▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – SYMDEKO (TEZACAFTOR/IVACAFTOR, IVACAFTOR) FILM –COATED TABLETS

1 NAME OF THE MEDICINE

Tezacaftor and ivacaftor in combination; and Ivacaftor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Morning dose
Each film-coated tablet contains 100 mg of tezacaftor and 150 mg of ivacaftor as a fixed-dose combination tablet.

Evening dose
Each film-coated tablet contains 150 mg of ivacaftor.

Excipients with known effect:
lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Composite pack
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).

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).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Symdeko 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 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.

Refer to Table 1 for a list of responsive mutations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Symdeko should only be prescribed by physicians with experience in the treatment of CF. 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 Table 1).

Table 1 below lists mutations that are responsive to tezacaftor/ivacaftor based on positive clinical response and/or in-vitro data obtained from FRT cells (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Table 1 : List of *CFTR* Gene Mutations that Produce CFTR Protein Responsive to Symdeko

*E56K***	*R117C*	*F508del**	*S977F*	*F1074L***	*3849+10kbC→T*
P67L	*E193K***	*D579G*	*F1052V***	*D1152H*	
*R74W***	*L206W*	*711+3A→G*	*K1060T***	*D1270N***	
*D110E***	*R352Q*	*E831X*	*A1067T***	*2789+5G→A*	
D110H	*A455E*	*S945L*	*R1070W*	*3272-26A→G*	

*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 1 to be indicated.
**responsive to tezacaftor/ivacaftor based on *in-vitro* data only obtained from FRT cells.

Dosage
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.

Missed Dose
If 6 hours or less have passed since a 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 should be taken at the usual time.

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

Method of administration
For oral use. Patients should be instructed to 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 (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Food or drink containing grapefruit or Seville oranges should be avoided during treatment with Symdeko (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Dosage adjustment
Hepatic impairment
For dose adjustment for patients with hepatic impairment, refer to Table 2. There is no experience in patients with severe hepatic impairment (Child-Pugh Class C); the exposure of

tezacaftor and ivacaftor in these patients is expected to be higher than in patients with moderate hepatic impairment. Therefore, caution is recommended in these patients. After weighing the risks and benefits of treatment, Symdeko should be used with caution at a reduced dose (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Table 2: 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	No ivacaftor 150 mg dose
Severe (Child-Pugh Class C)	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily (or less frequently)	

Renal impairment
No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment (creatinine clearance less than or equal to 30mL/min) or end-stage renal disease (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Concomitant use of CYP3A inhibitors
The dose of Symdeko should be adjusted when co-administered with moderate and strong CYP3A inhibitors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the dose should be adjusted as in Table 3 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 3: Dosing schedule for concomitant use of Symdeko with Moderate and Strong CYP3A inhibitors				
Moderate CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose				
Tezacaftor 100 mg/ ivacaftor 150 mg tablet	ü	-	ü	-
Ivacaftor 150 mg tablet	-	ü	-	ü
Evening Dose				
Ivacaftor 150 mg tablet	-	-	-	-
*Continue dosing with tezacaftor 100 mg/ivacaftor 150 mg or ivacaftor 150 mg tablets on alternate days.				
Strong CYP3A Inhibitors				
	Day 1	**Day 2 and Day 3**		**Day 4#**
Morning Dose				
Tezacaftor 100 mg/ ivacaftor 150 mg tablet	ü	-		-
Evening Dose^				
Ivacaftor 150 mg tablet	-	-		-

#Dosing with tezacaftor 100 mg/ivacaftor 150 mg twice a week, taken approximately 3 to 4 days apart.
^ The evening dose of ivacaftor 150 mg should not be taken (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE & 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.3 CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of this medication, patients should not be treated with this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric 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 paediatric patients initiating treatment with Symdeko (see Section 5.3 PRECLINICAL SAFETY DATA).

Cataracts were seen in juvenile rats treated with ivacaftor from postnatal Day 7 through 35 at oral dose levels of 10 mg/kg/day and higher, yielding exposure to ivacaftor and its major metabolites approximately 3–5 times lower than in patients at the maximum recommended human dose of Symdeko (based on summed AUCs). This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Interactions with other medicinal products

CYP3A inducers

Exposure to tezacaftor and ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Symdeko efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CYP3A inhibitors

The dose of Symdeko should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see Table 3 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Effect on Liver Function Tests

Elevated transaminases are common in patients with CF, and have been observed in some 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 >5x 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Patients after organ transplantation

Symdeko has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended (see Sections 4.5 INTERACTIONS

WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for interactions with ciclosporin or tacrolimus).

