BlueCross BlueShield Federal Employee Program

SYMDEKO
(tezacaftor and ivacaftor)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Cystic Fibrosis (CF) is caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encode for proteins called CFTR proteins. The CFTR proteins function as channels for chloride ions to go in and out of epithelial cells, which can be found on various parts of the body including the lungs and pancreas. Because these CFTR protein channels are mutated in CF patients, chloride (and therefore fluids) cannot be transported appropriately across cell membranes, causing a build-up of abnormally thick mucus in the lungs, pancreas, and other organs with the CFTR channels. Symdeko is a combination medication of CFTR potentiators (tezacaftor and ivacaftor) that works within cells to increase the quantity and function of the CFTR protein at the cell surface, resulting in increased chloride transport, in CF patients with certain *CFTR* gene mutations (1-2).

Regulatory Status

FDA-approved indication: Symdeko is a combination of tezacaftor and ivacaftor, 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 (1).

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 (1).

List of *CFTR* Gene Mutations that are Responsive to Symdeko					
546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
711+3A→G	*E116K*	*G576A;R668*	*L967S*	*R117H*	*S737F*
2789+5G→A	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
3272-26A→G	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L*
3849+10kbC→T	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F*
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251*
A455E	*F311del*	*H939R*	*M952I*	*R347H*	*S1255*

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A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036*
A1067T	*F508C;S1251*	*I148T*	*P67L*	*R352Q*	*T1053I*
D110E	*F508del* ^	*I175V*	*P205S*	*R352W*	*V201M*
D110H	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153*
D579G	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240*
D614G	*G126D*	*I1027T*	*R31L*	*R1066*	*V1293*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070*	*W1282*
D924N	*G178R*	*I1269N*	*R74W*	*R1070*	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N* †	*R1162L*	*Y161S*
D1152H	*G194V*	*K1060T*	*R74W;V201M* †	*R1283*	*Y1014*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270*	*R1283*	*Y1032*
E56K	*G551D*	*L206W*	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C*	*S549R*	

^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented above to be indicated.

† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Elevated transaminases have been observed in patients with CF treated with Symdeko, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations more frequent monitoring should be considered. In the event of significant elevations of transaminases, e.g., patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment (1).

Additionally, participants were excluded if they 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. The primary efficacy endpoint was change in lung function determined by absolute change from baseline in $ppFEV_1$ (1).

The safety and efficacy of Symdeko in patients with CF younger than 6 years of age have not been studied (1).

Summary

Cystic Fibrosis (CF) is caused by mutations to the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encode for proteins called CFTR proteins. Mutations in these regulators lead to a build-up of sticky mucus in the lungs, pancreas, and other organs of the body. Symdeko is a combination of tezacaftor and ivacaftor, 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. The use of this medication can improve the quantity and quality of the CFTR channels on the cell membranes and can help decrease the build-up of mucus in CF patients (1-2).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Symdeko while maintaining optimal therapeutic outcomes.

References

1. Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals, Inc.; August 2023.
2. Farinha CM, Paulo M, and Amaral MD. Control of cystic fibrosis transmembrane conductance regulator membrane trafficking: not just from the endoplasmic reticulum to the Golgi. FEBS Journal 280 (2013) 4396–4406.