Original Effective Date: 06/2012
Current Effective Date: 12/01/2025
Last P&T Approval/Version: 10/29/2025
Next Review Due By: 04/2026
Policy Number: C2436-A

Cystic Fibrosis Agents

PRODUCTS AFFECTED

Alyftrek (vanzacaftor-tezacaftor-deutivacaftor), 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

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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
   OR
   (e) For Alyftrek: 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), Alyftrek (vanzacaftor-tezacaftor-deutivacaftor)] 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]

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,

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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) 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:
Alyftrek (vanzacaftor-tezacaftor-deutivacaftor): 6 years of age and older
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:
Alyftrek (vanzacaftor-tezacaftor-deutivacaftor): Tablets: 3 tablets per day
Kalydeco (ivacaftor): Tablets: 2 tablets per day; OR Oral granules: 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:
Alyftrek (vanzacaftor-tezacaftor-deutivacaftor): Indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation or another responsive mutation in the CFTR gene.

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

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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 *	

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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.

Table 6: List of CFTR Gene Mutations Responsive to TRIKAFTA				
Mutations responsive to TRIKAFTA based on clinical data^{*}				
2789+5G→A	D1152H^{†}	L206W^{†}	R1066H^{†}	S945L^{†}
3272-26A→G	F508del^{†}	L997F^{†}	R117C^{†}	T338I^{†}
3849+10kbC→T	G85E^{†}	M1101K^{†}	R347H^{†}	V232D^{†}
A455E^{†}	L1077P^{†}	P5L^{†}	R347P^{†}	
Mutations responsive to TRIKAFTA based on in vitro data^{‡}				
N1303K	F200I	I1139V	P574H	S1045Y
1507_1515del9	F311del	I125T	P67L	S108F
2183A→G	F311L	I1269N	P750L	S1118F
3141del9	F508C	I1366N	Q1291R	S1159F

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

546insCTA	F508C;S1251N	I148N	Q1313K	S1159P
A1006E	F575Y	I148T	Q237E	S1235R
A1067P	F587I	I175V	Q237H	S1251N
A1067T	G1047R	I331N	Q359R	S1255P
A107G	G1061R	I336K	Q372H	S13F
A120T	G1069R	I502T	Q493R	S341P
A234D	G1123R	I506L	Q552P	S364P
A309D	G1244E	I556V	Q98R	S492F
A349V	G1247R	I601F	R1048G	S549I
A46D	G1249R	I618T	R1070Q	S549N
A554E	G126D	I807M	R1070W	S549R
A62P	G1349D	I980K	R1162L	S589N
C491R	G178E	K1060T	R117C;G576A;R668C	S737F
D110E	G178R	K162E	R117G	S912L
D110H	G194R	K464E	R117H	S977F
D1270N	G194V	L1011S	R117L	T1036N
D1445N	G27E	L1324P	R117P	T1053I
D192G	G27R	L1335P	R1283M	T1086I
D443Y	G314E	L137P	R1283S	T1246I
D443Y;G576A;R668C	G424S	L1480P	R170H	T1299I
D565G	G463V	L15P	R258G	T351I
D579G	G480C	L165S	R297Q	V1153E
D614G	G480S	L320V	R31C	V1240G
D836Y	G551A	L333F	R31L	V1293G
D924N	G551D	L333H	R334L	V201M
D979V	G551S	L346P	R334Q	V392G
D993Y	G576A	L441P	R347L	V456A
E116K	G576A;R668C	L453S	R352Q	V456F
E116Q	G622D	L619S	R352W	V562I
E193K	G628R	L967S	R516S	V603F
E292K	G970D	M1137V	R553Q	V754M
E403D	G970S	M150K	R555G	W1098C
E474K	H1054D	M152V	R668C	W1282R
E56K	H1085P	M265R	R709Q	W361R
E588V	H1085R	M952I	R74Q	Y1014C
E60K	H1375P	M952T	R74W	Y1032C
E822K	H139R	N1088D	R74W;D1270N	Y109N
E92K	H199Y	N1303I	R74W;V201M	Y161D
F1016S	H620P	N186K	R74W;V201M;D1270N	Y161S
F1052V	H620Q	N187K	R751L	Y301C
F1074L	H939R	N418S	R75L	Y563N
F1099L	H939R;H949L	P140S	R75Q	

HIGHEST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

F1107L	I1027T	P205S	R792G	
F191V	I105N	P499A	R933G	
Mutations responsive to TRIKAFTA based on extrapolation from Trial 5^{§}				
4005+2T→C	2789+2insA	3849+40A→G	5T;TG13	
1341G→A	296+28A→G	3849+4A→G	621+3A→G	
1898+3A→G	3041-15T→G	3850-3T→G	711+3A→G	
2752-26A→G	3600G→A	5T;TG12	E831X	

