

5.45.012

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	1 of 7

Last Review Date: December 13, 2024

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 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 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 *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 *F508del* mutation or a mutation that is responsive to Trikafta based on *in vitro* data (1).

List of <i>CFTR</i> Gene Mutations that are Responsive to Trikafta					
3141del9	E822K	G1069R	L967S	R117L	S912L

5.45.012

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	2 of 7

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 2 years of age have not been established (1).

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	3 of 7

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, and bilirubin levels will be obtained and prescriber agrees to monitor every 3 months during the first year of treatment, 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

Section: Prescription Drugs	Effective Date: January 1, 2025
Subsection: Respiratory Agents	Original Policy Date: November 1, 2019
Subject: Trikafta	Page: 4 of 7

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 ppFEV₁ from baseline **OR** reduced number of pulmonary exacerbations
3. Prescriber agrees to monitor ALT, AST, 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 6 months

Prior – Approval *Renewal* Limits

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	5 of 7

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

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 *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.; August 2023.

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 <i>F508del</i> mutation and <i>CFTR</i> 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

5.45.012

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	6 of 7

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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 13, 2024 and is effective on January 1, 2025.

Section:	Prescription Drugs	Effective Date:	January 1, 2025
Subsection:	Respiratory Agents	Original Policy Date:	November 1, 2019
Subject:	Trikafta	Page:	7 of 7

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
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.