FOR PATIENTS WITH CF WITH RESPONSIVE MUTATIONS

PROVIDING A CFTR-TARGETED THERAPY AS EARLY AS AGE 6 YEARS

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
CF is a genetic, systemic disease that results in progressive lung disease and can ultimately lead to pulmonary failure.1,2

**CF Causes an Average Annual Decline of 1-3% in Lung Function**

<table>
<thead>
<tr>
<th>Estimated Decline in Lung Function in Patients With CF With Certain Genotypes From 2006 to 2014 Based on Analysis of the CFFPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Group</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>6-12</td>
</tr>
<tr>
<td>13-17</td>
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<tr>
<td>18-24</td>
</tr>
<tr>
<td>251</td>
</tr>
</tbody>
</table>


**Study Overview**

Retrospective analysis of patients in the US CFFPR from 2006 to 2014. Objective was to characterize and compare rate of decline of ppFEV1 in patients homozygous for F508del with patients heterozygous for F508del and a mutation associated with residual CFTR activity.

**Limitations and Disclosures**

The severity of disease in patients with CF and a mutation associated with residual CFTR activity is highly variable. Analysis of patients with genotypes with residual CFTR activity only included patients heterozygous for F508del and may not be applicable to other genotypes.

**Pulmonary Exacerbations Significantly Contribute to Lung Function Decline**

- By age 12, ~30% of patients will experience ≥1 pulmonary exacerbation(s) per year2
- In patients with CF, 52% of FEV1 decline is associated with pulmonary exacerbations1,3
- 25% of patients do not recover to baseline FEV1 within 3 months after treatment1,4
- Pulmonary exacerbations may have devastating effects on patients, including being associated with subsequent reductions in lung function, which may be permanent.5-7

*This was a retrospective cohort study of lung function decline in pediatric and adult patients with CF. The data were extracted from the Toronto CF Database. From 1997 to 2008, 851 patients were included, and 45% of patients had at least 1 pulmonary exacerbation requiring hospitalization and antibiotics. Patients were followed for a median of 6.7 years.5 1 pulmonary exacerbation requiring hospitalization and antibiotics. Patients were followed for a median of 6.7 years.1 Pulmonary exacerbations are defined as the requirement for hospitalization or antibiotics. The study included those who were treated for at least 1 pulmonary exacerbation between January 1, 2003 and December 1, 2006. One randomly selected pulmonary exacerbation was analyzed per patient.*

**Structural Lung Damage May Occur Before Spirometry Detects Loss of Lung Function**

<table>
<thead>
<tr>
<th>HRCT scans below show evidence of pulmonary abnormalities in 2 patients with CF with high ppFEV1, of 94%.*1,6,18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30-YEAR-OLD patient with ppFEV1, of 94%</strong></td>
</tr>
</tbody>
</table>

Reprinted from Chest. 130(5): Judge EP et al. Pulmonary Abnormalities on High-Resolution CT Demonstrate More Rapid Decline Than FEV1, in Adults With Cystic Fibrosis, 1424-1432, © 2006 with permission from Elsevier.


*Case scenario of a patient from a retrospective study of 19 patients studied at the Irish National Referral Centre for Adult CF who received 3 HRCT scans ≥9 months apart. The mean age was 22 years, and all patients had documented clinical, radiological, or genotypic features of CF as well as sweat sodium and chloride >60 mmol/L. Image shows a patient at age 30 with ppFEV1 of 80% HRCT shows moderate bronchiectasis (straight arrow), peribronchial wall thickening (curved arrow), and an apical bulla (arrowhead).3

*Case scenario of a patient from a study of 48 patients studied at Sophia Children’s Hospital in the Netherlands who received annual PFT and biannual HRCT scans. The mean age was 22 years, and all patients had documented clinical, radiological, or genotypic features of CF as well as sweat sodium and chloride >60 mmol/L. Image shows a patient at age 30 with ppFEV1 of 80%. HRCT shows moderate bronchiectasis (straight arrow), peribronchial wall thickening (curved arrow), and an apical bulla (arrowhead).1,3

**EVEN PATIENTS WHO HAVE NORMAL ppFEV1 MAY HAVE EVIDENCE OF STRUCTURAL LUNG DAMAGE**

<table>
<thead>
<tr>
<th>13-YEAR-OLD patient with ppFEV1, of 96%*9,16</th>
</tr>
</thead>
</table>

Reprinted from Chest. 130(5): Judge EP et al. Pulmonary Abnormalities on High-Resolution CT Demonstrate More Rapid Decline Than FEV1, in Adults With Cystic Fibrosis, 1424-1432, © 2006 with permission from Elsevier.


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**Indications and Usage**

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) targets CFTR protein defects in specific mutations. SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to SYMDEKO/ivacaftor based on in vitro data and/or clinical evidence. 

If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. 

**Clinical data for these mutations in Clinical Studies see Clinical Studies in USPI (14.1 and 14.2)**

† Complex/compound mutations in which a single allele of the CFTR indicated for SYMDEKO. 

A patient must have 2 copies of the presence of mutations on the other allele.

**Warning and Precautions**

**Transaminase (ALT or AST) Elevations**

- Elevated transaminases have been observed in patients with CF receiving SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered.

- Dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST >5x upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN) and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment.

**Hypersensitivity Reactions, Including Anaphylaxis**

- Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue SYMDEKO and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with SYMDEKO.

**Concomitant Use With CYP3A Inducers**

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort, is not recommended. 

**Cataracts**

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO.

**Serious Adverse Reactions**

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients.

**Most Common Adverse Reactions**

- The most common adverse reactions in Trials 1 and 3 occurring in ≥3% of patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness.

**Use in Specific Populations**

**Pediatric Use**

- The safety and effectiveness of SYMDEKO in patients with CF younger than 6 years of age have not been studied. Please click for full prescribing information for SYMDEKO.

