MEDICAL MUTUAL®

Drug Policy

Policy:	Alyftrek (Vanzacaftor/Tezacaftor/Deutivacaftor) Tablets	**Annual Review Date:** **03/20/2025** **Last Revised Date:** **03/20/2025**

OVERVIEW

Alyftrek is a combination of deutivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and vanzacaftor. It is indicated for the **treatment of cystic fibrosis (CF)** in patients ≥ 6 years of age who have at least one F508del mutation or another responsive mutation in the CFTR gene.[1]

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.[1]

Table 1 lists responsive CFTR mutations based on clinical response, and/or *in vitro* data in Fischer Rat Thyroid cells or human bronchial endothelial cells or based on extrapolation of efficacy.

Table 1 (continued). List of CFTR Gene Mutations that are Responsive to Alyftrek.[1]

L1480P	*Q372H*	*R74Q*	*Y161D*	*C491R*
L441P	*R1066L*	*R792G*	*D192G*	*G1247R*
M1101R	*R117C*	*S1159P*	*D579G*	*G178E*
M952I	*R117P*	*S364P*	*D993Y*	*G27R*
N186K	*R297Q*	*S912L*	*3141del9*	*E292K*
P205S	*R334Q*	*T1086I*	*A1067P*	*E60K*
P750L	*R516G*	*T604I*	*A309D*	*F1074L*
Q237E	*R560T*	*V232D*	*A559V*	*F311del*
Q493R	*R74W;D1270N*	*V603F*	*Y563N*	*1507_1515del9*
R1066H	*S1251N*	*V562I*	*D110H*	*G1061R*
R1070Q	*S1045Y*	*Y301C*	*G149R*	*I1366N*
R117L	*S341P*	*D565G*	*G27E*	*I502T*
R258G	*S737F*	*D979V*	*E474K*	*G551A*
R347L	*T1299I*	*3199del6*	*E92K*	*G628R*
R553Q	*V1240G*	*A107G*	*F1107L*	*H1085R*
R709Q	*V456A*	*A46D*	*A613T*	*F508C*
R74W;V201M;D	*1270N*	*Y1014C*	*F575Y*	*H620Q*
R751L	*Y109N*	*A72D*	*H1054D*	*M1101K*
R75Q	*S549R*	*W1098C*	*G1123R*	*I1139V*
S1118F	*Y913C*	*D1445N*	*G1244E*	*I336K*
S1159F	*S945L*	*W1282R*	*I331N*	*M265R*
S13F	*D513G*	*G1349D*	*G85E*	*L206W*
S549N	*V754M*	*D1152H*	*I175V*	*N1303K*
S589N	*D924N*	*G194V*	*G463V*	*I601F*

T1053I	*2183A→G*	*E193K*	*G576A*	*K162E*
T351I	*A1006E*	*E588V*	*G970D*	*L1324P*
V201M	*A234D*	*F1052V*	*H139R*	*L165S*
V520F	*A559T*	*F200I*	*H939R;H949L*	*L619S*
Y161S	*D110E*	*G1047R*		

CFTR – Cystic Fibrosis Transmembrane Conductance Regulator.

POLICY STATEMENT

This policy involves the use of Alyftrek Prior authorization is recommended for pharmacy benefit coverage of Alyftrek Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Alyftrek as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Alyftrek be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Alyftrek is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Cystic Fibrosis (CF); Initial Use.** Approve for 6 months (can be extended to 12 months based on patient's response) if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 6 years of age; AND
   - **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.
   - **C)** Patient has at least ONE of the following variants in the cystic fibrosis conductance regulator gene that is considered to be a pathogenic or likely pathogenic variant: F508del, A455E, G551D, L1077P, R352Q, S549N, V754M, D1152H, G85E, L206W, R75Q, S549R, W1098C, H1054D, M1101K, S1159F, S945L, W1282R, G1244E, I336K, R1066H, S1251N, V562I, Y563N, 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, 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, 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; AND

D) Patient meets at least ONE of the following (i, ii, or iii):
- **i.** Positive cystic fibrosis newborn screening test; OR
- **ii.** Family history of cystic fibrosis; OR
- **iii.** Clinical presentation consistent with signs and symptoms of cystic fibrosis; AND
  Note: Examples of clinical presentation of cystic fibrosis include but are not limited to meconium ileus, sino-pulmonary symptoms (e.g., persistent cough, wheezing, pulmonary function tests consistent with obstructive airway disease, excess sputum production), bronchiectasis, sinusitis, failure to thrive, pancreatic insufficiency.

E) Patient has evidence of abnormal cystic fibrosis transmembrane conductance regulator function as demonstrated by at least ONE of the following (i, ii, or iii):
- **i.** Elevated sweat chloride test; OR
- **ii.** Two cystic fibrosis-causing cystic fibrosis transmembrane conductance regulator mutations; OR
- **iii.** Abnormal nasal potential difference.

Cystic Fibrosis (CF); Continuation of Therapy

Criteria. *Patient must meet the following criteria (A, B, and C):*

A. The patient continues to meet all criteria in (1) above for new starts; AND
B. The patient has been using Alyftrek for at least 6 months; AND
C. The patient has experienced an adequate response to therapy (e.g. improvement in FEV1 and/or other lung function tests, improvement in sweat chloride, decrease in pulmonary exacerbations or infections, increase in weight, decrease in hospitalizations, etc.) compared to baseline.

Initial Approval/ Extended Approval.
A) *Initial Approval:* 6 months
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alyftrek has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

Coverage of Alyftrek is not recommended in the following situations:

1. **Cystic Fibrosis, Patient with Unknown Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutation.** An FDA-cleared cystic fibrosis mutation test should be used to detect the presence of at least one indicated mutation prior to use of Alyftrek.[1]

2. **Combination Therapy with other Cystic Fibrosis Transmembrane Conductance Regulator Modulator(s).** Alyftrek contains tezacaftor, which is a component of Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets) and Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor tablets and granules). Note: Examples of other cystic fibrosis transmembrane conductance regulator modulators are: Kalydeco® (ivacaftor tablets and oral granules), Orkambi® (lumacaftor/ivacaftor tablets and oral granules), Symdeko® (tezacaftor/ivacaftor; ivacaftor tablets), Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor tablets and oral granules).

3. **Infertility.** Alyftrek is indicated for the treatment of cystic fibrosis in patients ≥ 6 years of age who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator gene. Note: A patient with a diagnosis of cystic fibrosis should be reviewed using criteria for the FDA-approved indication, above.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational, or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or

performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Alyftrek™ tablets [prescribing information]. Cambridge, MA: Vertex; December 2024.
2. Southern KW, Castellani C, Lammertyn E, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *J Cyst Fibros.* 2023;17-30.
3. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr.* 2017;181S:S4-S15.
4. Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. *J Pediatr.* 2017;181S:S33-S44.
5. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. *J Cyst Fibros.* 2024;21-28.