PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis Transmembrane Conductance Regulator – Alyftrek Prior Authorization Policy
- Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets – Vertex)

REVIEW DATE: 01/02/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

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]

1341G→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*
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.

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.

Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets – Vertex) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

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, 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

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 COVERED

Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor tablets – Vertex) is(are) considered experimental, investigational or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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.

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