symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Consider SYMDEKO for patients with cystic fibrosis (CF) age 12 years and older who are homozygous for the *F508del* mutation

RESULTS OF 2 CLINICAL TRIALS IN PATIENTS 12 YEARS AND OLDER

- **EVOLVE (Trial 1):** Phase 3 trial evaluating SYMDEKO vs placebo in patients with CF who are homozygous for *F508del*
- **ENCOURAGE (Trial 661-114):** A trial evaluating SYMDEKO vs placebo in patients who discontinued lumacaftor/ivacaftor due to respiratory adverse events

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) 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.

Important Safety Information

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), 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

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

Pediatric Use

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

(continued on page 3)

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Please click for full Prescribing Information for SYMDEKO.

Important Safety Information

(continued)

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) 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
- The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3

Please click for full Prescribing Information for SYMDEKO.

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

A CF treatment for indicated patients not currently on a CFTR modulator or for those considering another option

EVOLVE (TRIAL 1)

The pivotal trial in patients with CF age 12 years and older who are homozygous for the *F508del* mutation[1]

ENCOURAGE (TRIAL 661-114)

A trial in patients with CF age 12 years and older who are homozygous for the *F508del* mutation and who previously discontinued lumacaftor/ivacaftor due to respiratory adverse events[2]

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

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

EVOLVE (TRIAL 1)

Patients with CF age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene

EVOLVE Study Design	**Phase 3, 24-week, randomized, double-blind, placebo-controlled, two-arm study evaluating efficacy and safety of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**[1,3] • Patients (N=504) were randomized to receive either tezacaftor/ivacaftor 100 mg/150 mg qd and ivacaftor 150 mg qd 12 hours apart (n=248) or placebo q12h (n=256) with fat-containing food, in addition to their currently prescribed CF therapies
EVOLVE Study Population	• Selected inclusion criteria[1,3] — Confirmed CF diagnosis and clinically stable — Patients ≥12 years of age (mean age, 26.3 years) and homozygous for the *F508del* mutation — Percent predicted FEV_1 ($ppFEV_1$) ≥40% and ≤90% at screening (mean baseline $ppFEV_1$, 60.0%) • Selected exclusion criteria[1] — History of colonization with organisms associated with a more rapid decline in pulmonary status, such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* — Two or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN), or AST or ALT ≥5 x ULN
EVOLVE Endpoints	• Primary endpoint: Mean absolute change in $ppFEV_1$ from baseline through Week 24 (please see page 5)[1] • Key secondary endpoints: Relative change 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 Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score from baseline through Week 24 (please see pages 5 and 6)[1,3] • 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 $P \leq 0.05$[1,4]

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; BMI, body mass index; GGT, gamma-glutamyl transferase; IV, intravenous; q12h, every 12 hours; qd, once a day; ULN, upper limit of normal.

A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.[1]

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

EVOLVE (Trial 1): Improvements in lung function

Lung function[1,3]

SIGNIFICANT IMPROVEMENT IN PRIMARY ENDPOINT

4.0 PERCENTAGE POINTS IMPROVEMENT VS PLACEBO in mean absolute change in $ppFEV_1$ from baseline through Week 24
(95% CI: 3.1, 4.8; *P*<0.0001)

SIGNIFICANT IMPROVEMENT IN KEY SECONDARY ENDPOINT

6.8 PERCENT IMPROVEMENT VS PLACEBO in relative change in $ppFEV_1$ from baseline through Week 24
(95% CI: 5.3, 8.3; *P*<0.0001)

Changes in $ppFEV_1$ from baseline vs placebo through Week 24[1,3-5,a]

Subgroups by baseline $ppFEV_1$	Absolute change in $ppFEV_1$ from baseline (percentage points)
(SYMDEKO n=23; placebo n=24; range 27.8% to <40%) **<40%**	**+3.5** (95% CI: 1.0, 6.1)
(SYMDEKO n=156; placebo n=152) **≥40 to <70%**	**+4.2** (95% CI: 3.1, 5.2)
(SYMDEKO n=66; placebo n=80; range ≥70% to 96.2%) **≥70%**	**+3.7** (95% CI: 2.2, 5.2)

IMPORTANT SAFETY INFORMATION

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), 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

[a]In EVOLVE, while $ppFEV_1$ at screening was 40-90%, changes may have occurred before baseline.[1,3]

CI, confidence interval.

