

tezacaftor/ivacaftor (Symdeko™)

Policy # 00620

Original Effective Date: 05/16/2018

Current Effective Date: 01/13/2025

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 tezacaftor/ivacaftor (Symdeko™)‡ for the treatment of cystic fibrosis to be **eligible for coverage.****

Patient Selection Criteria

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

- Patient has a documented diagnosis of cystic fibrosis; AND
- Patient is 6 years of age or older; AND
- Patient meets ONE of the following criteria:
 - The patient is homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene as detected by an FDA-cleared test; OR
 - The patient has confirmation of a mutations in the *CFTR* gene that is responsive to tezacaftor/ivacaftor (Symdeko) as detected by an FDA cleared test; AND
- The drug will not be used in combination with ivacaftor (Kalydeco®)‡, lumacaftor/ivacaftor (Orkambi®)‡, or elexacaftor/tezacaftor/ivacaftor (Trikafta™)‡.

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 tezacaftor/ivacaftor (Symdeko) 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 Symdeko

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|--------------------------|---------------------|--------------------|--------------------|---------------|---------------|
| <i>546insCTA</i> | <i>E92K</i> | <i>G576A</i> | <i>L346P</i> | <i>R117G</i> | <i>S589N</i> |
| <i>711+3A →G</i> | <i>E116K</i> | <i>G576A;R668C</i> | <i>L967S</i> | <i>R117H</i> | <i>S737F</i> |
| <i>2789+5G →A</i> | <i>E193K</i> | <i>G622D</i> | <i>L997F</i> | <i>R117L</i> | <i>S912L</i> |
| <i>3272-26A →G</i> | <i>E403D</i> | <i>G970D</i> | <i>L1324P</i> | <i>R117P</i> | <i>S945L</i> |
| <i>3849+10kbC →T</i> | <i>E588V</i> | <i>G1069R</i> | <i>L1335P</i> | <i>R170H</i> | <i>S977F</i> |
| <i>A120T</i> | <i>E822K</i> | <i>G1244E</i> | <i>L1480P</i> | <i>R258G</i> | <i>S1159F</i> |
| <i>A234D</i> | <i>E831X</i> | <i>G1249R</i> | <i>M152V</i> | <i>R334L</i> | <i>S1159P</i> |
| <i>A349V</i> | <i>F191V</i> | <i>G1349D</i> | <i>M265R</i> | <i>R334Q</i> | <i>S1251N</i> |
| <i>A455E</i> | <i>F311del</i> | <i>H939R</i> | <i>M952I</i> | <i>R347H</i> | <i>S1255P</i> |
| <i>A554E</i> | <i>F311L</i> | <i>H1054D</i> | <i>M952T</i> | <i>R348L</i> | <i>T338I</i> |
| <i>A1006E</i> | <i>F508C</i> | <i>H1375P</i> | <i>P5L</i> | <i>R347P</i> | <i>T1036N</i> |
| <i>A1067T</i> | <i>F508C;S1251N</i> | <i>I148T</i> | <i>P67L</i> | <i>R352Q</i> | <i>T1053I</i> |
| <i>D110E</i> | <i>F508del</i> | <i>I175V</i> | <i>P205S</i> | <i>R352W</i> | <i>V201M</i> |
| <i>D110H</i> | <i>F575Y</i> | <i>I336K</i> | <i>Q98R</i> | <i>R553Q</i> | <i>V232D</i> |
| <i>D192G</i> | <i>F1016S</i> | <i>I601F</i> | <i>Q237E</i> | <i>R668C</i> | <i>V562I</i> |
| <i>D443Y</i> | <i>F1052V</i> | <i>I618T</i> | <i>Q237H</i> | <i>R751L</i> | <i>V754M</i> |
| <i>D443Y;G576A;R668C</i> | <i>F1074L</i> | <i>I807M</i> | <i>Q359R</i> | <i>R792G</i> | <i>V1153E</i> |
| <i>D579G</i> | <i>F1099L</i> | <i>I980K</i> | <i>Q1291R</i> | <i>R933G</i> | <i>V1240G</i> |
| <i>D614G</i> | <i>G126D</i> | <i>I1027T</i> | <i>R31L</i> | <i>R1066H</i> | <i>V1293G</i> |
| <i>D836Y</i> | <i>G178E</i> | <i>I1139V</i> | <i>R74Q</i> | <i>R1070Q</i> | <i>W1282R</i> |
| <i>D924N</i> | <i>G178R</i> | <i>I1269N</i> | <i>R74W</i> | <i>R1070W</i> | <i>Y109N</i> |
| <i>D979V</i> | <i>G194R</i> | <i>I1366N</i> | <i>R74W;D1270N</i> | <i>R1162L</i> | <i>Y161S</i> |
| <i>D1152H</i> | <i>G194V</i> | <i>K1060T</i> | <i>R74W;V201M</i> | <i>R1283M</i> | <i>Y1014C</i> |