**Indications and Usage**

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) targets CFTR protein defects in specific mutations. 

| CFTR Mutations That Produce CFTR Protein and Are Responsive to SYMDEKO1-14 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| S464fsCTA       | E19K            | G576A           | L348P           | R117H           | S589N           |
| 2765..G        | E19K            | G576A           | G692D           | R117H           | S589N           |
| 5727..26A..G   | E403D           | G937D           | L1224P          | R117H           | S548L           |
| 3849..10kbC..J | E588V           | G1069R          | L1335P          | R117H           | S57P            |
| A20KT          | E82K2           | G1448E          | R258G           | S193P           |
| A234D          | E83K            | G1448E          | M532V           | R334L           | S193P           |
| A314V          | F190V           | G1349D          | H255X           | R334R           | S253H           |
| A455E          | F316H           | M929X           | R347P           | T338E           |
| A546E          | F505C           | H1375P          | P33L            | R347V           | T1053N          |
| A606E          | F505R;S521N     | I487T           | P476L           | T1083E          |
| D107C          | F508del*        | I775V           | P205S           | R352W           | V201M           |
| D110H          | F575Y           | L336K           | Q88R            | R352S           | V232O           |
| D129C          | F587S           | R373F           | Q88R            | R568C           | V362I           |
| D445Y          | F587V           | I683T           | Q237E           | R568C           | V362I           |
| D445Y          | F587V           | I683T           | Q237E           | R568C           | V362I           |
| D445Y          | F587V           | I683T           | Q237E           | R568C           | V362I           |
| D445Y          | F587V           | I683T           | Q237E           | R568C           | V362I           |
| D445Y          | F587V           | I683T           | Q237E           | R568C           | V362I           |

*Clinical data for these mutations in Clinical Studies (see Clinical Studies in USPI 14.1 and 14.2).

† A patient must have 2 copies of the F508del mutation or at least 1 copy of a responsive mutation listed above in this table to be indicated for SYMDEKO.

**Complex/compound mutations in which a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.**

Visit SYMDEKOhcp.com or refer to the full Prescribing Information to see which mutations are eligible.
**OVERVIEW OF CLINICAL TRIAL EXPERIENCE**

**TRIAL 4**

Homozygous for the F508del mutation or heterozygous for the F508del mutation with a mutation predicted to be responsive to SYMDEKO®

(see table on page 4 for a list of these mutations)*

Patients do not need to have an F508del mutation if they have a mutation responsive to SYMDEKO to be indicated for SYMDEKO.10

**EVOLVE (TRIAL 1)**

Homozygous for the F508del mutation in the CFTR gene

**EXPAND (TRIAL 2)**

Heterozygous for the F508del mutation with a mutation predicted to be responsive to SYMDEKO®

(see table on page 4 for a list of these mutations)*

Patients do not need to have an F508del mutation if they have a mutation responsive to SYMDEKO to be indicated for SYMDEKO.10

**EXTEND (TRIAL 661-110)**

96-week, open-label Extension Study of patients completing EVOLVE and EXPAND

DESIGN

- Phase 3, 24-week, open-label, multicenter study evaluating pharmacokinetics, safety, and tolerability.12,18
- Placebo (n=256)19
- Ivacaftor 150 mg q12h (n=156)20
- Placebo q12h (n=248)19

DOING

- Ivacaftor 150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=1042)15
- Placebo q12h (n=161)20

**MUTATIONS ENROLLED IN STUDY**

F508del

- 50 mg qd + ivacaftor 75 mg qd
- 100 mg qd + ivacaftor 75 mg qd
- 100 mg qd 12 hours apart (patients ≥40 kg, n=62)8

**REQUIRED ppFEV1 AT SCREENING**

≥90%12

**REFERENCE**

12鎗14

Additional mutations determined to be responsive to tezacaftor/ivacaftor based on in vitro data and eligible for but not enrolled in EXPAND were A1067T, D110E, D1270N, E193K, F1052V, L206W, R352Q, S945L, R74W, and F508del to be included in the full prescribing information approved for SYMDEKO.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Safety results through Week 24 were similar to those observed in patients age 12 years and older (cont’d)

• 1 patient experienced liver enzyme elevations that led to study drug interruption

• 4 patients experienced total bilirubin >1 to ≤1.5 x ULN

No patients experienced total bilirubin >1.5 x ULN

Incidence of maximum transaminases

<table>
<thead>
<tr>
<th>Elevated ALT or AST</th>
<th>SYMDEKO (N=70) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>7 (10.0)*</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>3 (4.5)*</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

*Includes all patients who experienced transaminase elevations >3 x ULN, including those who experienced >5 and >8 x ULN

†Includes all patients who experienced transaminase elevations >5 x ULN, including those who experienced >8 x ULN

• The proportion of patients who discontinued study drug due to adverse events was:

1.4% of patients treated with SYMDEKO (tezacaftor/ivacaftor and ivacaftor) (n=70)

• The discontinuation was due to constipation, which was considered unlikely related to study drug

• No deaths occurred in patients taking SYMDEKO

• There were no treatment discontinuations due to respiratory adverse events or transaminase elevations

• 4 patients had adverse events that led to treatment interruption; none were considered serious and all resolved

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.

TRIAL 4 limitations and disclosures

• The study was open label and not placebo controlled; therefore, causality cannot be attributed to SYMDEKO

• Trial 4 was conducted using a weight-based dosing regimen that differs from the FDA-approved dosing regimen for patients age 6 through 11 years

• The dosing regimen studied in Trial 4 had a 40 kg weight-based dosing cutoff

• The FDA-approved dosing regimen for patients age 6 through 11 years is:

— <30 kg: tezacaftor/ivacaftor (50 mg/75 mg qd + ivacaftor 75 mg qd) approximately 12 hours apart

— ≥30 kg: tezacaftor/ivacaftor (100 mg/150 mg qd + ivacaftor 150 mg qd) approximately 12 hours apart

Transaminase Elevations

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Safety results through Week 24 were similar to those observed in patients age 12 years and older (cont’d)

• Trial 4 was conducted using a weight-based dosing regimen that differs from the FDA-approved dosing regimen for patients age 6 through 11 years. See FDA-approved dosing and administration details on page 2 and limitations and disclosures on page 8.