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

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

EVOLVE (Trial 1): Additional key secondary endpoints

Pulmonary exacerbations[1,3]

35% SIGNIFICANT REDUCTION VS PLACEBO
RR: 0.65

in the estimated annualized event rate of pulmonary exacerbations from baseline through Week 24 (95% CI: 0.48, 0.88) *P*=0.0054

Body mass index (BMI)[1,3,a]

+0.06 kg/m² VS PLACEBO

in mean absolute change in BMI from baseline at Week 24
(95% CI: -0.08, 0.19; **not statistically significant**)

CFQ-R Respiratory Domain score[1,3,b]

5.1 POINT INCREASE VS PLACEBO

in absolute change from baseline through Week 24
(95% CI: 3.2, 7.0; **not statistically significant due to testing hierarchy**)

IMPORTANT SAFETY INFORMATION

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® (tezacaftor/ivacaftor and ivacaftor). 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

[a]Placebo baseline BMI: 21.12 kg/m²; SYMDEKO baseline BMI: 20.96 kg/m².[3]
[b]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.[6]

MCID, minimal clinically important difference; RR, relative risk.

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials

Safety data from 3 placebo-controlled clinical trials[1]

- The overall safety profile is based on data from three double-blind, placebo-controlled Phase 3 clinical trials: 2 parallel-group trials of 12- and 24-week duration and one 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 three placebo-controlled Phase 3 trials, a total of 496 patients with CF aged 12 years and older received at least one 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 ppFEV$_1$, and geographic regions
- There were no deaths in the placebo-controlled studies, and one death in the open-label extension study due to respiratory failure and influenza infection in a patient who had discontinued SYMDEKO 7 weeks prior, which was not considered to be related to the study drug by the investigator[1,7]

Laboratory abnormalities: Transaminase elevations[1]

Incidence of maximum transaminases during placebo-controlled trials

Elevated ALT or AST	SYMDEKO %	Placebo %
>3 X ULN	3.4	3.4
>5 X ULN	1.0	1.0
>8 X ULN	0.2	0.4

- The incidence of transaminase elevations was similar between treatment groups
- One 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

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) safety profile demonstrated in clinical trials (cont)

Cataracts[1]

- 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[1]

- 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[1]

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

Adverse Reactions (Preferred Term)	**SYMDEKO** (N=334) n (%)	**Placebo** (N=343) n (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	12 (4)	8 (2)

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

*Trial 3 was a two-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.[1]

†Trial 2 was a 2-period, 3-treatment study that compared SYMDEKO to ivacaftor and placebo in patients with CF aged ≥12 years who were heterozygous for the *F508del* mutation and a mutation predicted to be responsive to tezacaftor/ivacaftor.[1]

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

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[8,a]

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[8]

Pooled analysis of respiratory events[8,a]

Respiratory Events	**SYMDEKO** (N=496) Patients with events, n (%)	**Placebo** (N=505) Patients with events, n (%)
Dyspnea	30 (6.0)	36 (7.1)
Respiration abnormal	15 (3.0)	20 (4.0)
Wheezing	9 (1.8)	13 (2.6)
Asthma	4 (0.8)	6 (1.2)
Chest discomfort	3 (0.6)	3 (0.6)
Bronchospasm	2 (0.4)	4 (0.8)
Bronchial hyperreactivity	0	0

Respiratory event rates by baseline $ppFEV_1$ subgroups[8,a]

Baseline $ppFEV_1$	**SYMDEKO** % (n/n)	**Placebo** % (n/n)
<40 (SYMDEKO range: 30.3 to <40; Placebo range: 27.8 to <40)	14.3% (7/49)	27.9% (12/43)
≥40 to <70	12.5% (38/304)	16.8% (52/310)
≥70 (SYMDEKO range: 70 to 96.7; Placebo range: 70 to 96.2)	7.7% (11/142)	6.6% (10/152)

[a]Data pooled from EVOLVE (Trial 1), EXPAND (Trial 2), and Trial 3.

