Clinical Policy: Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek)

Reference Number: PA.CP.PHAR.700
Effective Date: 05/2025
Last Review Date: 04/2025

Description

Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek®) is a combination of deutivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, tezacaftor, and vanzacaftor.

- Vanzacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular process 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.

FDA Approved Indication(s)

Alyftrek is 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Alyftrek is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all)**:**

1. Diagnosis of CF;
2. Prescribed by or in consultation with a pulmonologist or cystic fibrosis specialist;
3. Age ≥ 6 years;
4. Documentation of member's baseline precent predicted forced expiratory volume in 1 second (ppFEV1), performed within the last 90 days;
5. Alyftrek is not prescribed concurrently with other CFTR modulators (e.g., Trikafta, Orkambi®, Kalydeco®, Symdeko®);
6. Dose does not exceed one of the following (a, b, or c):
   a. Age 6 to < 12 years and weight < 40 kg (both i and ii):
      i. Vanzacaftor 12 mg/tezacaftor 60 mg/deutivacaftor 150 mg per day;
      ii. 3 tablets (vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg) per day;
   b. Age 6 to < 12 years and weight ≥ 40 kg (both i and ii):
      i. Vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg per day;
      ii. 2 tablets (vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg) per day;
   c. Age ≥ 12 years (both i and ii):

i. Vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg per day;
ii. 2 tablets (vanzacaftor 10 mg/tezacaftor 50 mg/deutvacaftor 125 mg) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Cystic Fibrosis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is benefiting from Alyftrek based on the prescriber's assessment;
3. Alyftrek is not prescribed concurrently with other CFTR modulators (e.g., Trikafta, Orkambi, Kalydeco, Symdeko);
4. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
   a. Age 6 to < 12 years and weight < 40 kg (both i and ii):
      i. Vanzacaftor 12 mg/tezacaftor 60 mg/deutivacaftor 150 mg per day;
      ii. 3 tablets (vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg) per day;
   b. Age 6 to < 12 years and weight ≥ 40 kg (both i and ii):
      i. Vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg per day;
      ii. 2 tablets (vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg) per day;
   c. Age ≥ 12 years (both i and ii):
      i. Vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg per day;
      ii. 2 tablets (vanzacaftor 10 mg/tezacaftor 50 mg/deutvacaftor 125 mg) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CF: cystic fibrosis
CFF: Cystic Fibrosis Foundation
CFTR: cystic fibrosis transmembrane conductance regulator

FDA: Food and Drug Administration

ppFEV1: precent predicted forced expiratory volume in 1 second

Appendix B: Therapeutic Alternatives

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Trikafta (elexacaftor/ivacaftor/ tezacaftor)	Pediatric patients age 6 years to less than 12 years weighing less than 30 kg: • Morning dose: 2 tablets (each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg) • Evening dose: 1 tablet of ivacaftor 75 mg Adults, pediatric patients age 12 years and older, or pediatric patients age 6 years to less than 12 years weighing 30 kg or more: • Morning dose: 2 tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) • Evening dose: 1 tablet of ivacaftor 150 mg Morning and evening dose should be taken PO approximately 12 hours apart with fat-containing food	Age 6 years to less than 12 years weighing less than 30 kg: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg per day Adults, pediatric patients age 12 years and older, or pediatric patients age 6 years to less than 12 years weighing 30 kg or more: elexacaftor 200 mg/ tezacaftor 100 mg/ ivacaftor 300 mg per day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): drug-induced liver injury and liver failure

Appendix D: General Information

- The Cystic Fibrosis Foundation (CFF) Mutation Analysis Program (MAP) is a free and confidential genetic testing program for people with a strongly suspected or confirmed diagnosis of CF. It is available here: https://www.cff.org/medical-professionals/mutation-analysis-program.
- Diagnostic criteria for CF:
  - The CFF guidelines state that CFTR dysfunction needs to be confirmed with an elevated sweat chloride ≥ 60 mmol/L.
  - "Genetic testing confirming the presence of two disease-causing mutations in CFTR gene" is used to ensure that whether heterozygous or homozygous, there are two

disease-causing mutations in the CFTR gene, one from each parental allele. One of those two mutations must be an *F508del* mutation but does not necessarily require both.

Appendix E: CFTR Gene Mutations that are Responsive to Alyftrek

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_1515 del9	*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*

List of CFTR Gene Mutations that are Responsive to Alyftrek						
D110H	*G1061R*	*I1027T*	*L967S*	*R1070W*	*S108F*	*Y569C*
D1270N	*G1069R*	*I105N*	*L997F*	*R1162L*	*S1118F*	*Y913C*
D1445N	*G1123R*	*I1139V*	*M1101R*	*R117C*	*S1159P*	
D192G	*G1247R*	*I1234Vdel6 aa*	*M1137V*	*R117C;G 576A;R 668C*	*S1235R*	
D443Y	*G1249R*	*I125T*	*M150K*	*R117G*	*S1255P*	
D443Y;G5 76A;R 668C§	*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+2ins A*	*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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CF	<u>Pediatric patients age 6 to less than 12 years weighing less than 40 kg:</u> 3 tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg PO QD <u>Pediatric patients age 6 to less than 12 years weighing ≥ 40 kg:</u>	<u>Pediatric patients age 6 to less than 12 years weighing less than 40 kg:</u> vanzacaftor 12 mg/tezacaftor 60 mg/deutivacaftor 150 mg/ day

Indication	Dosing Regimen	Maximum Dose
	2 tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg PO QD Adults and pediatric patients age ≥ 12 years: 2 tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg PO QD	Pediatric patients age 6 to less than 12 years weighing ≥ 40 kg: vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg/day Adults and pediatric patients age > 12 years: vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg/day

VI. Product Availability

Tablets: fixed-dose combination containing vanzacaftor 4 mg (equivalent to 4.24 mg of vanzacaftor calcium dihydrate)/tezacaftor 20 mg/deutivacaftor 50 mg; fixed-dose combination containing vanzacaftor 10 mg (equivalent to 10.6 mg of vanzacaftor calcium dihyrdrate)/tezacaftor 50 mg/deutivacaftor 125 mg

VII. References

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