PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSYMDEKO™

Tezacaftor / Ivacaftor Tablets and Ivacaftor Tablets

Tezacaftor 100 mg / Ivacaftor 150 mg Tablets
and
Ivacaftor 150 mg Tablets, Oral

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

ATC R07AX31

Distributed by:
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PrSYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *P67L, D110H*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T*.

1.1 Pediatrics

Pediatrics (<12 years of age): No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in this age group.

1.2 Geriatrics

Geriatrics (≥65 years of age): 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.

2 CONTRAINDICATIONS

SYMDEKO is contraindicated in patients who are hypersensitive to tezacaftor, ivacaftor or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *Dosage Forms, Strengths, Composition and Packaging (6)*.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

SYMDEKO should only be administered to patients who have a mutation in the *CFTR* gene that is responsive to SYMDEKO. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of an indicated mutation [see *Action and Clinical Pharmacology (10) and Clinical Trials (14)*].

SYMDEKO dosing may be impacted in the following patient groups:

- Hepatic Impairment – Moderate or severe hepatic impairment
- Interactions with Medicinal Products - Concomitant use of moderate and strong CYP3A inhibitors
- Interactions with Medicinal Products - Concomitant use of strong CYP3A inducers

- Renal Impairment – Severe renal impairment or end-stage renal disease
- Elevated transaminase (AST/ALT) levels - patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN

4.2 Recommended Dose and Dosage Adjustment

Adults, adolescents, and children aged 12 years and older
The recommended dose is one tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart with fat-containing food. Health Canada has not authorized an indication for use in pediatric patients less than 12 years of age [see *Special Populations (7.1) and Pharmacokinetics (10.3)*].

Hepatic impairment
A dose reduction to 1 tablet of tezacaftor/ivacaftor in the morning is recommended for patients with moderate hepatic impairment (Child-Pugh Class B). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution after weighing the risks and benefits of treatment and reduce the dose accordingly in these patients. For dose adjustment for patients with hepatic impairment, refer to Table 1.

Table 1: Dosing recommendations for patients with hepatic impairment

	Morning	Evening
Mild (Child-Pugh Class A)	No dose adjustment	No dose adjustment
Moderate (Child-Pugh Class B)	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily with fat-containing food	No ivacaftor 150 mg dose
Severe (Child-Pugh Class C)	Starting dose: One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily with fat-containing food. If required dosing intervals should be lengthened to reduce the dosage further, according to clinical response and tolerability.	

Renal impairment
No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment (creatinine clearance ≤30 mL/min) or end-stage renal disease [see *Warnings and Precautions (7) and Pharmacokinetics (10.3)*].

Concomitant use of CYP3A inhibitors
The dose of SYMDEKO should be adjusted when co-administered with moderate and strong CYP3A inhibitors [see *Warnings and Precautions (7) and Drug-Drug Interactions (9.3)*].

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the dose should be adjusted as in Table 2.

When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin), the dose should be adjusted as in Table 2 [see *Warnings and Precautions (7) and Drug-Drug Interactions (9.3)*].

Table 2: Dosing schedule for concomitant use of Tezacaftor/Ivacaftor or Ivacaftor with moderate CYP3A inhibitors

Moderate CYP3A inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose				
Tezacaftor 100 mg/ ivacaftor 150 mg tablet	✓	-	✓	-
Ivacaftor 150 mg tablet	-	✓	-	✓
Evening Dose^				
Ivacaftor 150 mg tablet	-	-	-	-
*Continue dosing with tezacaftor 100 mg/ivacaftor 150 mg or ivacaftor 150 mg tablets on alternate days. ^The evening dose of ivacaftor 150 mg should not be taken				

Strong CYP3A inhibitors			
	Day 1	**Day 2 and Day 3**	**Day 4[#]**
Morning Dose			
Tezacaftor 100 mg/ivacaftor 150 mg tablet	✓	-	✓
Evening Dose^			
Ivacaftor 150 mg tablet	-	-	-
[#]Dosing with tezacaftor 100 mg/ivacaftor 150 mg tablets twice a week, taken approximately 3 to 4 days apart. ^The evening dose of ivacaftor 150 mg should not be taken.			

Concomitant use of strong CYP3A inducers
Co administration with strong CYP3A inducers (e.g. rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (Hypericum perforatum) is not recommended [see *Warnings and Precautions (7) and Drug-Drug Interactions (9.3)*].

Elevated transaminase (AST/ALT) levels
Elevated transaminases have been observed in CF patients treated with SYMDEKO, as well as with ivacaftor monotherapy. In the event of significant elevations of transaminases, e.g., patients with ALT or AST >5 x 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 *Warnings and Precautions (7) and Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data (8.4)*].

4.3 Administration

For oral use. Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break, or dissolve the tablets).

SYMDEKO should be taken with fat-containing food, such as food recommended in CF guidelines or in standard nutritional guidelines. Examples of meals or snacks that contain adequate amounts of fat are those prepared with butter or oils or those containing eggs,

cheeses, nuts, whole milk, or meats [see *Drug-Food Interactions (9.4) and Pharmacokinetics (10.3)*].

Morning dose: 100 mg of tezacaftor and 150 mg of ivacaftor as a fixed-dose combination tablet.
Evening dose: 150 mg of ivacaftor.

Food or drink containing grapefruit or Seville oranges should be avoided during treatment with SYMDEKO [see *Drug-Food Interactions (9.4)*].

4.5 Missed Dose

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 with fat-containing food 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 should be taken at the usual time.

More than one dose should not be taken at the same time.