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Pooled analysis of respiratory adverse events in clinical trials of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (cont)

Post-dose spirometry assessments[4,9]

- During initiation of treatment with SYMDEKO, spirometry showed no evidence of an acute drop (defined as a decrease in ppFEV$_1$ of ≥10 percentage points) in a subset of patients age 12 to <18 years

Absolute change in ppFEV$_1$ from pre-dose to post-dose in patients age 12 to <18 years at screening[9]

Time point		SYMDEKO mean (SD)	Placebo mean (SD)
DAY 1	Pre-dose	69.5 (13.8) n=51	68.9 (12.2) n=51
DAY 1	2 hours post-dose	0.0 (3.6) n=45	-0.5 (3.6) n=48
	4 hours post-dose	0.4 (4.3) n=46	-0.5 (3.5) n=49
DAY 15	2 hours post-dose	0.4 (3.3) n=48	0.5 (3.9) n=46
	4 hours post-dose	0.7 (5.1) n=46	0.4 (4.3) n=45

The analysis included all subjects age 12 to <18 years who had a non-missing assessment at the pre-dose time point and at least 1 non-missing post-dose assessment. The sample size for this assessment was limited by the number of subjects who completed the Day 1 and Day 15 visits. Data were pooled from EVOLVE, EXPAND (Trial 2)*, and Trial 3†. Due to the crossover design of EXPAND, patients may have received 2 periods of treatment, and therefore, may have results for both SYMDEKO and placebo.

Safety profile in a specific population: Patients with severe lung dysfunction (ppFEV$_1$ <40)[1]

- EVOLVE and EXPAND included a total of 39 patients treated with SYMDEKO with ppFEV$_1$ <40 at baseline (range 30 to 40)
  - In EVOLVE, 23 patients treated with SYMDEKO and 24 placebo-treated patients had ppFEV$_1$ <40
  - In EXPAND, 16 patients treated with SYMDEKO, 15 placebo-treated, and 13 ivacaftor-treated patients had ppFEV$_1$ <40
- The safety profile in this subgroup was comparable to the overall results observed in both EVOLVE and EXPAND

*Trial 2 was a 2-period, 3-treatment study that compared SYMDEKO to ivacaftor and placebo in patients with CF aged ≥12 years who were heterozygous for the *F508del* mutation and a mutation predicted to be responsive to tezacaftor/ivacaftor.[1]

†Trial 3 was a two-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.[1]

SD, standard deviation.

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

ENCOURAGE (TRIAL 661-114)

Patients with CF age 12 years and older who are homozygous for *F508del* mutation and who previously discontinued lumacaftor/ivacaftor due to respiratory adverse events

Study Design	**Phase 3b, 8-week, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor)**[2] • Patients (N=97) received tezacaftor/ivacaftor (100 mg/150 mg qd) and ivacaftor (150 mg qd) 12 hours apart (n=50) or placebo q12h (n=47)[2,10] — Treatment was taken with fat-containing food — Patients continued to take their prescribed CF therapies
Study Population	• Selected inclusion criteria[2,10] — Confirmed CF diagnosis and clinically stable — Patients aged ≥12 years of age (mean age, 34.3 years for SYMDEKO and 33.3 for placebo) and homozygous for the *F508del* mutation — Percent predicted FEV_1 ($ppFEV_1$) ≥25 and ≤90 at screening (mean baseline $ppFEV_1$, 44.6 for SYMDEKO and 48.0 for placebo) — Prior discontinuation of lumacaftor/ivacaftor due to respiratory adverse events*, with at least 1 respiratory sign or symptom considered related to treatment, including asymptomatic reduction in relative change in $ppFEV_1$ >12% within 2 weeks after starting lumacaftor/ivacaftor — Discontinuation of lumacaftor/ivacaftor must have occurred within approximately 12 weeks from the most recent initiation of lumacaftor/ivacaftor, and events had to resolve or stabilize >28 days prior to screening • Selected exclusion criteria[10] — History of colonization with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* — Two or more abnormal liver function tests at screening (ALT, AST, ALP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN), or ALT or AST ≥5 x ULN — Hepatic impairment (Child-Pugh Class B or C) — History of lung transplantation since most recent initiation of lumacaftor/ivacaftor — Acute upper or lower respiratory infection, pulmonary exacerbation, or change in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug)

