SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
SYMDEKO 50 mg/75 mg & 75 mg
SYMDEKO 100 mg/150 mg & 150 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
SYMDEKO 50 mg/75 mg & 75 mg
Tezacaftor/Ivacaftor tablet:
Each film-coated tablet contains 75 mg ivacaftor and 50 mg tezacaftor.

Ivacaftor tablet:
Each film-coated tablet contains 75 mg ivacaftor.

Excipients with known effect:
Each Ivacaftor film-coated tablet contains 83.6 mg of lactose.

SYMDEKO 100 mg/150 mg & 150 mg
Tezacaftor/Ivacaftor tablet:
Each film-coated tablet contains 150 mg ivacaftor and 100 mg tezacaftor.

Ivacaftor tablet:
Each film-coated tablet contains 150 mg ivacaftor.

Excipients with known effect:
Each Ivacaftor film-coated tablet contains 167.2 mg of lactose.

For the full list of excipients, *[see Description (12)]*.

3 PHARMACEUTICAL FORM
Film-coated tablets

SYMDEKO 50 mg/75 mg & 75 mg
Tezacaftor/ivacaftor tablet:
White film-coated tablet, debossed with "V 50" on one face.

Ivacaftor tablet:
Light blue capsule-shaped tablet printed with "V 75" in black ink on one face.

SYMDEKO 100 mg/150 mg & 150 mg
Tezacaftor/ivacaftor tablet:
Yellow film-coated tablet, debossed with "V 100" on one face.

Ivacaftor tablet:
Light blue capsule-shaped tablet printed with "V 150" in black ink on one face.

4 THERAPEUTIC INDICATION
SYMDEKO is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 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 *[see Clinical Pharmacology (13.1)]*.

If the patient's genotype is unknown, a health authority 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.

5 DOSAGE AND ADMINISTRATION
5.1 General Dosage Information
Swallow the tablets whole.
SYMDEKO should be taken with fat-containing food, such as food recommended in standard nutritional guidelines. 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, etc. *[see Clinical Pharmacology (13.3)]*.

5.2 Recommended Dosage in Adults, Adolescents, and Children Aged 6 Years and Older
Adults, adolescents, and children aged 6 years and older should be dosed according to Table 1. The morning and the evening doses should be taken approximately 12 hours apart.

Table 1: Recommended Dosage for Patients Aged 6 Years and Older

Age	Morning (one tablet)	Evening (one tablet)
6 to <12 years weighing <30 kg	tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 75 mg
6 to <12 years weighing ≥30 kg	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg
≥12 years	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

Information for Missed Doses:
If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule. If more than 6 hours have passed since the missed morning or evening dose, the patient should not take the missed dose. The next scheduled dose can be taken at the usual time. More than one dose should not be taken at the same time.

5.3 Recommended Dosage for Patients with Hepatic Impairment
For dosage adjustment for patients with hepatic impairment, refer to Table 2.
Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure of tezacaftor and ivacaftor is expected to be higher than in patients with moderate hepatic impairment. Therefore, SYMDEKO should be used with caution at an adjusted dosage after weighing the risks and benefits of treatment in these patients *[see Use in Specific Populations (10.5) and Clinical Pharmacology (13.3)]*.

Table 2: Recommended Dosage for Patients with Hepatic Impairment

Hepatic Impairment	Morning		Evening
	Patients Aged 6 to <12 Years Weighing <30 kg	Patients Aged 6 to <12 Years Weighing ≥30 kg and Patients Age ≥12 Years	All Patients
Mild (Child-Pugh Class A)	No dose adjustment	No dose adjustment	No dose adjustment
Moderate (Child-Pugh Class B)	One tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily	No ivacaftor dose
Severe (Child-Pugh Class C)	One tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily (or less frequently)	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily (or less frequently)	

5.4 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors
The dosing regimen of SYMDEKO should be adjusted when co-administered with moderate and strong CYP3A inhibitors.

Moderate CYP3A inhibitors:
When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin), the dosing regimen should be adjusted as in Table 3 *[see Drug Interactions (9.2) and Clinical Pharmacology (13.3)]*.

Table 3: Dosing Schedule for Concomitant Use of SYMDEKO with Moderate CYP3A Inhibitors

	Day 1	Day 2	Day 3	Day 4*
Patients Aged 6 to <12 Years Weighing <30 kg				
Morning				
Tezacaftor 50 mg/ivacaftor 75 mg tablet	✓	-	✓	-
Ivacaftor 75 mg tablet	-	✓	-	✓
Evening				
Ivacaftor 75 mg tablet	-	-	-	-
Patients Aged 6 to <12 Years Weighing ≥30 kg and Patients Age ≥12 Years				
Morning				
Tezacaftor 100 mg/ivacaftor 150 mg tablet	✓	-	✓	-
Ivacaftor 150 mg tablet	-	✓	-	✓
Evening				
Ivacaftor 150 mg tablet	-	-	-	-

* Continue dosing with tezacaftor/ivacaftor or ivacaftor tablets on alternate days.

Strong CYP3A inhibitors:
When co-administered with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dosing regimen should be adjusted as in Table 4 *[see Drug Interactions (9.2) and Clinical Pharmacology (13.3)]*.

Table 4: Dosing Schedule for Concomitant Use of SYMDEKO with Strong CYP3A Inhibitors

	Day 1	Day 2 and Day 3	Day 4*
Patients Aged 6 to <12 Years Weighing <30 kg			
Morning			
Tezacaftor 50 mg/ivacaftor 75 mg tablet	✓	-	✓
Evening†			
Ivacaftor 75 mg tablet	-	-	-
Patients Aged 6 to <12 Years Weighing ≥30 kg and Patients Age ≥12 Years			
Morning			
Tezacaftor 100 mg/ivacaftor 150 mg tablet	✓	-	✓
Evening†			
Ivacaftor 150 mg tablet	-	-	-

* Continue dosing with tezacaftor/ivacaftor tablets twice a week, taken approximately 3 to 4 days apart.
† The evening dose of ivacaftor should not be taken on any day.

Food or drink containing grapefruit should be avoided during treatment with SYMDEKO *[see Drug Interactions (9.2)]*.

