAIL ☐ HAND

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/s/

BRANDI E WHEELER
11/15/2023 02:24:19 PM

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ADVICE / INFORMATION REQUEST

DATE: October 23, 2023

To: Sheila Ehrenberg Regulatory Program Management	**From:** Brandi Wheeler, PharmD, RAC Regulatory Project Manager
Company: Genentech, Inc.	Division of Pulmonology, Allergy, and Critical Care
Email: sheila.ehrenberg@contractors.roche.com	**Email:** Brandi.Wheeler@fda.hhs.gov
Subject: BLA 103532 S-5194 Information Request	

Comments:

We are currently reviewing your submission dated May 11, 2023, and have the following requests for information:

In Table P.2.3-26, we note that two of the vibrating mesh nebulizers – [redacted] InnoSpire Go and [redacted] Pulmogine – have average delivered doses of [redacted]% and [redacted]%, respectively, which are outside of the [redacted]% accepted range. You state that these results are within safe and effective dose limits and are considered passing results, based on previous clinical trials. Provide justification, including information from the referenced trials, for the safety and acceptability of the higher doses delivered by the [redacted] InnoSpire Go and [redacted] Pulmogine nebulizers.

Submit your response to the BLA by October 26, 2023.

If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at Brandi.Wheeler@fda.hhs.gov.

Drafted by: L Kim / E Boulos 10/23/23
Initialed by: L Jafari 10/23/23
Finalized by: B Wheeler 10/23/23

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/s/

BRANDI E WHEELER
10/23/2023 12:45:33 PM

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Immunology and Inflammation

ADVICE / INFORMATION REQUEST

DATE: September 15, 2023

To: Sheila Ehrenberg Regulatory Program Management	**From:** Brandi Wheeler, PharmD, RAC Regulatory Project Manager
Company: Genentech, Inc.	Division of Pulmonology, Allergy, and Critical Care
Email: sheila.ehrenberg@contractors.roche.com	**Email:** Brandi.Wheeler@fda.hhs.gov

Subject: BLA 103532 S-5194 Carton and Container Labeling Comments

Comments:

Please respond by Monday, September 25, 2023.

We have the following comments regarding your proposed container labels and carton labeling submitted on May 11, 2023.

A. General Comments

1. The format for expiration date is not defined. Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or forward slash be used to separate the portions of the expiration date.

B. Carton Labeling

1. Remove the statement "(b) (4)." from the carton labeling because (b) (4).

2. Revise the country-of-origin labeling statement from "(b) (4)" to appear as "Product of Singapore".

Submit your response to the BLA by September 25, 2023. Please note these are not our final labeling recommendations and that additional comments or requests may be forthcoming as we continue to review this application.

If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at Brandi.Wheeler@fda.hhs.gov.

Drafted by: Luming Lu / Lissa Owens 9/12/23
Initialed by: L Jafari 09/15/23
Finalized by: B Wheeler 09/15/23

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/s/

BRANDI E WHEELER
09/15/2023 01:50:07 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:
CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Brandi Wheeler, RPM, DPACC, 6-4495

REQUEST DATE:
06/02/23

BLA NO.: 103532
S – 5194
(b) (4)

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
Pulmozyme

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
DNase enzyme

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
10/10/23

SPONSOR:
Genentech

PDUFA Date: 11/11/23

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\BLA103532\0433

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Genentech submitted a supplement in order to support the addition of four 510(k) cleared vibrating mesh nebulizers to the USPI and the IFU. We would like PLT to review the IFU.

(b) (4)

SIGNATURE OF REQUESTER
Brandi Wheeler

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

BRANDI E WHEELER
06/02/2023 10:07:56 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE			Brandi Wheeler, RPM, DPACC, 6-4495	
DATE 06/02/23	IND NO.	BLA NO. 103532/5194	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT 05/11/23
NAME OF DRUG Pulmozyme	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG DNase enzyme	DESIRED COMPLETION DATE 10/10/23

NAME OF FIRM: Genentech

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☑ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Genentech submitted a supplement in order to support the addition of four 510(k) cleared vibrating mesh nebulizers to the USPI and the IFU. We would like OSE to review.

(b) (4)

[redacted]

SIGNATURE OF REQUESTER Brandi Wheeler	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

BRANDI E WHEELER
06/02/2023 10:10:31 AM

BLA 103532/S-5194

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Attention: Sheila Ehrenberg
Regulatory Program Management

Dear Ms. Ehrenberg:

We have received your supplemental biologics license application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER: 103532

SUPPLEMENT NUMBER: 5194

PRODUCT NAME: PULMOZYME (dornase alfa) inhalation solution

DATE OF SUBMISSION: May 11, 2023

DATE OF RECEIPT: May 11, 2023

This supplemental application proposes the following change for Pulmozyme: to provide for additional vibrating mesh nebulizers in the USPI.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 10, 2023, in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be November 11, 2023

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call me, at (301)796-4495.

Sincerely,

{See appended electronic signature page}

Brandi Wheeler, PharmD, RAC
Senior Regulatory Project Manager
Pulmonology, Allergy, and Critical Care
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

BRANDI E WHEELER
05/31/2023 09:30:18 AM