TRIAL 4 PRIMARY ENDPOINT: SAFETY (cont’d)

Serious Adverse Events\(^{18, a}\)

• Serious adverse events occurred in 6 patients (8.6%) on SYMDEKO\(^{a}\) (tezacaftor/ivacaftor and ivacaftor)

• Serious adverse events, which were not considered drug-related by the investigators, that occurred in patients treated with SYMDEKO included infective pulmonary exacerbation of CF, 2 (2.9%); breath odor, 1 (1.4%); snoring, 1 (1.4%); failure to thrive, 1 (1.4%); sinusitis, 1 (1.4%); and constipation, 1 (1.4%)

Most Common Adverse Events\(^{18}\)

Incidence of adverse reactions in ≥10% of patients taking SYMDEKO

<table>
<thead>
<tr>
<th>Adverse Reactions (Preferred Term)</th>
<th>SYMDEKO (N=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>25 (35.7)</td>
</tr>
<tr>
<td>Infective pulmonary exacerbation of CF</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10 (14.3)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (10)</td>
</tr>
</tbody>
</table>

• 92.9% of patients (n=65) experienced at least 1 adverse event

Respiratory Adverse Events

• 2 patients (2.9%) experienced abnormal respiration (eg, chest tightness), which did not result in treatment discontinuation

Results for secondary endpoints: sweat chloride, lung function, BMI, and CFQ-R Respiratory Domain score

• Trial 4 was open label and not placebo controlled; therefore, causality cannot be attributed to SYMDEKO\(^a\) (tezacaftor/ivacaftor and ivacaftor)

TRIAL 4 SECONDARY ENDPOINTS

Sweat Chloride\(^{17, 18}\)

• Reductions in sweat chloride were seen in the overall study population

Lung Function\(^{18}\)

0.9 PERCENTAGE POINTS LS mean absolute change in ppFEV\(_1\) from baseline through Week 24 (Baseline 91.1%; 95% CI: -0.6, 2.3)

1.4 PERCENT LS mean relative change in ppFEV\(_1\) from baseline through Week 24 (Baseline 91.1%; 95% CI: -0.4, 3.1)

BMI\(^{18}\)

+0.23 kg/m\(^2\) LS mean absolute change in BMI from baseline at Week 24 (Baseline 17.44; 95% CI: 0.06, 0.40)

-0.03 LS mean absolute change in BMI-for-age z-score from baseline at Week 24 (Baseline 0.37; 95% CI: -0.10, 0.04)

CFQ-R Respiratory Domain Score (Child Version)\(^{18}\)

3.4 POINT LS mean absolute change in CFQ-R Respiratory Domain score from baseline through Week 24 (95% CI: 1.4, 5.5)

• The CFQ-R Respiratory Domain score evaluated respiratory symptoms, including cough, sputum production, and difficulty breathing\(^22\)

CI, confidence interval; LS, least squares.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.

*Serious adverse events included any adverse event that was fatal or life-threatening or resulted in hospitalization or prolonged hospitalization, disability/incapacity, congenital anomaly or birth defect, or an important medical event that required professional medical intervention.*
Evolve (Evolve) Extend

Patients with CF age 12 years and older, homozygous for the F508del mutation

Improvements in lung function in Evolve were generally maintained in extend.

Study Designs\(^{12,19}\)

- Evolve: Phase 3, 24-week, randomized, double-blind, placebo-controlled, 2-arm study evaluating efficacy and safety of Symdeko\(^*\) (tezacaftor/ivacaftor and ivacaftor).
  
  - A hierarchical testing procedure was performed for primary and key secondary endpoints. For an endpoint to be significant, both it and all previous tests in the hierarchy had to achieve P<0.05.\(^{12,13}\)
  
  - The primary endpoint was mean absolute change in ppFEV\(_1\) from baseline through Week 24\(^\dagger\).
  
  - Key secondary endpoints were relative change from baseline in ppFEV\(_1\), through Week 24; number of pulmonary exacerbations from baseline through Week 24; absolute change in BMI from baseline at Week 24; and absolute change in C-FG R Respiratory score from baseline through Week 24.\(^\dagger\)

- Extend: Phase 3, 96-week, open-label Extension Study of patients completing Evolve\(^\dagger\)
  
  - The primary endpoint was the long-term safety and tolerability of Symdeko (see page 19 for results); the secondary endpoint was long-term efficacy.


Improvements in other key secondary endpoints were seen in 24 weeks of Evolve and persisted for up to an additional 96 weeks in extend.

**Lung Function**

**Evolve & Extend**: Improvements in lung function were seen by Day 15 of Evolve and were generally maintained for an additional 96 weeks in extend\(^{12,15,19}\).

**Absolute Change in ppFEV**\(_1\), Evolve vs Placebo\(^{12,19}\)

**Pulmonary Exacerbations**

**Estimated event rate per year**

**SYMDEKO vs Placebo**

- **35% Reduction in Estimated Event Rate per Year**
  
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Estimated Event Rate</th>
<th>Placebo (95% CI)</th>
<th>SYMDEKO (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Exacerbations</td>
<td>0.76</td>
<td>(95% CI: 0.63, 0.92)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Tolerability**

**Absolute Change in CFQ-R Respiratory Domain Score**

**Estimated event rate per year calculated using 48 weeks per year.**\(^{12,12,17}\)

**Significantly different from placebo with a 95% confidence interval of 0.5 to 0.9.**\(^{12,12,17}\)

**The minimal clinically important difference (MCID) threshold for C-FG R Respiratory Domain scores is 4 points in patients with CF with stable respiratory symptoms, which is the minimal change a patient can detect.**\(^{12,12,17}\)

**Please see pages 6 and 7 for limitations and disclosures of Extend.**

**Important Safety Information**

**Warnings and Precautions**

- **Transaminase (ALT or AST) Elevations**
  
  - Elevated transaminases have been observed in patients with CF receiving Symdeko, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered.

