Clinical Policy Title:	elexacaftor/ivacaftor/tezacaftor; ivacaftor
Policy Number:	RxA.523
Drug(s) Applied:	Trikafta®
Original Policy Date:	09/05/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Trikafta®is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 6 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.

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
elexacaftor/ivacaftor/tezacaftor; ivacaftor (Trikafta®)	CF	<u>Age 6 to less than 12 years weighing less than 30 kgs</u>: • Morning dose: Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg • Evening dose: One tablet of ivacaftor 75 mg <u>Age 6 to less than 12 years weighing 30 kgs or more</u>: • Morning dose: Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg • Evening dose: One tablet of ivacaftor 150 mg <u>12 years and older:</u> • Morning dose: 2 tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) • Evening dose: 1 tablet of ivacaftor 150 mg	<u>For 6 to less than 12 years weighing less than 30 kgs:</u> elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg <u>6 to less than 12 years weighing 30 kgs or more & 12 years and older:</u> elexacaftor 200 mg/ tezacaftor 100 mg/ ivacaftor 300 mg per day

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		• Morning and evening dose should be taken approximately 12 hours apart with fat- containing food. <u>For Hepatic impairment:</u> Moderate impairment (Child-Pugh Class B): 2 tablets containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg orally once daily; NO ivacaftor 150 mg dose.	

Dosage Forms

- Tablets: co-packaged fixed dose combination containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 150 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all)**:**

1. Diagnosis of CF;
2. Member has at least one of the following mutations in the CFTR gene (a or b);
   a. At least one F508del mutation;
   b. A mutation that is responsive based on in vitro data (see appendix D)*;*
3. Age ≥ 6 years;
4. Prescribed by or in consultation with a pulmonologist;
5. Chart notes indicate that pulmonary function tests, performed within the last 90 days, show a percent predicted forced expiratory volume in 1 second (ppFEV1) that is between 40-90%;
6. Trikafta® is not prescribed concurrently with other CFTR modulators (e.g., Orkambi®, Kalydeco®, Symdeko®);
7. Dose does not exceed any of the following (a or b)):
   a. 6 years to less than 12 years weighing less than 30 kgs: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg per day;
   b. 6 years to less than 12 years weighing 30 kgs or more & 12 years and older: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg per day;

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Cystic Fibrosis (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy as evidenced by both of the following (a and b):
   a. Stabilization in ppFEV1 if baseline was ≥ 70% or increase in ppFEV1 if baseline was < 70%;
   b. Increase in chloride transport ≥ 10% since baseline;
3. Trikafta® is not prescribed concurrently with other CFTR modulators (e.g., Orkambi®, Kalydeco®, Symdeko®);
4. If request is for a dose increase, new dose does not exceed any of the following (a or b):
   a. 6 years to less than 12 years weighing less than 30 kgs: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 150 mg per day;
   b. 6 years to less than 12 years weighing 30 kgs or more & 12 years and older: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg per day;

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
FDA: Food and Drug Administration
ppFEV1: percent predicted forced expiratory volume in 1 second

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Orkambi®	Adults and pediatric patients aged 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally every 12 hours Pediatric patients age 6 to 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) PO every 12 hours	Adults and pediatric patients age 12 years and older: lumacaftor 800 mg/ivacaftor 500 mg per day Pediatric patients age 6 to 11 years: lumacaftor 400 mg/ivacaftor 500 mg per day
Symdeko®	Age ≥ 12 years OR age 6 to 11 years weighing ≥ 30 kg: 1 tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and 1 tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart with fat-containing food.	tezacaftor 100 mg/day ivacaftor 300 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Kalydeco®	Adults and pediatric patients aged 6 years and older: one 150 mg tablet orally every 12 hours with fat containing food.	Age ≥ 6 years: 300 mg/day

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of 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 F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.
- Should not be used in patients with severe hepatic impairment.
- List of CFTR Gene Mutations that are Responsive to Trikafta®

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;R6	G126D	I502T	P574H	R792G	V562I

List of CFTR Gene Mutations that are Responsive to Trikafta®					
68C†					
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 [see Clinical Studies (14)].
†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.

