OPTUMRx

Therapeutic Class Overview

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators and dornase alfa

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 200 have been confirmed to cause CF (*Quon et al 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*). The most common *CFTR* mutation leading to CF is the *F508del* mutation; approximately 50% of patients with CF are homozygous for this mutation, and 90% carry at least 1 copy (*Katkin 2018*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon et al 2016*).
  - Inhaled antibiotics have commonly been used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF. A reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, and oral macrolide antibiotics and high dose ibuprofen have been used to reduce inflammation (*Quon et al 2016*).
    - Pulmozyme (dornase alfa), initially approved by the Food and Drug Administration (FDA) in 1993, is a recombinant DNase enzyme. In CF patients, retention of viscous purulent secretions in the airways contributes to reduced pulmonary function and to exacerbations of infection. Dornase alfa hydrolyzes deoxyribonucleic acid (DNA) in the sputum of CF patients, reducing sputum viscoelasticity. Guidelines recommend the use of dornase alfa for patients with CF aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations) (*Drugs@FDA 2018, Mogayzel et al 2013*).
- More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), and Symdeko (tezacaftor/ivacaftor) (*Drugs@FDA 2018, Elborn 2016*). The CFTR modulators facilitate processing and trafficking of CFTR to the cell surface (CFTR correctors [tezacaftor and lumacaftor]) or facilitate increased chloride transport at the cell surface (CFTR potentiator [ivacaftor]).
  - Approximately 55% of patients with CF in the U.S. who have a known genotype are eligible for CFTR modulator therapy (*Vertex CF portfolio guide 2018*), and these products are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the 3 available CFTR modulators and dornase alfa.
- Medispan Class: CF Agents, CFTR Potentiators (Kalydeco); CF Agents, CF Agent-Combinations (Orkambi and Symdeko); and CF Agents, Hydrolytic Enzymes (Pulmozyme)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
CFTR Modulators	
Kalydeco (ivacaftor)	-
Orkambi (lumacaftor/ivacaftor)	-
Symdeko (tezacaftor/ivacaftor)	-
DNase enzyme	
Pulmozyme (dornase alfa)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	CFTR Modulators			DNase Enzyme
	Kalydeco (ivacaftor)	Orkambi (lumacaftor/ ivacaftor)	Symdeko (tezacaftor/ ivacaftor	Pulmozyme (dornase alfa)
Treatment of CF in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data*	✔			
Treatment of CF in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene		✔		
Treatment of patients with CF aged 12 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence†			✔	
For daily administration in conjunction with standard therapies for the management of CF patients to improve pulmonary function‡				✔

* The following 38 mutations are included: *E56K, P67L, R74W, D110E, D110H, R117C,* ***R117H****,* ***G178R****, E193K, L206W, R347H, R352Q, A455E,* ***S549N****,* ***S549R****,* ***G551D****,* ***G551S****, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T,* ***G1069R****,* ***R1070Q****, R1070W, F1074L, D1152H,* ***G1244E****,* ***S1251N****,* ***S1255P****, D1270N,* ***G1349D****, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: Bolded mutations are unique to the indication for Kalydeco and are not covered by another CFTR modulator.

† The following 27 mutations are included (patients must have 2 copies of the *F508del* mutation, or at least 1 copy of another listed medication, for Symdeko to be indicated): *E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, F508del, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T*. Note: All of these mutations are also covered by either Kalydeco or Orkambi.

‡ In CF patients with a forced vital capacity (FVC) ≥ 40% of predicted, daily administration of dornase alfa has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

(*Prescribing information: Kalydeco 2017, Orkambi 2018, Pulmozyme 2014, Symdeko 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

CFTR Modulators

Note: The following is a brief overview of the clinical evidence supporting the efficacy of the CFTR modulators. Please also refer to Appendix A, which provides an overview of key clinical trials for CFTR modulators in a table format. Appendix B provides a description of study endpoints.

- The safety and efficacy of ivacaftor have been evaluated in a number of trials in patients with a variety of *CFTR* mutations. In addition to the clinical evidence available, ivacaftor has been FDA-approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.

