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Policy Number: C2436-A

Cystic Fibrosis Agents

PRODUCTS AFFECTED

Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor-ivacaftor), Trikafta (elexacaftor, tezacaftor, ivacaftor)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Cystic fibrosis

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. CYSTIC FIBROSIS:

1. Documented diagnosis of Cystic Fibrosis

Drug and Biologic Coverage Criteria

AND

2. Documentation the member has a responsive mutation to the product requested [DOCUMENTATION REQUIRED]:
 - (a) For Kalydeco: Documentation member as at least ONE of the mutations in the CFTR gene responsive to ivacaftor based on clinical and/or in vitro assay data (see Appendix)
 - OR
 - (b) For Orkambi: Documentation member is homozygous for the F508del mutation in the CFTR gene
 - OR
 - (c) For Symdeko: Documentation member is homozygous for the F508del mutation; OR the member has at least ONE of the mutations in the CFTR gene responsive to tezacaftor/ivacaftor based on clinical and/or in vitro assay data (see Appendix)
 - OR
 - (d) For Trikafta: Documentation member has at least ONE F508del mutation in the CFTR gene OR a mutation in the CFTR gene that is responsive based on in vitro data
- AND
3. Prescriber attests that CFTR agents will not be used concurrently with another CFTR agent [e.g., Kalydeco (ivacaftor), Orkambi (lumacaftor-ivacaftor), Symdeko (tezacaftor/ivacaftor), Trikafta (elexacaftor, tezacaftor, ivacaftor)] OR Strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)
- AND
4. FOR ORAL GRANULE REQUESTS:
 - (a) For Kalydeco member is 1 month to 5 years of age OR
 - (b) For Orkambi member is 1 to 5 years of age OR
 - (c) For Trikafta member is 2 to 5 years of age OR
 - (d) Documentation member is unable to ingest solid oral dosage form (i.e., tablet) due to ONE of the following: age, oral/motor difficulties, dysphagia, or member utilizes a feeding tube for medical administration
- AND
5. Documentation of baseline status to evaluate efficacy of therapy at renewal (i.e., predicted FEV1, lung clearance index, sweat chloride concentration, BMI, amount/frequency of pulmonary exacerbations, etc.) [DOCUMENTATION REQUIRED]
- AND
6. Prescriber attests that the appropriate baseline lab measures were performed prior to initiation of therapy and will be monitored per FDA drug label (i.e., liver function testing, eye exam)

CONTINUATION OF THERAPY:

A. CYSTIC FIBROSIS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
- AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., elevated transaminases, cataracts, chest discomfort, dyspnea, increased blood pressure)
- AND
3. Documentation of improvement or stabilization of lung function as measured by the FEV1 compared to pretreatment baseline when the member is clinically stable OR positive clinical response to therapy (e.g., reduction in lung clearance index, reduction in sweat chloride concentration, a significant improvement in BMI from baseline, reduction in the incidence of pulmonary exacerbations) [DOCUMENTATION REQUIRED]
- AND
4. Prescriber attests a recent review of member's current medication has been completed and there is no concomitant use of strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)

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AND

5. FOR ORAL GRANULE REQUESTS:

- (a) For Kalydeco member is 1 month to 5 years of age OR
- (b) For Orkambi member is 1 to 5 years of age OR
- (c) For Trikafta member is 2 to 5 years of age OR
- (d) Documentation member is unable to ingest solid oral dosage form (i.e., tablet) due to ONE of the following: age, oral/motor difficulties, dysphagia, or member utilizes a feeding tube for medical administration

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a pulmonologist, cystic fibrosis specialist or physician from a CF center accredited by the Cystic Fibrosis Foundation. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.]

AGE RESTRICTIONS:

Kalydeco (ivacaftor): 1 month of age and older

Orkambi (lumacaftor-ivacaftor): 1 year of age and older

Symdeko (tezacaftor-ivacaftor): 6 years of age and older

Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor): 2 years of age and older

QUANTITY:

Kalydeco (ivacaftor): Tablets: 150mg twice daily; OR Packets: 2 packets per day

Orkambi (lumacaftor-ivacaftor): Oral tablets: 4 tablets per day; OR Oral granules: 2 packets per day

Symdeko (tezacaftor-ivacaftor, ivacaftor): 2 tablets per day

Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor): Oral tablets: 3 tablets per day; OR Oral granules: 2 packets per day

