UnitedHealthcare Pharmacy
Clinical Pharmacy Programs

Program Number	2025 P 2180-8
Program	Prior Authorization/Medical Necessity
Medication	Trikafta® (elexacaftor/tezacaftor/ivacaftor)
P&T Approval Date	11/2019, 11/2020, 3/2021, 7/2021, 7/2022, 6/2023, 6/2024, 2/2025
Effective Date	5/1/2025

1. Background:

Trikafta is a combination of elexacaftor, tezacaftor, and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or a mutation in the CFTR gene that is responsive based on clinical and/or *in vitro* data.

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.

Members will be required to meet the coverage criteria below.

2. Coverage Criteria[a]:

A. Initial Authorization

1. **Trikafta** will be approved based upon **all** of the following criteria:

   a. Diagnosis of cystic fibrosis (CF)

   -AND-

   b. Submission of laboratory results documenting that the patient has at least **one** of the following responsive mutations in the CFTR gene:*

   (1) F508del mutation
   (2) A mutation that is responsive based on clinical data
   (3) A mutation that is responsive based on *in vitro* data
   (4) A mutation that is responsive based on extrapolated data

*List of CFTR gene mutations responsive to Trikafta. A complete up to date list of responsive mutations can be referenced in the Trikafta Prescribing Information.				
Based on clinical data**				
2789+5G→A	*D1152H†*	*L206W†*	*R1066H†*	*S945L†*
3272-26A→G	*F508del†*	*L997F†*	*R117C†*	*T338I†*
3849+10kbC→T	*G85E†*	*M1101K†*	*R347H†*	*V232D†*
A455E†	*L1077P†*	*P5L†*	*R347P†*	
Based on *in vitro* data‡				
N1303K	*F200I*	*I1139V*	*P574H*	*S1045Y*
1507_1515del9	*F311del*	*I125T*	*P67L*	*S108F*
2183A→G	*F311L*	*I1269N*	*P750L*	*S1118F*
3141del9	*F508C*	*I1366N*	*Q1291R*	*S1159F*

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546insCTA	*F508C; S1251N*	*I148N*	*Q1313K*	*S1159P*
A1006E	*F575Y*	*I148T*	*Q237E*	*S1235R*
A1067P	*F587I*	*I175V*	*Q237H*	*S1251N*
A1067T	*G1047R*	*I331N*	*Q359R*	*S1255P*
A107G	*G1061R*	*I336K*	*Q372H*	*S13F*
A120T	*G1069R*	*I502T*	*Q493R*	*S341P*
A234D	*G1123R*	*I506L*	*Q552P*	*S364P*
A309D	*G1244E*	*I556V*	*Q98R*	*S492F*
A349V	*G1247R*	*I601F*	*R1048G*	*S549I*
A46D	*G1249R*	*I618T*	*R1070Q*	*S549N*
A554E	*G126D*	*I807M*	*R1070W*	*S549R*
A62P	*G1349D*	*I980K*	*R1162L*	*S589N*
C491R	*G178E*	*K1060T*	*R117C; G576A; R668C*	*S737F*
D110E	*G178R*	*K162E*	*R117G*	*S912L*
D110H	*G194R*	*K464E*	*R117H*	*S977F*
D1270N	*G194V*	*L1011S*	*R117L*	*T1036N*
D1445N	*G27E*	*L1324P*	*R117P*	*T1053I*
D192G	*G27R*	*L1335P*	*R1283M*	*T1086I*
D443Y	*G314E*	*L137P*	*R1283S*	*T1246I*
D443Y; G576A; R668C	*G424S*	*L1480P*	*R170H*	*T1299I*
D565G	*G463V*	*L15P*	*R258G*	*T351I*
D579G	*G480C*	*L165S*	*R297Q*	*V1153E*
D614G	*G480S*	*L320V*	*R31C*	*V1240G*
D836Y	*G551A*	*L333F*	*R31L*	*V1293G*
D924N	*G551D*	*L333H*	*R334L*	*V201M*
D979V	*G551S*	*L346P*	*R334Q*	*V392G*
D993Y	*G576A*	*L441P*	*R347L*	*V456A*
E116K	*G576A; R668C*	*L453S*	*R352Q*	*V456F*
E116Q	*G622D*	*L619S*	*R352W*	*V562I*
E193K	*G628R*	*L967S*	*R516S*	*V603F*
E292K	*G970D*	*M1137V*	*R553Q*	*V754M*
E474K	*H1054D*	*M152V*	*R668C*	*W1282R*
E56K	*H1085P*	*M265R*	*R709Q*	*W361R*
E588V	*H1085R*	*M952I*	*R74Q*	*Y1014C*
E60K	*H1375P*	*M952T*	*R74W*	*Y1032C*
E92K	*H199Y*	*N1303I*	*R74W; V201M*	*Y161D*
F1016S	*H620P*	*N186K*	*R74W; V201M; D1270N*	*Y161S*
F1052V	*H620Q*	*N187K*	*R751L*	*Y301C*
F1074L	*H939R*	*N418S*	*R75L*	*Y563N*
F1099L	*H939R; H949L*	*P140S*	*R75Q*	
F1107L	*I1027T*	*P205S*	*R792G*	
F191V	*I105N*	*P499A*	*R933G*	
Based on extrapolation from Trial 5[§]				
4005+2T→C	*2789+2insA*	*3849+40A→G*	*5T; TG13*	
1341G→A	*296+28A→G*	*3849+4A→G*	*621+3A→G*	
1898+3A→G	*3041-15T→G*	*3850-3T→G*	*711+3A→G*	
2752-26A→G	*3600G→A*	*5T; TG12*	*E831X*	