6 CONTRAINDICATIONS
Hypersensitivity to the active substances or to any of the excipients *[see Description (12)]*.

7 WARNINGS AND PRECAUTIONS
7.1 Transaminase (AST/ALT) Elevations
Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended for all patients 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. In the event of significant elevations of transaminases, e.g., patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment *[see Adverse Reactions (8)]*.

7.2 Hypersensitivity Reactions, Including Anaphylaxis
Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the postmarketing setting *[see Adverse Reactions (8.2)]*. 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.

7.3 Intracranial Hypertension
Cases of intracranial hypertension (IH) have been reported in the postmarketing setting with the use of drugs containing the same or similar active ingredients as SYMDEKO *[see Adverse Reactions (8.2)]*. Clinical manifestations of IH include headache, blurred vision, diplopia, and potential vision loss; papilledema can be found on fundoscopy. If an unusual headache or visual disturbances occur during treatment, and IH is suspected, interrupt SYMDEKO and refer for prompt medical evaluation. Consider the benefits and risks for the individual patient to determine whether to resume treatment with SYMDEKO. Patients should be monitored until IH resolution and for recurrence. Patients with elevated vitamin A levels may be at increased risk.

7.4 Concomitant Use with CYP3A Inducers
Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by the concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Therefore, co-administration with strong CYP3A inducers is not recommended *[see Drug Interactions (9.1) and Clinical Pharmacology (13.3)]*.

7.5 Cataracts
Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with SYMDEKO cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO *[see Use in Specific Populations (10.3)]*.

8 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Transaminase Elevations *[see Warnings and Precautions (7.1)]*
- Hypersensitivity Reactions, Including Anaphylaxis *[see Warnings and Precautions (7.2)]*
- Intracranial Hypertension *[see Warnings and Precautions (7.3)]*
- Cataracts *[see Warnings and Precautions (7.5)]*

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

The overall safety profile of SYMDEKO is based on data from 1001 patients in three double-blind, placebo-controlled, clinical trials: two parallel-group trials of 12 and 24-week duration and one cross-over design trial of 8 weeks duration. Eligible patients were also able to participate in an open-label extension safety study (up to 96 weeks of SYMDEKO). In the three placebo-controlled trials (Trials 1, 2, and 3), 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 reactions was 1.6% for SYMDEKO-treated patients and 2.0% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in SYMDEKO-treated patients compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) SYMDEKO-treated patients vs. 0 placebo. There were no deaths in the placebo-controlled trials, and one death in the open-label extension study due to respiratory failure and influenza infection in a patient who had discontinued SYMDEKO seven weeks prior.

The safety profile of SYMDEKO was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Table 5 shows adverse reactions occurring in ≥3% of SYMDEKO-treated patients that also occurred at a higher rate than in the placebo-treated patients in the 12- and 24-week placebo-controlled, parallel-group trials (Trials 1 and 3).

Table 5: Incidence of Adverse Drug Reactions in ≥3% of SYMDEKO-Treated Patients and Greater than Placebo

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 data from the following trials are similar to that observed in Trials 1 and 3:

- an 8-week randomized, double-blind, placebo-controlled crossover study in 244 patients with CF aged 12 years and older who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (Trial 2).
- a 24-week open-label study in 70 patients with CF aged 6 to less than 12 years who were either homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (Trial 4).

Laboratory abnormalities

Transaminase elevations

During the placebo-controlled trials in patients aged 12 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the upper limit of normal (ULN) was similar between SYMDEKO-treated patients and placebo-treated patients; 0.2%, 1.0%, and 3.4% in SYMDEKO-treated patients, and 0.4%, 1.0%, and 3.4% in placebo-treated patients. One patient (0.2%) on SYMDEKO and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. No SYMDEKO-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

During the 24-week, open-label study in patients aged 6 to less than 12 years (Trial 4), the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 x ULN were 1.4%, 4.3%, and 10.0%, respectively. No SYMDEKO-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN or discontinued SYMDEKO treatment due to transaminase elevations.

8.2 Postmarketing Experience

Postmarketing Adverse Reactions with SYMDEKO

The following adverse reactions have been identified during post approval use of SYMDEKO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: anaphylaxis
Skin: rash

Postmarketing Adverse Reactions with Other Drugs Containing the Same or Similar Active Ingredients as SYMDEKO

The following adverse reactions have been identified during post approval use of drugs containing the same or similar active ingredients as SYMDEKO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders: intracranial hypertension

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form. https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

Potential for other drugs to affect tezacaftor/ivacaftor

9.1 Inducers of CYP3A

Tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced SYMDEKO efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (area under the curve [AUC]) by 89%. Tezacaftor exposures can also be expected to decrease significantly during co-administration with strong CYP3A inducers. Therefore, co-administration of SYMDEKO with strong CYP3A inducers is not recommended *[see Warnings and Precautions (7.4) and Clinical Pharmacology (13.3)]*.

Examples of strong CYP3A inducers include:

- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

9.2 Inhibitors of CYP3A

Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (AUC) by 4.0-fold and ivacaftor by 15.6-fold. When co-administered with strong CYP3A inhibitors, the dosing regimen of SYMDEKO should be adjusted *[see Dosage and Administration (5.4) and Clinical Pharmacology (13.3)]*.

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Co-administration of fluconazole increased ivacaftor exposure (AUC) by 3.0-fold. Simulation suggested co-administration with fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor exposure (AUC) by approximately 2.0-fold. When co-administered with moderate CYP3A inhibitors, the dosing regimen of SYMDEKO should be adjusted *[see Dosage and Administration (5.4) and Clinical Pharmacology (13.3)]*.

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

Co-administration of SYMDEKO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of tezacaftor and ivacaftor; therefore, food or drink containing grapefruit should be avoided during treatment with SYMDEKO *[see Dosage and Administration (5.4) and Clinical Pharmacology (13.3)]*.

9.3 Ciprofloxacin
Co-administration of SYMDEKO with ciprofloxacin had no significant effect on the exposure of tezacaftor or ivacaftor. Therefore, no dosage adjustment is necessary during concomitant administration of SYMDEKO with ciprofloxacin *[see Clinical Pharmacology (13.3)]*.