- A 48-week, double-blind trial demonstrated improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and exacerbations for ivacaftor vs placebo in 167 patients with CF aged ≥ 12 years with ≥ 1 *G551D* mutation (*Ramsey et al 2011*). A separate, placebo-controlled, 48-week double-blind trial in 52 patients aged 6 to 11 years with this mutation demonstrated improvement in $ppFEV_1$ (*Davies et al 2013*), and an open-label extension study of these 2 trials demonstrated sustained $ppFEV_1$ improvement over 96 weeks (*McKone et al 2014*).
- A placebo-controlled crossover trial with two 8-week treatment periods demonstrated improved $ppFEV_1$ with ivacaftor in 39 patients with CF aged ≥ 6 years with a non-*G551D* gating mutation (*De Boeck et al 2014*).
- A 24-week, double-blind, placebo-controlled trial evaluated the safety and efficacy of ivacaftor vs placebo in 69 patients aged ≥ 6 years with an *R117H* mutation (*Moss et al 2015*). In this trial, improvement in $ppFEV_1$ was demonstrated in adults but not in children aged 6 to 11 years; the authors suggested that the lack of effect may have been related to the high baseline $ppFEV_1$ in the pediatric patients enrolled.
- A crossover study with two 8-week treatment arms enrolled a total of 246 patients aged ≥ 12 years with CF who were heterozygous for *F508del* and a residual function mutation (*Rowe et al 2017*). A comparison of the ivacaftor and placebo arms demonstrated an improvement in $ppFEV_1$ with ivacaftor. (Please see the tezacaftor/ivacaftor section below for information on comparisons of tezacaftor/ivacaftor to ivacaftor and placebo in this study).
- An open-label study in 34 patients aged 2 to 5 years with CF and ≥ 1 *CFTR* gating mutation evaluated weight-based dosing of ivacaftor in this younger age group (*Davies et al 2016*). Patients weighing < 14 kg received a dose of 50 mg and those ≥ 14 kg received a dose of 75 mg. Pharmacokinetic analyses demonstrated that exposure was similar to that reported with the approved dosing in adults. No meaningful data on lung function were available, as the accuracy of spirometry results is limited in this age group.
- Support for ivacaftor's efficacy for additional mutations is available from *in vitro* assay data (*Kalydeco prescribing information 2017*). This assay was based on CFTR chloride transport in Fisher Rat Thyroid cells expressing mutant *CFTR*. An increase in chloride transport of ≥ 10% was designated as the response threshold because it is predictive or reasonably expected to predict clinical benefit. Mutations meeting this threshold were considered responsive, and a patient must have at least 1 responsive mutation in order for ivacaftor to be indicated.

- A number of trials have evaluated the safety and efficacy of lumacaftor/ivacaftor for the treatment of patients with CF homozygous for the *F508del* mutation.
  - Two 24-week, double-blind, placebo-controlled trials evaluated the efficacy of lumacaftor/ivacaftor in a total of 1122 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Wainright et al 2015*). Pooled data demonstrated an improvement in $ppFEV_1$ as well as exacerbations. Based on a 96-week open-label extension study, the $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor; however, the improvement was not statistically significant (*Konstan et al 2017*).
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 58 patients with CF aged 6 to 11 years who were homozygous for *F508del* (*Milla et al 2017*). At 24 weeks, there was a small improvement in $ppFEV_1$ that failed to reach statistical significance ($p = 0.0671$); the authors suggested that the lack of a significant effect might have been due to the small sample size and relatively mild lung disease in this population. A separate double-blind, placebo-controlled trial in 206 patients in this age group demonstrated a small but statistically significant effect on $ppFEV_1$ (*Ratjen et al 2017*).
- Two published Phase 3 trials have evaluated the safety and efficacy of tezacaftor/ivacaftor in patients with CF. As with ivacaftor, tezacaftor/ivacaftor has additionally been FDA approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 24-week, double-blind trial compared tezacaftor/ivacaftor to placebo in 509 patients with CF ≥ 12 years of age who were homozygous for the *F508del* mutation (*Taylor-Cousar et al 2017*). The improvement in $ppFEV_1$ was greater with tezacaftor/ivacaftor vs placebo, and the rate of pulmonary exacerbations also favored tezacaftor/ivacaftor treatment.
  - A double-blind, crossover trial with two 8-week treatment periods evaluated tezacaftor/ivacaftor, ivacaftor monotherapy, and placebo in 246 patients with CF ≥ 12 years of age who were heterozygous for *F508del* and a second allele with a residual function mutation (*Rowe et al 2017*). Both tezacaftor/ivacaftor and ivacaftor monotherapy improved $ppFEV_1$ vs placebo, with tezacaftor/ivacaftor having a slightly larger effect than ivacaftor alone.