Maximum Quantity Limits – Based on FDA labeled recommendations for age/weight

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral

DRUG CLASS:

CFTR Potentiators and combinations

FDA-APPROVED USES:

Kalydeco (ivacaftor): Indicated for the treatment of cystic fibrosis in patients age 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data

Orkambi (lumacaftor-ivacaftor): Indicated for the treatment of cystic fibrosis in patients aged 1 year and older who are homozygous for the F508del mutation in the CFTR gene

Limitations of Use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the F508del mutation

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Symdeko (tezacaftor-ivacaftor): Indicated for the treatment of cystic fibrosis (CF) in patients age 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 based on in vitro data and/or clinical evidence.

Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor): Indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro 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.

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Mutation	CFTR Gene Mutation	CFTR Protein	CFTR Protein	CFTR Protein
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 *	

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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.

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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 copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 6 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.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Kalydeco, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, is indicated for the treatment of cystic fibrosis (CF) in patients ≥ 1 years of age who have one mutation in the CFTR gene that is responsive to Kalydeco potentiation based on clinical and/or in vitro assay data. Mutations with an increase in chloride transport of 10% or greater are considered responsive and include: E56K, P67L, R74W, D110E, D110H, R117C, R117H, G178R, E193K, L206W, R347H, R352Q, A455E, S549N, S549R, G551D, G551S, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T,

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G1069R, R1070Q, R1070W, F1074L, D1152H, G1244E, S1251N, S1255P, D1270N, G1349D, 2789+5G→A, 3272-26A→G OR 3849+10kbC→T. In patients with unknown genotype, a Food and Drug Administration (FDA)- cleared CF mutation test should be used to detect the presence of the CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Kalydeco is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.

Orkambi is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who 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.

Symdeko is indicated for the treatment of patients ≥ 6 years of age with cystic fibrosis (CF) 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. Table 1 lists responsive CFTR mutations based on: 1) a clinical forced expiratory volume in 1 second (FEV1) response and/or 2) in vitro data in FRT cells, indicating that tezacaftor/ivacaftor increases chloride transport to ≥10% of untreated normal over baseline.

CFTR gene mutations that are not responsive to ivacaftor alone are not expected to respond to Symdeko except for F508del homozygotes.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of CFTR Potentiators are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Labeled contraindications to CFTR potentiators include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

Kalydeco (ivacaftor): For cystic fibrosis patients who are homozygous for the F508del mutation, evidence demonstrates a lack of net benefit; additional research is recommended. A systematic review found no improvement in lung function or quality of life for cystic fibrosis patients with homozygous F508del mutations treated with ivacaftor. A specialty society guideline notes that the use of ivacaftor in cystic fibrosis patients who are homozygous for the F508del CFTR mutation is not effective.

For cystic fibrosis patients with a G970R mutation, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. (RG B) The efficacy of ivacaftor could not be established in patients with a G970R mutation in a double-blind crossover study (ivacaftor and placebo) with an open-label extension of 39 cystic fibrosis patients 6 years of age and older with an FEV1 40% of predicted or higher.

Use with strong CYP3A inducers substantially decreases the exposure of ivacaftor, which may reduce the effectiveness of these agents. Therefore, coadministration should be avoided.

CODING/BILLING INFORMATION

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina

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adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
N/A	N/A

AVAILABLE DOSAGE FORMS:

Kalydeco TABS 150MG
Kalydeco PACK 5.8MG
Kalydeco PACK 13.4MG
Kalydeco PACK 25MG
Kalydeco PACK 50MG
Kalydeco PACK 75MG
Orkambi TABS 100-125MG
Orkambi TABS 200-125MG
Orkambi PACK 75-94MG
Orkambi PACK 100-125MG
Orkambi PACK 150-188MG
Symdeko TBPK 50-75 & 75MG
Symdeko TBPK 100-150 & 150MG
Trikafta TBPK 50-25-37.5 & 75MG
Trikafta TBPK 100-50-75 & 150MG
Trikafta THPK 80-40-60 & 59.5MG
Trikafta THPK 100-50-75 & 75MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Coding/Billing Information Template Update	Q4 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q4 2023

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REVISION- Notable revisions: Required Medical Information Age Restrictions Quantity FDA-Approved Uses Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Age Restrictions Appendix Available Dosage Forms References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file

HIGH RISK ALERT