Use in elderly
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.

Paediatric use
The safety and efficacy of Symdeko in children aged less than 12 years has not yet been studied (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Effects on laboratory tests
See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Effect on Liver Function Tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products affecting the pharmacokinetics of Symdeko
CYP3A inducers
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.

Examples of strong CYP3A inducers include:
- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

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. When co-administered with strong CYP3A inhibitors, the dose of Symdeko should be reduced (see Table 3 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Examples of strong CYP3A inhibitors include:
- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Physiologically based pharmacokinetic modeling suggested co-administration with fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor exposure (AUC) by approximately 2-fold. Co-administration of fluconazole increased ivacaftor AUC by 3-fold. When co-administered with moderate CYP3A inhibitors, the dose of Symdeko should be reduced (see Table 3 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 ivacaftor and tezacaftor; therefore, food or drink containing grapefruit or Seville oranges should be avoided during treatment with Symdeko (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

No dose adjustment is necessary for Symdeko when administered concomitantly with ciprofloxacin.

Medicinal products affected by Symdeko

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 normalised ratio (INR) during co-administration of Symdeko with warfarin is recommended. Other drugs for which exposure may be increased by Symdeko include glimepiride and glipizide; these drugs should be used with caution.

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 ciclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Hormonal contraceptives

Symdeko has been studied with an estrogen/progesterone 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Tezacaftor did not affect fertility or reproductive performance indices in male and female rats at oral doses up to 100 mg/kg/day (yielding systemic exposure in animals approximately 3 times greater than that in patients at the maximum recommended human dose [MRHD] based on summed AUCs of tezacaftor and its pharmacologically active M1 metabolite).

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding approximately 12 and 6 times, respectively, the systemic exposure anticipated in patients at the MRHD based on summed AUCs of ivacaftor and its major metabolites when dams were dosed prior to and during early pregnancy. The pregnancy rate was decreased, oestrus cycling was disrupted and pre-implantation loss was increased. These effects occurred in the presence of significant maternal toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (yielding approximately 6.5 and 4 times, respectively, the exposure at the MRHD of the ivacaftor component of Symdeko based on summed AUCs of ivacaftor and its metabolites).

Use in Pregnancy
Category B3
Category B3 drugs have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Tezacaftor, ivacaftor and/or their metabolites were shown to cross the placenta in laboratory animal species (rats and/or rabbits).

Tezacaftor
No evidence of harm to the fetus was observed with tezacaftor in a developmental toxicity study in rats at oral doses up to 100mg/kg/day (yielding 3 times the exposure at the MRHD (based on summed AUCs for tezacaftor and its M1 metabolite). In the rabbit, lower foetal body weights were noted at an oral dose of 50mg/kg/day (the highest dose tested; yielding exposure around the same as at the MRHD), which occurred in conjunction with significant maternotoxicity. However, no effects on embryofoetal survival and no teratogencity were observed with tezacaftor in the species. Foetal body weight was unaffected in rabbits at 25mg/kg/day (yielding exposure 4 times lower than that at the MRHD based on summed AUCs of tezacaftor and its M1 metabolite).

Ivacaftor
Developmental toxicity studies with ivacaftor revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day (yielding 6 times the summed AUC for ivacaftor and its major metabolites anticipated in patients) or in rabbits at up to 100 mg/kg/day (relative exposure based on summed AUCs, ≥3.4). Foetal weight was decreased and the incidence of minor foetal skeletal abnormalities was increased in rats treated at 200 mg/kg/day; these effects were observed in conjunction with maternal toxicity.

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.

Use in lactation
Both tezacaftor and ivacaftor are excreted into the milk of lactating female rats. Exposure of ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 2 and 1.5 times, respectively, 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness has been reported in patients receiving Symdeko, which could influence the ability to drive or operate machines (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile of Symdeko is based on pooled data from three double-blind, placebo-controlled, Phase 3 clinical studies in patients with CF aged 12 years and older, including: a 24-week study in patients homozygous for the F508del mutation in the CFTR gene, a 8-week cross-over study in patients heterozygous for the F508del-CFTR mutation and a second mutation associated with residual CFTR activity and a 12-week study in patients heterozygous for the F508del mutation and a second mutation not responsive to tezacaftor/ivacaftor. In these studies, a total of 496 patients received at least one dose of Symdeko. The proportion of patients who discontinued study drug prematurely due to adverse events was 1.6% for Symdeko treated patients and 2.0% for placebo-treated patients. The safety profile of Symdeko also includes data from a 24 week interim analysis, from a 96-week open-label extension study.