Dornase alfa

- Pivotal trials have been conducted in CF patients with an FVC > 40% predicted and in patients with advanced lung disease (FVC < 40% predicted) (*Fuchs et al 1994, McCoy et al 1996*).
  - A 24-week, randomized, double-blind, placebo-controlled trial was conducted in 968 adults and children aged ≥ 5 years with clinically stable CF and FVC > 40% predicted (*Fuchs et al 1994*). Patients received dornase alfa 2.5 mcg

once daily, dornase alfa 2.5 mcg twice daily, or placebo. A T-Updraft II Nebu-u-mist nebulizer with PulmoAide compressor was used for drug administration.
  - The administration of dornase alfa once or twice daily reduced the risk of an exacerbation requiring parenteral antibiotic treatment, although only the reduction with twice-daily dosing was statistically significant. Exacerbations requiring parenteral antibiotic therapy occurred in 27%, 22%, and 19% of patients in the placebo, once-daily, and twice-daily groups, respectively. The relative risk vs placebo was 0.78 (95% confidence interval [CI], 0.57 to 1.06; p = 0.11) in the once-daily dornase alfa group and 0.66 (95% CI, 0.48 to 0.91; p = 0.01) in the twice-daily group. When adjusted based on the estimated relative risk of exacerbation by patient age, the exacerbation reduction was statistically significant with both dose regimens (once daily: relative risk, 0.72; 95% CI, 0.52 to 0.98; p = 0.04; twice daily: relative risk, 0.63; 95% CI, 0.46 to 0.87; p < 0.01).
  - Dornase alfa also improved pulmonary function. FEV_1 improved an average of 5.8% and 5.6% with once- and twice-daily dosing, respectively, throughout the study, while placebo-treated patients did not improve (change of 0.0%) (p < 0.01 for both dose regimens vs placebo).
  - Dornase alfa also improved quality of life compared to placebo.
- A 12-week, randomized, double-blind, placebo-controlled trial was conducted in 320 patients (age range, 7 to 57 years) with clinically stable CF and FVC < 40% predicted (*McCoy et al 1996*). Patients received dornase alfa 2.5 mg once daily or placebo.
  - There were no statistically significant differences in the incidence of pulmonary exacerbations; the age-adjusted relative risk for patients treated with dornase alfa vs placebo was 0.925 (95% CI, 0.69 to 1.21; p = 0.52). However, the study may have been underpowered to detect a difference.
  - Dornase alfa significantly improved pulmonary function. The mean improvements in FEV_1 were 9.4% and 2.1% in the dornase alfa and placebo groups, respectively (p < 0.001), and the mean improvements in FVC were 12.4% and 7.3%, respectively (p < 0.01).
  - No differences were observed in dyspnea scores.