5 OVERDOSAGE

The highest repeated dose for tezacaftor was 300 mg once daily administered to 47 healthy subjects for 7 days in an ECG assessment study, following 7 days of tezacaftor dosed 100 mg once daily. The most common adverse events reported during dosing of tezacaftor 300 mg once daily and which were more common than during dosing of tezacaftor 100 mg once daily were headache and nausea.

The highest repeated dose for ivacaftor was 450 mg every 12 hours for 4.5 days (9 doses) in an ECG assessment study with 72 healthy subjects. Adverse events reported at a higher incidence compared to placebo included dizziness and diarrhea.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging		
Route of Administration	**Dosage Form / Strength/Composition**	**Non-medicinal Ingredients**
Oral	tablet 100 mg of tezacaftor/150 mg of ivacaftor (fixed-dose combination) and 150 mg of ivacaftor	Tezacaftor/Ivacaftor *Tablet core* Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate *Tablet film coat* HPMC/hypromellose 2910, hydroxypropyl cellulose, iron oxide yellow, talc, titanium dioxide Ivacaftor *Tablet core* Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate *Tablet film coat* Carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, titanium dioxide *Printing ink* Ammonium hydroxide, iron oxide black, propylene glycol, shellac

Physical Characteristics

Morning dose

Film-coated tablet

Yellow, capsule-shaped tablet debossed with “V100” on one side and plain on the other (15.9 mm x 8.5 mm). Contains 100 mg of tezacaftor and 150 mg of ivacaftor as a fixed-dose combination tablet.

Evening dose

Film-coated tablet

Light blue, capsule-shaped tablet, printed with “V150” in black ink on one side and plain on the other (16.5 mm x 8.4 mm). Contains 150 mg of ivacaftor.

Nature and contents of container

Blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminum foil lidding.

Pack size
Monthly pack of 56 tablets (4 weekly blister cards, each with 14 tablets).
Tezacaftor/Ivacaftor 100 mg/150 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets.

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery
Dizziness has been reported in patients receiving SYMDEKO, which could influence the ability to drive or operate machines [see *Clinical Trial Adverse Reactions (8.2)*]. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

Hepatic/Biliary/Pancreatic
If SYMDEKO is used in patients with moderate to severe hepatic impairment, they should be closely monitored after the initiation of treatment and the dose should be reduced as recommended [see *Recommended Dose and Dosage Adjustment (4.2) and Pharmacokinetics (10.3)*].

Elevated transaminase (AST/ALT) levels
Elevated transaminases have been observed in CF patients treated with SYMDEKO, as well as with ivacaftor monotherapy. In the event of significant elevations of transaminases, e.g., patients with ALT AST >5 x 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 *Recommended Dose and Dosage Adjustment (4.2) and Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data (8.4)*].

Concomitant Use with CYP3A inducers
Exposure to tezacaftor and ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in the loss of SYMDEKO efficacy; therefore, co-administration with strong CYP3A inducers is not recommended [see *Recommended Dose and Dosage Adjustment (4.2) and Drug-Drug Interactions (9.3)*].

Concomitant Use with CYP3A inhibitors
The dose of SYMDEKO should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors [see Table 2 in *Recommended Dose and Dosage Adjustment (4.2)*].

Monitoring and Laboratory Tests
Effect on liver function tests
Elevated transaminases have been observed in CF patients 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 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 *Recommended Dose and Dosage Adjustment (4.2) and Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data (8.4)*].

Patients should be advised to contact their doctor immediately if they develop symptoms suggestive of increased transaminases (e.g., abdominal pain, anorexia, jaundice, dark urine, pale stools, pruritus).

Ophthalmologic
Cataracts
Cases of non-congenital lens opacities without impact on vision 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 and 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 *Non-Clinical Toxicology (16)*].

Renal
Caution is recommended while using SYMDEKO in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease [see *Recommended Dose and Dosage Adjustment (4.2) and Pharmacokinetics (10.3)*].

Sexual Health
Fertility
Tezacaftor had no effects on fertility and reproductive performance indices in male and female rats at doses up to 100 mg/kg/day (approximately 3 times the maximum recommended human dose [MRHD] based on summed area under the curve (AUCs) of tezacaftor and M1 metabolite).

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 extrapolated from Day 90 exposures at 150 mg/kg/day in the 6-month, repeat-dose toxicity trial in this species) when dams were dosed prior to and during early pregnancy [see *Non-Clinical Toxicology (16)*]. 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 of the ivacaftor component of tezacaftor/ivacaftor based on summed AUCs of ivacaftor and its metabolites).

7.1 Special Populations

7.1.1 Pregnant Women

The extent of exposure to SYMDEKO in pregnant women during clinical trials is very limited. No adequate and well-controlled studies of SYMDEKO in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, SYMDEKO should be used during pregnancy only if the potential benefits outweigh the potential risks.

Tezacaftor
No evidence of harm to the fetus was observed in developmental toxicity trials in rats at daily doses up to 3 times the MRHD (based on summed AUCs for tezacaftor and its M1 metabolite) [see *Non-Clinical Toxicology (16)*]. Tezacaftor was not teratogenic in rabbits at any dose and did not affect fetal development or survival at exposures up to 0.2 times the MRHD (based on summed AUCs of tezacaftor and M1 metabolite at maternal oral doses up to 25 mg/kg/day). In the rabbit at maternally toxic doses that produced exposures approximately 1 time the MRHD (at a maternal dose of 50 mg/kg/day), lower fetal body weights were noted; however, no effects on intrauterine survival or fetal morphology were noted at any dose. Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor
No evidence of harm to the fetus was observed in developmental toxicity trials in rats and rabbits at daily doses up to 6 and 16 times, respectively, the MRHD based on the summed AUCs of ivacaftor and its metabolites [see *Non-Clinical Toxicology (16)*].

Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from gestation Day 7 through lactation Day 20 at 100 mg/kg/day (approximately 4 times the MRHD based on the summed AUCs of ivacaftor and its metabolites). Doses above this resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights. Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

7.1.2 Breastfeeding

Both tezacaftor and ivacaftor are excreted into the milk of lactating female rats. 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 $AUC_{0\text{-}24h}$). 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 $AUC_{0\text{-}24h}$). Because it is not known if tezacaftor, ivacaftor, or their metabolites are excreted in human milk, SYMDEKO should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant.

7.1.3 Pediatrics (<12 years of age)

No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in this age group.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of SYMDEKO is based on pooled data from three double-blind, placebo-controlled, Phase 3 clinical trials (2 parallel-group trials of 12 and 24 weeks 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. The 12-week parallel arm study was terminated following the planned interim analysis since the pre-specified futility criteria had been met. 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 trial drug prematurely due to adverse events 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 subjects vs. 0 placebo-treated patients.

The most common adverse drug reactions experienced by patients who received SYMDEKO in the pooled, placebo-controlled phase 3 studies were headache (14%) and nasopharyngitis (12%).

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.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The incidence of adverse reactions below is based on pooled data from three double-blind, placebo-controlled, Phase 3 clinical trials.

Table 4 shows adverse reactions occurring in ≥3% of SYMDEKO-treated patients and at a frequency higher than placebo by ≥1%.

Table 4: Adverse Reactions by Preferred Term and Incidence			
System Organ Class (SOC)	**Adverse Reactions (Preferred Term)**	**SYMDEKO N=496 n (%)**	**Placebo N=505 n (%)**
Infections and infestations	Nasopharyngitis	57 (12)	49 (10)
Nervous system disorder	Headache	68 (14)	57 (11)
	Dizziness	15 (3.0)	10 (2.0)
Respiratory, thoracic and mediastinal disorders	Sinus congestion	17 (3)	11 (2)
Gastrointestinal disorders	Nausea	38 (8)	34 (7)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory Abnormalities

Transaminase elevations

During the placebo-controlled Phase 3 trials (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN was similar between SYMDEKO-treated patients and placebo-treated patients.

Table 5: Threshold Analysis of Liver Function Tests During Overall Treatment-emergent Period: Placebo-controlled Safety Set		
LFT Analyte (Unit) Threshold Analysis Criteria	**Placebo N = 505 n/N1 (%)**	**SYMDEKO N = 496 n/N1 (%)**
ALT or AST (U/L)		
>3 × ULN	17/504 (3.4)	17/494 (3.4)
>5 × ULN	5/504 (1.0)	5/494 (1.0)
>8 × ULN	2/504 (0.4)	1/494 (0.2)
ALT or AST and total bilirubin ALT or AST >3 × ULN and Total Bilirubin >2 × ULN	1/504 (0.2)	0/494
ALT: alanine aminotransferase; AST: aspartate aminotransferase; LFT: liver function test; ULN: upper limit of normal		

One patient (0.2%) on SYMDEKO and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

The safety profile is generally consistent among adolescents (between 12 and 18 years of age) and adult patients. Pediatric patients under the age of 12 years old have not been studied.

9 DRUG INTERACTIONS

9.2 Overview

In vitro studies showed that tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Exposure to ivacaftor and tezacaftor may be reduced by concomitant use of CYP3A inducers and increased by concomitant use of CYP3A inhibitors.

Clinical studies showed that ivacaftor is not an inhibitor of CYP2C8 or CYP2D6. In vitro, ivacaftor was not an inducer of CYP isozymes. Ivacaftor is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3. *In vitro* studies showed that ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-gp.

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.
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, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

9.3 Drug-Drug Interactions

The drugs listed in Table 6 are based on either drug interaction case reports or trials, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those where co-administration is not recommended).

Table 6: Established or Potential Drug-Drug Interactions - Effect of Other Drugs on Tezacaftor/Ivacaftor or Ivacaftor			
Drug	**Source of Evidence**	**Effect**	**Clinical comment**
Strong CYP3A Inducers			
Rifampin	CT (ivacaftor)	↓AUC of ivacaftor by 89%	Co-administration is not recommended. Concomitant use can substantially decrease exposure of ivacaftor and may decrease the exposure of tezacaftor which may reduce therapeutic effectiveness.
	T (tezacaftor)	↓AUC of tezacaftor	
Phenobarbital Carbamazepine Phenytoin Rifabutin	T	↓AUC of ivacaftor ↓AUC of tezacaftor	
Strong CYP3A Inhibitors			
Itraconazole	CT	↑15.6-fold in ivacaftor AUC ↑4-fold in tezacaftor AUC	Doses of SYMDEKO must be reduced [see Table 2].
Ketoconazole Posaconazole Voricanozole Clarithromycin	T	↑ AUC of tezacaftor and ivacaftor	
Moderate CYP3A Inhibitors			
Fluconazole	CT	↑3-fold in ivacaftor AUC	Doses of SYMDEKO must be reduced [see Table 2].
	T	↑2-fold in tezacaftor AUC	
Erythromycin	T	↑ AUC of tezacaftor and ivacaftor	
↑ = increase, ↓ = decrease Legend: CT = Clinical Trial; T = Theoretical; AUC = Area Under the Curve			

Effect of Other Drugs on SYMDEKO

CYP3A inducers

Co-administration of SYMDEKO with strong CYP3A inducers is not recommended. 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 efficacy of SYMDEKO. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by 89%. Tezacaftor exposures can also be expected to decrease significantly during co-administration with strong CYP3A inducers [see *Recommended Dose and Dosage Adjustment (4.2); Warnings and Precautions (7)].*

CYP3A inhibitors

The dose of SYMDEKO should be reduced when co-administered with strong CYP3A inhibitors. Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure

(measured as AUC) by 4.0-fold and increased ivacaftor AUC by 15.6-fold [see Table 2 in *Recommended Dose and Dosage Adjustment (4.2)*].

