

5.45.016

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<b>Subsection:</b>	Respiratory Agents	<b>Original Policy Date:</b>	January 24, 2025
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**Last Review Date:** June 12, 2025

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## Alyftrek

### Description

#### Alyftrek (vanzacaftor/tezacaftor/deutivacaftor)

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#### 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

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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).

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**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

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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)

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## 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<sub>1</sub> 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

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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

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### 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

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

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

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

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## Appendix 2 - List of *CFTR* Gene Mutations that are Responsive to Alyftrek

Based on Clinical Data <sup>†</sup>						
A455E	G551D	L1077P <sup>†</sup>	R352Q	S549N	V754M	
D1152H	G85E <sup>†</sup>	L206W	R75Q	S549R	W1098C <sup>†</sup>	
F508del <sup>†</sup>	H1054D	M1101K <sup>†</sup>	S1159F	S945L	W1282R	
G1244E	I336K	R1066H	S1251N	V562I	Y563N <sup>†</sup>	
Based on in vitro Data <sup>‡</sup>						
I507_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
546msCTA	E56K	G551S	K1060T	P67L	R352W	T351I
A1006E	E588V	G576A	K162E	P750L	R516G	T604I
A1067P	E60K	G576A;R668C <sup>§</sup>	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 <sup>§</sup>	V603F
A559V	F311del	H199R	L320V	Q552P	R74W;V201M <sup>§</sup>	W361R
A561E	F311L	H199Y	L333F	Q98R	R74W;V201M;D1270N <sup>§</sup>	Y1014C
A613T	F508C	H609R	L333H	R1048G	R75L	Y1032C
A62P	F508C;S1251N <sup>§</sup>	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 <sup>§</sup>	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 <sup>‡</sup>	R258G	S737F	
D979V	G27E	I502T	N186K	R297Q	S912L	
D993Y	G27R	I506L	N187K	R31C	S977F	

<i>E116K</i>	<i>G314E</i>	<i>I506T</i>	<i>N418S</i>	<i>R31L</i>	<i>T1036N</i>	
<b>Based on Extrapolation<sup>‡</sup></b>						
<i>1341G→A</i>	<i>2789+2insA</i>	<i>3041-15T→G</i>	<i>3849+10kbC→T</i>	<i>3850-3T→G</i>	<i>5T,TG13</i>	<i>711+3A→G</i>
<i>1898+3A→G</i>	<i>2789+5G→A</i>	<i>3272-26A→G</i>	<i>3849+4A→G</i>	<i>4005+2T→C</i>	<i>621+3A→G</i>	<i>E831X</i>
<i>2752-26A→G</i>	<i>296+28A→G</i>	<i>3600G→A</i>	<i>3849+40A→G</i>	<i>5T,TG12</i>		

\* 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.