- A 2-year, randomized, double-blind, placebo-controlled trial was conducted in 474 children aged 6 to 10 years with CF and mild lung function abnormalities (FVC ≥ 85% predicted) (*Quan et al 2001*). Patients received dornase alfa 2.5 mg daily or placebo with a jet nebulizer and compressor.
  - After 2 years of therapy, patients treated with dornase alfa maintained their $ppFEV_1$ (mean change from baseline, 0.04% predicted), whereas patients treated with placebo had a decrease from baseline of 3.2% predicted (p = 0.006). Lung function benefit was also shown for the forced expiratory flow between 25% and 75% of vital capacity (difference, 7.9% predicted; p = 0.0008) and maximal expiratory flow rate at 50% of vital capacity (difference, 8.2% predicted; p = 0.0002); however, the treatment difference in FVC was not statistically significant (difference, 0.7% predicted; p = 0.51).
  - Use of dornase alfa also reduced pulmonary exacerbations. In the dornase alfa group, 40 patients (17%) had a total of 62 exacerbations, compared to 56 patients (24%) and 92 exacerbations in the placebo group (relative risk, 0.66; 95% CI, 0.44 to 1.00; p = 0.048).
- A randomized, crossover study in 87 patients with CF aged ≥ 6 years compared administration of dornase alfa via a jet nebulizer to administration using the Pari eRapid electronic nebulizer (*Sawicki et al 2015*). The 2 devices led to comparable efficacy and safety, while the eRapid nebulizer was associated with shorter administration times and higher patient preference.
- A systematic review and meta-analysis evaluated the use of dornase alfa in patients with CF (*Yang et al 2016*). The review included randomized and quasi-randomized controlled trials comparing dornase alfa to placebo, standard therapy, or other medications that improve airway clearance. In all, 19 trials (2565 patients) were included, most of which compared dornase alfa to placebo. Trial duration ranged from 6 days to 3 years. Of the 19 trials included in the qualitative synthesis, 13 trials were included in the meta-analysis.
  - Compared to placebo or no dornase alfa treatment, dornase alfa was demonstrated to improve FEV_1 at various time points ranging from 1 month to 2 years. Results for efficacy at 1 month of treatment were pooled from 4 trials and demonstrated a mean improvement vs placebo of 9.51% (95% CI, 0.67 to 18.35). Results for later time points were based on a smaller number of trials and generally showed smaller improvements.
  - Pooled data for pulmonary exacerbations from 4 trials found a significant exacerbation reduction, with a risk ratio of 0.78 (95% CI, 0.62 to 0.96).
  - Effects on quality of life measurements such as symptoms, activity limitation, fatigue, and emotional well-being varied among trials, with some (but not all) showing significant benefits.

- Based on 7 trials, mortality was not significantly different between dornase alfa and control groups (risk ratio, 1.7; 95% CI, 0.70 to 4.14). The majority of deaths were reported from trials in patients with severe lung disease.
- Overall, voice alteration and rash were the only adverse events (AEs) associated with dornase alfa.
- Evidence comparing dornase alfa to other medications was limited.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF) – CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. It has not been updated since 2013 and thus does not include recommendations for lumacaftor/ivacaftor or tezacaftor/ivacaftor; recommendations also do not reflect the expanded indications for ivacaftor.
  - For these guidelines, the severity of lung disease is defined by $ppFEV_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
  - Recommendations specific to CFTR modulators and dornase alfa are shown in Table 3.

Table 3. CFF recommendations for CFTR modulators and dornase alfa in CF treatment

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Dornase alfa – moderate-to-severe disease	For individuals with CF, 6 years of age and older, with moderate-to-severe lung disease, the CFF strongly recommends the chronic use of dornase alfa to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa – mild disease	For individuals with CF, 6 years of age and older, with asymptomatic or mild lung disease, the CFF recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
2013 new or modified recommendations				
Ivacaftor	For individuals with CF, 6 years of age and older, with at least 1 *G551D CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.
B: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

- **CFF - Clinical Practice Guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children ages 2 to 5 years with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 4 highlights recommendations relevant to CFTR modulators and dornase alfa. The guideline does not include the more recent expanded indications for ivacaftor.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force.