The dose of SYMDEKO should be reduced when co-administered with moderate CYP3A inhibitors. Co-administration of fluconazole increased ivacaftor AUC by 3-fold. Physiologically-based pharmacokinetic modeling suggested co-administration with fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor exposure (AUC) by approximately 2-fold [see Table 2 in *Recommended Dose and Dosage Adjustment (4.2)*].

The effects of tezacaftor and ivacaftor (or ivacaftor alone) on the exposure of co-administered drugs are shown in Table 7.

Table 7: Established or Potential Drug-Drug Interactions - Effect of Tezacaftor/Ivacaftor or Ivacaftor on Other Drugs

Drug	Source of Evidence	Effect	Clinical comment
CYP3A substrates			
Midazolam	CT	↔ Midazolam	No dose adjustment for midazolam is recommended.
CYP2C9 Substrates			
Warfarin Glimepiride Glipizide	T	↑ exposures	Caution is warranted; monitoring of international normalized ratio (INR) ratio is recommended when SYMDEKO is co-administered with warfarin or other CYP2C9 substrates.
P-Glycoprotein Substrates			
Digoxin	CT	↑ 1.3-fold Digoxin	Caution is warranted and therapeutic concentration monitoring of digoxin is recommended.
Cyclosporine Everolimus Sirolimus Tacrolimus	T	↑ exposures	Caution is warranted and therapeutic concentration monitoring of sensitive P-gp substrates is recommended.
Hormonal Contraceptives			
Oral Contraceptive	CT	↔ Ethinyl estradiol ↔ Norethindrone	No dose adjustment of the hormonal contraceptive is recommended.

↑ = increase, ↔ = no change
Legend: CT = Clinical Trial; T = Theoretical

Effect of SYMDEKO on Other Drugs

CYP3A substrates

Co-administration with (oral) midazolam, a sensitive CYP3A substrate, did not affect midazolam exposure. No dose adjustment of CYP3A substrates is required when co-administered with SYMDEKO.

CYP2C9 substrates
Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) is recommended during co-administration of warfarin with SYMDEKO.

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, caution and appropriate monitoring should be used.

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.

9.4 Drug-Food Interactions

SYMDEKO should be administered with fat-containing food. The AUC of ivacaftor, when given in combination with tezacaftor, increased approximately 3-fold when given with fat-containing food. The AUC of tezacaftor did not change when given with fat-containing food relative to fasted conditions [see *Pharmacokinetics (10.3)*].

Food or drink containing grapefruit or Seville oranges should be avoided during treatment with SYMDEKO. Co-administration of SYMDEKO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor and tezacaftor [see *Administration (4.3)*].

9.5 Drug-Herb Interactions

Co-administration with St. John's wort (*Hypericum perforatum*) is not recommended. As with other strong CYP3A inducers, concomitant use may decrease the exposure of tezacaftor and substantially decrease exposure of ivacaftor, which may reduce the therapeutic effectiveness of SYMDEKO.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tezacaftor is a CFTR corrector that facilitates the processing and trafficking of 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 CFTR 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.

10.2 Pharmacodynamics

Effects on Sweat Chloride
In Trial 1 (patients 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 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 to the average of Week 4 and 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.

There was no direct correlation between decrease in sweat chloride levels and improvement in lung function ($ppFEV_1$).

In a randomized, double-blind, placebo- and positive-controlled, parallel group (nested crossover cohorts for positive control and placebo) ECG assessment study in healthy subjects (N=48/treatment), tezacaftor was administered at the therapeutic dose of 100 mg once daily from days 1 to 7 and at a supratherapeutic dose of 300 mg once daily from days 8 to 14. On days 7 and 14, there was no evidence of any meaningful effect on the QTcF interval, the QRS duration, the PR interval or heart rate.

In a double-blind, randomized, placebo- and positive-controlled, 4-period crossover ECG assessment study in healthy subjects (N=72), the ivacaftor 150 mg twice daily (therapeutic dose) and 450 mg twice daily (3X multiple of therapeutic dose) treatments administered for 5 days were not associated with any meaningful effect on the QTcF interval, the QRS duration, the PR interval, or heart rate.

10.3 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. Upon dosing tezacaftor/ivacaftor to steady-state, the accumulation ratio is approximately 1.6 for tezacaftor and 2.6 for ivacaftor. Exposures of tezacaftor (administered alone or in combination with ivacaftor) increase in an approximately dose-proportional manner, with increasing doses from 10 mg to 150 mg once daily. Key pharmacokinetic parameters for tezacaftor and ivacaftor at steady state are shown in Table 8.