- **Hypersensitivity Reactions, Including Anaphylaxis**
  
  - Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue SYMDEKO and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with SYMDEKO. Please click for additional Important Safety Information and full Prescribing Information for SYMDEKO.

**Please see pages 6 and 7 for limitations and disclosures of Extend.**
Adding tezacaftor to ivacaftor led to improvement in lung function in EXPAND that was generally maintained in EXTEND

STUDY DESIGNS

• EXPAND: Phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor). This was a 2-period, 5-treatment, 8-week crossover study
  — There were two 8-week dosing periods separated by an 8-week washout
  — The primary endpoint was the mean absolute change in ppFEV1 from baseline to the average of Weeks 4 and 8
  — The key secondary endpoint was the absolute change in CFQ-R Respiratory Domain Score from baseline to the average of Weeks 4 and 8
• EXTEND: 96-week, open-label Extension Study of patients completing EXPAND
  — The key secondary endpoint was the long-term safety and tolerability of SYMDEKO (see page 19 for results), the secondary endpoint was long-term efficacy

Lung Function

EXPAND & EXTEND: Improvements in lung function (ppFEV1) were seen by Day 15 in EXPAND and were maintained in EXTEND12,20

EXPAND: SIGNIFICANT IMPROVEMENT IN PRIMARY ENDPOINT

6.8 PERCENTAGE POINTS IMPROVEMENT vs PLACEBO in LS mean absolute change in ppFEV1 from baseline to the average of Weeks 4 and 8 (95% CI: 5.7, 7.8; P<0.0001)

EXPAND: SIGNIFICANT IMPROVEMENT IN OTHER EFFICACY ANALYSIS

2.1 PERCENTAGE POINTS IMPROVEMENT vs IVACAFTOR in LS mean absolute change in ppFEV1 from baseline to the average of Weeks 4 and 8 (95% CI: 1.2, 2.9; P<0.0001)

• For individual mutations, changes in ppFEV1 varied by genotype and ranged from -1.0 to 10.1; see full Prescribing Information for results by mutation. This was an ad hoc analysis20-22


KEY SECONDARY ENDPOINT: CFQ-R RESPIRATORY DOMAIN SCORE

IN EXPAND TO THE AVERAGE OF WEEKS 4 AND 8

+11.1 POINT SIGNIFICANT IMPROVEMENT VS PLACEBO 
In LS mean change from baseline (95% CI: 8.7, 13.6; P<0.0001)

+1.4 POINT TREATMENT DIFFERENCE VS IVACAFTOR 
In LS mean change from baseline (95% CI: -1.0, 3.9; not statistically significant)

IN EXTEND UP TO AN ADDITIONAL 96 WEEKS

+13.8 POINTS 
LS mean within-group absolute change from baseline in patients continuing on SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (95% CI: 10.2, 17.2)

+11.2 POINTS 
LS mean within-group absolute change from baseline in patients transitioning from ivacaftor to SYMDEKO (95% CI: 7.7, 14.7)

*The MCID threshold for CFQ-R Respiratory Domain scores is 4 points in patients with CF with stable respiratory symptoms, which is the minimal change a patient can detect.21

For individual mutations, changes in CFQ-R Respiratory Domain score varied by genotype and ranged from -11.1 to 29.2; see full Prescribing Information for results by mutation20-22

WARNINGS AND PRECAUTIONS (cont’d)

Concomitant Use With CYP3A Inducers

• Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John’s wort, is not recommended

Cataracts

• Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO
SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials

**Safety data from 3 placebo-controlled clinical trials**

- The overall safety profile is based on data from 3 double-blind, placebo-controlled, Phase 3 clinical trials: 2 parallel-group trials of 12- and 24-week durations and 1 cross-over design trial of 8-week duration. Eligible patients were also able to participate in an open-label extension safety study (up to 96 additional weeks of SYMDEKO).
- In the 3 placebo-controlled Phase 3 trials, a total of 496 patients with CF aged 12 years and older received at least 1 dose of SYMDEKO.
- The proportion of patients who discontinued study drug prematurely due to adverse events was:
  - 1.6% of patients treated with SYMDEKO
  - 2.0% of patients treated with placebo

The safety profile of SYMDEKO was generally similar across all subgroups of patients, including analysis by age, sex, baseline ppFEV₁, and geographic regions.

**Laboratory abnormalities: Transaminase elevations**

<table>
<thead>
<tr>
<th>Incidence of maximum transaminases during placebo-controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT or AST</td>
</tr>
<tr>
<td>&gt;3 x ULN</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
</tr>
</tbody>
</table>

- The incidence of transaminase elevations was similar between treatment groups.
- 1 patient (0.2%) on SYMDEKO and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases.
- No patients treated with SYMDEKO experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

**Adverse reactions in ≥3% of patients taking SYMDEKO and greater than placebo (EVOLVE [Trial 1] and Trial 3)*

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>SYMDEKO (N=334) n (%)</th>
<th>Placebo (N=343) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>49 (15)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (9)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Sinus congestion</td>
<td>13 (4)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (4)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

*Trial 3 was a 2-arm study that compared SYMDEKO to placebo in patients with CF aged 12 years and older who were heterozygous for the F508del mutation and had a second CFTR mutation not responsive to SYMDEKO. This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

- The safety profile for patients with CF enrolled in EXPAND (Trial 2) was similar to that observed in EVOLVE and Trial 3.

**Cataracts**

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO.

**Serious adverse reactions**

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs 0 placebo patients.

