UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2025 P 2363-2
Program	Prior Authorization/Medical Necessity
Medication	Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor)
P&T Approval Date	2/2025, 4/2025
Effective Date	7/1/2025

1. Background:

Alyftrek is a combination of deutivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor 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.

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.

Members will be required to meet the coverage criteria below.

2. Coverage Criteria[a]:

A. Initial Authorization

1. **Alyftrek** will be approved based upon **all** of the following criteria:

   a. Diagnosis of cystic fibrosis (CF)

   -AND-

   b. Submission of laboratory results documenting that the patient has at least **one** of the following responsive mutations in the CFTR gene*:

   (1) F508del mutation
   (2) A mutation that is responsive based on clinical data
   (3) A mutation that is responsive based on in vitro data
   (4) A mutation that is responsive based on extrapolated data

*List of CFTR gene mutations responsive to Alyftrek. A complete up to date list of responsive mutations can be referenced in the Alyftrek Prescribing Information.						
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*
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*
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*	*I331N*	*M26SR*	*R117L*	*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 Trial 1, NCT05033080 and Trial 2, NCT05076149.
† 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.

-AND-

c. The patient is ≥ 6 years of age

-AND-

d. **One** of the following:

(1) Submission of medical records demonstrating a history of trial and failure, contraindication, or intolerance to Trikafta (elexacaftor/tezacaftor/ivacaftor)

-OR-

(2) Patient has a documented CFTR gene mutation that is responsive to Alyftrek but is not responsive to Trikafta (a complete up to date list of responsive mutations can be referenced in the Trikafta Prescribing Information)

-OR-

(3) **Both** of the following:

(a) Patient is currently on Alyftrek therapy as documented by claims history or submission of medical records (document date and duration of therapy)

-AND-

(b) Patient has **not** received a manufacturer supplied sample at no cost in the prescriber's office, or any form of assistance from the Vertex GPS™: Guidance & Patient Support program or other Vertex co-pay assistance programs (e.g., sample card which can be redeemed at a pharmacy for a free supply of medication) as a means to establish as a current user of Alyftrek*

-AND-

e. Prescribed by or in consultation with a provider who specializes in the treatment of CF

***** Patients requesting initial authorization who were established on therapy via the receipt of a manufacturer supplied sample at no cost in the prescriber's office or any form of assistance from the Vertex GPS™: Guidance & Patient Support program or other Vertex co-pay assistance programs **shall be required** to meet initial authorization criteria as if patient were new to therapy.

Authorization will be issued for 12 months.

B. Reauthorization

1. **Alyftrek** will be approved based on the following criterion:

   a. Documentation of positive clinical response to Alyftrek therapy (e.g., improved lung function, stable lung function)

Authorization will be issued for 12 months.

[a] State mandates may apply. Any federal regulatory requirements and the member specific benefit plan coverage may also impact coverage criteria. Other policies and utilization management programs may apply.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limits may be in place.

4. References:

1. Alyftrek [package insert]. Boston, MA: Vertex Pharmaceuticals, Inc.; December 2024.
2. Trikafta [package insert]. Cambridge, MA: Vertex Pharmaceuticals, Inc.; December 2024

Program	Prior Authorization/Medical Necessity – Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor)
Change Control	
2/2025	New program
4/2025	Updated criteria to require history, contraindication, or intolerance to Trikafta, or member is currently on Alyftrek therapy. Added reference.