Table 8: Mean (SD) Pharmacokinetic Parameters of Tezacaftor and Ivacaftor at Steady State in Patients with CF						
	Drug	**C_{max} (mcg/mL)**	**$t_{½}$ (h)**	**AUC_{0-24h} or AUC_{0-12h} (mcg·h/mL)***	**Apparent Clearance (L/hr)**	**Apparent Volume of Distribution (L)**
Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Tezacaftor	6.52 (1.83)	156 (52.7)	82.7 (23.3)	1.31 (0.41)	271 (157)
	Ivacaftor	1.28 (0.440)	9.3 (1.7)	10.9 (3.89)	15.7 (6.38)	206 (82.9)
*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 6.0 hours (3 to 10 hours) in the fed state. The AUC of tezacaftor did not change when given with fat-containing food relative to fasted conditions. The AUC of ivacaftor, when given in combination with tezacaftor, increased approximately 3-fold when given with fat-containing food; therefore, SYMDEKO should be administered with fat-containing food.

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 in combination with 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.

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 3 major circulating metabolites of tezacaftor in humans. M1 has 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.

Elimination: After oral administration of tezacaftor 100 mg once daily in combination with 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 CF patients, the mean (SD) terminal half-lives of tezacaftor and ivacaftor were approximately 156 (52.7) and 9.3 (1.7) hours, respectively.

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%) was eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. 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). There was negligible urinary excretion of ivacaftor as unchanged drug.

Special Populations and Conditions

Pediatrics (<12 years of age): No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in this age group.

Geriatrics: 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.

Sex: The pharmacokinetic parameters of tezacaftor and ivacaftor are similar in males and females.

Pregnancy and Breast-feeding: The extent of exposure to SYMDEKO in pregnant women during clinical trials is very limited. No adequate and well-controlled studies of SYMDEKO in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, SYMDEKO should be used during pregnancy only if the potential benefits outweigh the potential risks [see *Special Populations (7.1)*].

Both tezacaftor and ivacaftor are excreted into the milk of lactating female rats. Because it is not known if tezacaftor, ivacaftor, or their metabolites are excreted in human milk, SYMDEKO should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant [see *Special Populations (7.1)*].

Hepatic Insufficiency: Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 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, subjects 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. Based on these results, a dose reduction of SYMDEKO is recommended for patients with moderate hepatic impairment [see Table 1 in *Recommended Dose and Dosage Adjustment (4.2)*].

The impact of severe hepatic impairment (Child-Pugh Class C, score 10 to 15) on the pharmacokinetics of tezacaftor and ivacaftor has not been studied. The magnitude of increase in exposure in these patients is unknown, but is expected to be higher than that observed in patients with moderate hepatic impairment. SYMDEKO should be used with caution and a dose reduction is recommended in patients with severe hepatic impairment [see Table 1 in *Recommended Dose and Dosage Adjustment (4.2)*].

No dose adjustment is considered necessary for patients with mild hepatic impairment.

Renal Insufficiency: 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 trial 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 trial 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 Phase 2/3 clinical trials indicated that mild renal impairment (n=147, estimated glomerular filtration rate, estimated by the modification of diet in renal disease method, 60 to ≤89 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly. No dose adjustment for SYMDEKO is recommended for mild and moderate renal impairment. Caution is recommended when administering SYMDEKO to patients with severe renal impairment or end-stage renal disease.

11 STORAGE, STABILITY AND DISPOSAL

Store at or below 30°C. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines:
No special requirements for disposal.

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Use established “collection systems” if available.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

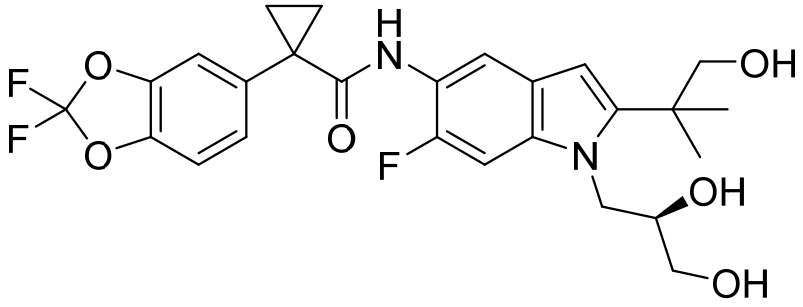
Proper name/Common name: tezacaftor/ivacaftor

Chemical name:

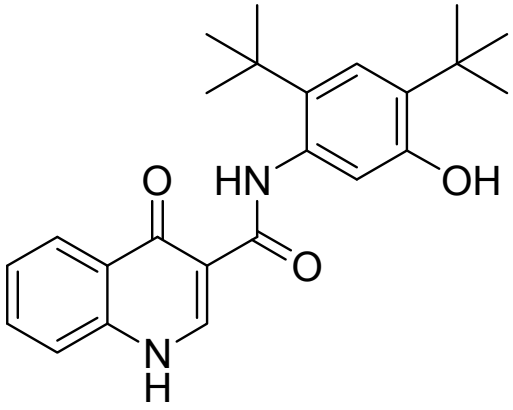
tezacaftor: 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide
ivacaftor : N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide.

Molecular formula and molecular mass: *tezacaftor*: C26H27N2F3O6; 520.50
ivacaftor: C24H28N2O3; 392.49

Structural formula:



tezacaftor



ivacaftor

Physicochemical properties: Tezacaftor is a white to off-white solid that is practically insoluble in water (<0.1 mg/mL).
Ivacaftor is a white to off-white solid that is practically insoluble in Water (<0.1 mg/mL).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of PrSYMDEKO™ (tezacaftor/ivacaftor; ivacaftor) in patients with CF was demonstrated in two Phase 3, randomized double-blind, placebo-controlled trials (Trial 1 and Trial 2).

