Clinical Policy: Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek)

Reference Number: CP.PHAR.700
Effective Date: 12.20.24
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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 confirmed by all of the following (a, b, and c):
   a. Clinical symptoms consistent with CF in at least one organ system, or positive newborn screen or genetic testing for siblings of patients with CF;
   b. Evidence of CFTR dysfunction confirmed by one of the following (i or ii, *see Appendix D*):
      i. Elevated sweat chloride ≥ 60 mmol/L;
      ii. Genetic testing confirming the presence of two disease-causing mutations in CFTR gene, one from each parental allele;
   c. Confirmation of one of the following (i or ii):
      i. Member has at least one *F508del* mutation in the CFTR gene;

ii. Member has at least one mutation in the CFTR gene that is responsive to Alyftrek (*see Appendix E*);

2. Prescribed by or in consultation with a pulmonologist;
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. Failure of Trikafta®, unless member meets one of the following (a or b):
   a. Presence of mutation in CFTR gene that is not responsive to Trikafta;
   b. Contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for Trikafta*
6. Alyftrek is not prescribed concurrently with other CFTR modulators (e.g., Trikafta, Orkambi®, Kalydeco®, Symdeko®);
7. 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Cystic Fibrosis (must meet all):

1. Member meets one of the following (a or b):

a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;

2. Member is responding positively to therapy as evidenced by a stabilization or improvement (e.g., increase) in ppFEV1 from baseline;
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

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*

List of CFTR Gene Mutations that are Responsive to Alyftrek						
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.

V. Dosage and Administration

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

1. Alyftrek Prescriber Information. Boston MA: Vertex Pharmaceuticals, Inc.; December 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218730s000lbl.pdf. Accessed January 13, 2025.
2. ClinicalTrials.gov. A Phase 3 Study of VX-121 Combination therapy in participants with cystic fibrosis heterozygous for F508del and a minimal function mutation. Available at: https://clinicaltrials.gov/study/NCT05033080. Accessed January 14, 2025.
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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	08.27.24	11.24
RT4: Drug is now FDA approved – criteria updated per FDA labeling; added redirection to Trikafta unless there is presence of mutation in CFTR gene that is not responsive to Trikafta; added Appendix E with CFTR gene mutations that are responsive to Alyftrek.	01.13.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.