References

1. Trikafta® Prescribing Information. Boston, MA: Vertex Pharmaceuticals, Inc.; June 2021. Available at: https://www.trikafta.com/. Accessed July 08, 2021.
2. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation pulmonary guidelines: Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018; 15(3): 271-280. Available at: https://pubmed.ncbi.nlm.nih.gov/29342367/. Accessed July 08, 2021.
3. Elexacaftor, Tezacaftor, and Ivacaftor, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed July 08, 2021.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2021. Accessed with subscription at: http://www.clinicalkey.com. Updated June 18, 2021. Accessed July 08, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	09/05/2020	09/14/2020
Policy was reviewed:	07/08/2021	09/14/2021

1. Background indicated ages of use was updated from “12 years and older” to “6 years and older.” 2. Background was updated to remove “Elexacaftor and tezacaftor bind to different sites on the cystic fibrosis transmembrane conductance regulator (CFTR) protein…”, “Ivafcaftor potentiates the channel open probability…”, and “the combined effect of elexacaftor, tezacaftor, and ivacaftor is increased quantity and function of…”. 3. Dosing Information dosing regimen was updated to include “Age 6 to less than 12 years weighing less than 30 kgs…”, “Age 6 to less than 12 years weighing 30 kgs or more…”, and “For Hepatic impairment: Moderate impairment (Child-Pugh Class B)…”. 4. Dosing Information maximum dose was updated to include “For 6 to less than 12 years weighing less than 30 kgs…” and “6 to less than 12 years weighing 30 kgs or more & 12 years and older…”. 5. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 6. Initial Approval Criteria I.A.1 was updated to remove “…with genetic testing confirming the presence of two disease causing mutations in CFTR gene.”. 7. Initial Approval Criteria I.A.2 was updated to include “Member has at least one of the following mutations in the CFTR gene (a or b)…”. 8. Initial Approval Criteria I.A.2.a was updated to include “At least one F508del mutation;”. 9. Initial Approval Criteria I.A.2.b was updated to include “A mutation that is responsive based on in vitro data (see appendix D)”. 10. Initial Approval Criteria I.A.3 was updated from “Age ≥ 12 years” to “Age ≥ 6 years”. 11. Initial Approval Criteria I.A.7.a was updated to include “6 years to less than 12 years weighing less than 30 kgs: elexacaftor 100		

mg/tezacaftor 50 mg/ivacaftor 150 mg per day". 12. Initial Approval Criteria I.A.7.b was updated to include "6 years to less than 12 years weighing 30 kgs or more & 12 years and older: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 300 mg per day". 13. Initial Approval Criteria I.A.7 was updated to remove "Moderate hepatic impairment: elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg per day". 14. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 15. Continued Therapy Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 16. Continued Therapy Approval Criteria II.A.2 was updated to include "…both of the following (a and b)…". 17. Continued Therapy Approval Criteria II.A.2.a was updated to include "Stabilization in ppFEV1 if baseline was ≥ 70% or increase in ppFEV1 if baseline was < 70%". 18. Continued Therapy Approval Criteria II.A.2.b was updated to include "Increase in chloride transport ≥ 10% since baseline". 19. Continued Therapy Approval Criteria II.A.4 was updated to include "dose does not exceed any of the following (a or b)…". 20. Continued Therapy Approval Criteria II.A.4.a was updated to include "6 years to less than 12 years weighing less than 30 kgs…". 21. Continued Therapy Approval Criteria II.A.4.b was updated to include "6 years to less than 12 years weighing 30 kgs or more & 12 years and older…". 22. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 23. Appendix B: Therapeutic Alternatives was updated to include alternative drug names		

Orkambi, Symdeko, and Kalydeco as well as their respective dosing regimens and dose limits. 24. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 25. Appendix D was updated to include “List of CFTR Gene Mutations that are Responsive to Trikafta®” and subsequent table. 26. References were reviewed and updated. 27.		