

# SmartPA Criteria Proposal

<b>Drug/Drug Class:</b>	Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators Clinical Edit
<b>First Implementation Date:</b>	April 23, 2020
<b>Proposed Date:</b>	December 15, 2022
<b>Prepared for:</b>	MO HealthNet
<b>Prepared by:</b>	MO HealthNet/Conduent
<b>Criteria Status:</b>	<input type="checkbox"/> Existing Criteria <input checked="" type="checkbox"/> Revision of Existing Criteria <input type="checkbox"/> New Criteria

## Executive Summary

**Purpose:** Ensure appropriate utilization and control of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

**Why Issue Selected:** Cystic fibrosis (CF) is a life-threatening autosomal recessive disease caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Mutations in the CFTR gene result in decreased amounts or function of the CFTR protein. The CFTR protein is found in the epithelial surfaces of various organs, including the lungs, pancreas, gastrointestinal (GI) tract, and urogenital tracts. This protein controls the movement of electrically charged particles, like chloride and sodium, in and out of these cells. When the protein is defective, as in CF, the salt balance in the epithelial surfaces is disturbed. This leads to increased viscosity of secretions in the respiratory and GI tracts. Abnormal viscosity, in turn, results in obstruction of the airways in the lungs and pancreatic ducts, and abnormal luminal contents in the GI tract. CF affects approximately 30,000 people in the US, with approximately 800 new cases diagnosed every year. The primary cause of death in CF is respiratory disease; median survival age in the US is 53.1 years.

In the last several years, CFTR modulators (which act by increasing the amount of or improving the function of the defective CF protein) have been developed for the treatment of cystic fibrosis. The efficacy of CFTR modulator therapy correlates to the specific mutation in the CFTR gene; over 2,000 mutations have been identified in human CFTR alleles. The *F508del* mutation is the most common CFTR mutation worldwide; 44.2% of Americans are homozygous for *F508del* with another 40.5% being heterozygous. Kalydeco® (ivacaftor) was first FDA approved in January 2012 and is currently indicated for the treatment of CF in patients aged 4 months and older who have a mutation in the CFTR gene that is responsive to ivacaftor therapy. Orkambi® (lumacaftor/ivacaftor) was first FDA approved in July 2015 and is currently indicated for the treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation in the CFTR gene. Symdeko® (tezacaftor/ivacaftor) was first FDA approved in February 2018 and is currently indicated for the treatment of CF in patients aged 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor therapy. Trikafta® was FDA approved in 2019 and is currently indicated for the treatment of CF in patients aged 6 years and

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older with at least one *F508del* mutation in the CFTR gene or at least one mutation in the CFTR gene that is responsive to Trikafta. Trikafta is a triple therapy agent, containing tezacaftor and ivacaftor, the ingredients in Symdeko, plus a second-generation corrector elexacaftor.

The prescribing of CFTR inhibitors has increased exponentially since their inception. For example, in 2016 amongst individuals 12 years of age and older, 35.4 percent of patients were prescribed a CFTR inhibitor. In 2021, that percentage has increased to 85.1. Trikafta usage in particular has increased, since approximately 92% of CF patients have a CFTR genotype that makes them eligible for this therapy once they reach the age of six.

Due to the high cost and specific approved indication, MO HealthNet will impose clinical criteria to ensure appropriate utilization of the CFTR inhibitors.

**Program-Specific Information:**

Date Range FFS 10/1/2021 to 9/30/2022			
Drug	Claims	Spend	Avg Spend per Claim
KALYDECO 25 MG GRANULES	1	\$10,261.23	\$10,261.23
KALYDECO 50MG GRANULES	37	\$810,285.47	\$21,899.61
KALYDECO 75MG GRANULES	56	\$1,173,500.65	\$20,955.37
KALYDECO 150 MG TAB	55	\$1,193,401.20	\$21,698.20
ORKAMBI 75/94 MG GRAN	0	-	-
ORKAMBI 100/125MG TAB	30	\$575,687.96	\$19,189.60
ORKAMBI 100/125MG GRAN	63	\$1,360,486.41	\$21,595.02
ORKAMBI 150/188MG GRAN	109	\$1,900,917.18	\$17,439.61
ORKAMBI 200/125MG TAB	0	-	-
SYMDEKO 50/75MG	0	-	-
SYMDEKO 100/150MG	26	\$506,022.63	\$19,462.41
TRIKAFTA 100/50/75MG	1,433	\$29,764,960.21	\$20,771.08
TRIKAFTA 50/25/37.5MG	286	\$6,071,161.45	\$21,227.84