The safety profile of Symdeko, including respiratory events (*e.g.*, chest discomfort, dyspnea, and respiration abnormal), was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Table 4 shows adverse events with an incidence of at least 10% in any treatment group from three double-blind, placebo-controlled, Phase 3 clinical studies (8, 12, and 24 weeks of treatment).

Table 4. Adverse Events With an Incidence of at Least 10% in Any Treatment Group of Patients Aged 12 Years and Older Who were Homozygous or heterogynous for the *F508del* Mutation in the CFTR Gene

Preferred Term	Symdeko N=496 n (%)	Placebo N=505 n (%)
Infective pulmonary exacerbation of cystic fibrosis	117 (23.6)	153 (30.3)
Cough	108 (21.8)	141 (27.9)
Headache	68 (13.7)	57 (11.3)
Nasopharyngitis	57 (11.5)	49 (9.7)
Sputum increased	57 (11.5)	65 (12.9)
Haemoptysis	48 (9.7)	56 (11.1)
Fatigue	38 (7.7)	51 (10.1)

Tabulated list of adverse reactions

Table 5 shows adverse events occurring in ≥3% of Symdeko-treated patients and at a frequency higher than placebo by ≥1%. Adverse events for Symdeko are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5: Adverse Reactions by Preferred Term, Incidence and Frequency

System Organ Class (SOC)	Adverse Events (Preferred Term)	Symdeko N=496 n (%)	Placebo N=505 n (%)	Frequency for Symdeko
Infections and infestations	Nasopharyngitis	57 (11.5)	49 (9.7)	very common
Nervous system	Headache	68 (13.7)	57 (11.3)	very common

disorder	Dizziness	15 (3.0)	10 (2.0)	common
Respiratory, thoracic and mediastinal disorders	Sinus congestion	17 (3.4)	11 (2.2)	common
Gastrointestinal disorders	Nausea	38 (7.7)	34 (6.7)	common

Safety data from an interim safety analysis performed on 867 patients in a long-term safety and efficacy rollover study (EXTEND), including 326 patients with ≥48 weeks of cumulative Symdeko treatment, were consistent with the safety data from the placebo-controlled Phase 3 studies.

Detailed description of selected adverse events
Laboratory Abnormalities
Transaminase elevations
During the placebo-controlled Phase 3 studies (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN were 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.

Reporting suspected adverse effects
Reporting of suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No specific antidote is available for 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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
CF is caused by mutations in the *CFTR* gene that result in the reduced function and/or quantity of the functional CFTR protein (responsible for chloride transport) to the cell surface in multiple organs including the lungs and pancreas. This is associated with persistent lung infections and progressive lung damage, characteristic of the morbidity and mortality associated with CF.

Tezacaftor is a broad-acting CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. 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, airway surface liquid height, and ciliary beat frequency. Symdeko targets the underlying cause of CF in patients who are homozygous for the F508del mutation or who have at least one tezacaftor/ivacaftor responsive mutation in the CFTR gene (see Table 1).

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR
In order to evaluate the response of mutant CFTR protein to tezacaftor/ivacaftor, chloride transport was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Mutations that are responsive to tezacaftor/ivacaftor resulted in increases in chloride transport to at least 10% of untreated normal over baseline.

Clinical trials

Pharmacodynamic effects

Effects on Sweat Chloride
In EVOLVE (Study 106; 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; nominal $P<0.0001$).

In EXPAND (Study 108; patients heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity), 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; nominal $P<0.0001$) between Symdeko and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3; nominal $P<0.0001$) between ivacaftor and placebo.

ECG Evaluation
The effect of multiple doses of tezacaftor 100 mg and 300 mg once daily on QTc interval was evaluated in a double-blind randomised, placebo- and active-controlled study with parallel design with nested crossover cohorts for moxifloxacin and placebo in 96 healthy subjects. No meaningful changes in QTc interval were observed with tezacaftor 100 mg or 300 mg once-daily dose groups.