^{*} Clinical data obtained from Trials 1, 2, and 5.
^{†} This mutation is also predicted to be responsive by FRT assay.
^{‡} The N1303K mutation is predicted to be responsive by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.
^{§} Efficacy is extrapolated from Trial 5 to non-canonical splice mutations because clinical trials in all mutations of this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

Table 5: List of CFTR Gene Mutations Responsive to ALYFTREK						
Based on Clinical Data^{*}						
A455E	G551D	L1077P^{†}	R352Q	S549N	V754M	
D1152H	G85E^{†}	L206W	R75Q	S549R	W1098C^{†}	
F508del^{†}	H1054D	M1101K^{†}	S1159F	S945L	W1282R	
G1244E	I336K	R1066H	S1251N	V562I	Y563N^{†}	
Based on in vitro Data^{‡}						
1507_1515del9	E116Q	G424S	I556V	P140S	R334L	T1053I
2183A→G	E193K	G463V	I601F	P205S	R334Q	T1086I
3141del9	E292K	G480C	I618T	P499A	R347H	T1246I
3195del6	E403D	G480S	I807M	P5L	R347L	T1299I
3199del6	E474K	G551A	I980K	P574H	R347P	T338I
546insCTA	E56K	G551S	K1060T	P67L	R352W	T351I
A1006E	E588V	G576A	K162E	P750L	R516G	T604I
A1067P	E60K	G576A;R668C^{§}	K464E	P99L	R516S	V1153E
A1067T	E822K	G622D	L1011S	Q1100P	R553Q	V1240G
A107G	E92K	G628R	L102R	Q1291R	R555G	V1293G
A120T	F1016S	G91R	L1065P	Q1313K	R560S	V201M
A234D	F1052V	G970D	L1324P	Q237E	R560T	V232D
A309D	F1074L	G970S	L1335P	Q237H	R668C	V392G
A349V	F1099L	H1085P	L137P	Q359R	R709Q	V456A
A46D	F1107L	H1085R	L1480P	Q372H	R74Q	V456F
A554E	F191V	H1375P	L15P	Q452P	R74W	V520F
A559T	F200I	H139R	L165S	Q493R	R74W;D1270N^{§}	V603F
A559V	F311del	H199R	L320V	Q552P	R74W;V201M^{§}	W361R
A561E	F311L	H199Y	L333F	Q98R	R74W;V201M;D 1270N^{§}	Y1014C
A613T	F508C	H609R	L333H	R1048G	R75L	Y1032C
A62P	F508C;S1251N^{§}	H620P	L346P	R1066C	R751L	Y109N

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

A72D	F575Y	H620Q	L441P	R1066L	R792G	Y161D
C491R	F587I	H939R	L453S	R1066M	R933G	Y161S
D110E	G1047R	H939R;H949L	L619S	R1070Q	S1045Y	Y301C
D110H	G1061R	I1027T	L967S	R1070W	S108F	Y569C
D1270N	G1069R	I105N	L997F	R1162L	S1118F	Y913C
D1445N	G1123R	I1139V	M1101R	R117C	S1159P	
D192G	G1247R	I1234Vdel6aa	M1137V	R117C;G576A;R668C	S1235R	
D443Y	G1249R	I125T	M150K	R117G	S1255P	
D443Y;G576A;R668C^{§}	G126D	I1269N	M152V	R117H	S13F	
D513G	G1349D	I331N	M265R	R117L	S341P	
D565G	G149R	I1366N	M952I	R117P	S364P	
D579G	G178E	I1398S	M952T	R1283M	S492F	
D614G	G178R	I148N	N1088D	R1283S	S549I	
D836Y	G194R	I148T	N1303I	R170H	S589N	
D924N	G194V	I175V	N1303K^{‡}	R258G	S737F	
D979V	G27E	I502T	N186K	R297Q	S912L	
D993Y	G27R	I506L	N187K	R31C	S977F	
E116K	G314E	I506T	N418S	R31L	T1036N	
Based on Extrapolation^{¶}						
1341G→A	2789+2insA	3041-15T→G	3849+10kbC→T	3850-3T→G	5T;TG13	711+3A→G
1898+3A→G	2789+5G→A	3272-26A→G	3849+4A→G	4005+2T→C	621+3A→G	E831X
2752-26A→G	296+28A→G	3600G→A	3849+40A→G	5T;TG12		

^{*} Clinical data is obtained from Trials 1 and 2.
^{†} This mutation is also predicted to be responsive by FRT assay with ALYFTREK.
^{‡} The N1303K mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.
^{§} 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.
^{¶} Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

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

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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 modulators are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Labeled contraindications to CFTR modulators include: No labeled contraindications.