Potential for tezacaftor/ivacaftor to affect other drugs

9.4 CYP3A Substrates
Co-administration of SYMDEKO with midazolam (oral), a sensitive CYP3A substrate, did not affect midazolam exposure. No dosage adjustment of CYP3A substrates is required when co-administered with SYMDEKO *[see Clinical Pharmacology (13.3)]*.

9.5 CYP2C9 Substrates
Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of SYMDEKO with warfarin is recommended. Other medicinal products for which exposure may be increased by SYMDEKO include glimepiride and glipizide; these medicinal products should be used with caution *[see Clinical Pharmacology (13.3)]*.

9.6 Digoxin and Other P-gp Substrates
Co-administration of SYMDEKO with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold consistent with weak inhibition of P-gp by ivacaftor. Administration of SYMDEKO may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used *[see Clinical Pharmacology (13.3)]*.

9.7 Hormonal Contraceptives
SYMDEKO has been studied with an ethinyl estradiol/norethindrone oral contraceptive and was found to have no significant effect on the exposures of the hormonal contraceptive. SYMDEKO is not expected to modify the efficacy of hormonal contraceptives *[see Clinical Pharmacology (13.3)]*.

10 USE IN SPECIFIC POPULATIONS
10.1 Pregnancy
Risk Summary
There are limited and incomplete human data from clinical trials and postmarketing reports on the use of SYMDEKO or its individual components, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk. Although there are no animal reproduction studies with the concomitant administration of tezacaftor and ivacaftor, separate reproductive and developmental studies were conducted with tezacaftor and ivacaftor in pregnant rats and rabbits. In animal reproduction studies, oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the maximum recommended human dose (MRHD) in rats and 0.2 times the MRHD in rabbits (based on summed AUCs for tezacaftor and M1 metabolite). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 6 and 16 times the exposure at the MRHD, respectively. No adverse developmental effects were observed after oral administration of either tezacaftor or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 1 and 4 times the exposures at the MRHD, respectively (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
Tezacaftor
In an embryo fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 3 times the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at maternal oral doses up to 100 mg/kg/day). In an embryo fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 0.2 times the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at maternal oral doses up to 25 mg/kg/day). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 1 time the MRHD (at a maternal dose of 50 mg/kg/day). In a pre- and postnatal development (PPND) study in pregnant rats dosed from gestation Day 6 through lactation Day 18, tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening, and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 2 times the exposure at the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at a maternal oral dose of 50 mg/kg/day). Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor
In an embryo fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7-17, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 6 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at a maternal oral dose of 200 mg/kg/day). In an embryo fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-19, ivacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 16 times the MRHD (on an ivacaftor AUC basis at maternal oral doses up to 100 mg/kg/day). In a PPND study in pregnant rats dosed from gestation Day 7 through lactation Day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 4 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 6 times the MRHD. Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

10.2 Lactation

Risk Summary

There is no information regarding the presence of tezacaftor or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Both tezacaftor and ivacaftor are excreted into the milk of lactating rats (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYMDEKO and any potential adverse effects on the breastfed child from SYMDEKO or from the underlying maternal condition.

Data

Tezacaftor

Lacteal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C-tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-tezacaftor in milk was approximately 3 times higher than in plasma (based on $AUC_{0\text{-}72h}$).

Ivacaftor

Lacteal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ^{14}C-ivacaftor in milk was approximately 1.5 times higher than in plasma (based on $AUC_{0\text{-}24h}$).

10.3 Pediatric Use

The safety and effectiveness of SYMDEKO for the treatment of CF have been established in pediatric patients aged 6 to less than 18 years who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence *[see Clinical Pharmacology (13.1) and Clinical Studies (15)]*.

Clinical trials included the following patients with CF:

- 12 to less than 18 years of age who are homozygous for the *F508del* mutation *[see Adverse Reactions (8) and Clinical Studies (15)]*.
- 12 to less than 18 years of age who are heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor *[see Adverse Reactions (8) and Clinical Studies (15)]*.
- 6 to less than 12 years of age who are either homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor *[see Adverse Reactions (8) and Clinical Pharmacology (13)]*.

The effectiveness of SYMDEKO in patients aged 6 to less than 12 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing similar tezacaftor and ivacaftor exposure levels in patients aged 6 to less than 12 years and in patients aged 12 years and older *[see Clinical Pharmacology (13.3)]*. Safety of SYMDEKO in this population was derived from a 24-week, open-label, clinical trial in 70 patients aged 6 to less than 12 years
(mean age at screening 8.1 years) administered either tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 75 mg or tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg, 12 hours apart (Trial 4). The safety profile for patients in this trial was similar to that observed in Trials 1 and 3 *[see Adverse Reactions (8.1)]*.

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

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.25 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals.

10.4 Geriatric Use

Clinical trials of SYMDEKO did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

10.5 Hepatic Impairment

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dosage of SYMDEKO is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There is no experience in patients with severe hepatic impairment (Child-Pugh Class C), but tezacaftor/ivacaftor exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a reduced dosage in patients with severe hepatic impairment after weighing the risks and benefits of treatment *[see Dosage and Administration (5.3) and Clinical Pharmacology (13.3)]*.

10.6 Renal Impairment

SYMDEKO has not been studied in patients with moderate or severe renal impairment or in patients with end-stage renal disease. No dosage adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment or end-stage renal disease *[see Clinical Pharmacology (13.3)]*.

10.7 Patients with Severe Lung Dysfunction

Trial 1 and Trial 2 included a total of 39 SYMDEKO-treated patients with $ppFEV_1$ <40 at baseline (range: 30-40); 23 patients in Trial 1 and 16 patients in Trial 2. There were 24 placebo-treated patients in Trial 1, and 15 placebo- and 13 ivacaftor-treated patients in Trial 2, with $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to the overall results observed in both Trials 1 and 2.

11 OVERDOSAGE

No specific antidote is available for overdose with SYMDEKO. Treatment of overdosage consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

12 DESCRIPTION

SYMDEKO is co-packaged as a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet. Both tablets are for oral administration.