In a separate study, the effect of multiple doses of ivacaftor 150 mg and 450 mg twice daily on QTc interval was evaluated in a randomised, placebo- and active-controlled (moxifloxacin 400 mg), four-period, crossover QT study in 72 healthy subjects. No meaningful changes in QTc interval were observed with ivacaftor 150 mg or 450 mg twice-daily dose groups.

Efficacy
The efficacy of Symdeko in patients with CF was demonstrated in two Phase 3, double-blind, controlled studies entitled EVOLVE (Study 106) and EXPAND (Study 108) and one Phase 3, open-label extension study entitled EXTEND (Study 110).

Patients in EVOLVE and EXPAND 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 EXTEND (Study 110), a 96-week open-label extension study. 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 studies.

EVOLVE – A study in patients with CF who were homozygous for the* F508del *mutation in the* CFTR *gene (Study 106)

EVOLVE (Study 106) was a 24-week, randomised, double-blind, placebo-controlled study. 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 randomised (1:1 randomisation: 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%]. In EVOLVE (Study 106) treatment with Symdeko resulted in a statistically significant improvement in $ppFEV_1$ (Table 6). The treatment difference between Symdeko and placebo for the primary endpoint of mean absolute change (95% CI) in $ppFEV_1$ from baseline through Week 24 was 4.0 percentage points (95% CI: 3.1, 4.8; $P<0.0001$). Mean improvement in $ppFEV_1$ was sustained throughout the 24-week treatment period (Figure 2). 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 6 for a summary of primary and key secondary outcomes.

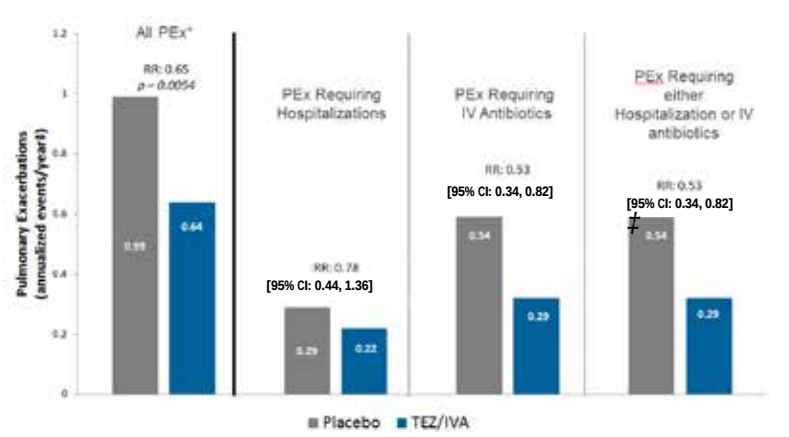
Table 6: Primary and Key Secondary Efficacy Analyses, Full Analysis Set in EVOLVE (Study 106)

Analysis	Statistic	Placebo N=256	Symdeko N=248
Primary			
Average absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI)	NA	4.0 (3.1, 4.8)
	P value	NA	*P*<0.0001*
Key Secondary			
Relative change in $ppFEV_1$ from baseline through Week 24 (%)	Treatment difference (95% CI)	NA	6.8 (5.3, 8.3)
	P value	NA	*P*<0.0001*
Number of pulmonary exacerbations from baseline through Week 24	Rate ratio (95% CI)	NA	0.65 (0.48, 0.88)
	P value	NA	*P*=0.0054*
	Number of events (event rate per year†)	122 (0.99)	78 (0.64)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (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 (95% CI)	NA	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.
* Indicates statistical significance confirmed in the hierarchical testing procedure.
† Estimated event rate per year calculated using 48 weeks per year.

At Week 24 the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with Symdeko compared with placebo. The rate ratio of exacerbations through Week 24 in patients treated with Symdeko was 0.65 (95% CI: 0.48, 0.88; *P*=0.0054), representing a reduction relative to placebo of 35% (see Figure 1).

Figure 1: Pulmonary Exacerbations at week 24 in EVOLVE (Study 106)



**PEx defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of 12 specified signs/symptoms*

‡ *Year defined as 48 weeks*

BMI increased in both treatment groups in EVOLVE (Symdeko: 0.18 kg/m^2, placebo: 0.12 kg/m^2). The treatment difference of 0.06 kg/m^2 mean change in BMI from baseline to Week 24 (95% CI: -0.08, 0.19) in EVOLVE was not statistically significant.

