

FOR CERTAIN PATIENTS WITH CF AGE 6 YEARS AND OLDER
**SYMDEKO targets CFTR protein defects
in a diverse range of genotypes¹**

**CFTR Mutations That Produce CFTR Protein
Responsive to SYMDEKO^{1-3*}**

F508del/F508del* c.1521_1523delCTT	E56K c.166G>A	R347H c.1040G>A
A1067T c.3199G>A	E831X c.2491G>T	R352Q c.1055G>A
A455E c.1364C>A	F1052V c.3154T>G	R74W c.220C>T
D110E c.330C>A	F1074L c.3222T>A	S945L c.2834C>T
D110H c.328G>C	K1060T c.3179A>C	S977F c.2930C>T
D1152H c.3454G>C	L206W c.617T>G	2789+5G>A c.2657+5G>A
D1270N c.3808G>A	P67L c.200C>T	3272-26A>G c.3140-26A>G
D579G c.1736A>G	R1070W c.3208C>T	3849+10kbC>T c.3718-2477C>T
E193K c.577G>A	R117C c.349C>T	711+3A>G c.579+3A>G

*A patient must have 2 copies of the *F508del* mutation or at least one copy of a responsive mutation listed above in this table to be indicated.

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

IMPORTANT SAFETY INFORMATION

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered
- Dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST >5x upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN) and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment

Please click for additional [Important Safety Information and full Prescribing Information for SYMDEKO.](#)

IMPORTANT SAFETY INFORMATION (CONT)

Concomitant Use With CYP3A Inducers

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, is not recommended

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO

Pediatric Use

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

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients

Most Common Adverse Reactions

- The most common adverse reactions in Trials 1 and 3 occurring in $\geq 3\%$ of patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness
- The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3

Please click for additional [Important Safety Information](#) and [full Prescribing Information](#) for SYMDEKO. For more information, visit SYMDEKOhcp.com.

References: **1.** SYMDEKO [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; June 2019. **2.** The Clinical and Functional TRanslation of CFTR (CFTR2); available at <http://cftr2.org>. List of CFTR2 mutations. https://www.cftr2.org/mutations_history/CFTR2_11March2019.xlsx. Accessed June 7, 2019. **3.** National Center for Biotechnology Information. ClinVar. Available at <https://www.ncbi.nlm.nih.gov/clinvar/>. Accessed June 7, 2019.



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