Exclusions/Discontinuation:

Elevated transaminases have been reported in patients with CF receiving CFTR modulators. ALT and AST should be assessed prior to initiating CFTR modulators, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, consider more frequent monitoring of liver function tests. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming CFTR modulators.

Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with CFTR modulators. Although other risk factors were present in some cases (such as corticosteroid use and/or exposure to radiation), a possible risk attributable to CFTR modulators cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating CFTR modulator treatment.

Co-administration with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended due to the risk of decrease exposure or CFTR modulators, which may reduce the therapeutic effect.

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

HIGH COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

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.

Trikafta and Alyftrek have a Black Box Warning for drug-induced liver injury and liver failure.

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 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:
Alyftrek TABS 4-20-50 MG
Alyftrek TABS 10-50-125 MG
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

REFERENCES

1. Kalydeco (ivacaftor) tablets, for oral use and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; May 2025.
2. Symdeko (tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; January 2025.

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

PRIOR COST AGENT

3. Orkambi (lumacaftor and ivacaftor) tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; December 2024.
4. Trikafta (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use, (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules), co-packaged [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2024.
5. Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor tablets), for oral use [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2025.
6. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. JPediatr. 2008;153:S4-S14.
7. De Bock K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014;13:674- 680
8. Institute for Clinical and Economic Review (ICER). Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. May 3,2018
9. Davies, JC, Wainwright, CE, Canny, GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. American journal of respiratory and critical care medicine. 2013 Jun 01;187(11):1219-25. PMID: 23590265
10. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014; 13(6): 674–680.
11. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordonez CL, Geller DE. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest 2012;142:718–724.
12. Moss, RB, Flume, PA, Elborn, JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. The Lancet Respiratory medicine.2015 Jul;3(7):524-33. PMID:26070913
13. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD009841. DOI: 10.1002/14651858.CD009841.pub2.
14. Ramsey BW, Davies J, McElvaney NG, et. al.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011 Nov 3;365(18):1663-72. PubMed PMID: 22047557.
15. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation member registry 2015 annual data report. Available at: https://www.cff.org/Our-Research/CF-Patient-Registry/2015-Patient- Registry-Annual-Data-Report.pdf. Accessed July 2017.
16. CF Clinical Care Guidelines. Available at: https://www.cff.org/For-Caregivers/CF-Clinical- Care-Guidelines/. Accessed July 2017.
17. Clancy JP, Johnson SG, Yee SW, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014; 95(6): 592-597. DOI:10.1038/clpt.2014.54.
18. Lahiri T, Hempstead SE, Brady C, et al. Clinical Practice Guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics Mar 2016, peds.2015-1784; DOI: 10.1542/peds.2015- 1784
19. Mogayzel Jr PJ, Naureckas ET, Robinson KA, et al. for the Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013; 187(7): 680-689. DOI: 10.1164/rccm.201207-1160OE. Available at: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201207-1160OE. Accessed July 2017.
20. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220-23. DOI:10.1056/NEJMoa1409547.
21. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr1;187(7):680-9.
22. Milla, Carlos E., et al. “Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis and Homozygous for F508del-CFTR.” American Journal of Respiratory and Critical Care Medicine, vol. 195, no. 7, 2017, pp. 912–920., doi:10.1164/rccm.201608- 1754oc.nwright CE, Elborn JS, Ramsey G, et al. Lumacaftor-ivacaftor in patients with cystic
23. Goralski, J. L., Hoppe, J. E., Mall, M. A., McColley, S. A., McKone, E., Ramsey, B., … Rosenfeld, M. (2023). Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

Through 5 Years with Cystic Fibrosis and at Least One F508del Allele. American Journal of Respiratory Critical Care Medicine, 208(1). https://doi.org/10.1164/rccm.202301-0084oc

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Contraindications/Exclusions/Dis continuation References	Q4 2025
REVISION- Notable revisions: Products Affected Required Medical Information Age Restrictions Quantity FDA-Approved Uses Appendix Other Special Considerations Available Dosage Forms References	Q2 2025
REVISION- Notable revisions: Coding/Billing Information Template Update Required Medical Information Continuation of Therapy Quantity Other Special Considerations Available Dosage Forms References	Q4 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q4 2023
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 COST ALERT

Molina Healthcare, Inc. confidential and proprietary © 2025
This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.