# PDL DRUG REVIEW

**Proprietary Name: Symdeko®**
**Common Name: tezacaftor & ivacaftor**
**PDL Category: Cystic Fibrosis Agents**

| Comparable Products | Preferred Drug List Status |
|---|---|
| Kalydeko | Non-Preferred with Conditions |
| Orkambi | Non-Preferred with Conditions |

## Summary


**Pharmacology/Usage:** Symdeko® is a fixed-dose combination tablet containing tezacaftor and ivacaftor that is co-packaged with ivacaftor tablets. Tezacaftor facilitates the cellular processing and trafficking of normal and select mutant forms of cystic fibrosis transmembrane conductance regulator (CFTR; including F508del-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport.

**Indication:** For the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508de*l mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

There is no pregnancy category for this medication; however, the risk summary indicates that there are limited and incomplete human data from clinical trials and post-marketing reports on the use of Symdeko® or its individual components in pregnant women to inform a drug-associated risk. No adverse developmental effects were seen after oral administration of either active ingredient to pregnant animals. The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

**Dosage Forms:** Co-packaged tezacaftor 100mg/ivacaftor 150mg fixed-dose combination tablets and ivacaftor 150mg tablets

**Recommended Dosage:** Take one tablet (tezacaftor/ivacaftor) in the morning and one ivacaftor 150mg tablet in the evening (about 12 hours apart) with fat-containing food such as food prepped with butter or oils or those containing eggs, cheese, nuts whole milk, or meats.

Dose adjustments are not required for mild or moderate renal impairment, but use treatment with caution in patients with severe impairment or end-stage renal disease. Dose adjustments are not required with mild hepatic impairment. A reduced dose is recommended with moderate hepatic impairment (one tablet once daily with no ivacaftor 150mg dose). Use with caution at a reduced dose in patients with severe hepatic impairment after weighing the risks and benefits of treatment (one tablet once daily or less frequently with no ivacaftor 150mg dose).

**Drug Interactions:** Food or drink containing grapefruit or Seville oranges should be avoided during treatment with Symdeko®. Concomitant use of Symdeko® with strong CYP3A inducers (such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort) is not recommended. When Symdeko® is co-administered with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate CYP3A inhibitors (e.g. fluconazole, erythromycin), the dosing of Symdeko® should be adjusted. Refer to the prescribing information for specific information regarding dose adjustments for patients taking CYP3A inhibitors.

Concomitant use of Symdeko® with digoxin increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of Symdeko® may increase systemic exposure of sensitive substrates of P-gp. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, use caution and monitor appropriately.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Symdeko®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included headache (2%), nausea (2%), sinus congestion (2%), and dizziness (2%).

Elevated transaminases have been seen in patients treated with Symdeko®, as well as with ivacaftor monotherapy. It is recommended to assess transaminases (ALT and AST) prior to starting treatment, every 3 months during the first year of treatment, and annually thereafter. For those with a history of elevated transaminases, more frequent monitoring should be considered. If significant elevations occur (e.g. patients with ALT or AST >5 times upper limit of normal (ULN) or ALT or AST >3 times ULN with bilirubin >2 times ULN), dosing should be interrupted and lab testing should be followed closely until the abnormalities resolve.

Cases of non-congenital lens opacities have been reported in pediatric patients treated with Symdeko®, as well as with ivacaftor monotherapy. While risk factors were present in some cases, a potential risk attributed to Symdeko® cannot be excluded. It is recommended that baseline and follow-up ophthalmological exams be conducted in pediatric patients starting treatment with Symdeko®.

**Contraindications:** There are no contraindications listed with this product.

**Manufacturer:** Vertex Pharmaceuticals

**Analysis:** The safety and efficacy of Symdeko® were assessed in CF pediatric patients ≥12 years of age in three phase 3, double-blind, placebo-controlled trials. Patients in all trials continued on their standard-of-care CF therapies (e.g. bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline) and were eligible to roll over into a 96-week open-label extension. Patients had a percent predicted FEV1 (ppFEV1) at screening between 40-90%. In addition, 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 abnormal liver function tests at screening or AST or ALT ≥5 times ULN, were excluded from the trials.