*Respiratory adverse events of special interest (RAESI) included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasm, and wheezing.[2]

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

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

ENCOURAGE (TRIAL 661-114)

Patients with CF age 12 years and older who are homozygous for *F508del* mutation and who previously discontinued lumacaftor/ivacaftor due to respiratory adverse events (cont)

Endpoints	• Primary endpoint[2] — Incidence of respiratory adverse events of special interest (please see page 14)* • Key secondary endpoint[2] — Absolute change in ppFEV$_1$ from baseline to the average of the Day 28 and Day 56 measurements (please see page 18) • Secondary endpoints[2,10] — Relative change in ppFEV$_1$ from baseline to the average of the Day 28 and Day 56 measurements (please see page 18) — Absolute change in CFQ-R Respiratory Domain score from baseline to the average of the Day 28 and Day 56 measurements (please see page 18) — Tolerability based on study drug discontinuation through Day 56 — Safety assessments based on adverse events, clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis), vital signs, pulse oximetry, and post-dose spirometry (please see pages 14, 15, 16, and 17)

ENCOURAGE (Trial 661-114): Limitations and Disclosures

- Enrollment was limited to only those patients who met strict inclusion criteria and elected to enroll
- Hypothesis testing was not planned or performed to compare SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and placebo for efficacy results in this trial; therefore, statistical significance cannot be determined
- Trial results are not included in the approved full Prescribing Information and the FDA did not consider this study in approving SYMDEKO

*Respiratory adverse events of special interest (RAESI) included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasm, and wheezing.[2]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Primary endpoint: Incidence of respiratory adverse events

Overall rates of respiratory adverse events of special interest[2]

14.0% **of patients treated with SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) (n=7)**

21.3% **of patients treated with placebo (n=10)**

Analysis of respiratory adverse events assessed in Trial 661-114

Respiratory Events	**SYMDEKO** (N=50) Patients with events, n (%)	**Placebo** (N=47) Patients with events, n (%)
Dyspnea	5 (10.0)	5 (10.6)
Respiration abnormal	3 (6.0)	1 (2.1)
Chest discomfort	0	1 (2.1)
Asthma	0	1 (2.1)
Bronchospasm	0	2 (4.3)
Wheezing	0	2 (4.3)
Bronchial hyperreactivity	0	0

No patients had respiratory adverse events that were classified as serious or led to treatment discontinuation[2]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Safety results of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) in Trial 661-114

Discontinuations[2]

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

4.0% OF PATIENTS TREATED WITH SYMDEKO **2.1% OF PATIENTS TREATED WITH PLACEBO**

- 1 death occurred in a patient taking SYMDEKO due to sepsis and multiple organ dysfunction following influenza infection, which was not considered to be related to study drug by the investigator

Transaminase elevations[2]

- No patients experienced ALT or AST elevations >3 x ULN in Trial 661-114
  - —Note: Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Click here for Important Safety Information

Serious adverse events

- Serious adverse events occurred in 5 patients (10.0%) on SYMDEKO and 9 patients (19.1%) on placebo[2]
- Serious adverse events, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included constipation, 1 (2.0%); multiple organ dysfunction syndrome, 1 (2.0%); sepsis, 1 (2.0%); and suicidal ideation, 1 (2.0%)[10]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Safety results of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) in Trial 661-114 (cont)

Most common adverse events[2]

- Adverse events occurred in 37 patients (74.0%) on SYMDEKO and 39 patients (83.0%) on placebo

Incidence of adverse events occurring at a rate of ≥3% of patients taking SYMDEKO and greater than placebo[2,10]

