| Pharmacy Policy Bulletin: J-0724 CFTR Modulators – Commercial and Healthcare Reform | |
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| **Number:** J-0724 | **Category:** Prior Authorization |
| **Line(s) of Business:**<br>☒ Commercial<br>☒ Healthcare Reform<br>☐ Medicare | **Benefit(s):**<br>**Commercial:**<br>**Prior Authorization (1.)**:<br>**1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization<br><br>**Healthcare Reform**: Not Applicable |
| **Region(s):**<br>☒ All<br>☐ Delaware<br>☐ New York<br>☐ Pennsylvania<br>☐ West Virginia | **Additional Restriction(s):**<br>None |
| **Version:** J-0724-015 | **Original Date:** 05/02/2018 |
| **Effective Date: 04/25/2025** | **Review Date:** 04/09/2025 |

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| **Drugs Product(s):** | • Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor tablets)<br>• Kalydeco (ivacaftor)<br>• Orkambi (lumacaftor/ivacaftor)<br>• Symdeko (tezacaftor/ivacaftor)<br>• Trikafta (elexacaftor/tezacaftor/ivacaftor) |
| **FDA-Approved Indication(s):** | • Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor tablets)<br>  ○ 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 cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see *Table 1*).<br>• Kalydeco (ivacaftor)<br>  ○ Treatment of CF 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 (see *Table 2*).<br>• Orkambi (lumacaftor/ivacaftor)<br>  ○ Treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation in the CFTR gene.<br>• Symdeko (tezacaftor/ivacaftor)<br>  ○ Treatment of CF in patients ages 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 (see *Table 3*).<br>• Trikafta (elexacaftor/tezacaftor/ivacaftor)<br>  ○ Treatment of 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 clinical and/or *in vitro* data (see *Table 4*). |

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| **Background:** | • CFTR modulators improve the quality and quantity of CFTR at the cell surface, ultimately resulting in an increase of chloride transport which helps to maintain moisture within mucous membranes. |

- CF is a life-threatening, multi-system disorder caused by defective or deficient CFTR protein activity. The protein is responsible for moving chloride to the cell surface, which attracts water. The lack of chloride and resulting absence of water leads to thick, viscous mucus in the lungs, pancreas, liver, intestine, and reproductive tract. *F508del* is the most common CFTR mutation.
- CF is characterized by progressive lung disease, gastrointestinal and nutritional abnormalities, and genital abnormalities in males. Pulmonary disease is the leading cause of morbidity and mortality in patients with CF.
- About 10 percent of patients with CF in the United States carry mutations that are responsive to ivacaftor. Approximately 50 percent of patients with CF are homozygous for the mutation F508del, and another 40 percent are heterozygous for this mutation.
- F508del results in folding defects leading to decreased CFTR at the cell surface as well as gating defects causing decreased conductance. Lumacaftor can partially correct the folding defect in F508del-CFTR, resulting in slightly increased surface protein, but ivacaftor is also needed to improve conductance.

**Table 1: 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;D1270N*§ | *Y1014C* |
| *A613T* | *F508C* | *H609R* | *L333H* | *R1048G* | *R75L* | *Y1032C* |
| *A62P* | *F508C;S1251N*§ | *H620P* | *L346P* | *R1066C* | *R751L* | *Y109N* |
| *A72D* | *F575Y* | *H620Q* | *L441P* | *R1066L* | *R792G* | *Y161D* |
| *C491R* | *F587I* | *H939R* | *L453S* | *R1066M* | *R933G* | *Y161S* |
| *D110E* | *G1047R* | *H939R;H949L* | *L619S* | *R1070Q* | *S1045Y* | *Y301C* |

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|---|---|---|---|---|---|---|
| *D110H* | *G1061R* | *I1027T* | *L967S* | *R1070W* | *S108F* | *Y569C* |
| *D1270N* | *G1069R* | *I105N* | *L997F* | *R1162L* | *S1118F* | *Y913C* |
| *D1445N* | *G1123R* | *I1139V* | *M1101R* | *R117C* | *S1159P* | |
| *D192G* | *G1247R* | *I1234Vdel 6aa* | *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* | |
| **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.

**Table 2: Examples 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 ** | |

† 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 3: Examples 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* | |

† 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.
^ A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented to be indicated.

**Table 4: 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* |
| *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;D1* | *Y161S* |

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|---|---|---|---|---|
| | | | *270N* | |
| *F1052V* | *H620Q* | *N187K* | *R751L* | *Y301C* |
| *F1074L* | *H939R* | *N418S* | *R75L* | *Y563N* |
| *F1099L* | *H939R;H949L* | *P140S* | *R75Q* | |
| *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.

