**Original Effective Date: 06/2012**
**Current Effective Date: 11/23/2023**
**Last P&T Approval/Version: 10/25/2023**
**Next Review Due By: 10/2024**
**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

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) 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, 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. Documentation of adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Prescriber attests, or clinical reviewer has found, that member has NOT experienced any toxicity related to the drug which may include elevated transaminases, cataracts, chest discomfort, dyspnea, or 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., 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)
   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) 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): max 60/30 150mg tablets or max 75mg packets (56 packets/28 days)
Orkambi (lumacaftor-Ivacaftor): Oral tablets: 4 tablets per day; 112 tablets per 28 days (package size is 28) OR Oral granules: 2 packets per day; 56 packets per 28 days (package size is 56)
Symdeko (tezacaftor-ivacaftor, ivacaftor): 56 tablets per 28 days
Trikafta (elexacaftor, tezacaftor and ivacaftor; ivacaftor): Oral tablets: max of 84 per 28 days OR Oral granules: 2 packets per day; 56 packets per 28 days (package size is 56)

**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*

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:**

| Table 3: 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 * | |

| Table 5: 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.

| Table 6: 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 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,

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.

## CODING/BILLING INFORMATION

*Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement*

| HCPCS CODE | DESCRIPTION |
|---|---|
| N/A | N/A |

**AVAILABLE DOSAGE FORMS**:

Kalydeco TABS 150MG
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

## REFERENCES


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2. Symdeko tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; August 2023.
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| SUMMARY OF REVIEW/REVISIONS | DATE |
|---|---|
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>FDA-Approved Uses<br>Contraindications/Exclusions/Discontinuation<br>References | Q4 2023 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Age Restrictions<br>Quantity<br>FDA-Approved Uses<br>Available Dosage Forms<br>References | Q3 2023 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Prescriber Requirements<br>Age Restrictions<br>Appendix<br>Available Dosage Forms<br>References | Q4 2022 |
| Q2 2022 Established tracking in new format | Historical changes on file |
| | |