**Most common adverse reactions**

**Incidence of adverse reactions in ≥3% of patients taking SYMDEKO and greater than placebo (EVOLVE [Trial 1] and Trial 3)**

Please click for [Important Safety Information](#) and full [Prescribing Information for SYMDEKO](#).
Pooled analysis of respiratory adverse events in clinical trials of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

### Rates of Respiratory Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>SYMDEKO (n=496)</th>
<th>Placebo (n=505)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>30 (6.0)</td>
<td>36 (7.1)</td>
</tr>
<tr>
<td>Respiration abnormal</td>
<td>15 (3.0)</td>
<td>20 (4.0)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>9 (1.8)</td>
<td>13 (2.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>4 (0.8)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>2 (0.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.27*

11.3% OF PATIENTS TREATED WITH SYMDEKO (n = 56)

14.7% OF PATIENTS TREATED WITH PLACEBO (n = 74)

- The median time to onset for any respiratory adverse event was 59 days with SYMDEKO vs 38 days with placebo.

### Pooled analysis of respiratory events

<table>
<thead>
<tr>
<th>Respiratory Events</th>
<th>SYMDEKO (N=496)</th>
<th>Placebo (N=505)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>30 (6.0)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.27*

14.7% OF PATIENTS TREATED WITH SYMDEKO (n=56)

### Respiratory Event Rates by Baseline ppFEV1 Subgroups

<table>
<thead>
<tr>
<th>Baseline ppFEV1</th>
<th>SYMDEKO % (n/n)</th>
<th>Placebo % (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>14.3% (7/49)</td>
<td>27.9% (12/43)</td>
</tr>
<tr>
<td>(SYMDEKO range: 30.3 to &lt;40; Placebo range: 27.8 to &lt;40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 to &lt;70</td>
<td>12.5% (38/304)</td>
<td>16.8% (52/310)</td>
</tr>
<tr>
<td>(SYMDEKO range: 70 to 96.7; Placebo range: 70 to 96.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>7.7% (11/142)</td>
<td>6.6% (10/152)</td>
</tr>
</tbody>
</table>

*Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.27*

### EXTEND primary endpoint: long-term safety and tolerability up to 96 weeks

1042 PATIENTS RECEIVED ≥1 DOSE OF SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

- 253 patients (24.3%) were from parent studies that did not meet their primary endpoints15
- 682 patients completed the 96-week regimen; reasons for discontinuation included:
  - 24 patients (3.0%) had adverse events that led to discontinuation. Those that occurred in ≥2 patients were AST and ALT increased (n=4), blood creatine phosphokinase increased (n=4), and infective pulmonary exacerbation of CF (n=2).
  - 83 patients (10.5%) discontinued for other reasons15
- 2 deaths occurred after the treatment-emergent period. There was 1 death due to respiratory failure and influenza in a patient who had discontinued SYMDEKO 7 weeks prior and 1 death due to esophageal carcinoma in a patient who had discontinued SYMDEKO 6 weeks prior28
- Serious adverse events occurred in 351 patients (33.7%); those that occurred in ≥1% of patients included infective pulmonary exacerbation of CF in 243 patients (23.3%), hemoptysis in 25 patients (2.4%), and distal intestinal obstruction syndrome in 12 patients (1.2%)15
- 95.5% of patients (n=995) experienced at least 1 adverse event15

### Preferred Term Safety Set (N=1042)

<table>
<thead>
<tr>
<th>Safety Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective pulmonary exacerbation of cystic fibrosis</td>
<td>549 (52.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>374 (35.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>227 (21.8)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>224 (21.5)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>179 (17.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>147 (14.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>136 (13.1)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>136 (13.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>135 (13.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>107 (10.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>107 (10.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>105 (10.1)</td>
</tr>
</tbody>
</table>

- 6.1% of patients (n=63) had ALT and/or AST elevations ≥3 X ULN, 28 patients (2.7%) had elevations ≥5 X ULN, and 13 patients (1.3%) had elevations ≥8 X ULN15

- 4 patients (0.4%) discontinued treatment due to both ALT and AST elevations15
- One patient had hypertransaminasemia, leading to treatment discontinuation15
- Respiratory events of special interest led to one treatment interruption and no treatment discontinuations15

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.
Potential drug interactions with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Clinical considerations are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

Drugs shown within a therapeutic class do not represent all possible drugs within the class. Drugs within a class may have different metabolic profiles, and therefore, clinical recommendations apply only to the drugs named and not the class. The table does not represent all possible drugs or drug classes that a patient could be receiving.

### Reduced Blood Levels of SYMDEKO expected with strong CYP3A inducers

The concomitant use of CYP3A inducers may reduce tezacaftor and ivacaftor blood levels, potentially resulting in reduced SYMDEKO efficacy. Co-administration of SYMDEKO with strong CYP3A inducers is not recommended.

<table>
<thead>
<tr>
<th>EXAMPLES OF STRONG CYP3A INDUCERS</th>
<th>EFFECT</th>
<th>EXAMPLES OF MODERATE CYP3A INDUCERS</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin¹</td>
<td>Decrease</td>
<td>Ketoconazole</td>
<td>Decrease</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Decrease</td>
<td>Itraconazole</td>
<td>Decrease</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Decrease</td>
<td>Erythromycin¹</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

### Increased Blood Levels of SYMDEKO expected with strong or moderate CYP3A inhibitors

Co-administration of SYMDEKO with strong or moderate CYP3A inhibitors may increase SYMDEKO exposure.

<table>
<thead>
<tr>
<th>EXAMPLES OF STRONG CYP3A INHIBITORS</th>
<th>EFFECT</th>
<th>EXAMPLES OF MODERATE CYP3A INHIBITORS</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Increase</td>
<td>Fluconazole¹</td>
<td>Increase</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Increase</td>
<td>Erythromycin¹</td>
<td>Increase</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Increase</td>
<td>Voriconazole</td>
<td>Increase</td>
</tr>
</tbody>
</table>

### Increased Exposure to these Drugs may occur with SYMDEKO

Ivacaftor may inhibit CYP2C9 and increase exposures of CYP2C9 substrates.