Tezacaftor 50 mg/ivacaftor 75 mg fixed-dose combination tablets and ivacaftor 75 mg tablets:

The tezacaftor/ivacaftor fixed-dose combination tablet is available as a white film-coated tablet containing 50 mg of tezacaftor, 75 mg of ivacaftor, and the following inactive ingredients: microcrystalline cellulose, hypromellose acetate succinate (HPMCAS), croscarmellose sodium, hypromellose (HPMC), magnesium stearate and sodium lauryl sulfate. The tablet film coat contains opadry white 20A180008 (HPMC 2910/hypromellose, hydroxypropyl cellulose, talc and titanium dioxide).

The ivacaftor tablet is available as a light blue, capsule-shaped, film-coated tablet containing 75 mg of ivacaftor and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide and sodium lauryl sulfate. The

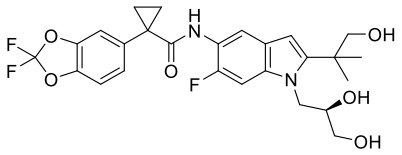
tablet film coat contains opadry II (blue) 85F105098 (polyvinyl alcohol, titanium dioxide, PEG 3350, talc, FD&C Blue #2/Indigo Carmine Aluminum Lake) and carnauba wax. The printing ink contains opacode black s-1-17823 (shellac, iron oxide black, propylene glycol and ammonium hydroxide).

Tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablets and ivacaftor 150 mg tablets:
The tezacaftor/ivacaftor fixed-dose combination tablet is available as a yellow film-coated tablet containing 100 mg of tezacaftor, 150 mg of ivacaftor, and the following inactive ingredients: microcrystalline cellulose, hypromellose acetate succinate (HPMCAS), croscarmellose sodium, hypromellose (HPMC), magnesium stearate and sodium lauryl sulfate. The tablet film coat contains opadry yellow (HPMC/hypromellose 2910, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow).

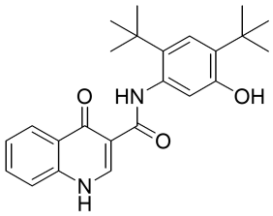
The ivacaftor tablet is available as a light blue, capsule-shaped, film-coated tablet containing 150 mg of ivacaftor and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide and sodium lauryl sulfate. The tablet film coat contains opadry II (blue) 85F90614 (polyvinyl alcohol, titanium dioxide, PEG 3350, talc, FD&C Blue #2/indigo carmine aluminum lake) and carnauba wax. The printing ink contains opacode black s-1-17823 (shellac, isopropyl alcohol, iron oxide black, propylene glycol, ammonium hydroxide).

The active ingredients of SYMDEKO are described below.

Tezacaftor
Tezacaftor is a white to off-white solid that is practically insoluble in water (<5 microgram/mL). Its chemical name of tezacaftor is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is $C_{26}H_{27}N_2F_3O_6$ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Ivacaftor
Ivacaftor is a white to off-white crystalline solid that is practically insoluble in water (<0.05 microgram/mL). Pharmacologically it is a CFTR potentiator. Its chemical name is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



13 CLINICAL PHARMACOLOGY
13.1 Mechanism of Action
Tezacaftor facilitates the cellular processing and trafficking of select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect of tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR
The chloride transport response of mutant CFTR protein to tezacaftor/ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Tezacaftor/ivacaftor increased chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

The *in vitro* chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

Note that splice site mutations cannot be studied in the FRT assay.

Table 6 lists responsive *CFTR* mutations based on (1) a clinical FEV_1 response and/or (2) *in vitro* data in FRT cells, indicating that tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline. *CFTR* gene mutations that are not responsive to ivacaftor alone are not expected to respond to SYMDEKO except for *F508del* homozygotes.

Table 6: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO					
546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
711+3A→G *	*E116K*	*G576A;R668C* †	*L967S*	*R117H*	*S737F*
2789+5G→A *	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
3272-26A→G *	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L* *
3849+10kbC→T *	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F* *
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
A455E *	*F311del*	*H939R*	*M952I*	*R347H* *	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C;S1251N* †	*I148T*	*P67L* *	*R352Q* *	*T1053I*
D110E	*F508del* ^	*I175V*	*P205S*	*R352W*	*V201M*
D110H *	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668C †	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
D579G *	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W* *	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N* †	*R1162L*	*Y161S*
D1152H *	*G194V*	*K1060T*	*R74W;V201M* †	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270N* †	*R1283S*	*Y1032C*
E56K	*G551D*	*L206W* *	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C* *	*S549R*	

* Clinical data for these mutations in Clinical Studies *[see Clinical Studies (15.1 and 15.2)]*.
^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

13.2 Pharmacodynamics

Effects on Sweat Chloride

In Trial 1 (patients aged 12 years and older who were homozygous for the *F508del* mutation), the treatment difference between SYMDEKO and placebo in mean absolute change from baseline in sweat chloride through Week 24 was -10.1 mmol/L (95% CI: -11.4, -8.8).

In Trial 2 (patients aged 12 years and older who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor), the treatment difference in mean absolute change from baseline in sweat chloride through Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between SYMDEKO and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo.

In Trial 4 (patients aged 6 to less than 12 years) a reduction in sweat chloride was observed from baseline through Week 4 and sustained throughout the 24-week treatment period. Mean absolute change in sweat chloride from baseline through Week 24 was -14.5 mmol/L (95% CI: -17.4, -11.6).

Cardiac Electrophysiology

At a dose 3 times the maximum approved recommended dose, tezacaftor does not prolong the QT interval to any clinically relevant extent.

In a separate study of ivacaftor evaluating doses up to 3 times the maximum approved recommended dose, ivacaftor does not prolong the QT interval to any clinically relevant extent.