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** Clinical data obtained from Trials 1 (NCT03525444), 2 (NCT03525548), and 5 (NCT05274269).
† This mutation is also predicted to be responsive by FRT assay.
‡ The N1303K mutation is predicted to be responsive by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.
§ Efficacy is extrapolated from Trial 5 to non-canonical splice mutations because clinical trials in all mutations of this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

-AND-

c. The patient is ≥ 2 years of age

-AND-

d. Prescribed by or in consultation with a provider who specializes in the treatment of CF

Authorization will be issued for 12 months.

B. Reauthorization

1. **Trikafta** will be approved based on the following criterion:

   a. Documentation of positive clinical response to Trikafta therapy (e.g., improved lung function, stable lung function)

Authorization will be issued for 12 months.

[a] State mandates may apply. Any federal regulatory requirements and the member specific benefit plan coverage may also impact coverage criteria. Other policies and utilization management programs may apply.

3. Additional Clinical Rules:

- Notwithstanding Coverage Criteria, UnitedHealthcare may approve initial and re-authorization based solely on previous claim/medication history, diagnosis codes (ICD-10) and/or claim logic. Use of automated approval and re-approval processes varies by program and/or therapeutic class.
- Supply limits may be in place.

4. References:

1. Trikafta [package insert]. Cambridge, MA: Vertex Pharmaceuticals, Inc.; December 2024.

Program	Prior Authorization/Medical Necessity – Trikafta (elexacaftor/tezacaftor/ivacaftor)
Change Control	
11/2019	New program
11/2020	Annual review. Updated reference.
3/2021	Updated criteria due to expanded indication approved for additional mutations.

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7/2021	Updated criteria due to expanded indication approved for patients 6 years and older.
7/2022	Annal review with no change to coverage criteria. Updated reauthorization duration to 12 months and reference.
6/2023	Updated criteria due to expanded indication approved for patients two years and older. Updated prescriber requirement, simplified reauthorization criteria, and updated reference.
6/2024	Annual review. Increased initial authorization approval duration to 12 months. Removed prescriber requirement from reauthorization criteria. Updated reference.
2/2025	Updated list of CFTR responsive gene mutations. Updated background and reference.

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