<table>
<thead>
<tr>
<th>EXAMPLES OF CYP2C9 SUBSTRATES</th>
<th>EFFICACY</th>
<th>EXAMPLES OF P-GP SUBSTRATES</th>
<th>EFFICACY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor international normalized ratio of:</td>
<td>Use with caution:</td>
<td>Caution and appropriate monitoring should be used with:</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Glimepiride</td>
<td>Digoxin</td>
<td>Siroliimus</td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dosing and administration

A regimen of a tezacaftor/ivacaftor tablet taken in the morning and an ivacaftor tablet taken in the evening, approximately 12 hours apart.

- SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) should always be taken with fat-containing food to ensure adequate absorption. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats.

#### Recommended Dose Adjustments

| SEVERE HEPATIC IMPAIRMENT (Child-Pugh Class C) | MODERATE HEPATIC IMPAIRMENT (Child-Pugh Class B) | Dosing for concomitant use with CYP3A inhibitors or inhibitors¹
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wear moderate hepatic impairment</td>
<td>Wear moderate hepatic impairment</td>
<td>Use with caution or less frequently¹</td>
</tr>
<tr>
<td>No recommended dose</td>
<td>No recommended dose</td>
<td>No recommended dose</td>
</tr>
</tbody>
</table>

#### Dosing for hepatic impairment

- No dose adjustments are necessary for mild hepatic impairment.
- Studies have not been conducted in patients with severe hepatic impairment.
- Use with caution at an adjusted dose after weighing the risks and benefits of treatment.
- No dose adjustment necessary for mild/moderate CYP3A inhibitors or mild moderate CYP3A inhibitors.
- Continue to alternate tablets every day.

- **Recommended Dose**
  - **Patients aged 6 through 11 years, weighing ≥40 kg**
    - Tezacaftor 50 mg
    - Ivacaftor 150 mg
  - **Patients aged 12 years and older**
    - Tezacaftor 75 mg
    - Ivacaftor 150 mg

- **Patients aged 6 through 11 years, weighing ≤40 kg**
  - Tezacaftor 25 mg
  - Ivacaftor 100 mg

#### Food and drink containing grapefruit

- Food or drink containing grapefruit should be avoided during treatment with SYMDEKO.

- Patients should continue taking their other CF therapies as prescribed.

- SYMDEKO has not been studied in patients with moderate or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment or end-stage renal disease.

- The safety and effectiveness of SYMDEKO in patients with CF younger than 6 years of age have not been studied.

Please click for Important Safety Information and full Prescribing Information for SYMDEKO.

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¹Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by 89%; ivacaftor exposures can also be expected to decrease significantly.

²Co-administration with rifampin, a strong CYP3A inducer, increased tezacaftor exposure (AUC) by 4.0-fold and ivacaftor by 15.6-fold.

³Co-administration with fluconazole, a moderate CYP3A inhibitor, increased ivacaftor exposure (AUC) by 3.0-fold and may increase tezacaftor exposure by approximately 2.0-fold.

⁴Co-administration of ivacaftor on rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by 89%; ivacaftor exposures can also be expected to decrease significantly.

⁵Co-administration with fluconazole, a moderate CYP3A inhibitor, increased ivacaftor exposure (AUC) by 3.0-fold and may increase tezacaftor exposure by approximately 2.0-fold.
SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) packaging and missed dose information

**Missed Dose**

<table>
<thead>
<tr>
<th>IF ≤6 HOURS</th>
<th>NEXT SCHEDULED DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF &gt;6 HOURS</td>
<td>have passed since the missed morning or evening dose, the patient should not take the missed dose.</td>
</tr>
<tr>
<td>NEXT SCHEDULED DOSE can be taken at the usual time. More than one dose should not be taken at the same time.</td>
<td></td>
</tr>
</tbody>
</table>

**Packaging**

- **SYMDEKO** is supplied in cartons containing 4 weekly blister cards, each with 14 tablets.
- **SYMDEKO** is co-packaged with a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet.

**Packaging for Patients Age 6 Through 11 Years Weighing ≥30 KG and Patients Age ≥12 Years**

- The tezacaftor/ivacaftor fixed-dose combination tablets are supplied as yellow, capsule-shaped tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor.
- Ivacaftor tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor.

**Packaging for Patients Age 6 Through 11 Years Weighing <30 KG**

- The tezacaftor/ivacaftor fixed-dose combination tablets are supplied as white, capsule-shaped tablets containing 50 mg of tezacaftor and 75 mg of ivacaftor.
- Ivacaftor tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 75 mg of ivacaftor.

**Considerations for Initiating Patients Previously Treated with Another CFTR Modulator**

Transition information provided is not intended to imply clinical comparison between products.

- **KALYDECO® (ivacaftor)**
  
  Trial 2 (EXPAND), which evaluated SYMDEKO in comparison to KALYDECO, was not designed to demonstrate the safety or efficacy of transitioning to SYMDEKO and transitioning has not been evaluated in a clinical setting.

- **ORKAMBI® (lumacaftor/ivacaftor)**
  
  SYMDEKO was not evaluated in comparison to ORKAMBI; nor has the safety or efficacy of transitioning to SYMDEKO from ORKAMBI been evaluated in a clinical setting.

Considerations for transitioning patients are intended only for patients eligible for SYMDEKO. These are patients who are aged 6 years and older who are homozygous for the F508del mutation or who have at least one CFTR mutation that is responsive to tezacaftor/ivacaftor.