13.3 Pharmacokinetics

The pharmacokinetics of tezacaftor and ivacaftor are similar between healthy adult volunteers and patients with CF. Following once daily dosing of tezacaftor and twice-daily dosing of ivacaftor in patients with CF, plasma concentrations of tezacaftor and ivacaftor reach steady-state within 8 days and within 3 to 5 days, respectively, after starting treatment. At steady-state, the accumulation ratio is approximately 1.5 for tezacaftor and 2.2 for ivacaftor. Exposures of tezacaftor (administered alone or in combination with ivacaftor) increased in an approximately dose-proportional manner with increasing doses from 10 mg to 300 mg once daily. Key pharmacokinetic parameters for tezacaftor and ivacaftor at steady state are shown in Table 7.

Table 7: Mean (SD) Pharmacokinetic Parameters of Tezacaftor and Ivacaftor at Steady State in Patients with CF				
	Drug	**C_{max} (mcg/mL)**	**Effective $t_{½}$ (h)**	**AUC_{0-24h} or AUC_{0-12h} (mcg·h/mL)***
Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Tezacaftor	5.95 (1.50)	15.0 (3.44)	84.5 (27.8)
	Ivacaftor	1.17 (0.424)	13.7 (6.06)	11.3 (4.60)
*AUC_{0-24h} for tezacaftor and AUC_{0-12h} for ivacaftor				

Absorption
After a single dose in healthy subjects in the fed state, tezacaftor was absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 4 hours (2 to 6 hours). The median (range) t_{max} of ivacaftor was approximately 6 hours (3 to 10 hours) in the fed state.
When a single dose of tezacaftor/ivacaftor was administered with fat-containing foods, tezacaftor exposure was similar and ivacaftor exposure was approximately 3 times higher than when taken in a fasting state.

Distribution
Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin. Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. After oral administration of tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent volume of distribution of tezacaftor and ivacaftor was 271 (157) L and 206 (82.9) L, respectively. Neither tezacaftor nor ivacaftor partition preferentially into human red blood cells.

Elimination
After oral administration of tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent clearance values of tezacaftor and ivacaftor were 1.31 (0.41) and 15.7 (6.38) L/h, respectively. After steady-state dosing of tezacaftor in combination with ivacaftor in patients with CF, the effective half-lives of tezacaftor and ivacaftor were approximately 15 (3.44) and 13.7 (6.06) hours, respectively.

Metabolism
Tezacaftor is metabolized extensively in humans. *In vitro* data suggested that tezacaftor is metabolized mainly by CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1, M2, and M5 were the three major circulating metabolites of tezacaftor in humans. M1 has the similar potency to that of tezacaftor and is considered pharmacologically active. M2 is much less pharmacologically active than tezacaftor or M1, and M5 is not considered pharmacologically active. Another minor circulating metabolite, M3, is formed by direct glucuronidation of tezacaftor.

Ivacaftor is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolized primarily by CYP3A4 and CYP3A5. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 is not considered pharmacologically active.

Excretion
Following oral administration of ^{14}C-tezacaftor, the majority of the dose (72%) was excreted in the feces (unchanged or as the M2 metabolite) and about 14% was recovered in urine (mostly as M2 metabolite), resulting in a mean overall recovery of 86% up to 21 days after the dose. Less than 1% of the administrated dose was excreted in urine as unchanged tezacaftor, showing that renal excretion is not the major pathway of tezacaftor elimination in humans.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine), and there was negligible urinary excretion of ivacaftor as unchanged drug.

Specific Populations
Based on population PK analyses, the PK exposure parameters of tezacaftor/ivacaftor in children and adolescents (aged 6 to <18 years) are similar to the AUCss range observed in adults when given in combination.

Pediatric patients aged 6 to less than 12 years

Table 8: Tezacaftor/Ivacaftor Exposure by Age Group, Mean (SD)			
Age Group	**Dose**	**tezacaftor AUCss mcg·h/mL***	**ivacaftor AUCss mcg·h/mL***
6 to <12 years ^		71.3 (28.3)	8.5 (3.34)
6 to <12 years (<30 kg)	tezacaftor 50 mg/ivacaftor 75 mg	56.7 (22.3)	6.92 (2.07)
6 to <12 years (≥30 kg) ^	tezacaftor 100 mg/ivacaftor 150 mg	92.7 (21.9)	10.8 (3.52)
^ Exposures in ≥30 kg weight range are predictions derived from the population PK model *AUC_{0-24h} for tezacaftor and AUC_{0-12h} for ivacaftor			

Pediatric patients aged 12 to less than 18 years
Following oral administration of SYMDEKO tablets, tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours, the mean (±SD) AUCss for tezacaftor and ivacaftor was 97.1 (35.8) mcg·h/mL and 11.4 (5.50) mcg·h/mL, respectively, similar to the mean AUCss in adult patients administered SYMDEKO tablets, tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours.

Patients with Hepatic Impairment
Following multiple doses of tezacaftor and ivacaftor for 10 days, patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had an approximately 36% increase in AUC and a 10% increase in C_{max} for tezacaftor, and a 1.5-fold increase in ivacaftor AUC compared with healthy subjects matched for

demographics. In a separate study, patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had similar ivacaftor C_{max}, but an approximately 2.0-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics.

Pharmacokinetic studies have not been conducted in patients with mild (Child-Pugh Class A, score 5-6) or severe hepatic impairment (Child-Pugh Class C, score 10 - 15) receiving SYMDEKO. The magnitude of increase in exposure in patients with severe hepatic impairment is unknown but is expected to be higher than that observed in patients with moderate hepatic impairment *[see Dosage and Administration (5.3) and Use in Specific Populations (10.5)]*.

Patients with Renal Impairment
SYMDEKO has not been studied in patients with moderate or severe renal impairment (creatinine clearance ≤30 mL/min) or in patients with end-stage renal disease. In a human pharmacokinetic study with tezacaftor alone, there was minimal elimination of tezacaftor and its metabolites in urine (only 13.7% of total radioactivity was recovered in the urine with 0.79% as unchanged drug).

In a human pharmacokinetic study with ivacaftor alone, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine).

In population pharmacokinetic analysis, data from 665 patients on tezacaftor or tezacaftor in combination with ivacaftor in clinical trials indicated that mild renal impairment (N=147; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N=7; eGFR 30 to less than 60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly *[see Use in Specific Populations (10.6)]*.

Male and Female Patients
The pharmacokinetic parameters of tezacaftor and ivacaftor are similar in males and females.