Events	**SYMDEKO** (N=50) Patients with events, n (%)	**Placebo** (N=47) Patients with events, n (%)
Cough	9 (18.0)	8 (17.0)
Nasopharyngitis	6 (12.0)	0
Constipation	5 (10.0)	0
Nausea	4 (8.0)	2 (4.3)
Bacterial test positive	3 (6.0)	0
Hemoptysis	3 (6.0)	2 (4.3)
Respiration abnormal	3 (6.0)	1 (2.1)
Chronic sinusitis	2 (4.0)	1 (2.1)
Increased viscosity of bronchial secretion	2 (4.0)	1 (2.1)
Musculoskeletal chest pain	2 (4.0)	1 (2.1)
Neck pain	2 (4.0)	0
Productive cough	2 (4.0)	1 (2.1)
Pruritus	2 (4.0)	1 (2.1)
Tonsillitis	2 (4.0)	0

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Safety results of SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) in Trial 661-114 (cont)

Post-dose spirometry assessments

Absolute change in $ppFEV_1$ from pre-dose to post-dose on Day 1[2,10]			
Time point		**SYMDEKO** mean (SD)	**Placebo** mean (SD)
DAY 1	Pre-dose	45.1 (16.2) n=48	48.0 (18.1) n=47
DAY 1	2 hours post-dose	-0.6 (2.1) n=45	0.3 (1.9) n=43
DAY 1	4 hours post-dose	-0.8 (4.3) n=45	0.0 (1.9) n=43

The analysis included all patients who had a non-missing assessment at the pre-dose time point and at least 1 non-missing post-dose assessment.[10]

- During initiation of treatment, 1 patient (2.2%) on SYMDEKO experienced a ≥20% absolute decline in $ppFEV_1$ 4 hours post-dose on Day 1[10]

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

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Results for key and other secondary efficacy endpoints

Results for absolute and relative change in ppFEV$_1$[2]

KEY SECONDARY ENDPOINT

2.7 PERCENTAGE POINTS TREATMENT DIFFERENCE VS PLACEBO in absolute change in ppFEV$_1$ from baseline to the average of the Day 28 and Day 56 measurements (95% CI: 1.0, 4.4)

SECONDARY ENDPOINT

6.7 PERCENT TREATMENT DIFFERENCE VS PLACEBO in relative change in ppFEV$_1$ from baseline to the average of the Day 28 and Day 56 measurements (95% CI: 2.5, 10.9)

Results for CFQ-R Respiratory Domain score[2]

SECONDARY ENDPOINT

1.1 POINT MEAN TREATMENT DIFFERENCE VS PLACEBO in absolute change in CFQ-R Respiratory Domain score from baseline to the average of the Day 28 and Day 56 measurements (95% CI: -4.9, 7.0)

- The mean score was 5.7 points for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and 4.7 points for placebo

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.[6]

Hypothesis testing was not planned or performed to compare SYMDEKO and placebo for efficacy results in this trial; therefore, statistical significance cannot be determined

IMPORTANT SAFETY INFORMATION

Pediatric Use

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

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

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

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

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Consider SYMDEKO for patients with CF age 12 years and older who are homozygous for the *F508del* mutation

IMPORTANT SAFETY INFORMATION

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
- The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3

For more information, visit **SYMDEKOhcp.com**.

References: 1. SYMDEKO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; June 2019. **2.** Schwarz C, Sutharsan S, Epaud R, et al. Safety, efficacy, and tolerability of tezacaftor/ivacaftor in cystic fibrosis patients who previously discontinued lumacaftor/ivacaftor due to respiratory adverse events: a randomized, double-blind, placebo-controlled phase 3b study. Poster presented at: Deutsche Mukoviszidose Tagung (DMT) Conference; November 22-24, 2018; Würzburg, Germany. **3.** Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del. *N Engl J Med.* 2017;377(21):2013-2023. **4.** Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del. *N Engl J Med.* 2017;377(21) (suppl1-29):2013-2023. **5.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0258; 2019. **6.** Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic pseudomonas aeruginosa airway infection. *Chest*. 2009;135(6):1610-1618. **7.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0547 (v2.0); 2017. **8.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-0004 (v2.0); 2019. **9.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-HQ-88-00227; 2018. **10.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. US-23-1800043; 2018.

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

VERTEX®