Symdeko demonstrated improvements in CFQ-R Respiratory Domain (a measure of respiratory symptoms relevant to patients with CF including cough, sputum production, and difficulty breathing) compared to placebo. The treatment difference through Week 24 was 5.1 points (95% CI: 3.2, 7.0). The percentage of subjects with at least a 4 point-increase from baseline was higher in the Symdeko group than in the placebo group at all visits. The odds ratio for Symdeko versus placebo through Week 24 was 2.171 (95% CI: 1.469, 3.208).

EXPAND – A Study in patients with CF who were heterozygous for the* F508del-CFTR *mutation and a second mutation associated with residual CFTR activity (Study 108)

In the 244 patients enrolled the following indicated mutations associated with residual CFTR activity were represented: *2789+5G→A*, *3272-26A→G*, *3849+10kbC→T*, *711+3A→G*, *A455E*, *D110H*, *D1152H*, *D579G*, *E831X*, *L206W*, *P67L*, *R1070W*, *R117C*, *R352Q*, *S945L*, and *S977F.*

EXPAND (Study 108) was a randomised, double-blind, placebo controlled, 2-period, 3-treatment, 8-week crossover study. 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 associated with residual CFTR activity were randomised to and received sequences of treatment that included Symdeko, ivacaftor, and placebo. 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%].

In EXPAND (Study 108), treatment with Symdeko resulted in a statistically significant improvement in $ppFEV_1$ (Table 7). The treatment difference between Symdeko- and placebo-treated patients for the primary endpoint of mean absolute change in $ppFEV_1$ from study baseline to the average of Week 4 and Week 8 was 6.8 percentage points (95% CI: 5.7, 7.8; P<0.0001).

Treatment difference 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. Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained throughout the 8-week treatment period (see Figure 3). 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 7 for a summary of primary and key secondary outcomes.

Table 7: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 108)

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)
	P value	NA	NA	*P*=0.2578

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

Subgroup analysis of patients with severe lung dysfunction ($ppFEV_1$ <40):
EVOLVE and EXPAND included a total of 39 Symdeko-treated patients with $ppFEV_1$ <40 at baseline (range 30.3, 39.9); 23 patients from EVOLVE and 16 patients from EXPAND. There were 24 placebo treated patients in EVOLVE, and 15 placebo- and 13 ivacaftor-treated patients in EXPAND with $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to the overall results observed in both EVOLVE and EXPAND.

Study in patients with CF who were heterozygous for the F508del mutation and a second mutation not responsive to tezacaftor/ivacaftor (Study107)
Study 107 was a Phase 3, randomised, double-blind, placebo-controlled, two-arm study that compared Symdeko to placebo in patients with CF aged 12 years and older who were heterozygous for the F508del mutation and had a second CFTR mutation not responsive to tezacaftor/ivacaftor. The primary endpoint of the study was change from baseline in absolute ppFEV1. This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

EXTEND – A long-term safety and efficacy rollover study (Study 110)

An ongoing, Phase 3, open-label, multicenter, rollover, 96-week study to evaluate the safety and efficacy of long-term treatment of Symdeko is being conducted with patients from EVOLVE (n=462) and EXPAND (n=223). When all patients had completed participation in EVOLVE or EXPAND, an interim analysis was conducted for EXTEND. Efficacy analyses for EXTEND were conducted through the last time point in which approximately 70% of subjects had completed

the visit (*i.e.*, Week 24 for patients from EVOLVE and Week 16 for patients from EXPAND). For patients in EXPAND only the Period 2 treatment assignments were considered in the analysis for EXTEND.

Patients who received placebo in both EVOLVE and EXPAND demonstrated improvements in $ppFEV_1$ when receiving Symdeko in EXTEND. These improvements were observed as early as Day 15 of EXTEND (EVOLVE: within-group change = 3.7 percentage points, EXPAND: within-group change 3.9 percentage points). Improvements were sustained for patients from both EVOLVE and EXPAND. Patients who received Symdeko in EVOLVE and EXPAND showed sustained improvements in $ppFEV_1$ through 48 weeks (i.e. Week 24 in EXTEND) and through 24 weeks (i.e. Week 16 EXTEND), respectively. Both magnitude and trend of improvement in $ppFEV_1$ observed in EXTEND were similar to those observed for patients who received Symdeko in EVOLVE and EXPAND (see Figure 2 and 3). Similar trends were observed for CFQ-R as in the parent studies. BMI continued to increase for patients in EVOLVE and EXPAND when enrolled into EXTEND.