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study that included CF patients (N=504) who were homozygous for the *F508del* mutation in the *CFTR* gene. The mean ppFEV1 at baseline was 60%. The primary endpoint was the change in lung function as determined by absolute change from baseline in ppFEV1 through week 24. Results suggested that treatment with Symdeko® resulted in a statistically significant improvement in

ppFEV1 as compared with placebo. The treatment difference for the mean absolute change in ppFEV1 from baseline through week 24 was 4.0 percentage points (p<0.0001).

Main secondary endpoints included relative change from baseline in ppFEV1 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 the CF Questionnaire-Revised (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. Results can be seen in the table below, which was adapted from the prescribing information.

| | | Placebo (N=256) | Symdeko® (N=248) |
|---|---|---|---|
| Relative change in ppFEV1 from baseline to week 24 (%) | Treatment difference | | 6.8 |
| | p-value | p<0.0001 | |
| # of pulmonary exacerbations from baseline to week 24 | # events (event rate/year) | 122 | 78 |
| | Rate Ratio; p-value | 0.65; p=0.0054 | |
| Absolute change in BMI from baseline at week 24 ($kg/m^2$) | Treatment difference | - | 0.06 |
| Absolute change in CFQ-R Respiratory Domain Score from baseline to week 24 | Treatment difference (points) | - | 5.1 |

Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (N=244). Mutations predicted to be responsive were selected for the study based on clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor. The mean ppFEV1 at baseline was 62.3%. Of the total group, 146 had a splice mutation and 98 had a missense mutation as the second allele. Patients were randomized to placebo, Symdeko®, or ivacaftor. The primary endpoint was the mean absolute change from study baseline in percent predicted FEV1 averaged at weeks 4 and 8 of treatment. The main secondary endpoint was absolute change in CFQ-R Respiratory Domain Score from study baseline averaged at weeks 4 and 8 of treatment.

For the overall population, Symdeko® as compared with placebo resulted in significant improvement in ppFEV1 (6.8 percentage points treatment difference, p<0.0001) and CFQ-R Respiratory Domain Score (11.1 points, p<0.0001). Treatment difference for ppFEV1 between ivacaftor- and placebo-treated patients was 4.7 percentage points (p<0.0001) and 2.1 percentage points (p<0.0001) between Symdeko®- and ivacaftor-treated patients, which were statistically significant. Statistically significant improvements compared to placebo were also seen in the subgroup of patients with splice mutations and missense mutations.

In an analysis of BMI at week 8, an exploratory endpoint, the Symdeko® group had a mean improvement of $0.2kg/m^2$, $0.1kg/m^2$, and $0.3kg/m^2$ versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

Trial 3 was a 12-week, randomized, double-blind, placebo-controlled, two-arm study in CF patients ≥12 years of age (N=168) who were heterozygous for the F508del mutation and a second CFTR mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor.

CF patients with the F508del mutation and one of the following mutations in the CFTR gene were enrolled in the study (listed in decreasing frequency): W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, CFTRdele2,3, 2183delAA>G, 2184insA, R1162X, R553X, 3659delC, 3905insT, G970R, I507del, R1066C, R347P,

1154insTC, 1811+1.6kbA>G, 2184delA, 405+1G>A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G>A, 1677delTA, 1812-1G>A, 2869INSG, 3120+1G>A, 394delTT, 457TAT>G, 711+1G>T, 711+5G>A, 712-1G>T, G673x, L1065P, Q220X, Q493X, R709X, V520F.

The mean ppFEV1 at baseline was 57.5%. The primary endpoint was the change from baseline in absolute ppFEV1 through week 12. The overall treatment difference between Symdeko® and placebo for the mean absolute change in ppFEV1 from baseline through week 12 was 1.2 percentage points. This study was terminated after the planned interim analysis as the pre-specified futility criteria were met.

**Place in Therapy:** Symdeko® is a combination product of tezacaftor/ivacaftor co-packaged with ivacaftor oral tablets indicated for the treatment of patients with CF aged ≥12 years who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence. If the patient's genotype is not known, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. The efficacy of Symdeko® was established in CF patients as compared with placebo.

There is no evidence that Symdeko® is safer or more effective than the currently available medications. It is therefore recommended that Symdeko® remain non-preferred to ensure it is used in clinically appropriate situations.

**PDL Placement:** ☐ **Preferred**
☒ **Non-Preferred with Conditions**

## References

[1] Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals; 2018.