Drug Interactions Studies
Drug interaction studies were performed with SYMDEKO and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies *[see Drug Interactions (9)]*.

Potential for Tezacaftor/Ivacaftor to Affect Other Drugs
Clinical studies (with rosiglitazone and desipramine – see Table 9) showed that ivacaftor is not an inhibitor of CYP2C8 or CYP2D6. Based on *in vitro* results, ivacaftor has the potential to inhibit CYP3A and P-gp, and may also inhibit CYP2C9. *In vitro*, ivacaftor was not an inducer of CYP isozymes. Ivacaftor is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3.

Based on *in vitro* results, tezacaftor has a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Tezacaftor has a low potential to induce CYP3A, but it is not an inducer of CYP1A2 and CYP2B6. Tezacaftor has a low potential to inhibit transporters P-gp, BCRP, OATP1B3, OCT2, OAT1, or OAT3.

Clinical studies with midazolam showed that SYMDEKO is not an inhibitor of CYP3A. Co-administration of SYMDEKO with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold. Co-administration of SYMDEKO with an ethinyl estradiol/ norethindrone oral contraceptive had no significant effect on the exposures of the hormonal contraceptives. Co-administration of SYMDEKO with pitavastatin, an OATP1B1 substrate, had no clinically relevant effect on the exposure of pitavastatin.

The effects of tezacaftor and ivacaftor (or ivacaftor alone) on the exposure of co-administered drugs are shown in Table 9 *[see Drug Interactions (9)]*.

Potential for Other Drugs to Affect Tezacaftor/Ivacaftor
In vitro studies showed that ivacaftor and tezacaftor were substrates of CYP3A enzymes (*i.e.*, CYP3A4 and CYP3A5). Exposure to ivacaftor and tezacaftor will be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors.

In vitro studies showed that tezacaftor is a substrate for the uptake transporter OATP1B1, and efflux transporters P-gp and BCRP. Tezacaftor is not a substrate for OATP1B3. *In vitro* studies showed that ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-gp.

The effects of co-administered drugs on the exposure of tezacaftor and ivacaftor (or ivacaftor alone) are shown in Table 10 *[see Dosage and Administration (5.4) and Drug Interactions (9)]*.

Table 9: Impact of Tezacaftor/Ivacaftor or Ivacaftor on Other Drugs					
	Dose and Schedule			Mean Ratio (90% CI) of Other Drugs No Effect=1.0	
Drug	**Dose**	**TEZ/IVA or IVA**	**Effect on Drug PK**	**AUC**	**C_{max}**
Midazolam	2 mg single oral dose	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin	0.5 mg single dose	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive	Ethinyl estradiol/ Norethindrone 0.035 mg/1.0 mg once daily	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Ethinyl estradiol	1.12 (1.03, 1.22)	1.15 (0.99, 1.33)
			↔ Norethindrone	1.05 (0.98, 1.12)	1.01 (0.87, 1.19)
Pitavastatin	2 mg single dose	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↑ Pitavastatin*	1.24 (1.17, 1.31)	0.977 (0.841, 1.14)
Rosiglitazone	4 mg single oral dose	IVA 150 mg twice daily	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine	50 mg single dose	IVA 150 mg twice daily	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939, 1.07)

↑=increase, ↓=decrease, ↔=no change. CI=Confidence interval; TEZ=tezacaftor; IVA=ivacaftor; PK=Pharmacokinetics
* Effect is not clinically significant– no dosage adjustment is necessary

Table 10: Impact of Other Drugs on Tezacaftor/Ivacaftor or Ivacaftor					
	Dose and Schedule			Mean Ratio (90% CI) of Tezacaftor and Ivacaftor No Effect=1.0	
Drug	**Dose**	**TEZ/IVA or IVA**	**Effect on TEZ/IVA PK**	**AUC**	**C_{max}**
Itraconazole	200 mg twice a day on Day 1, followed by 200 mg once daily	TEZ 25 mg + IVA 50 mg once daily	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
			↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Ciprofloxacin	750 mg twice daily	TEZ 50 mg + IVA 150 mg twice daily	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
			↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Oral Contraceptive	Norethindrone/ethinyl estradiol 1.0 mg/0.035 mg once daily	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Tezacaftor	1.01 (0.963, 1.05)	1.01 (0.933, 1.09)
			↔ Ivacaftor	1.03 (0.960, 1.11)	1.03 (0.941, 1.14)
Rifampin	600 mg once daily	IVA 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole	400 mg single dose on Day 1, followed by 200 mg once daily	IVA 150 mg twice daily	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)

↑=increase, ↓=decrease, ↔=no change. CI=Confidence interval; TEZ=tezacaftor; IVA=ivacaftor; PK=Pharmacokinetics
*Effect is not clinically significant – no dosage adjustment is necessary

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of tezacaftor and ivacaftor, however, separate studies of tezacaftor and ivacaftor are described below.

Tezacaftor

A 2-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 2 and 3 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1 metabolite).

Ivacaftor
Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 9 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 9 and 6 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 6 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 6 and 4 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites).

15 CLINICAL STUDIES

Dose Ranging:
Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF (homozygous for the *F508del* mutation) 18 years of age and older with a screening $ppFEV_1 \geq 40$. In the study, 34 and 106 patients, respectively, received tezacaftor at once daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean $ppFEV_1$ change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily.

Efficacy:
The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three double-blind, placebo-controlled trials (Trials1, 2, and 3).

Trial 1 was a 24-week randomized, double-blind, placebo-controlled, two-arm study in patients with CF who were homozygous for the *F508del* mutation in the *CFTR* gene.

Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in patients with CF who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and *in vitro* responsiveness to tezacaftor/ivacaftor *[see Clinical Studies (15.2)]*. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo.

Trial 3 was a 12-week randomized, double-blind, placebo-controlled, two-arm study in patients with CF who were heterozygous for the *F508del* mutation and a second *CFTR* mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and *in vitro* testing to tezacaftor and/or ivacaftor.

Patients in all trials continued on their standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline) and were eligible to roll over into a 96-week open-label extension. Patients had a $ppFEV_1$ at screening between 40-90%. Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 2 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, were excluded from the trials.