Patients who continued on Symdeko from EVOLVE to EXTEND maintained an event rate of pulmonary exacerbations (0.72) that was lower than the placebo event rate per year in EVOLVE (0.99).

Patients who received placebo in EVOLVE and then received Symdeko in EXTEND had a reduction in event rate per year of pulmonary exacerbations from 0.99 to 0.58.

Patients who continued on Symdeko from EXPAND to EXTEND had an event rate of pulmonary exacerbations of 0.20 that was lower than the placebo event rate per year in EXPAND (0.63).

Patients who received placebo in EXPAND and switched to Symdeko in EXTEND had an event rate per year of pulmonary exacerbations (0.34) similar to the event rate observed in Symdeko-treated patients in EXPAND.

Figure 2: Absolute Change From Baseline in Percent Predicted FEV_1 at Each Visit in EVOLVE (Study 106) and for Patients from EVOLVE that Enrolled into EXTEND (Study 110)

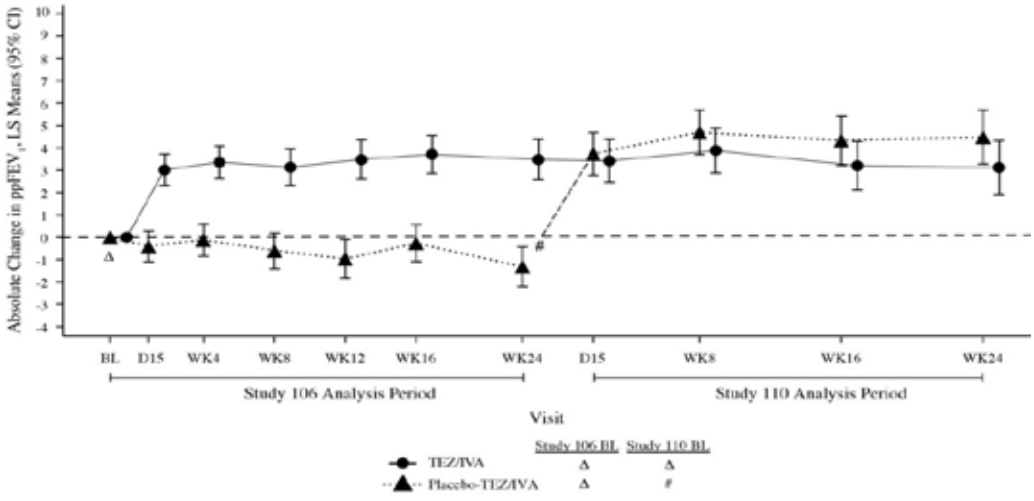
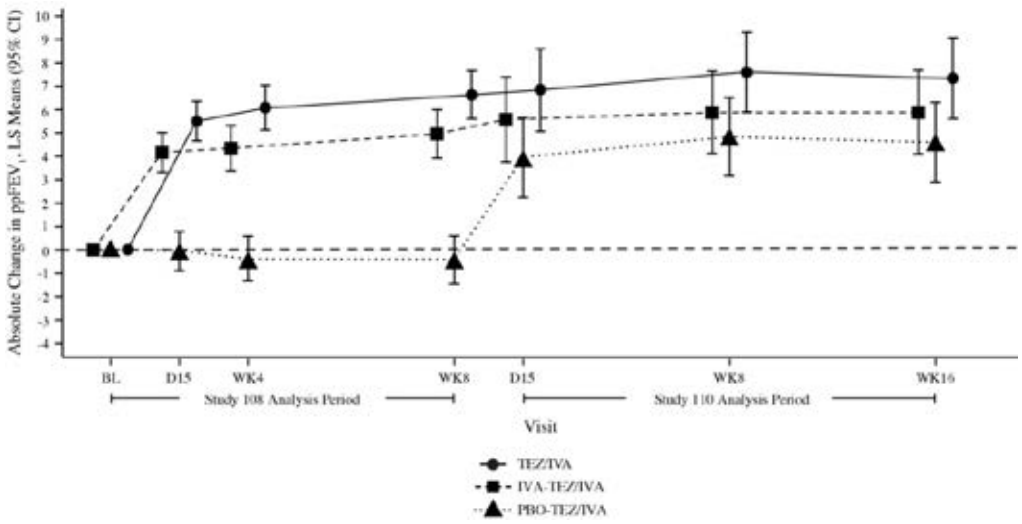