Table 9: Summary of Patient Demographics for Clinical Trials in CF Patients with selected CFTR mutations

Trial #	Trial design	Dosage, route of administration and duration	Number of Subjects (N)	Mean age (Range)	Sex
Trial 1 (subjects homozygous for the *F508del* mutation)	Randomized, double-blind, placebo-controlled, parallel-group, multicentre	Tezacaftor 100 mg once daily (qd)/ivacaftor 150 mg every 12 hours (q12h), or placebo; Oral 24 weeks	504	26.3 years (range: 12 to 64 years)	Male: 51.2% Female: 48.8%
Trial 2 (subjects heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ ivacaftor)	Randomized, double-blind, placebo-controlled, crossover, multicentre	Tezacaftor 100 mg qd/ ivacaftor q12h, or Ivacaftor 150 mg q12h, or matching placebo Oral Two 8-week treatment periods, with a washout of 8 weeks between each treatment period	244	34.8 years (range: 12 to 72 years)	Male: 45.1% Female: 54.9%

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled trial. A total of 504 patients aged 12 years and older (mean age 26.3 years), who were homozygous for the *F508del* mutation in the *CFTR* gene, were randomized (1:1 randomization: 248 SYMDEKO, 256 placebo). Patients had a $ppFEV_1$ at screening between 40-90%. 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. 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.

Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover trial. A total of 244 patients aged 12 years and older (mean age 34.8 years), who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor, were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo. In the 244 patients enrolled, the following CFTR mutations were represented: *P67L, D110H*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T.* Patients had a $ppFEV_1$ at screening between 40-90%. 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.

Patients in Trials 1 and 2 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 trial. Patients had a confirmed genotype of a protocol-specified *CFTR* mutation and a confirmed diagnosis of CF.

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 both trials.

14.2 Study Results

Trial in patients with CF who were homozygous for the* F508del *mutation in the CFTR gene (Trial 1)

In Trial 1, treatment with SYMDEKO resulted in a statistically-significant improvement in $ppFEV_1$ (Table 10). These changes persisted throughout the 24-week treatment period (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. See Table 10 for a summary of primary and key secondary outcomes.

Table 10: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 1)‡			
Analysis	**Statistic**	**Placebo N=256**	**SYMDEKO N=248**
Primary			
Average absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference[a] (95% CI) *P* value	NA NA	4.0 (3.1, 4.8) *P*<0.0001*
Key Secondary			
Relative change in $ppFEV_1$ from baseline through Week 24 (%)	Treatment difference[a] (95% CI) *P* value	NA NA	6.8 (5.3, 8.3) *P*<0.0001*
Number of pulmonary exacerbations from baseline through Week 24	Rate ratio[b] (95% CI) *P* value Number of events (event rate per year†)	NA NA 122 (0.99)	0.65 (0.48, 0.88) *P*=0.0054* 78 (0.64)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference[a] (95% CI)	NA	0.06 (-0.08, 0.19)
Absolute change in CFQ-R Respiratory Domain Score from baseline through Week 24 (points)	Treatment difference[a] (95% CI)	NA	5.1 (3.2, 7.0)

BMI: body mass index; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; NA: not applicable; $ppFEV_1$: percent predicted forced expiratory volume in 1 second.

‡ A hierarchical testing procedure was performed for primary and key 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.

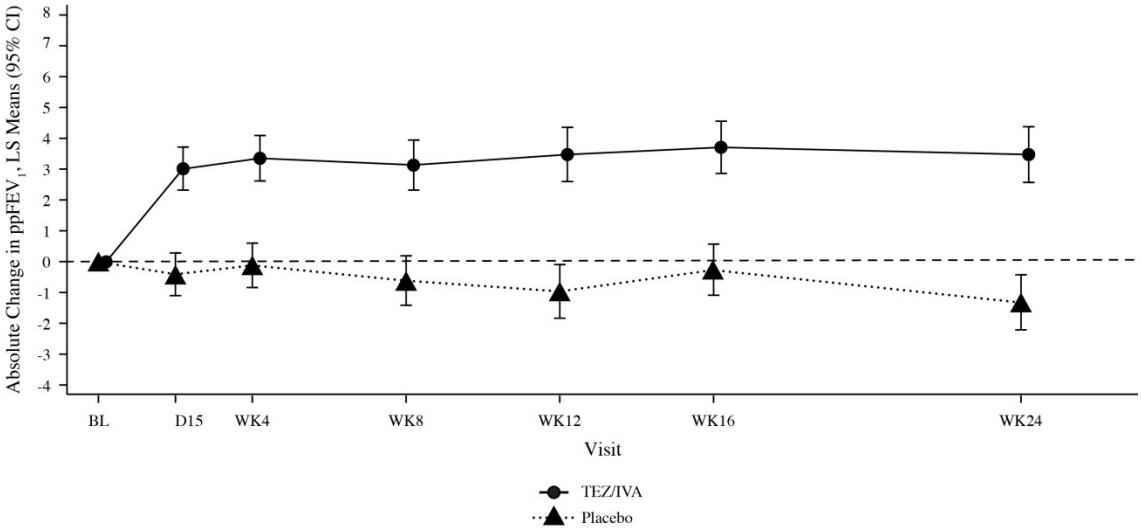
* Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures considered not statistically significant.

† Estimated event rate per year calculated using 48 weeks per year.

[a] Treatment difference = effect of SYMDEKO – effect of placebo

[b] Estimated rate ratio (SYMDEKO vs. placebo): event rate of SYMDEKO divided by event rate of placebo

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



Trial in patients with CF who were heterozygous for the* F508del-CFTR *mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (Trial 2)

In Trial 2, treatment with SYMDEKO resulted in a statistically significant improvement in $ppFEV_1$ (Table 11). Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex, mutation class, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region. See Table 11 for a summary of primary and key secondary outcomes.

