LOUISIANA BLUE

elexacaftor/tezacaftor/ivacaftor (Trikafta™)

Policy # 00697
Original Effective Date: 01/08/2020
Current Effective Date: 02/10/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider elexacaftor/tezacaftor/ivacaftor (Trikafta™)‡ for the treatment of cystic fibrosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for elexacaftor/tezacaftor/ivacaftor (Trikafta) will be considered when the following criteria are met:

- Patient has a documented diagnosis of cystic fibrosis; AND
- Patient is 2 years of age or older; AND
- Patient meets ONE of the following:
    - Patient has at least 1 copy of the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene as detected by an FDA-cleared test; OR
    - Patient has confirmation of a mutation in the *CFTR* gene that is responsive to Trikafta as detected by an FDA-cleared test; AND
- Trikafta will not be used in combination with other disease modifying therapies for cystic fibrosis (i.e., ivacaftor [Kalydeco®]‡, lumacaftor/ivacaftor [Orkambi®]‡, or tezacaftor/ivacaftor [Symdeko®]‡).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers elexacaftor/tezacaftor/ivacaftor (Trikafta) when patient selection criteria are not met to be **investigational.***

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Policy Guidelines

***CFTR* Gene Mutations that Produce CFTR Protein and 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;D1270N*	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1060R*	*L453S*	*R117H*	*S737F*	

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Background/Overview

Cystic fibrosis (CF) is a serious genetic disorder affecting the lungs and other organs that ultimately leads to an early death. It is caused by mutations in a gene that encodes for a protein called CFTR that regulates ion (such as chloride) and water transport in the body. The defect in chloride and water transport results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body leading to severe respiratory and digestive problems, as well as other complications such as infections and diabetes.

Trikafta is a combination of three drugs, two of which are available in other products. Both elexacaftor and tezacaftor work by binding to different sites on the CFTR protein to facilitate the cellular processing and trafficking of the protein and increase the amount of CFTR protein delivered to the cell surface. The third drug, ivacaftor, works by potentiating the channel open probability (or gating) of the CFTR protein at the cell surface. These drugs all work together to increase CFTR activity in patients who have at least one *F508del* mutation or another mutation responsive to Trikafta in the *CFTR* gene. If a patient's mutation status is not known, an FDA-cleared cystic fibrosis mutation test should be used to determine whether a *CFTR* mutation is present. Trikafta is supplied in fixed dose combination tablets with different doses available depending on the patient's age and weight. It is also available as fixed dose combination oral granules. See Food and Drug Administration (FDA) package insert for detailed dosing information. Regardless of the strength used, the recommended dose is two combination tablets (or one packet of granules) taken in the morning and one ivacaftor tablet taken in the evening. Both doses should be taken with fat-containing food such as those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats. Since Trikafta contains ivacaftor, the active agent in Kalydeco and part of both Orkambi and Symdeko, and tezacaftor, the active agent in Symdeko, it should not be used in combination with Kalydeco, Orkambi, or Symdeko.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Trikafta was approved by the FDA in October 2019 for the treatment of cystic fibrosis in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. In 2021, the indication was updated to include patients aged 6-12 years as well as 178 additional *CFTR* mutations. In 2023, the indication was further updated to include patients aged 2-6 years.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Trikafta in patients with CF aged 12 years and older was evaluated in two phase 3, double blind, controlled trials (Trials 1 and 2).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in 403 patients aged ≥12 years who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. An interim analysis was planned when at least 140 patients completed week 4 and at least 100 patients completed week 12. The primary endpoint assessed at the time of interim analysis was mean absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at week 4. The final analysis tested all key secondary endpoints in the 403 patients who completed the 24-week study participation, including absolute change in $ppFEV_1$ from baseline through week 24, absolute change in sweat chloride from baseline at week 4 and through week 24, number of pulmonary exacerbations through week 24, absolute change in BMI from baseline at week 24, and absolute change in the CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF) from baseline at week 4 and through week 24.

In the interim analysis, the treatment difference between Trikafta and placebo for the mean absolute change from baseline in $ppFEV_1$ at week 4 was 13.8% (95% CI: 12.1, 15.4, $P<0.0001$). The treatment difference between Trikafta and placebo for mean absolute change in $ppFEV_1$ from baseline through week 24 was 14.3% (95% CI: 12.7, 15.8, $P<0.0001$). Mean improvement in $ppFEV_1$ was observed at the first assessment on day 14 and sustained through the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region. All secondary endpoints showed a statistically significant improvement with Trikafta compared to placebo.

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in 107 patients with CF aged 12 years and older who were homozygous for the *F508del* mutation. Patients received Symdeko during a 4-week open-label run-in period and were then randomized and dosed to receive Trikafta or Symdeko during a 4-week double-blind treatment period. The primary endpoint was mean absolute change in $ppFEV_1$ from baseline at week 4 of the double-blind treatment period.

Treatment with Trikafta compared to Symdeko resulted in a statistically significant improvement in ppFEV1 of 10.0% (95% CI: 7.4, 12.6; P<0.0001). Mean improvement in $ppFEV_1$ was observed at the first assessment on day 15. Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region.

The efficacy of Trikafta in patients aged 2 to less than 12 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing elexacaftor, tezacaftor, and ivacaftor exposure levels in patients aged 2 to less than 12 years within the range of exposures observed in patients aged 12 years and older. Safety of Trikafta in patients aged 6 to less than 12 years was derived from a 24-week open-label, clinical trial in 66 patients aged 6 to less than 12 years administered either a total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening (for patients weighing less than 30 kg) or a total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening (for patients weighing 30 kg or more). The safety of Trikafta in patients aged 2 to less than 6 years was derived from a 24-week, open-label, clinical trial in 75 patients aged 2 to less than 6 years administered either a total dose of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg in the morning and ivacaftor 59.5 in the evening (for patients weighing 10 kg or less than 14 kg) or a total dose of elexacaftor 100 mg/tezacaftor 50 mg/ ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening (for patients weighing 14 kg or more). The safety profile of patients in these trials was similar to that observed in Trial 1.

References

1. Trikafta [package insert]. Vertex Pharmaceuticals, Boston, MA. Updated October 2023.

Policy History

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01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. New policy.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. Updated criteria and background information to include newly approved age and *CFTR* mutations.
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2024	Medical Policy Committee review
01/10/2024	Medical Policy Implementation Committee approval. Updated age requirement to 2 years or older based on FDA label update.

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01/02/2025 Medical Policy Committee review
01/08/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 01/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.