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Section:	Prescription Drugs	**Effective Date:**	July 1, 2025
Subsection:	Respiratory Agents	**Original Policy Date:**	January 24, 2025
Subject:	Alyftrek	**Page:**	1 of 7

Last Review Date: June 12, 2025

Alyftrek

Description

Alyftrek (vanzacaftor/tezacaftor/deutivacaftor)

Background
Alyftrek is a combination of vanzacaftor, tezacaftor, and deutivacaftor. Vanzacaftor and tezacaftor bind to different sites on the cystic fibrosis transmembrane conductance regulator (CFTR) protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Deutivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of vanzacaftor, tezacaftor and deutivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured both by CFTR mediated chloride transport in vitro and by sweat chlorine in patients with cystic fibrosis (CF) (1).

Regulatory Status
FDA-approved indication: 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 (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 (see Appendix 2) (1).

Alyftrek carries a boxed warning regarding drug-induced liver injury and liver failure. Liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) should be assessed prior to

initiating Alyftrek, every month for the first 6 months, every 3 months for the next 12 months, then at least annually thereafter. In patients with a history of liver disease or liver function test elevations, more frequent monitoring should be considered. Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with Alyftrek (1).

Concomitant use with strong CYP3A inducers may lead to reduced effectiveness of Alyftrek, while concomitant use with strong CYP3A inhibitors may increase the risk of Alyftrek-associated adverse reactions. Therefore, co-administration with either is not recommended (1).

The safety and effectiveness of Alyftrek in pediatric patients less than 6 years of age have not been established (1).

Related policies
Kalydeco, Orkambi, Pulmozyme, Symdeko, Trikafta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Alyftrek may be considered **medically necessary** if the conditions indicated below are met.

Alyftrek may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 6 years of age and older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL the following:

1. At least one *F508del* mutation in the *CFTR* gene confirmed by an FDA-cleared CF mutation test or a mutation that is responsive to Alyftrek (see Appendix 2)
2. Pretreatment percent predicted forced expiratory volume (ppFEV) must be provided

3. Baseline ALT, AST, alkaline phosphatase, and bilirubin levels will be obtained and prescriber agrees to monitor every month for the first 6 months, every 3 months for the next 12 months, and annually thereafter
4. Must be prescribed by a pulmonologist or gastroenterologist
5. **NO** severe hepatic impairment (Child-Pugh Class C)
6. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 6 years of age and older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL of the following:

1. Stable or improvement of ppFEV$_1$ from baseline **OR** reduced number of pulmonary exacerbations
2. Prescriber agrees to monitor ALT, AST, alkaline phosphatase, and bilirubin levels annually
3. **NO** severe hepatic impairment (Child-Pugh Class C)
4. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre – PA Allowance

None

Prior – Approval Limits

Quantity

Age	Weight	Strength	Quantity Limit
6 to 11 years	< 40 kg	4 mg vanzacaftor/ 20 mg tezacaftor/ 50 mg deutivacaftor	12 wallets per 84 days

6 to 11 years	≥ 40 kg	10 mg vanzacaftor/ 50 mg tezacaftor/ 125 mg deutivacaftor	12 wallets per 84 days
≥ 12 years	Any weight	10 mg vanzacaftor/ 50 mg tezacaftor/ 125 mg deutivacaftor	12 wallets per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Alyftrek is a combination of deutivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor. Alyftrek is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 and older who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene. Alyftrek has a boxed warning for drug-induced liver injury and liver failure. The safety and effectiveness of Alyftrek in pediatric patients less than 6 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Alyftrek while maintaining optimal therapeutic outcomes.

References

1. Alyftrek [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; January 2025.

Policy History

Date	Action
January 2025	Addition to PA
June 2025	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 12, 2025 and is effective on July 1, 2025.

Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta
vanzacaftor/tezacaftor/deutivacaftor	Alyftrek

Appendix 2 - List of *CFTR* Gene Mutations that are 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*
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.