- Prescribing Considerations:
  - CFTR Modulators will not be approved in patients with CF who do not have a mutation responsive to the respective agent.
  - CFTR Modulators should be prescribed by or in consultation with a pulmonologist or CF specialist.
  - Hepatic impairment and CYP3A inhibitor dosage adjustments:
    - Alyftrek: Alyftrek should not be used in patients with severe hepatic impairment (Child-Pugh Class C). Alyftrek is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B). Use of Alyftrek should only be considered in patients with hepatic impairment when there is a clear medical need, and the benefit outweighs the risk. If used, the recommended dosage in patients with moderate hepatic impairment is the same as for patients with normal hepatic function. The recommended dosage of Alyftrek in patients with mild hepatic impairment (Child-Pugh Class A) is the same as in patients with normal hepatic function. Alyftrek is not recommended to be used concomitantly with strong or moderate CYP3A inducers. Reduce the dose of Alyftrek when used concomitantly with strong or moderate CYP3A inhibitors.
    - Kalydeco: Reduce dose in moderate and severe hepatic impairment and with moderate and strong CYP3A inhibitors.
    - Orkambi: Reduce dose in moderate and severe hepatic impairment and with strong CYP3A inhibitors. If treatment is interrupted for more than 1 week and then re-initiated while taking strong CYP3A inhibitors, patients should reduce dose to 1 tablet daily for the first week of treatment re-initiation. Following this period, continue with the recommended daily dose.
    - Symdeko: Reduce morning dose and eliminate evening dose in moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment and with moderate and strong CYP3A inhibitors. Co-administration with strong CYP3A4 inducers is not recommended.
    - Trikafta: Treatment is not recommended for patients with moderate hepatic impairment. Use should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used, reduce dose and eliminate evening dose. Reduce dose and eliminate evening dose with moderate and strong CYP3A inhibitors. Do not use in severe hepatic impairment.

| | |
|---|---|
| | ○ Orkambi and Kalydeco tablets may be crushed for patient administration. |

## Approval Criteria

**I. Initial Authorization**

**A. Alyftrek**

When a benefit, coverage of Alyftrek may be approved when all of the following criteria are met **(1., 2., and 3.):**

**1.** The member is 6 years of age of age or older.
**2.** The member has a diagnosis of cystic fibrosis. (ICD-10: E84)
**3.** The member has least one *F508del* mutation or another responsive mutation in the *CFTR* gene (see *Table 1*) as detected by an FDA-approved test.

**B. Kalydeco**

When a benefit, coverage of Kalydeco may be approved when all of the following criteria are met **(1., 2., and 3.):**

**1.** The member is 1 month of age or older.
**2.** The member has a diagnosis of cystic fibrosis. (ICD-10: E84)
**3.** The member has at least one mutation from *Table 2* as detected by an FDA-approved test.

**C. Orkambi**

When a benefit, coverage of Orkambi may be approved when all of the following criteria are met **(1., 2., and 3.)**:

**1.** The member is 1 year of age or older.
**2.** The member has a diagnosis of cystic fibrosis. (ICD-10: E84)
**3.** The member has the homozygous *F508del* mutation as detected by an FDA-approved test.

**D. Symdeko**

When a benefit, coverage of Symdeko may be approved when all of the following criteria are met **(1., 2., and 3.)**:

**1.** The member is 6 years of age or older.
**2.** The member has a diagnosis of cystic fibrosis. (ICD-10: E84)
**3.** The member has the homozygous *F508del* mutation or has at least one mutation from *Table 3* as detected by an FDA-approved test.

**E. Trikafta**

When a benefit, coverage of Trikafta may be approved all of the following criteria are met **(1., 2., and 3.)**

**1.** The member is 2 years of age or older.
**2.** The member has a diagnosis of cystic fibrosis. (ICD-10: E84)
**3.** The member has at least one mutation from *Table 4* as detected by an FDA-approved test.

**II. Reauthorization**

When a benefit, reauthorization of a CFTR modulator may be approved when one (1) of the following criteria is met **(A. through D.)**:

**A.** Documented improvement or stabilization of forced expiratory volume ($FEV_1$) compared to baseline $FEV_1$.
**B.** Increased Body Mass Index.
**C.** Decreased pulmonary exacerbations.
**D.** Improved quality of life as demonstrated by Cystic Fibrosis Questionnaire.

**III.** An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

## Limitations of Coverage

**I.** Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

**II.** For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

## Authorization Duration

**Initial Authorization**

- Commercial and HCR plans: If approved, up to a 6 month authorization may be granted.
- For Delaware Commercial fully-insured and ACA members, a 12 month authorization must be granted pursuant to 18 Del. C. §§3376(a) and 3586(a) and market conduct examination docket #5467 (Exam Authority #53287-22-701).

**Reauthorization**

- Commercial and HCR plans: If approved, up to a 12 month authorization may be granted.

## Automatic Approval Criteria

None

**References:**


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3. Orkambi [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; August 2023.
4. Kalydeco [package insert]. Boston, MA: Vertex Pharmaceutics Inc; August 2023.
5. Trikafta [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; August 2023.
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9. Flume PA, Borowitz D, Liou T, et al. VX-770 in subjects with CF and homozygous for the F508del-CFTR mutation [abstract]. *Pediatr Pulmonol*. 2011;46(suppl 34):284-85.
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12. Cystic Fibrosis Foundation. About cystic fibrosis. Available at: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. Accessed January 29, 2025.