**Remind Patients That SYMDEKO Should Be Taken As Directed and Discuss Any Necessary Dose Adjustments**

Please click for Important Safety Information for SYMDEKO, KALYDECO, and ORKAMBI, and full Prescribing Information for SYMDEKO, KALYDECO, and ORKAMBI.
Transitioning patients from KALYDECO® (ivacaftor) to SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Clinical considerations are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

### KALYDECO SYMDEKO

- Patients age 6 through 11 weighing ≥30 kg or patients age 12 years and older will still be receiving the same amount of ivacaftor, but tezacaftor will be added with the transition to SYMDEKO.
- Patients age 6 through 11 and weighing <30 kg will be receiving 75 mg of ivacaftor twice a day (a lower amount), and tezacaftor will be added with the transition to SYMDEKO.
- The initial dose of SYMDEKO should be taken in the morning, approximately 12 hours after the final dose of KALYDECO.
- During approximately the first 2 weeks after transition:
  - In patients age 6 through 11 and weighing ≥30 kg or age 12 years and older, blood levels of ivacaftor are expected to be maintained.
  - In patients age 6 through 11 and weighing <30 kg, blood levels of ivacaftor are expected to decrease before establishing a new steady state.

Blood levels of tezacaftor will be increasing in all patients.

Tezacaftor and ivacaftor are expected to reach steady state within 1-2 weeks.

#### Selected drug-drug interactions to consider in patients transitioning from KALYDECO to SYMDEKO

- All recommendations in this brochure with regard to drug interactions for KALYDECO also apply to SYMDEKO, with the exception of the drugs listed below.
- Drugs shown within a therapeutic class do not represent all possible drugs within the class. Drugs within a class may have different metabolic profiles, and therefore, clinical recommendations apply only to the drugs listed here and not the class.
- Caution and appropriate monitoring are recommended with KALYDECO.
- No dose adjustments or additional monitoring is considered necessary with SYMDEKO.

Benzodiazepines:
- alprazolam, diazepam, midazolam, and triazolam

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See SYMDEKO drug-drug interactions in the Table on page 20 and dose adjustments on page 21.

Please click for Important Safety Information for SYMDEKO and full Prescribing Information for SYMDEKO and KALYDECO.
Transitioning patients from ORKAMBI® (lumacaftor/ivacaftor) to SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)

Clinical considerations are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

**ORKAMBI**

• Patients will still be receiving ivacaftor, but in combination with tezacaftor instead of lumacaftor
• The initial dose of SYMDEKO should be taken in the morning, approximately 12 hours after the final dose of ORKAMBI
• During approximately the first 2 weeks after transition:
  - Blood levels of lumacaftor will be decreasing
  - Blood levels of tezacaftor will be increasing
  - Blood levels of ivacaftor may decrease before establishing a new steady state

**SYMDEKO**

Tezacaftor and ivacaftor are expected to reach steady state within 1-2 weeks

• Based on pharmacokinetic modeling (which has not been directly evaluated in patients), ivacaftor exposures may decline slightly for a short period, but ivacaftor and either lumacaftor or tezacaftor exposures are expected to remain above their respective EC50 values throughout the transition period
• During the first 1-2 weeks after transitioning, some lumacaftor-mediated CYP3A induction may remain, and interactions related to this should be considered30
• When patients have no identified drug-drug interactions at the time of transition to SYMDEKO, consider waiting 2 weeks before initiating any new concomitant medications that interact with ORKAMBI as lumacaftor-mediated interactions may persist during this period12

Selected drug-drug interactions to consider when transitioning from ORKAMBI to SYMDEKO

<table>
<thead>
<tr>
<th>Category</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal contraceptives</td>
<td>Recommended contraceptives should not be considered effective for at least 2 weeks after transition30</td>
</tr>
<tr>
<td>CYP3A inhibitors</td>
<td>- Co-administration of ORKAMBI is not recommended with these drugs</td>
</tr>
<tr>
<td>- Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition30</td>
<td></td>
</tr>
<tr>
<td>- After 2 weeks, no dose adjustment is necessary; caution is warranted and appropriate monitoring should be used</td>
<td></td>
</tr>
</tbody>
</table>

**Consider waiting 2 weeks before using midazolam or triazolam30**

- Co-administration with ORKAMBI is not recommended30
- Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition30
- No dose adjustments of these drugs are recommended with SYMDEKO12

**Consider waiting 2 weeks before starting certain antibiotics and antifungals; dose adjustment of SYMDEKO is recommended if used31**

- Co-administration with ORKAMBI may reduce the exposure and effectiveness of these drugs31
- Consider alternative to these antibiotics during concomitant use with ORKAMBI
- Concomitant use of these antifungals with ORKAMBI is not recommended
- Due to residual CYP3A induction by lumacaftor with the potential to reduce drug exposures, consider waiting to initiate these drugs until 2 weeks after transition30
- Co-administration of strong and moderate CYP3A inhibitors, such as those listed, increased exposures to tezacaftor and ivacaftor. Dose adjustment of SYMDEKO is recommended; see the dosing and administration table on page 27

See SYMDEKO drug-drug interactions in the table on page 20 and dose adjustments on page 21.

Please click for Important Safety Information for SYMDEKO and Important Safety Information for ORKAMBI, and full Prescribing Information for SYMDEKO and ORKAMBI.
Selected drug-drug interactions to consider when transitioning from ORKAMBI to SYMDEKO (cont’d)

Dose adjustment of SYMDEKO recommended with fluconazole

Antifungals
- Fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor and ivacaftor exposures
- When co-administered with fluconazole and other moderate CYP3A inhibitors, the dose of SYMDEKO should be reduced; see the dosing and administration table on page 21

Drugs whose dosage may have been increased during ORKAMBI treatment: Consider dose reduction during the transition if dosage of any drug below was increased during treatment with ORKAMBI

Antidepressants
- ORKAMBI may reduce or alter the exposure of these drugs, which may require a higher dose during co-administration to obtain desired clinical effect

Antihypertensives
- Lumacaftor-mediated CYP3A induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to SYMDEKO