Table 4. CFF recommendations for CFTR modulators and dornase alfa in preschoolers age 2 to 5 with CF

Topic	Recommendation	Grade or Consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Dornase alfa	The CFF recommends that dornase alfa be selectively offered to patients based on individual circumstances.	Moderate	Low	C
Ivacaftor	The Preschool Guidelines Committee recommends the routine use of ivacaftor in those with specific gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, and *S549R*), and a consideration for those with a confirmed diagnosis of CF and a *R117H* mutation.	Consensus Recommendation		

*__C__: The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

SAFETY SUMMARY

- **Kalydeco (ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been reported. It is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Kalydeco with strong cytochrome P450 (CYP) 3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor and is not recommended.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Kalydeco treatment.
  - The most common adverse reactions (≥ 8% in patients with CF who have a *G551D* mutation) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.
- **Orkambi (lumacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Worsening of liver function in patients with advanced liver disease has been reported. Orkambi should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, the patients should be closely monitored and the dose should be reduced.
    - Serious adverse reactions related to elevated transaminases have been reported; in some cases associated with concomitant elevations in total serum bilirubin. ALT, AST, and bilirubin should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. Dosage interruptions may be necessary in patients with significant transaminase or bilirubin elevations.
    - Respiratory events (eg, chest discomfort, dyspnea, and abnormal respiration) were observed more commonly in patients during initiation of Orkambi compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease ($ppFEV_1$ < 40%). Clinical experience in patients with $ppFEV_1$ < 40% is limited, and additional monitoring of these patients is recommended during initiation of therapy.
    - Increased blood pressure has been observed in some patients treated with Orkambi. Blood pressure should be monitored periodically.
    - Drug interactions:

- Lumacaftor is a strong inducer of CYP3A. Administration of Orkambi may decrease systemic exposure of CYP3A substrates. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.
- Orkambi may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, eg, amenorrhea, dysmenorrhea, menorrhagia, and irregular menstruation (27% in women using hormonal contraceptives compared with 3% in women not using hormonal contraceptives). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.
- Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of Orkambi with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure and is not recommended.

▪ Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Orkambi treatment.

○ The most common adverse reactions (≥ 5% in patients with CF who are homozygous for the *F508del* mutation) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, abnormal respiration, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza.

- **Symdeko (tezacaftor/ivacaftor):**
  - ○ Contraindications: none
  - ○ Warnings/precautions:
    - ▪ Elevated transaminases have been observed in patients treated with Symdeko, as well as with ivacaftor monotherapy. Assessments of ALT and AST are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - ▪ Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and may decrease exposure to tezacaftor; co-administration is not recommended.
    - ▪ Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with Symdeko, as well as with ivacaftor monotherapy. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Symdeko.
  - ○ The most common adverse reactions (≥ 3% of patients) were headache, nausea, sinus congestion, and dizziness.
- **Pulmozyme (dornase alfa):**
  - ○ Pulmozyme is contraindicated in patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product.
  - ○ Warnings/precautions: None
  - ○ The most common adverse reactions (≥ 3% of patients) were voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥ 10%, fever, and dyspnea.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
CFTR Modulators				
Kalydeco (ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Orkambi (lumacaftor/ ivacaftor)	Tablets	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Dose should be reduced for the first week of Orkambi treatment when co-administered with strong CYP3A inhibitors.
Symdeko (tezacaftor/ ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is a tezacaftor/ivacaftor combination tablet and the evening dose is ivacaftor only. • Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
DNase Enzyme				
Pulmozyme (dornase alfa)	Inhalation solution	Inhalation (with nebulizer)	Once daily; some patients may benefit from twice-daily administration	• Administered using a recommended jet nebulizer/compressor system or eRapid Nebulizer System.

See the current prescribing information for full details.

CONCLUSION

- The CFTR modulators, Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), and Symdeko (tezacaftor/ivacaftor), are used in the long-term management of CF in patients eligible for such treatment based on their age and specific *CFTR* mutations. These products act to facilitate processing and trafficking of CFTR to the cell surface or to increase chloride transport at the cell surface. Slightly over half of patients with CF are eligible for CFTR modulator therapy. These products have been demonstrated to improve lung function; some trials also demonstrated improvement in reducing pulmonary exacerbations and/or improving quality of life.
  - Key warnings/precautions with the CFTR modulators include the risk of elevated transaminases, cataracts, and drug interactions. A key additional warning for Orkambi is the risk of respiratory events (eg, chest discomfort, dyspnea, and abnormal respiration). Orkambi has also been associated with worsening of liver function in patients with advanced liver disease, and has more significant drug interactions than the other CFTR modulators.
  - The CFTR modulators are dosed orally twice daily.
- Pulmozyme (dornase alfa) is another key treatment used in the long-term management of CF. It works to reduce sputum viscoelasticity. Guidelines recommend its use in patients aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations).
  - Pulmozyme has no warnings/precautions listed in its prescribing information.
  - Pulmozyme is administered by inhalation with a nebulizer. Recommended dosing is once daily, although some patients may benefit from twice-daily administration.

