Cystic Fibrosis Agents (Kalydeco, Orkambi, Symdeko, and Trikafta)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Cystic Fibrosis Agent Policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies for Kalydeco (ivacaftor), Orkambi (ivacaftor/lumacaftor), Symdeko (tezacaftor/ivacaftor) and Trikafta (elexacaftor/tezacaftor/ivacaftor).

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Kalydeco is a cystic fibrosis transmembrane conductance regulator (*CFTR*) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Orkambi (lumacaftor/ivacaftor) is approved by the FDA for the treatment of CF in patients age 2 years and older that are homozygous for the *F508del* mutation in the *CFTR* gene.
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.
The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation.

Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 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 *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Trikafta, a triple combination of elexacaftor, tezacaftor, and ivacaftor, is indicated for patients 12 years and older with cystic fibrosis who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* assay data.
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation or a mutation that is responsive based on in vitro data.

POLICY

Required Documentation
The following information is necessary to initiate the prior authorization review:

- Genetic testing report confirming the presence of the appropriate *CFTR* gene mutation
- Submission of medical records (e.g., chart notes, laboratory values, pulmonary function tests, CFQ-R score) documenting clinical benefit from therapy

Criteria for Initial Approval

I. Kalydeco (ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:
   - Genetic testing was conducted to detect a mutation in the *CFTR* gene.
   - The member has one of the mutations in the *CFTR* gene listed Appendix A
   - The patient is at least 4 months of age
   - Kalydeco will not be used in combination with Orkambi, Symdeko or Trikafta

   Initial approval will be for **6 months.**

II. Orkambi (lumacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:
   - The patient is at least 2 years of age
   - Genetic testing was conducted to detect a mutation in the *CFTR* gene
   - The patient is positive for the *F508del* mutation on both alleles of the *CFTR* gene
   - The patient will not be using Orkambi in combination with Kalydeco, Symdeko or Trikafta

   Initial approval will be for **6 months.**

III. Symdeko (tezacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:
   - Genetic testing was conducted to detect a mutation in the *CFTR* gene.
   - The member has one of the mutations in the *CFTR* gene listed in Appendix B, or the member is homozygous for the F508del mutation.
   - The member is at least 6 years of age.
   - Symdeko will not be used in combination with Kalydeco, Orkambi or Trikafta

   Initial approval will be for **6 months.**

IV. Trikafta (elexacaftor/tezacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:
- The patient is at least 12 years of age
- Genetic testing was conducted to detect a mutation in the *CFTR* gene
- The patient is positive for at least one *F508del* mutation of the *CFTR* gene OR has one of the mutations in the *CFTR* gene listed in Appendix C
- The patient will not be using Trikafta in combination with Kalydeco, Orkambi, or Symdeko.

Initial approval will be for **6 months.**

V. Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria and achieve a clinically meaningful response as demonstrated by any of the following:
- Improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline
- Increased body mass index (BMI)
- Decreased pulmonary exacerbations
- Improvement in quality of life from baseline as demonstrated by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

Approval will be for **12 months**.

Quantity Limits Apply:
- Kalydeco 56 tablets/28 days
- Kalydeco Pak 56 packets/28 days
- Orkambi 112 tablets/28 days
- Symdeko 56 tablets/28 days
- Trikafta 84 tablets/28 days

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Appendices

Appendix A: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco (Kalydeco package insert Section 12.1, Table 3)

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*	

*Clinical data exist for these mutations [See Clinical Studies (14)].

**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.

Appendix B: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko (Symdeko package insert Section 12.1, Table 6)

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	

*Clinical data for these mutations in Clinical Studies *[see Clinical Studies (14.1 and 14.2)].*

^A patient must have two copes of the *F508del* mutation or at least one copy of a responsive mutation presented in Appendix B 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.

Appendix C: List of *CFTR* Gene Mutations that are Responsive to Trikafta (Trikafta package insert Section 12.1, Table 4)

Appendix C: List of *CFTR* Gene Mutations that 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	

**F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)].*
**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.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- No applicable codes

REFERENCES

- Kalydeco [package insert]. Cambridge, MA: Vertex Pharmaceuticals Inc; December 2020.
- Orkambi [package insert]. Boston, MA. Vertex Pharmaceuticals Inc.; July 2019.
- Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; December 2020.
- Trikafta [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; December 2020.

- Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. Tezacaftor-Ivacaftor in Residual Funtion Heterzygotes with Cystic Fibrosis. *N Engl J Med*. 2017; 377:2024-2035
- Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *N Engl J Med* 2017; 377:2013-2023
- Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187:680-689.

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POLICY HISTORY

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