- Type of Criteria:**  Increased risk of ADE  Preferred Drug List  
 Appropriate Indications  Clinical Edit
- Data Sources:**  Only Administrative Databases  Databases + Prescriber-Supplied

**Setting & Population**

- Drug class for review: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators
- Age range: All appropriate MO HealthNet participants aged 4 months and older

**Approval Criteria**

- Documented diagnosis of cystic fibrosis **AND**
- Prescribed by or in consultation with an appropriate specialist for the treated disease state, preferably associated with a CF Care Center **AND**
- Participant is of the appropriate age for product prescribed:
  - Kalydeco – aged 4 months and older
  - Orkambi – aged 1 year and older
  - Symdeko – aged 6 years and older

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- Trikafta – aged 6 years and older **AND**
- ~~Documented genetic testing results showing a gene mutation responsive to product prescribed:~~
  - ~~Kalydeco – one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data (see Appendix A)~~
  - ~~Orkambi – homozygous for the F508del mutation in the CFTR gene~~
  - ~~Symdeko:~~
    - ~~homozygous for the F508del mutation in the CFTR gene OR~~
    - ~~one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence (see Appendix B)~~
  - ~~Trikafta:~~
    - ~~at least one F508del mutation in the CFTR gene OR~~
    - ~~one mutation in the CFTR gene that is responsive to Trikafta based on in vitro data (see Appendix C) AND~~
- ~~Documented recent baseline AST, ALT, and bilirubin AND~~
- ~~Documented recent baseline pulmonary function test results (ppFEV<sub>1</sub>) for participants aged ≥ 5 years AND~~
- ~~Documented recent baseline eye exam for participants aged < 18 years to monitor for lens opacities or cataracts~~
- ~~Renewal of prior authorization may be up to 12 months following documentation of the following:~~
  - ~~Annual review at minimum at a CF Care Center AND~~
  - ~~Annual ophthalmic examinations for participants aged < 18 years AND~~
  - ~~AST, ALT, and bilirubin at least every 3 months during the first year of treatment and annually thereafter:~~
    - ~~Serum ALT or AST < 5 times the upper limit of normal (ULN) OR~~
    - ~~Serum ALT or AST < 3 times the ULN with bilirubin < 2 times the ULN AND~~
  - ~~Annual documentation of benefit of therapy (less than expected decline in disease progression), examples include:~~
    - ~~Decrease in hospitalizations~~
    - ~~Increase in BMI~~
    - ~~Decrease in pulmonary exacerbations~~
    - ~~Number percent increase in ppFEV<sub>1</sub> and/or other lung function tests~~

## Denial Criteria

- Therapy will be denied if all approval criteria are not met
- Participant claim history demonstrates concurrent therapy with any other CFTR modulator in the past 25 days
- For Trikafta: documented severe hepatic impairment (Child-Pugh Class C)
- Claim exceeds maximum dosing limitation for the following:

Drug Description	Generic Equivalent	Max Dosing Limitation
TRIKAFTA 100/50/75 MG-150 MG	ELEXACAFTOR/TEZACAFTOR/IVACAFT	3 tablets per day
TRIKAFTA 50/25/37.5 MG-75 MG	ELEXACAFTOR/TEZACAFTOR/IVACAFT	3 tablets per day

## Required Documentation

Laboratory Results:

MedWatch Form:

Progress Notes:

Other:

## Disposition of Edit

Denial: Exception code "0682" (Clinical Edit)  
 Rule Type: CE

## Default Approval Period

1 year

## Appendix A: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco

<i>711+3A→G</i>	<i>F311del</i>	<i>I148T</i>	<i>R75Q</i>	<i>S589N</i>
<i>2789+5G→A</i>	<i>F311L</i>	<i>I175V</i>	<i>R117C</i>	<i>S737F</i>
<i>3272-26A→G</i>	<i>F508C</i>	<i>I807M</i>	<i>R117G</i>	<i>S945L</i>
<i>3849+10kbC→T</i>	<i>F508C;S1251N</i>	<i>I1027T</i>	<i>R117H</i>	<i>S977F</i>
<i>A120T</i>	<i>F1052V</i>	<i>I1139V</i>	<i>R117L</i>	<i>S1159F</i>
<i>A234D</i>	<i>F1074L</i>	<i>K1060T</i>	<i>R117P</i>	<i>S1159P</i>
<i>A349V</i>	<i>G178E</i>	<i>L206W</i>	<i>R170H</i>	<i>S1251N</i>
<i>A455E</i>	<i>G178R</i>	<i>L320V</i>	<i>R347H</i>	<i>S1255P</i>
<i>A1067T</i>	<i>G194R</i>	<i>L967S</i>	<i>R347L</i>	<i>T338I</i>
<i>D110E</i>	<i>G314E</i>	<i>L997F</i>	<i>R352Q</i>	<i>T1053I</i>
<i>D110H</i>	<i>G551D</i>	<i>L1480P</i>	<i>R553Q</i>	<i>V232D</i>
<i>D192G</i>	<i>G551S</i>	<i>M152V</i>	<i>R668C</i>	<i>V562I</i>
<i>D579G</i>	<i>G576A</i>	<i>M952I</i>	<i>R792G</i>	<i>V754M</i>
<i>D924N</i>	<i>G970D</i>	<i>M952T</i>	<i>R933G</i>	<i>V1293G</i>
<i>D1152H</i>	<i>G1069R</i>	<i>P67L</i>	<i>R1070Q</i>	<i>W1282R</i>
<i>D1270N</i>	<i>G1244E</i>	<i>Q237E</i>	<i>R1070W</i>	<i>Y1014C</i>
<i>E56K</i>	<i>G1249R</i>	<i>Q237H</i>	<i>R1162L</i>	<i>Y1032C</i>
<i>E193K</i>	<i>G1349D</i>	<i>Q359R</i>	<i>R1283M</i>	
<i>E822K</i>	<i>H939R</i>	<i>Q1291R</i>	<i>S549N</i>	
<i>E831X</i>	<i>H1375P</i>	<i>R74W</i>	<i>S549R</i>	