15.1 Trial in Patients with CF Who Were Homozygous for the *F508del* Mutation in the *CFTR* Gene (Trial 1)

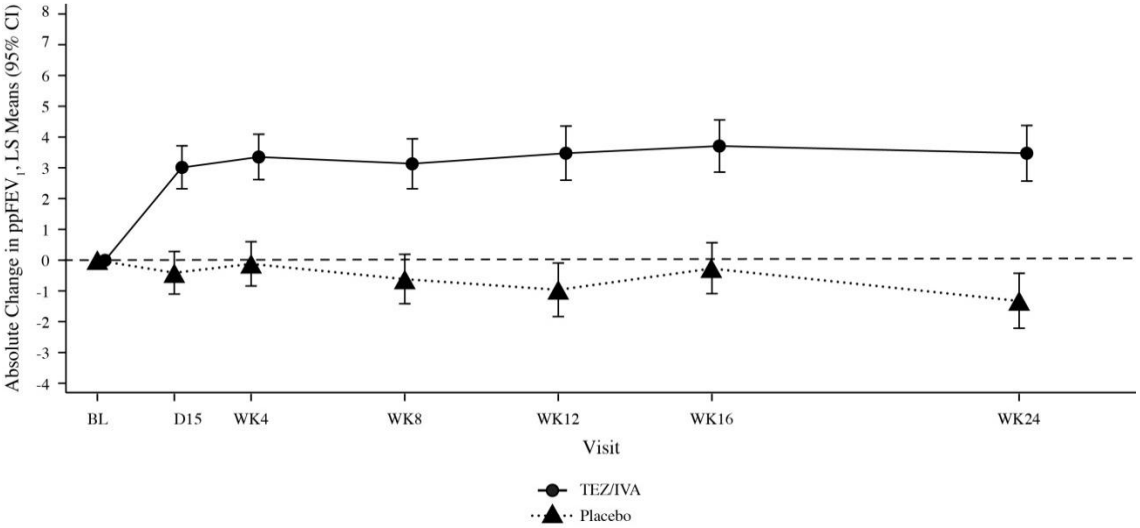
Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean $ppFEV_1$ at baseline was 60.0% (range: 27.8% to 96.2%). The primary efficacy endpoint was change in lung function as determined by absolute change from baseline in $ppFEV_1$ through Week 24. Treatment with SYMDEKO resulted in a statistically significant improvement in $ppFEV_1$. The treatment difference between SYMDEKO and placebo for the mean absolute change in $ppFEV_1$ from baseline through Week 24 was 4.0 percentage points (95% CI: 3.1, 4.8; $P<0.0001$). These changes persisted throughout the 24-week treatment period (see Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region.

Key secondary efficacy variables included 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 CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production, and difficulty breathing) from baseline through Week 24. For the purposes of this trial, 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. See Table 11 for a summary of key secondary outcomes in Trial 1.

Table 11: Key Secondary Efficacy Analyses, Full Analysis Set (Trial 1)*			
		Placebo N=256	**SYMDEKO N=248**
Relative change in $ppFEV_1$ from baseline through Week 24 (%)	Treatment difference (95% CI) *P* value	- NA	6.8 (5.3, 8.3) *P*<0.0001‡
Number of pulmonary exacerbations from baseline through Week 24	Number of events (event rate per year†) Rate ratio (95% CI) *P* value	122 (0.99) NA	78 (0.64) 0.65 (0.48, 0.88) *P*=0.0054‡
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI)	-	0.06 (-0.08, 0.19)
Absolute change in CFQ-R Respiratory Domain Score from baseline through Week 24 (points)	Treatment difference (95% CI)	-	5.1 (3.2, 7.0)

BMI: body mass index; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; IVA: ivacaftor; NA: not applicable; $ppFEV_1$: percent predicted forced expiratory volume in 1 second;
*A hierarchical testing procedure was performed for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.05$ and all previous tests also meeting this level of significance were required for statistical significance.
‡ Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures considered not statistically significant.
† Estimated event rate per year calculated using 48 weeks per year.

Figure 1: Absolute Change From Baseline in Percent Predicted FEV_1 at Each Visit in Trial 1



15.2 Trial in Patients with CF Who Were Heterozygous for the *F508del* Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 2)

Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean $ppFEV_1$ at baseline was 62.3% (range: 34.6 to 93.5). Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. 161 patients received SYMDEKO, 156 patients received ivacaftor, and 161 patients received placebo. The primary efficacy endpoint was the mean absolute change from study baseline in percent predicted FEV_1 averaged at Weeks 4 and 8 of treatment. The key secondary efficacy endpoint was absolute change in CFQ-R Respiratory Domain Score from study baseline averaged at Weeks 4 and 8 of treatment. For the overall population, treatment with SYMDEKO compared to placebo resulted in significant improvement in $ppFEV_1$ (6.8 percentage points [95% CI: 5.7, 7.8]; *P*<0.0001) and CFQ-R Respiratory Domain Score (11.1 points (95% CI: 8.7, 13.6); *P*<0.0001). Treatment difference for $ppFEV_1$ between ivacaftor- and placebo-treated patients was 4.7 percentage points (95% CI: 3.7, 5.8; *P*<0.0001) and 2.1 percentage points (95% CI: 1.2, 2.9; *P*<0.0001) between SYMDEKO- and ivacaftor-treated patients, which were statistically significant. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, mutation class, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (see Table 12).