APPENDICES

Appendix A: Additional Information on CFTR Modulators

Table 6. Overview of Key Clinical Trials for CFTR Modulators

Trial/Reference	Design/Population	Key Results	Comments/ Additional Data
Kalydeco (ivacaftor)			
STRIVE *Ramsey et al 2011*	Phase 3, 48-week, DB, PC trial in 167 patients aged ≥ 12 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 10.4 percentage points from baseline; difference from placebo, 10.6 percentage points (95% CI, 8.6 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, and sweat chloride. Improvements were maintained through week 48.
DISCOVER *Flume et al 2012*	Phase 2, 16-week, DB, PC trial in 140 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 1.5 percentage points from baseline; difference from placebo, 1.7 percentage points (95% CI, -0.6 to 4.1; p = 0.15)	Secondary endpoints: There was a small but statistically significant change in sweat chloride concentration (TD, -2.9 mmol/L; 95% CI, -5.6 to -0.2). There was no difference from placebo in CFQ-R score or patient weight. The study was terminated on the basis of futility; Kalydeco is not indicated for patients homozygous for *F508del*.
ENVISION *Davies et al 2013*	Phase 3, 48-week, DB, PC trial in 52 patients aged 6 to 11 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 12.6 percentage points from baseline; difference from placebo, 12.5 percentage points (95% CI, 6.6 to 18.3; p < 0.0001)	Secondary endpoints: Improvements were observed in weight and sweat chloride concentrations. The improvement in CFQ-R (child version) did not reach statistical significance (TD, 6.0 points; p = 0.109); however, the parent/caregiver version did (TD, 5.9 points; p = 0.033). No statistically significant difference in exacerbations was demonstrated.
PERSIST *McKone et al 2014*	Phase 3, 96-week, OLE study of STRIVE and ENVISION; enrolled 192 patients aged ≥ 6 yrs with ≥ 1 *G551D* mutation; all received ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate and resolved during the reporting period. Safety was consistent with the PC period of the trial. $ppFEV_1$ (secondary endpoint): Improvements in FEV_1 were sustained through the 96-week extension period.	Additional secondary endpoints: Improvements were sustained for weight gain, CFQ-R, and exacerbation rate.

KONNECTION *De Boeck et al 2014*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 39 patients aged ≥ 6 yrs with non-*G551D* gating mutation	ppFEV$_1$: 8 weeks: 7.5 percentage points from baseline; difference from placebo, 10.7 percentage points (95% CI, 7.3 to 14.1; p < 0.0001)	Secondary endpoints: Improvements were observed in weight, sweat chloride, and CFQ-R.
KONDUCT *Moss et al 2015*	Phase 3, 24-week, DB, PC trial in 69 patients aged ≥ 6 yrs with *R117H* mutation	ppFEV$_1$: 24 weeks: 2.6 percentage points from baseline; difference from placebo, 2.1 percentage points (95% CI, -1.13 to 5.35; p = 0.20); in a pre-specified subgroup analysis, ppFEV$_1$ significantly improved with ivacaftor in patients aged ≥ 18 yrs, with a TD vs placebo of 5.0 percentage points (95% CI, 1.15 to 8.78), but not in patients aged 6 to 11 yrs, with a TD vs placebo of -6.3 percentage points (95% CI, -11.96 to -0.71; p = 0.03)	Secondary endpoints: Improvements were observed in sweat chloride and CFQ-R. The lack of effect for ppFEV$_1$ in the pediatric and overall populations may be related in part to the fact that pediatric patients had a high baseline ppFEV$_1$. Most patients (N = 65) entered a washout period followed by an OLE period; at a 12-week analysis, patients in both the placebo-to-ivacaftor and ivacaftor-to-ivacaftor groups showed a significant ppFEV$_1$ improvement from post-washout baseline (5.0 [p = 0.0005] and 6.0 [p = 0.0006] percentage points, respectively).
EXPAND *Rowe et al 2017* *(ivacaftor and placebo arms)*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation (of these, 157 and 162 patients were treated with ivacaftor and placebo, respectively)	ppFEV$_1$: Average of 4 and 8 week assessments: difference from placebo, 4.7 percentage points (95% CI, 3.7 to 5.8; p < 0.001)	Secondary endpoint: Improvements were observed for ivacaftor vs placebo for CFQ-R. Benefits were also observed for other secondary endpoints, but statistical significance cannot be claimed due to the statistical design.
KIWI *Davies et al 2016*	Phase 3, 24-week, OL study in 34 patients aged 2 to 5 yrs with ≥ 1 *CFTR* gating mutation; patients received a dose of 50 mg (weight < 14 kg) or 75 mg (weight ≥ 14 kg)	Pharmacokinetics: Exposure was similar to that reported with the approved dosing in adults Safety: Safety was similar to use in adults, although there was an increased incidence of LFT elevations; most AEs were mild or moderate; common AEs included cough and vomiting	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. No meaningful data on lung function were available (spirometry results are limited in this age group).
Orkambi (lumacaftor/ivacaftor)			
TRAFFIC and **TRANSPORT**	Two Phase 3, 24-week, DB, PC trials in 1122	ppFEV$_1$:	Secondary endpoints: In the pooled analysis, there were improvements in