## Appendix B: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko

<i>546insCTA</i>	<i>E92K</i>	<i>G576A</i>	<i>L346P</i>	<i>R117G</i>	<i>S589N</i>
<i>711+3A→G</i>	<i>E116K</i>	<i>G576A;R668C</i>	<i>L967S</i>	<i>R117H</i>	<i>S737F</i>
<i>2789+5G→A</i>	<i>E193K</i>	<i>G622D</i>	<i>L997F</i>	<i>R117L</i>	<i>S912L</i>
<i>3272-26A→G</i>	<i>E403D</i>	<i>G970D</i>	<i>L1324P</i>	<i>R117P</i>	<i>S945L</i>
<i>3849+10kbC→T</i>	<i>E588V</i>	<i>G1069R</i>	<i>L1335P</i>	<i>R170H</i>	<i>S977F</i>
<i>A120T</i>	<i>E822K</i>	<i>G1244E</i>	<i>L1480P</i>	<i>R258G</i>	<i>S1159F</i>
<i>A234D</i>	<i>E831X</i>	<i>G1249R</i>	<i>M152V</i>	<i>R334L</i>	<i>S1159P</i>
<i>A349V</i>	<i>F191V</i>	<i>G1349D</i>	<i>M265R</i>	<i>R334Q</i>	<i>S1251N</i>
<i>A455E</i>	<i>F311del</i>	<i>H939R</i>	<i>M952I</i>	<i>R347H</i>	<i>S1255P</i>
<i>A554E</i>	<i>F311L</i>	<i>H1054D</i>	<i>M952T</i>	<i>R347L</i>	<i>T338I</i>
<i>A1006E</i>	<i>F508C</i>	<i>H1375P</i>	<i>P5L</i>	<i>R347P</i>	<i>T1036N</i>
<i>A1067T</i>	<i>F508C;S1251N</i>	<i>I148T</i>	<i>P67L</i>	<i>R352Q</i>	<i>T1053I</i>
<i>D110E</i>	<i>F508del*</i>	<i>I175V</i>	<i>P205S</i>	<i>R352W</i>	<i>V201M</i>
<i>D110H</i>	<i>F575Y</i>	<i>I336K</i>	<i>Q98R</i>	<i>R553Q</i>	<i>V232D</i>
<i>D192G</i>	<i>F1016S</i>	<i>I601F</i>	<i>Q237E</i>	<i>R668C</i>	<i>V562I</i>
<i>D443Y</i>	<i>F1052V</i>	<i>I618T</i>	<i>Q237H</i>	<i>R751L</i>	<i>V754M</i>

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<b>D443Y;G576A;R668C</b>	<b>F1074L</b>	<b>I807M</b>	<b>Q359R</b>	<b>R792G</b>	<b>V1153E</b>
<b>D579G</b>	<b>F1099L</b>	<b>I980K</b>	<b>Q1291R</b>	<b>R933G</b>	<b>V1240G</b>
<b>D614G</b>	<b>G126D</b>	<b>I1027T</b>	<b>R31L</b>	<b>R1066H</b>	<b>V1293G</b>
<b>D836Y</b>	<b>G178E</b>	<b>I1139V</b>	<b>R74Q</b>	<b>R1070Q</b>	<b>W1282R</b>
<b>D924N</b>	<b>G178R</b>	<b>I1269N</b>	<b>R74W</b>	<b>R1070W</b>	<b>Y109N</b>
<b>D979V</b>	<b>G194R</b>	<b>I1366N</b>	<b>R74W;D1270N</b>	<b>R1162L</b>	<b>Y161S</b>
<b>D1152H</b>	<b>G194V</b>	<b>K1060T</b>	<b>R74W;V201M</b>	<b>R1283M</b>	<b>Y1014C</b>
<b>D1270N</b>	<b>G314E</b>	<b>L15P</b>	<b>R74W;V201M;D1270N</b>	<b>R1283S</b>	<b>Y1032C</b>
<b>E56K</b>	<b>G551D</b>	<b>L206W</b>	<b>R75Q</b>	<b>S549N</b>	
<b>E60K</b>	<b>G551S</b>	<b>L320V</b>	<b>R117C</b>	<b>S549R</b>	

