SmartPA Criteria Proposal

Drug/Drug Class:	Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators Clinical Edit
First Implementation Date:	April 23, 2020
Proposed Date:	March 18, 2021
Prepared for:	MO HealthNet
Prepared by:	MO HealthNet/Conduent
Criteria Status:	☐Existing Criteria ☒Revision of Existing Criteria ☐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 about 1,000 new cases diagnosed every year. The primary cause of death in CF is respiratory disease; median survival age in the US is 44.4 years.

In the past, treatment of CF has focused on end organ effects (pancreatic insufficiency and treatment of lung disease); however, 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. 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. On October 21, 2019, Trikafta® was FDA approved for the treatment of CF in patients aged 12 years and older with at least one *F508del* mutation in the CFTR gene; this indication covered 90% of the cystic fibrosis population and opened CFTR modulator therapy to many patients who were previously ineligible. In December 2020, Trikafta, Symdeko®, and Kalydeco® received expanded indications to include more mutations responsive to each therapy. With this approval an additional 600 people with CF who were not previously eligible for modulators could benefit from Trikafta, Symdeko, or Kalydeco therapy for the first time. In January 2021, the FDA accepted a sNDA for Trikafta in a younger population (ages 6 through 11 years old) and granted Priority Review. If approved, up to 1,500 additional children would qualify to be treated with Trikafta.

Program-Specific Information:

Date Range FFS 1-1-2020 to 12-31-2020			
Drug	**Claims**	**Spend**	**Avg Spend per Claim**
KALYDECO 25 MG GRANULES	0	-	-
KALYDECO 50 MG GRANULES	45	$954,731.91	$21,216.26
KALYDECO 75 MG GRANULES	7	$166,986.32	$23,855.18
KALYDECO 150 MG TABLET	84	$1,812,910.29	$21,582.26
ORKAMBI 100 MG-125 MG TABLET	111	$2,077,271.71	$18,714.15
ORKAMBI 100-125 MG GRANULES	59	$1,477,724.42	$25,046.17
ORKAMBI 150-188 MG GRANULES	95	$1,397,495.77	$14,710.48
ORKAMBI 200 MG-125 MG TABLET	4	$83,394.86	$20,848.71
SYMDEKO 50/75 MG-75 MG TABLET	70	$1,395,961.45	$19,942.30
SYMDEKO 100/150 MG-150 MG TABLET	102	$1,986,632.83	$19,476.79
TRIKAFTA 100/50/75 MG-150 MG TABLET	1,078	$21,748,632.52	$20,174.98

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 2 years and older
  - Symdeko – aged 6 years and older
  - Trikafta – aged 12 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 ($ppFEV_1$) **AND**
- Documented recent baseline eye exam for participants aged < 18 years to monitor for lens opacities or cataracts

- Renewal Criteria:
  - Initial approval of prior authorization is **12** months
  - Renewal of prior authorization may be given 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 ppFEV1 and/or other lung function tests

Denial Criteria

- Therapy will be denied if no approval criteria are met
- For Trikafta: documented severe hepatic impairment (Child-Pugh Class C)

Required Documentation

Laboratory Results:	X	Progress Notes:	X
MedWatch Form:		Other:	

Disposition of Edit

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

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

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

E56K	G1249R	Q237H	R1162L	Y1032C
E193K	G1349D	Q359R	R1283M	
E822K	H939R	Q1291R	S549N	
E831X	H1375P	R74W	S549R	

Appendix B: List of CFTR Gene Mutations that Produce CFTR Protein and 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	

* 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

3141del9	E822K	G1069R	L967S	R117L	S912L
546insCTA	F191V	G1244E	L997F	R117P	S945L
A46D	F311del	G1249R	L1077P	R170H	S977F
A120T	F311L	G1349D	L1324P	R258G	S1159F
A234D	F508C	H139R	L1335P	R334L	S1159P
A349V	F508C;S1251N	H199Y	L1480P	R334Q	S1251N
A455E	F508del	H939R	M152V	R347H	S1255P
A554E	F575Y	H1054D	M265R	R347L	T338I
A1006E	F1016S	H1085P	M952I	R347P	T1036N
A1067T	F1052V	H1085R	M952T	R352Q	T1053I
D110E	F1074L	H1375P	M1101K	R352W	V201M
D110H	F1099L	I148T	P5L	R553Q	V232D

D192G	G27R	I175V	P67L	R668C	V456A
D443Y	G85E	I336K	P205S	R751L	V456F
D443Y;G576A;R668C	G126D	I502T	P574H	R792G	V562I
D579G	G178E	I601F	Q98R	R933G	V754M
D614G	G178R	I618T	Q237E	R1066H	V1153E
D836Y	G194R	I807M	Q237H	R1070Q	V1240G
D924N	G194V	I980K	Q359R	R1070W	V1293G
D979V	G314E	I1027T	Q1291R	R1162L	W361R
D1152H	G463V	I1139V	R31L	R1283M	W1098C
D1270N	G480C	I1269N	R74Q	R1283S	W1282R
E56K	G551D	I1366N	R74W	S13F	Y109N
E60K	G551S	K1060T	R74W;D1270N	S341P	Y161D
E92K	G576A	L15P	R74W;V201M	S364P	Y161S
E116K	G576A;R668C	L165S	R74W;V201M;D1270N	S492F	Y563N
E193K	G622D	L206W	R75Q	S549N	Y1014C
E403D	G628R	L320V	R117C	S549R	Y1032C
E474K	G970D	L346P	R117G	S589N	
E588V	G1061R	L453S	R117H	S737F	

References

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- ORKAMBI® (lumacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; July 2019.
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- TRIKAFTA™ (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2020.
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