

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis Transmembrane Conductance Regulator – Alyftrek Prior Authorization Policy

- Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets – Vertex)

REVIEW DATE: 01/02/2025

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. List of CFTR Gene Mutations that are Responsive to Alyftrek.¹

I341G→A	2789+2insA	3041-15T→G	3849+10kbC→T	3850-3T→G
3195del6	E403D	G480S	I807M	P5L
3600G→A	3849+40A→G	5T;TG12	E831X 2752-26A→G	296+28A→G
3849+4A→G	4005+2T→C	621+3A→G	2789+5G→A	3272-26A→G
5T;TG13	711+3A→G	1898+3A→G	L1011S	Q1100P
A1067T	E822K	G622D	L137P	Q359R
A349V	F1099L	H1085P	L333F	Q98R
A561E	F311L	H199Y	L346P	R1066C
A62P	F508C;S1251N	H620P	L997F	R1162L
D1270N	G1069R	I105N	M152V	R117H
D443Y;G576A;R668C	G126D	I1269N	N1303I	R170H
D836Y	G194R	I148T	P140S	R334L
E116Q	G424S	I556V	P67L	R352W
E56K	G551S	K1060T	Q1313K	R560S
F1016S	G91R	L1065P	Q452P	R74W
F191V	H1375P	L15P	L1077P	R352Q
F508del	A455E	G551D	R1066M	R933G
F587I	H939R	L453S	R117G	S1255P
G1249R	I125T	M150K	R1283S	S549I
G178R	I148N	N1088D	R31L	T1036N
G314E	I506T	N418S	R347H	T1246I
G480C	I618T	P499A	R516S	V1153E
G576A;R668C	K464E	P99L	R668C	V392G
G970S	L1335P	Q237H	R74W;V201M	W361R
H199R	L320V	Q552P	R75L	Y1032C
H609R	L333H	R1048G	S108F	Y569C
I1027T	L967S	R1070W	S1235R	D443Y
I1234Vdel6aa	M1137V	R117C;G576A;R668C	S492F	D614G
I1398S	M952T	R1283M	S977F	E116K
I506L	N187K	R31C	T338I	546insCTA
I980K	P574H	R347P	V1293G	A120T
L102R	Q1291R	R555G	V456F	A554E

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

L1480P	Q372H	R74Q	Y161D	C491R
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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	I270N	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.

Guidelines

Alyftrek is not addressed in available guidelines. The most current treatment recommendations are the Standards of Care for CFTR variant-specific therapy for people with CF, from the European Cystic Fibrosis Society (2023).² However, the Standards do not reflect the currently approved age indications for Kalydeco® (ivacaftor tablets and oral granules) [≥ 1 months of age], Orkambi® [lumacaftor/ivacaftor tablets and oral granules] (≥ 1 year of age), or Trikafta® [elexacaftor/tezacaftor/ivacaftor; ivacaftor tablets and oral granules] [≥ 2 years of age]. In general, Trikafta is recommended over other agents where indications overlap. The Standards recommend Trikafta in patients ≥ 6 years of age with CF who are homozygous or heterozygous for F508del. In patients with one or more responsive non-F508del variant, Kalydeco, Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets), or Trikafta are recommended. Kalydeco is recommended in patients ≥ 4 months of age with eligible CFTR gene variants. Orkambi is recommended for patients 2 to 5 years of age who are homozygous for F508del. Of note, the Standards state that after diagnosis, repeat sweat testing provides evidence of treatment effect on CFTR activity, but does not predict clinical response. The European Cystic Fibrosis Society Standards for establishing and maintaining health (2024) note that people with CF with eligible CFTR gene variants should be offered CFTR modulator therapy.⁵

According to the CF Foundation (2017), CF is diagnosed when an individual has both a clinical presentation of CF and evidence of CFTR dysfunction.^{3,4} Clinical presentation of CF includes a positive newborn screening, signs and/or symptoms of CF, and/or family history of CF. To establish a diagnosis of CF, sweat chloride tests should be considered first, then CFTR genetic analysis (CFTR genotype), and then CFTR physiologic tests (nasal potential difference [NPD] or intestinal current measurement [ICM]). However, tests of CFTR function are not always done in this order. All individuals diagnosed with CF should have a sweat chloride test and CFTR genetic analysis performed.

In a patient with a sweat chloride test ≥ 60 mmol/L, CF diagnosis is established and in patients with a sweat chloride test < 30 mmol/L, a diagnosis of CF is unlikely.^{3,4} Rarely, patients with a sweat chloride < 30 mmol/L may be considered to have CF if alternatives are excluded and other confirmatory tests (genetic and physiologic testing) support CF. In patients with a sweat chloride test of ≥ 30 to < 60 mmol/L, CFTR genetic analysis is undertaken. If the genetic analysis identifies two CF-causing CFTR mutations, CF is diagnosed, if no CFTR mutations are identified, a diagnosis of CF is unlikely. In patients with a CFTR genotype that is undefined or of varying clinical consequence, full gene CFTR sequencing (if not already performed) or CFTR physiologic testing is performed (NPD or ICM). If only one CFTR variant is identified on limited analysis, full gene CFTR sequencing should be performed. CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence mutations; CF is unlikely if only no CF-causing mutations are found. If results of the NPD or ICM show CFTR dysfunction, CF is diagnosed; when testing is unavailable or equivocal, the diagnosis of CF is not resolved, and when results of the physiologic testing show CFTR function is preserved, a diagnosis of CF is considered unlikely. It is recommended that patients with challenging diagnoses be evaluated at an accredited CF Foundation Care Center.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Alyftrek. All approvals are provided for the duration noted below. 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, approval requires Alyftrek to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
 - A) Patient is ≥ 6 years of age; AND
 - B) 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, I341G→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

C) 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.

D) 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; AND

E) The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

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.

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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/02/2025