\* Participant must have two copies of the *F508del* mutation

### Appendix C: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to Trikafta

<b>3141del9</b>	<b>E822K</b>	<b>G1069R</b>	<b>L967S</b>	<b>R117L</b>	<b>S912L</b>
<b>546insCTA</b>	<b>F191V</b>	<b>G1244E</b>	<b>L997F</b>	<b>R117P</b>	<b>S945L</b>
<b>A46D</b>	<b>F311del</b>	<b>G1249R</b>	<b>L1077P</b>	<b>R170H</b>	<b>S977F</b>
<b>A120T</b>	<b>F311L</b>	<b>G1349D</b>	<b>L1324P</b>	<b>R258G</b>	<b>S1159F</b>
<b>A234D</b>	<b>F508C</b>	<b>H139R</b>	<b>L1335P</b>	<b>R334L</b>	<b>S1159P</b>
<b>A349V</b>	<b>F508C;S1251N</b>	<b>H199Y</b>	<b>L1480P</b>	<b>R334Q</b>	<b>S1251N</b>
<b>A455E</b>	<b>F508del</b>	<b>H939R</b>	<b>M152V</b>	<b>R347H</b>	<b>S1255P</b>
<b>A554E</b>	<b>F575Y</b>	<b>H1054D</b>	<b>M265R</b>	<b>R347L</b>	<b>T338I</b>
<b>A1006E</b>	<b>F1016S</b>	<b>H1085P</b>	<b>M952I</b>	<b>R347P</b>	<b>T1036N</b>
<b>A1067T</b>	<b>F1052V</b>	<b>H1085R</b>	<b>M952T</b>	<b>R352Q</b>	<b>T1053I</b>
<b>D110E</b>	<b>F1074L</b>	<b>H1375P</b>	<b>M1101K</b>	<b>R352W</b>	<b>V201M</b>
<b>D110H</b>	<b>F1099L</b>	<b>I148T</b>	<b>P5L</b>	<b>R553Q</b>	<b>V232D</b>
<b>D192G</b>	<b>G27R</b>	<b>I175V</b>	<b>P67L</b>	<b>R668C</b>	<b>V456A</b>
<b>D443Y</b>	<b>G85E</b>	<b>I336K</b>	<b>P205S</b>	<b>R751L</b>	<b>V456F</b>
<b>D443Y;G576A;R668C</b>	<b>G126D</b>	<b>I502T</b>	<b>P574H</b>	<b>R792G</b>	<b>V562I</b>
<b>D579G</b>	<b>G178E</b>	<b>I601F</b>	<b>Q98R</b>	<b>R933G</b>	<b>V754M</b>
<b>D614G</b>	<b>G178R</b>	<b>I618T</b>	<b>Q237E</b>	<b>R1066H</b>	<b>V1153E</b>
<b>D836Y</b>	<b>G194R</b>	<b>I807M</b>	<b>Q237H</b>	<b>R1070Q</b>	<b>V1240G</b>
<b>D924N</b>	<b>G194V</b>	<b>I980K</b>	<b>Q359R</b>	<b>R1070W</b>	<b>V1293G</b>
<b>D979V</b>	<b>G314E</b>	<b>I1027T</b>	<b>Q1291R</b>	<b>R1162L</b>	<b>W361R</b>
<b>D1152H</b>	<b>G463V</b>	<b>I1139V</b>	<b>R31L</b>	<b>R1283M</b>	<b>W1098C</b>
<b>D1270N</b>	<b>G480C</b>	<b>I1269N</b>	<b>R74Q</b>	<b>R1283S</b>	<b>W1282R</b>
<b>E56K</b>	<b>G551D</b>	<b>I1366N</b>	<b>R74W</b>	<b>S13F</b>	<b>Y109N</b>
<b>E60K</b>	<b>G551S</b>	<b>K1060T</b>	<b>R74W;D1270N</b>	<b>S341P</b>	<b>Y161D</b>
<b>E92K</b>	<b>G576A</b>	<b>L15P</b>	<b>R74W;V201M</b>	<b>S364P</b>	<b>Y161S</b>
<b>E116K</b>	<b>G576A;R668C</b>	<b>L165S</b>	<b>R74W;V201M;D1270N</b>	<b>S492F</b>	<b>Y563N</b>
<b>E193K</b>	<b>G622D</b>	<b>L206W</b>	<b>R75Q</b>	<b>S549N</b>	<b>Y1014C</b>
<b>E403D</b>	<b>G628R</b>	<b>L320V</b>	<b>R117C</b>	<b>S549R</b>	<b>Y1032C</b>
<b>E474K</b>	<b>G970D</b>	<b>L346P</b>	<b>R117G</b>	<b>S589N</b>	
<b>E588V</b>	<b>G1061R</b>	<b>L453S</b>	<b>R117H</b>	<b>S737F</b>	

### References

- KALYDECO® (ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2020.
- ORKAMBI® (lumacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; September 2022.

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- SYMDEKO® (tezacaftor/ivacaftor) tablets and (ivacaftor) tablets [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2020.
- TRIKAFTA® (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; October 2021.
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