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5.45.012

Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Respiratory Agents	**Original Policy Date:**	November 1, 2019
Subject:	Trikafta	**Page:**	1 of 8

Last Review Date: March 7, 2025

Trikafta

Description

Trikafta (elexacaftor/tezacaftor/ivacaftor)

Background
Trikafta is a combination of ivacaftor, tezacaftor, and elexacaftor. Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing 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. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by both CFTR mediated chloride transport in vitro and by sweat chloride in patients with CF (1).

Regulatory Status
FDA-approved indication: Trikafta is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or in vitro data (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 (see Appendix 2) (1).

Liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) should be assessed prior to initiating Trikafta, every month during the first 6 months of treatment, then every 3 months for the next 12 months, and then at least annually thereafter. In patients with a history of hepatobiliary

disease or liver function test elevations, more frequent monitoring should be considered. Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with Trikafta (1).

Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's Wort) significantly decreases exposure of Trikafta which may diminish effectiveness. Therefore, co-administration is not recommended (1).

Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating treatment with Trikafta (1).

The safety and effectiveness of Trikafta in pediatric patients less than 2 years of age have not been established (1).

Related policies
Kalydeco, Orkambi, Pulmozyme, Symdeko

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Trikafta may be considered **medically necessary** if the conditions indicated below are met.

Trikafta may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 2 years of age and older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL the following:

1. At least one *F508del* mutation in the *CFTR* gene confirmed by an FDA-cleared CF mutation test or a mutation that is responsive to Trikafta (see Appendix 2)

2. Patients 6 years of age or older **only**: Pretreatment percent predicted forced expiratory volume (ppFEV) must be provided
3. Baseline ALT, AST, alkaline phosphatase, and bilirubin levels will be obtained and prescriber agrees to monitor every month for the first 6 months of treatment, every 3 months for the next 12 months, and annually thereafter
4. Must be prescribed by a pulmonologist or gastroenterologist
5. **NO** severe hepatic impairment (Child-Pugh Class C)
6. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 2 years of age and older

Diagnosis

Patient must have the following:

Cystic fibrosis (CF)

AND ALL of the following:

1. Patients less than 6 years of age **only**: Patient's symptoms have improved or stabilized from baseline **OR** reduced number of pulmonary exacerbations
2. Patients 6 years of age or older **only**: Stable or improvement of $ppFEV_1$ from baseline **OR** reduced number of pulmonary exacerbations
3. Prescriber agrees to monitor ALT, AST, alkaline phosphatase, and bilirubin levels annually
4. **NO** severe hepatic impairment (Child-Pugh Class C)
5. **NO** dual therapy with another cystic fibrosis transmembrane conductance regulator (CFTR) potentiator (see Appendix 1)

Policy Guidelines

Pre – PA Allowance

None

Prior – Approval Limits

Quantity

Dosage Form	Quantity Limit	Details
Tablets	12 blister packs (252 tablets) per 84 days	Blister packs contain 14 tablets of elexacaftor, tezacaftor, and ivacaftor and 7 tablets of ivacaftor for a 7 day supply
Oral granules	12 wallets (168 packets of granules) per 84 days	Wallets contain 7 packets of elexacaftor, tezacaftor, and ivacaftor and 7 packets of ivacaftor for a 7 day supply

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Trikafta is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor. Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or in vitro data. Trikafta has warnings for elevated liver function tests, concomitant use with CYP3A inducers, and cataracts. The safety and efficacy of Trikafta in pediatric patients less than 2 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Trikafta while maintaining optimal therapeutic outcomes.

References

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

Policy History

Date	Action
November 2019	Addition to PA
December 2019	Annual review

March 2020	Annual review. Added “reduced number of pulmonary exacerbations” option for renewal per SME
January 2021	Updated indication to include treatment of patients who have a mutation in the CFTR gene that is responsive to Trikafta. Added Appendix 2. Italicized every mention of the *F508del* mutation and *CFTR* gene mutation per FEP. Updated liver function monitoring to require every 3 months monitoring during the first year of treatment to be consistent with PI per FEP
March 2021	Annual review
June 2021	Changed age requirement to 6 and older from 12 and older per new package insert
September 2021	Annual review
December 2022	Annual review and reference update. Changed policy number to 5.45.012
May 2023	Per PI update, lowered age requirement from 6 to 2 and added packets of oral granules to quantity limit. Added caveat that only patients 6 and older need to do a ppFEV1 for initiation. Added continuation requirement that patients under 6 can have symptomatic improvement or stabilization
June 2023	Annual review
December 2023	Annual review and reference update
December 2024	Annual review
January 2025	Per PI update, revised LFT monitoring for initiation and also updated list of gene mutations that are responsive to Trikafta. Changed initiation approval duration to 12 months
March 2025	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.

Appendix 1 - List of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiators

Generic Name	Brand Name
ivacaftor	Kalydeco
ivacaftor/lumacaftor	Orkambi
ivacaftor/tezacaftor	Symdeko
ivacaftor/tezacaftor/elexacaftor	Trikafta

Appendix 2 - List of CFTR Gene Mutations Responsive to TRIKAFTA

Mutations responsive to TRIKAFTA 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†*	
Mutations responsive to TRIKAFTA 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*
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*
E403D	*G970S*	*M150K*	*R555G*	*W1098C*
E474K	*H1054D*	*M152V*	*R668C*	*W1282R*
E56K	*H1085P*	*M265R*	*R709Q*	*W361R*
E588V	*H1085R*	*M952I*	*R74Q*	*Y1014C*
E60K	*H1375P*	*M952T*	*R74W*	*Y1032C*
E822K	*H139R*	*N1088D*	*R74W;D1270N*	*Y109N*
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*	
Mutations responsive to TRIKAFTA 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*	

∗ Clinical data obtained from Trials 1, 2, and 5.
† 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.