Table 11: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 2)

Analysis	Statistic	Placebo N=161	Ivacaftor N=156	SYMDEKO N=161
Absolute change in $ppFEV_1$ from study baseline to the average of Week 4 and Week 8 (percentage points)	Treatment difference versus placebo (95% CI)	NA	4.7 (3.7, 5.8)	6.8 (5.7, 7.8)
	P value	NA	*P*<0.0001	*P*<0.0001
	Treatment difference versus IVA (95% CI)	NA	NA	2.1 (1.2, 2.9)
	P value	NA	NA	*P*<0.0001
Absolute change in CFQ-R respiratory domain score from study baseline to the average of Week 4 and Week 8 (points)	Treatment difference versus placebo (95% CI)	NA	9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
	P value	NA	*P*<0.0001	*P*<0.0001
	Treatment difference versus IVA (95% CI)	NA	NA	1.4 (-1.0, 3.9)

CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; NA: not applicable.

16 NON-CLINICAL TOXICOLOGY

Tezacaftor

Tezacaftor did not cause reproductive system toxicity in male and female rats at 100 mg/kg/day, the highest dose evaluated (approximately 3 times the MRHD based on summed AUCs of tezacaftor and M1 metabolite).

Tezacaftor was not teratogenic in pregnant rats and rabbits at doses approximately 3 times and 1 times, respectively, the tezacaftor exposure in humans at the therapeutic dose.

In a pre-and post-natal development study (PPND) tezacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally at 25 mg/kg/day (approximately ~~0.~~1 time~~s~~ the MRHD based on summed AUCs for tezacaftor and M1 metabolite). 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).

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.

Tezacaftor was shown to be non-carcinogenic in a 6-month trial in Tg.rasH2 transgenic mice and in a 2-year trial in Sprague-Dawley rats. Plasma exposures in male and female mice at the non-carcinogenic dose (500 mg/kg/day, the highest dose tested) were approximately 1.8-fold higher than the sum of plasma exposures of tezacaftor and its metabolite when measured in humans following tezacaftor/ivacaftor therapy. Plasma exposures in rats at the non-carcinogenic dose (50 mg/kg/day in males and 75 mg/kg/day in females, the highest doses tested) were approximately 2- to 3-fold higher than the sum of tezacaftor and its metabolite when measured in humans following tezacaftor/ivacaftor therapy.

Ivacaftor

Ivacaftor is not considered a potent hERG channel blocker. Ivacaftor-induced QT prolongation was not observed in a dog telemetry trial at single doses up to 60 mg/kg or in ECG measurements from repeat-dose trials of up to 1 year duration at the 60 mg/kg/day dose level in dogs. Ivacaftor produced a dose-related but transient increase in the blood pressure parameters in dogs at single oral doses up to 60 mg/kg.

Ivacaftor did not cause reproductive system toxicity in male and female rats at 100 mg/kg/day. A reduction in overall fertility index, numbers of pregnancies, number of corpora lutea and implantation sites, as well as changes in the estrous cycle, were observed in females at 200 mg/kg/day. Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day.

Ivacaftor was not teratogenic in rats at 200 mg/kg/day and rabbits at 100 mg/kg/day (approximately 6 and 16 times, respectively, the MRHD based on the summed AUCs of ivacaftor and its metabolites). Decreased fetal body weights and small increases in common variations in skeletal development were observed at a maternally toxic dose that produced exposures 6 times the MRHD.

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 when co-administered with tezacaftor as tezacaftor/ivacaftor). This finding has not been observed in fetuses derived from rat dams treated with ivacaftor on gestation Days 7 to 17, in rat pups exposed to ivacaftor to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 3.5- to 5-month-old dogs treated with ivacaftor.

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.

Two-year studies in CD-1 mice and Sprague-Dawley rats to assess carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures of ivacaftor on an AUC basis in mice at the non-carcinogenic dose (200 mg/kg/day, the highest dose tested) were approximately 2 times higher than the sum of plasma exposures of ivacaftor and its metabolites when measured in humans following tezacaftor/ivacaftor therapy. Plasma exposures of ivacaftor on an AUC basis in rats at the non-carcinogenic dose (50 mg/kg/day, the highest dose tested) were approximately 9 times higher than the sum of plasma exposures of ivacaftor and its metabolites when measured in humans following tezacaftor/ivacaftor therapy.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]SYMDEKO™
tezacaftor 100 mg / ivacaftor 150 mg tablets
and
ivacaftor 150 mg tablets

Read this carefully before you start taking **SYMDEKO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SYMDEKO.**

What is SYMDEKO used for?
SYMDEKO is used for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who:

- are homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene or
- are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, D110H*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T.*

It is not known if SYMDEKO is safe and effective in children under 12 years of age.

How does SYMDEKO work?

- The CFTR gene provides instructions to your cells to make the CFTR protein. This protein helps take chloride ions in and out of the cells in many organs of your body.
- People with CF have a lower amount of the CFTR protein and/or reduced function of the CFTR protein.
- SYMDEKO contains two ingredients:
    - Tezacaftor. This is a CFTR Corrector. It increases the amount of the CFTR protein at the surface of the cell.
    - Ivacaftor. This is a CFTR Potentiator. It makes the CFTR protein at the cell surface work better in allowing more chloride ions to pass through.

What are the ingredients in SYMDEKO?
Medicinal ingredients: tezacaftor and ivacaftor

Non-medicinal ingredients:
Tezacaftor/Ivacaftor tablet
Tablet core: Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

Tablet film coat: HPMC/hypromellose 2910, hydroxypropyl cellulose, iron oxide yellow, talc, and titanium dioxide.

