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Subsection:	Respiratory Agents	Original Policy Date:	March 9, 2018
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Last Review Date: March 12, 2021

Symdeko

Description

Symdeko (tezacaftor and ivacaftor)

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).

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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 <i>CFTR</i> Gene Mutations that are Responsive to Symdeko					
546insCTA	E92K	G576A	L346P	R117G	S589N
711+3A→G	E116K	G576A;R668C †	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	S1159P
A349V	F191V	G1349D	M265R	R334Q	S1251N
A455E	F311del	H939R	M952I	R347H	S1255P
A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C;S1251N †	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;R668C †	F1074L	I807M	Q359R	R792G	V1153E
D579G	F1099L	I980K	Q1291R	R933G	V1240G
D614G	G126D	I1027T	R31L	R1066H	V1293G
D836Y	G178E	I1139V	R74Q	R1070Q	W1282R
D924N	G178R	I1269N	R74W	R1070W	Y109N
D979V	G194R	I1366N	R74W;D1270N †	R1162L	Y161S
D1152H	G194V	K1060T	R74W;V201M †	R1283M	Y1014C
D1270N	G314E	L15P	R74W;V201M;D1270N †	R1283S	Y1032C
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

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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 ppFEV₁ (1).

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

Related policies

Kalydeco, Orkambi, Pulmozyme, Trikafta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Symdeko may be considered **medically necessary** for patients 6 years of age or older with cystic fibrosis and if all of the conditions indicated below are met

Symdeko may be considered **investigational** in patients less than 6 years of age and for all other indications.

Prior-Approval Requirements

Age 6 years of age or older

Diagnosis

Patient must have the following:

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Cystic fibrosis (CF)

AND ALL of the following

1. Homozygous for the *F508del* mutation or at least one mutation in the *CFTR* gene that is responsive to Symdeko (see Appendix 2)
2. Pretreatment percent predicted forced expiratory volume (ppFEV₁) must be provided
3. Baseline ALT, AST, and bilirubin must be obtained at baseline and tested every 3 months for the first year
4. Must be prescribed by a pulmonologist or gastroenterologist
5. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 6 years of age or older

Diagnosis

Patient must have the following:

Cystic Fibrosis (CF)

AND ALL of the following:

1. Stable or improvement of ppFEV₁ from baseline
2. Annual testing of ALT, AST, and bilirubin levels after the first year of therapy
3. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 168 tablets for 84 days

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Duration 6 months

Prior – Approval *Renewal* Limits

Quantity 168 tablets for 84 days

Duration 12 months

Rationale

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.; December 2020.
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

Policy History

Date	Action
March 2018	Addition to PA

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June 2018	Annual editorial review Removal of requirement: patient has had 2 negative respiratory cultures for any of the following organisms: burkholderia cenocepacia, burkholderia dolosa, or mycobacterium abscessus in the past 12 months per SME
March 2019	Annual review
July 2019	Decreased age requirement to 6 years or older from 12 years or older
September 2019	Annual review
March 2020	Annual review and reference update
January 2021	Updated the list of <i>CFTR</i> gene mutations with additional mutations that have been identified as responsive to Symdeko. Added Appendix 2. Italicized every mention of <i>F508del</i> mutation and <i>CFTR</i> gene mutation to be consistent with PI per FEP
March 2021	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

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Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta

Appendix 2 - List of CFTR Gene Mutations that are Responsive to Symdeko

546insCTA	E92K	G576A	L346P	R117G	S589N
711+3A→G	E116K	G576A;R668C †	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
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A455E	F311del	H939R	M952I	R347H	S1255P
A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C;S1251N †	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;R668C †	F1074L	I807M	Q359R	R792G	V1153E
D579G	F1099L	I980K	Q1291R	R933G	V1240G
D614G	G126D	I1027T	R31L	R1066H	V1293G
D836Y	G178E	I1139V	R74Q	R1070Q	W1282R
D924N	G178R	I1269N	R74W	R1070W	Y109N
D979V	G194R	I1366N	R74W;D1270N †	R1162L	Y161S
D1152H	G194V	K1060T	R74W;V201M †	R1283M	Y1014C
D1270N	G314E	L15P	R74W;V201M;D1270N †	R1283S	Y1032C
E56K	G551D	L206W	R75Q	S549N	
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