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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Respiratory Agents	**Original Policy Date:**	November 1, 2019
Subject:	Trikafta	**Page:**	1 of 7

Last Review Date: March 12, 2021

Trikafta

Description

Trikafta (elexacaftor/tezacaftor/ivacaftor)

Background
Trikafta is a combination of ivacaftor, tezacaftor, and elexacaftor. Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients 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 *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 *F508del* mutation or a mutation that is responsive based on *in vitro* data. 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 CFTR mediated chloride transport (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 12 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 *in vitro* data (1).

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of at least one *F508del* mutation or a mutation that is responsive to Trikafta based on *in vitro* data (1).

List of *CFTR* Gene Mutations that are Responsive to Trikafta					
3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N* †	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del* *	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C †	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N* †	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M* †	*S364P*	*Y161S*
E116K	*G576A;R668C* †	*L165S*	*R74W;V201M;D1270N* †	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data.
† 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.

Liver function tests (ALT, AST, and bilirubin) should be assessed prior to initiating Trikafta, every 3 months during the first year of treatment, and 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).

The safety and efficacy of Trikafta in pediatric patients less than 12 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** in patients 12 years of age and older for the treatment of cystic fibrosis (CF) and if the conditions indicated below are met.

Trikafta is considered **investigational** in patients less than 12 years of age and for all other indications.

Prior-Approval Requirements

Age 12 years of age and older

Diagnosis

The 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. Pretreatment percent predicted forced expiratory volume (ppFEV) must be provided
3. Baseline levels of ALT, AST and bilirubin must be obtained and prescriber agrees to monitor every 3 months during the first year of treatment, and at least yearly 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 12 years of age and older

Diagnosis

Patient must have the following:
Cystic fibrosis (CF)

AND ALL of the following:
1. Stable or improvement of ppFEV$_1$ from baseline **OR** reduced number of pulmonary exacerbations
2. Prescriber agrees to monitor ALT, AST and bilirubin levels at least yearly
3. **NO** severe hepatic impairment (Child-Pugh Class C)
4. **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 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)

Duration 6 months

Prior – Approval *Renewal* Limits

Quantity 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)

Duration 12 months

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 who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *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 *F508del* mutation or a mutation in the *CFTR* gene that is responsive based on *in vitro* data. 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 CFTR mediated chloride transport (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 2020.

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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

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 that are Responsive to Trikafta

3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
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A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
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D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
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E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
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