Table 12: Effect of SYMDEKO for Efficacy Variables in Splice and Missense CFTR Mutation Subgroups			
Mutation (n)	**Absolute Change in percent predicted FEV_1*†**	**Absolute Change in CFQ-R Respiratory Domain Score (Points)*‡**	**Absolute Change in Sweat Chloride (mmol/L)*‡**
Splice mutations (n= 93 for TEZ/IVA, n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	7.4 (6.0, 8.7)	9.5 (6.3, 12.7)	-5.4 (-8.0, -2.7)
By individual splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
2789+5G→A (25)	8.6 (-1.5, 23.4)	12.0 (-8.3, 38.9)	-3.2 (-16.5, 9.0)
3272-26A→G (23)	5.7 (-2.1, 25.9)	5.7 (-22.2, 44.4)	-3.8 (-22.3, 16.5)
3849+10kbC→T (43)	5.8 (-7.2, 22.3)	8.2 (-25.0, 47.2)	-5.6 (-27.0, 8.5)

Table 12: Effect of SYMDEKO for Efficacy Variables in Splice and Missense CFTR Mutation Subgroups			
Mutation (n)	**Absolute Change in percent predicted FEV_1[*†]**	**Absolute Change in CFQ-R Respiratory Domain Score (Points)[*‡]**	**Absolute Change in Sweat Chloride (mmol/L)[*‡]**
711+3A→G (2)	4.3 (2.0, 6.7)	-4.2 (-5.6, -2.8)	-15.4 (-21.0, -9.8)
E831X[§] (0)	NA	NA	NA
Missense mutations (n=66 for TEZ/IVA, n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	5.9 (4.2, 7.5)	13.4 (9.6, 17.3)	-16.3 (-19.7, -12.9)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
D579G (2)	8.1 (-0.2, 16.4)	11.1 (5.6, 16.7)	-23.1 (-24.8, -21.5)
D110H (1)	-1.0 (-1.0, -1.0)	-11.1 (-11.1, -11.1)	-22.5 (-22.5, -22.5)
D1152H (21)	3.8 (-2.5, 12.5)	15.2 (-8.3, 55.6)	-4.1 (-15.0, 11.5)
A455E (11)	8.5 (2.6, 16.1)	11.6 (-11.1, 44.4)	-0.3 (-8.8, 14.0)
L206W (4)	3.0 (-4.5, 10.2)	12.5 (-2.8, 38.9)	-36.1 (-44.5, -27.5)
P67L (11)	9.4 (0.0, 31.9)	11.7 (-12.5, 72.2)	-29.3 (-50.0, 0.8)
R1070W (2)	6.1 (2.0, 10.1)	29.2 (16.7, 41.7)	-13.8 (-26.8, -0.8)
R117C (1)	2.9 (2.9, 2.9)	16.7 (16.7, 16.7)	-38.8 (-38.8, -38.8)
R347H (2)	-0.5 (-2.8, 1.7)	5.6 (-5.6, 16.7)	-13.8 (-19.0, -8.5)
R352Q (2)	4.9 (2.6, 7.1)	8.3 (8.3, 8.3)	-43.3 (-49.8, -36.8)
S945L (7)	9.6 (0.7, 19.5)	11.3 (-4.2, 25.0)	-29.0 (-42.5, -8.0)
S977F (2)	10.1 (5.5, 14.7)	-1.4 (-8.3, 5.6)	-13.9 (-22.3, -5.5)

(n=) patient numbers analysed
[*]Average of Week 4 and 8 values
[†]Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
[‡]Absolute change in CFQ-R Respiratory Domain Score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.
[§]Patients enrolled did not receive tezacaftor/ivacaftor treatment.

In an analysis of BMI at Week 8, an exploratory endpoint, patients treated with SYMDEKO had a mean improvement of 0.2 kg/m^2 (95% CI [0.0, 0.3], 0.1 kg/m^2 (95% CI [-0.1, 0.3], and 0.3 kg/m^2 (95% CI [0.1, 0.5]) versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

15.3 Trial in Patients with CF Who Were Heterozygous for the *F508del* Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 3)

Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.1 years) who were heterozygous for the *F508del* mutation and had a second *CFTR* mutation predicted to be unresponsive to tezacaftor/ivacaftor. CF patients with the *F508del* mutation and one of the following mutations in the *CFTR* gene were enrolled in the study (listed in decreasing frequency): *W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, CFTRdele2,3*, *2183delAA>G*, *2184insA*, *R1162X*, *R553X, 3659delC, 3905insT, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1.6kbA>G, 2184delA, 405+1G>A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G>A, 1677delTA, 1812-1G>A, 2869INSG, 3120+1G>A, 394delTT, 457TAT>G, 711+1G>T, 711+5G>A, 712-1G>T, G673x, L1065P, Q220X, Q493X, R709X, V520F.* The mean $ppFEV_1$ at baseline was 57.5% (range: 31.0 to 96.7). The primary efficacy endpoint was changed from baseline in absolute $ppFEV_1$ through Week 12. The overall treatment difference between SYMDEKO and placebo for the mean absolute change in $ppFEV_1$ from baseline through Week 12 was 1.2 percentage points (95% CI: -0.3, 2.6). This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMDEKO (tezacaftor 50 mg/ivacaftor 75 mg fixed-dose combination tablets co-packaged with ivacaftor 75 mg tablet):
Tezacaftor 50 mg/ivacaftor 75 mg fixed-dose combination tablets are supplied as white film-coated tablets containing 50 mg of tezacaftor and 75 mg of ivacaftor. Each tablet is debossed with “V50” on one face. Ivacaftor 75 mg tablets are supplied as light blue capsule-shaped tablets containing 75 mg of ivacaftor. Each tablet is printed with “V 75” on one face.

SYMDEKO (tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablets co-packaged with ivacaftor 150 mg tablet):
Tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablets are supplied as yellow film-coated tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor. Each tablet is debossed with “V100” on one face. Ivacaftor 150 mg tablets are supplied as light blue, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with “V 150” on one face.

Each of the strengths of SYMDEKO is available in a pack containing 56 film-coated tablets. The tablets are packaged in 4 blisters. Each blister contains 14 tablets (7 tezacaftor/ivacaftor and 7 ivacaftor tablets).

Store below 25ºC.

The expiry date of the product is indicated on the packaging materials.

17 MANUFACTURER

Vertex Pharmaceuticals Inc.
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18 LICENSE HOLDER

Vertex Pharmaceuticals (Europe) Limited Israel Branch
7 Rival St., Tel Aviv – Yafo, 6777840, Israel

19 REGISTRATION NUMBER

SYMDEKO 50 mg/75 mg & 75 mg: 167-05-36310

SYMDEKO 100 mg/150 mg & 150 mg: 162-71-35683

Revised in October 2025.