Proton pump inhibitors (PPIs) and H2 blockers
- A dose reduction of the concomitant drug, as appropriate, should be considered at the time of transition
- No dose adjustments of these drugs are recommended during treatment with SYMDEKO

Systemic corticosteroids
- When co-administered with fluconazole and other moderate CYP3A inhibitors, the dose of SYMDEKO should be reduced; see the dosing and administration table on page 21

Food/drink
- advise patients to avoid grapefruit products during the first week after treatment initiation with ORKAMBI
- Co-administration of SYMDEKO with food or drink containing grapefruit, which contains one or more components that moderately inhibit CYP3A, may increase exposure of tezacaftor and ivacaftor
- Food or drink containing grapefruit should be avoided during treatment with SYMDEKO

Other drug interactions with ORKAMBI and/or SYMDEKO, including Panel

- Antiarrhythmics (digoxin)
- Anticoagulants (warfarin)
- Anticonvulsants (carbamazepine, phenobarbital, phenytoin)
- Herbals (St. John’s wort)

Please see additional information regarding these interactions on page 20.

INDICATION AND USAGE
ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the CFTR gene. If the patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

Limitations of Use
The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Use in Patients With Advanced Liver Disease
- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CP patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI. Use ORKAMBI 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, they should be closely monitored after the initiation of treatment and the dose should be reduced.

Liver-related Events
- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin.
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve.
- Dosing should be interrupted in patients with ALT or AST >5 × upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations >3 x ULN when associated with bilirubin elevations >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing.

Hypersensitivity Reactions, Including Anaphylaxis
- Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue ORKAMBI and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ORKAMBI.

Respiratory Events
- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) are common 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 (percent predicted FEV1, ppFEV1 <40). Clinical experience in patients with ppFEV1 <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 in all patients being treated with ORKAMBI.

Please click for Important Safety Information for SYMDEKO and additional Important Safety Information for ORKAMBI, and full Prescribing Information for SYMDEKO and ORKAMBI.
WARNINGS AND PRECAUTIONS (cont’d)

Drug Interactions

• Substrates of CYP3A

Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. 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-related symptoms such as amenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

• Strong CYP3A Inducers

Ivacaftor is a substrate of CYP2A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

Cataracts

• Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI

ADVERSE REACTIONS

Serious Adverse Reactions

• Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients

Most Common Adverse Reactions

The safety profile in patients age 6 through 11 years from a double-blind, placebo-controlled trial (Trials 3 and 4) in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, and influenza. The safety profile in patients age 6 through 11 years from an open-label trial (Trial 3; N=58) and a placebo-controlled trial (Trial 4: patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and spurted increased

The safety profile in patients age 2 through 5 years from an open-label trial (Trial 6; N=60) was similar to that in patients aged 6 years and older. The safety profile in patients age 1 through 2 years from an open-label trial (Trial 7; N=46) was similar to that in patients aged 2 years and older

USE IN SPECIFIC POPULATIONS

Pediatric Use

The safety and effectiveness of ORKAMBI in patients with CF younger than 1 year of age have not been established

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Please click for important Safety Information for SYMDEKO and additional important Safety Information for ORKAMBI, and full Prescribing Information for SYMDEKO and ORKAMBI.
For patients with CF age 6 years and older who are homozygous for the F508del mutation or have a mutation predicted to be responsive to SYMDEKO

**CFTR-TARGETED THERAPY CAN BEGIN AS EARLY AS AGE 6 YEARS**

### IMPROVEMENTS SEEN IN EVOLVE AND EXPAND WERE GENERALLY MAINTAINED UP TO 96 WEEKS IN EXTEND

#### SAFETY PROFILE WAS SIMILAR TO THAT OBSERVED IN PATIENTS AGE 12 YEARS AND OLDER

#### TRIAL 4

**Patients age 6 through 11 years who are homozygous or heterozygous for the F508del mutation or have a mutation predicted to be responsive to SYMDEKO**

#### SIGNIFICANT IMPROVEMENTS IN LUNG FUNCTION

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Placebo vs SYMDEKO</th>
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<tr>
<td>4.0 %</td>
<td>6.8 %</td>
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**4.0 % IMPROVEMENT VS PLACEBO**

*In mean absolute change in ppFEV₁ from baseline through Week 24 (95% CI: 3.1, 4.8; P<0.0001)*

**6.8 % IMPROVEMENT VS PLACEBO**

*In mean absolute change in ppFEV₁ from baseline to the average of Weeks 4 and 8 (95% CI: 5.7, 7.8; P<0.0001)*

### TRIALS

- **EVOLVE (Trial 1)**
  - Patients age 12 years and older homozygous for the F508del mutation

- **EXPAND (Trial 2)**
  - Patients age 12 years and older heterozygous for F508del with a mutation predicted to be responsive to tezacaftor/ivacaftor

### SAFETY RESULTS

- The proportion of patients who discontinued study drug prematurely due to adverse events was 1.6% of patients treated with SYMDEKO and 2.0% of patients treated with placebo.
- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs 0 placebo patients.
- The most common adverse reactions in patients treated with SYMDEKO (Trials 1 and 3) with an incidence of ≥3% and at a higher incidence for patients treated with SYMDEKO (N=334) than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness.
- During the placebo-controlled Phase 3 trials (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN were similar between patients treated with SYMDEKO and placebo-treated patients; 0.2%, 1.0%, and 3.4% in patients treated with SYMDEKO, and 0.4%, 1.0%, and 3.4% in placebo-treated patients.
- Safety results up to 96 weeks in EXTEND were consistent with those observed in placebo-controlled clinical trials.

### ADDITIONAL SAFETY PROFILE INFORMATION

- Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.
- Trial 3 was a 2-arm study that compared SYMDEKO to placebo in patients with CF age 12 years and older who were heterozygous for the F508del mutation and had a second CFTR mutation not responsive to SYMDEKO. This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

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