Ivacaftor tablet
Tablet core: Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

Tablet film coat: Carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide.

Printing ink: Ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

SYMDEKO comes in the following dosage forms:
Tablet: tezacaftor 100 mg / ivacaftor 150 mg and ivacaftor 150 mg

Do not use SYMDEKO if:

- You are allergic (hypersensitive) to:
    - tezacaftor
    - ivacaftor
    - any of the non-medicinal ingredients or any of the ingredients in the component of the container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SYMDEKO. Talk about any health conditions or problems you may have, including if you:

- Have liver disease. Your doctor may need to adjust your dose of SYMDEKO.
- Have kidney disease.
- Are pregnant or plan to become pregnant. It is not known if SYMDEKO will harm your unborn baby. You and your doctor should decide if you will take SYMDEKO while you are pregnant.
- Are breastfeeding or planning to breastfeed. It is not known if SYMDEKO can pass into your breast milk. You and your doctor should decide if you should take SYMDEKO while you are breastfeeding.

Other warnings you should know about:

Cataracts

Cloudiness of the eye lens (cataract) without any effect on vision has been seen in some children and adolescents while taking SYMDEKO. Your doctor may perform eye exams before you start taking SYMDEKO and during treatment with SYMDEKO to look for cataracts.

Abnormal test results

Abnormal blood tests of the liver have been seen in some people taking SYMDEKO.
Your doctor will order some blood tests to check your liver:

- before you take SYMDEKO,
- every 3 months of the first year while you are taking SYMDEKO, and
- every year while you are taking SYMDEKO.

If you have had abnormal blood tests of the liver in the past, your doctor may order blood tests to check your liver more often.

Tell your doctor right away if you have any of these symptoms, which may be a sign of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark urine
- pale stools
- itchy skin

Children

SYMDEKO is not for use in children under 12 years of age. It is not known if SYMDEKO is safe and effective in children under 12 years of age.

Driving and using machines

You may get dizzy when you take SYMDEKO. Wait to see how you feel after taking SYMDEKO before you drive or use machines. **For children**: you or your child's caregiver should supervise your child when they take SYMDEKO. Wait to see if your child is dizzy after taking it before they ride their bikes or do anything else that needs their full attention.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SYMDEKO:

- Medicines used to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole and fluconazole).
- Medicines used to treat bacterial infections (such as clarithromycin, erythromycin, rifampicin and rifabutin). You should not take SYMDEKO with rifampicin and rifabutin.
- Medicines used to treat seizures (such as phenobarbital, carbamazepine and phenytoin). You should not take SYMDEKO with these medicines.
- Warfarin (a medicine used to prevent blood clots from forming or growing larger).
- Medicines used to treat diabetes (such as glimepiride and glipizide).
- Digoxin (a medicine used to treat congestive heart failure or a heart rhythm problem called atrial fibrillation).
- Medicines used after an organ transplant (such as cyclosporine, tacrolimus and sirolimus).
- Everolimus (used to treat certain types of cancer).
- St. John's wort (*Hypericum perforatum*). You should not take SYMDEKO with this medicine.
- Food or drinks containing grapefruit or Seville oranges. You should avoid eating and drinking these.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How to take SYMDEKO:

- **In order to get the right amount of medicine in your body, SYMDEKO should always be taken with fat-containing food.** Meals and snacks recommended in CF guidelines contain acceptable amounts of fat. Examples of meals that contain fat are:
    - meals that have been prepared with butter or oils.
    - meals that have eggs, nuts, whole-milk dairy products (such as whole-milk, cheese, and yogurt) or meats.
- Take SYMDEKO exactly how your doctor tells you to take it, even if you feel well.
- Check with your doctor if you are not sure about how to take SYMDEKO.

Usual dose:
To remove the tablet, push it through the blister strip.

Morning dose: Take 1 yellow tablet (tezacaftor 100 mg / ivacaftor 150 mg). Swallow it **whole** with fat-containing food.

Evening dose: Take 1 light blue tablet (ivacaftor 150 mg) 12 hours after your morning dose. Swallow it **whole** with fat-containing food.

- Do not change the dose or stop taking SYMDEKO without first talking to your doctor.
- Your doctor may need to adjust your dose if you have liver disease or if you are taking medications that may interact with SYMDEKO.

Refilling your prescription:
Remember to get a new prescription from your doctor or a refill from your pharmacy 7-10 days before taking your last dose of SYMDEKO.

Overdose:

If you think you have taken too much SYMDEKO, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss your dose of SYMDEKO and:

- **it is 6 hours or less** from the time you usually take it, you should take the missed dose as soon as

possible with fat-containing food.
- **it has been more than 6 hours** from the time you usually take it, **do not** take the missed dose. Wait until it is time for your next dose and take it at the usual time.
- **Do not** take 2 doses at the same time to make up for your missed dose.

What are possible side effects from using SYMDEKO?
These are not all the possible side effects you may feel when taking SYMDEKO. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:
- Headache
- Common cold
- Nausea
- Stuffy nose
- Dizziness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Allergic reaction: rash; hives; swelling of the face, lips, tongue, or throat, difficult swallowing or breathing.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use this medicine after the expiry date that is stated on the package after EXP. The expiry date refers to the last day of that month.

Store at or below 30°C.

Keep out of reach and sight of children.

You may need to read this leaflet again. Do not throw this away.

If you want more information about SYMDEKO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.vrtx.ca; or by calling 1-877-634-VRTX (8789).

This leaflet was prepared by Vertex Pharmaceuticals (Canada) Incorporated.

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