Wainright et al 2015	patients aged ≥ 12 yrs homozygous for *F508del*	24 weeks, pooled data: 2.5 percentage points from baseline; difference from placebo, 2.8 percentage points (95% CI, 1.8 to 3.8; p < 0.001)	weight and exacerbations. The difference in CFQ-R did not reach statistical significance, with an improvement of 2.2 (95% CI, 0.0 to 4.5; p = 0.05).
PROGRESS *Konstan et al 2017*	Phase 3, 96-week, OLE study of TRAFFIC and TRANSPORT; enrolled 1030 patients aged ≥ 12 yrs homozygous for *F508del*; all received lumacaftor/ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate. Rates of AEs were similar or reduced to rates during the PC period of the trial. An increase in blood pressure was noted. $ppFEV_1$ (secondary endpoint): Mean $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor, but the improvement was not statistically significant.	Additional secondary endpoints: The pulmonary exacerbation rate remained low. Improvements in BMI and CFQ-R continued throughout the study. Analysis of lung function change over time showed a slower rate of decline compared to matched registry patients.
Milla et al 2017	Phase 3, 24-week, OL study in 58 patients aged 6 to 11 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 2.5 percentage points from baseline (95% CI, -0.2 to 5.2; p = 0.0671)	Secondary endpoints: Improvements from baseline were seen in sweat chloride, weight, and CFQ-R. The small sample size and relatively mild lung disease in this population may explain the lack of significant effect on $ppFEV_1$. The safety profile was similar to that seen in larger trials in older patients.
Ratjen et al 2017	Phase 3, 24-week, DB, PC trial in 206 patients aged 6 to 11 yrs homozygous for *F508del*	Mean change in lung clearance index ($LCI_{2.5}$; see Appendix B) from baseline to average of all visits up to and including week 24 (primary endpoint): -1.0 with lumacaftor/ ivacaftor vs 0.1 with placebo; TD, -1.1 (95% CI, -1.4 to -0.8; p < 0.0001) $ppFEV_1$: Average of all visits up to and including week 24: 1.1 percentage points from baseline; difference from placebo, 2.4	Additional secondary endpoints: Improvements were observed in sweat chloride. Changes in BMI and CFQ-R were not statistically significant.