Figure 3: Absolute Change From Baseline in Percent Predicted FEV_1 at Each Visit in EXPAND (Study 108) and for Patients from EXPAND that Enrolled into EXTEND (110)



5.2 PHARMACOKINETIC PROPERTIES

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 of tezacaftor is approximately 2.3 for tezacaftor and 3.0 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)*
Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Tezacaftor	6.52 (1.83)	156 (52.7)	82.7 (23.3)
	Ivacaftor	1.28 (0.440)	9.3 (1.7)	10.9 (3.89)
*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 metabolised extensively in humans. *In vitro* data suggested that tezacaftor is metabolised 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 apparent 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 metabolised extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolised 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
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%) is eliminated in the feces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged drug.

Hepatic impairment
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. Based on these results, a modified regimen of Symdeko is recommended for patients with moderate hepatic impairment (see Table 2 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
The impact of severe hepatic impairment (Child-Pugh Class C, score 10-15) 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 in patients with severe hepatic impairment (see Table 2 in Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

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 Phase 2/3 clinical studies indicated that mild renal impairment (N=147; eGFR 60 to 89 ml/min/1.73 m^2) and moderate rental impairment (N=7, eGFR 30 to 59 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.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Tezacaftor and ivacaftor were both 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.

Carcinogenicity
No evidence of tumourigenicity by tezacaftor was observed in a 6-month study in transgenic (Tg.rasH2) mice and in a conventional 2-year study in rats, conducted by the oral route. The highest doses tested (500 mg/kg/day in mice, 50 mg/kg/day in male rats and 75 mg/kg/day in female rats) yielded exposure to tezacaftor and its M1 and M2 metabolites that was 1.8 fold higher in mice, 1.5-fold higher in male rats, and 2.5-fold higher in female rats than in patients at the MRHD (based on summed AUCs).

Two-year oral studies in mice and rats demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 5- to 9-fold higher than the plasma levels measured in humans following Symdeko therapy, and at least 1.4- to 2.8-fold higher with respect to the summed AUC for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 21- to 39-fold higher than the plasma levels measured in humans following Symdeko therapy, and 7- to 11-fold higher with respect to the summed AUC for ivacaftor and its major metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tezacaftor/Ivacaftor Tablets
Hypromellose acetate succinate
Sodium lauryl sulfate
Hypromellose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Opadry complete film coating system 20A120010 Yellow (PI No. 111630)

Ivacaftor Tablets
Silicon dioxide
Croscarmellose sodium
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate
Carnauba wax
Opadry II complete film coating system 85F90614 Blue (PI No.108371)
OPACODE monogramming ink S-1-17823 BLACK (PI No.12108)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf-life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Store in original container.

6.5 NATURE AND CONTENTS OF THE CONTAINER

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

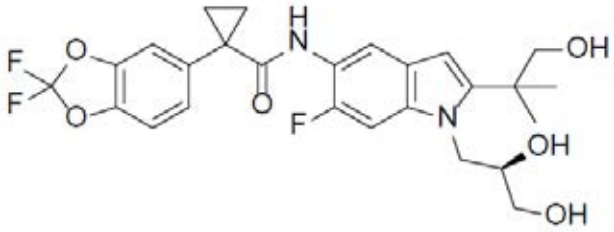
Symdeko Pack size:
56 tablets, monthly pack
Tezacaftor 100 mg/Ivacaftor 150 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

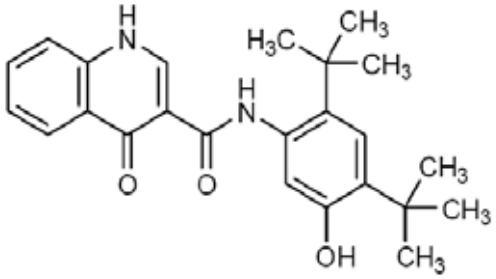
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



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)-4-oxo-1,4-dihydroquinoline-3-carboxamide

CAS Number

Tezacaftor: 1152311-62-0
Ivacaftor: 873054-44-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Vertex Pharmaceuticals (Australia) Pty Ltd
Suite 3, Level 3
601 Pacific Highway
St Leonards,
NSW 2065
Australia
Telephone: 1800 179 987

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

5 March 2019

10 DATE OF REVISION

Not applicable

Summary table of changes

Section Changed	Date Changed	Summary of new information