		percentage points (95% CI, 0.4 to 4.4; p = 0.0182)	
Symdeko (tezacaftor/ivacaftor)			
EVOLVE *Taylor-Cousar et al 2017)*	Phase 3, 24-week, DB, PC trial in 509 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 3.4 percentage points from baseline; difference from placebo, 4.0 percentage points (95% CI, 3.1 to 4.8; p < 0.001)	Secondary endpoints: Patients treated with tezacaftor/ivacaftor had a reduced number of pulmonary exacerbations. Numerical improvements were seen in BMI, CFR-Q, and sweat chloride. The change in BMI was not statistically significant, and the changes in CFQ-R and sweat chloride were not assessed for statistical significance due to the testing hierarchy. The rate of respiratory AEs was not higher in the tezacaftor/ ivacaftor group than the placebo group; this compares favorably to other studies with lumacaftor/ ivacaftor.
EXPAND *Rowe et al 2017*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation	$ppFEV_1$: 8 weeks: difference for tezacaftor/ivacaftor vs placebo, 6.8 percentage points (95% CI, 5.7 to 7.8; p < 0.0001); difference for tezacaftor/ivacaftor vs ivacaftor, 2.1 percentage points (95% CI, 1.2 to 2.9; p < 0.0001)	Secondary endpoints: Improvement was seen in CFQ-R for tezacaftor/ivacaftor vs placebo; the difference in CFQ-R between tezacaftor/ivacaftor and ivacaftor was not statistically significant. A numerical improvement was observed in sweat chloride, but significance was not assessed due to the statistical hierarchy.

Note: CFQ-R scores refer to the respiratory domain.
Abbreviations: AE = adverse event, BMI = body mass index, CFQ-R = cystic fibrosis questionnaire-revised, CI = confidence interval, DB = double-blind, LCI = lung clearance index, LFT = liver function test, OL = open-label, OLE = open-label extension, PC = placebo-controlled, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second, TD = treatment difference, XO = crossover, yrs = years

Appendix B: Study endpoint descriptions

- **CF Questionnaire (CFQ); CF Questionnaire-Revised (CFQ-R)** (*American Thoracic Society [ATS] 2002, Quittner et al 2009, University of Miami 2008*)
  - This is a disease-specific quality of life instrument designed to measure impact of CF on overall health, daily life, perceived well-being, and symptoms. It is used in clinical trials and in routine CF care.
  - The CFQ-R has 9 quality of life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, and health perceptions) and 3 symptom scales (weight, respiratory, and digestion).
  - Scaling of items uses 4-point Likert scales (eg, always/often/sometimes/never).
  - Each health-related quality of life domain is scored. Standardized scores range from 0 to 100, with higher scores indicating better quality of life.
  - The minimal clinically important difference in CFQ-R respiratory scores has been estimated to be approximately 8.5 points in patients experiencing a CF exacerbation and 4.0 points in stable CF patients.
- **Lung Clearance Index ($LCI_{2.5}$)** (*Ratjen et al 2017*)
  - This is a measure of the number of lung volume turnovers required to reach 2.5% of tracer gas concentration.
  - Elevated $LCI_{2.5}$ values reflect increasing unevenness of gas mixing within the lung caused by early lung disease secondary to mucus plugging and airway wall changes.
  - $LCI_{2.5}$ may be more sensitive than FEV_1 for the presence of early structural lung abnormalities, particularly in the pediatric population.

- **Sweat chloride test** (*Durmowicz et al 2013, Farrell et al 2017*)
  - This test measures the amount of chloride in a patient's sweat. It is considered the gold standard for diagnosis of CF.
  - A sweat test concentration of ≥ 60 mmol/L indicates a diagnosis of CF, and a concentration of < 30 mmol/L indicates that CF is unlikely. Patients with results in the intermediate range (30 to 59 mmol/L) and certain clinical characteristics (positive newborn screen, symptoms of CF, or a positive family history) may have CF and further testing should be considered.
  - Based on the diagnostic relationship between sweat chloride and CF, change in sweat chloride has been used as a measure of CFTR function and as a pharmacodynamic endpoint in clinical trials. A reduction in sweat chloride has been demonstrated in clinical trials of CFTR modulators. However, a correlation between changes in sweat chloride and improvements in FEV_1 has not been consistently demonstrated, and there is no specific improvement in sweat chloride concentration that can predict FEV_1 improvement. This may be related to the multiple physiologic, environmental, and genetic factors that modulate CF severity.

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