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|---------------|--------------|--------------|--------------------------|---------------|---------------|
| <i>D1270N</i> | <i>G314E</i> | <i>L15P</i> | <i>R74W;V201M;D1270N</i> | <i>R1283S</i> | <i>Y1032C</i> |
| <i>E56K</i> | <i>G551D</i> | <i>L206W</i> | <i>R75Q</i> | <i>S549N</i> | |
| <i>E60K</i> | <i>G551S</i> | <i>L320V</i> | <i>R117C</i> | <i>S549R</i> | |

Background/Overview

Cystic fibrosis 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.

Symdeko is a combination of the CFTR potentiator, ivacaftor, and tezacaftor which increases the amount of mature CFTR protein delivered to the cell surface. The combined effect of these two drugs is to increase the quantity and function of CFTR at the cell surface which results in increased chloride transport. Symdeko is indicated for treatment of cystic fibrosis in patients 6 years of age and older who are either homozygous for the *F508del* mutation in the *CFTR* gene (the most common *CFTR* genotype and associated with severe disease) or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor (Symdeko) based on clinical and/or *in vitro* assay data. 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. Symdeko is supplied as co-packaged tezacaftor 100mg/ivacaftor 150 mg fixed-dose combination tablets with ivacaftor 150 mg tablets and tezacaftor 50 mg/ivacaftor 75 mg tablets with ivacaftor 75 mg tablets. Patients should take one combination tablet in the morning and one ivacaftor tablet in the evening. Both doses should be taken with a fat-containing meal to ensure adequate absorption. Examples of foods that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats. Symdeko is not indicated for use in combination with other targeted cystic fibrosis therapies including Kalydeco, Orkambi, and Trikafta. It should be noted that all of these products contain ivacaftor as one of the active ingredients and Trikafta and Symdeko both contain tezacaftor as another active ingredient.



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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Symdeko was approved by the FDA in February 2018 for the treatment of patients with cystic fibrosis aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. In June 2019, the label was updated to include patients 6 years of age and older. In December 2020, the label was further expanded to include 127 additional mutations based on *in vitro* data.

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 Symdeko was evaluated in two trials in different patient populations. The EVOLVE trial evaluated 510 patients 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene. These subjects were randomized to placebo or Symdeko for 24 weeks. Treatment with Symdeko resulted in modest improvement in FEV₁ (absolute change, 4 percentage points versus placebo), and modest improvement in disease-related quality of life score (5.1 points versus placebo). The rate of pulmonary exacerbations was 35% lower in the treatment group compared with placebo (HR 0.64, 95% CI, 0.46-0.88). BMI increased slightly during the 24 week study, but was not significantly different between the study groups.

The EXPAND trial evaluated 248 patients 12 years and older who were heterozygous for the *F508del* mutation and had a residual function mutation and mild or moderate cystic fibrosis-related lung disease. The patients were randomized in a crossover study to Symdeko alone, ivacaftor (Kalydeco) monotherapy, or placebo. Treatment with Symdeko resulted in modest improvement in FEV₁ (absolute change, 6.8 percentage points versus placebo), as did ivacaftor monotherapy (absolute change, 4.7 percentage points versus placebo). The benefit of Symdeko compared to Kalydeco was slight, but statistically significant (absolute change, 2.1 percentage points). Symdeko also resulted in clinically significant improvements in a disease-related quality of life score (11.1 points versus placebo).

The efficacy of Symdeko in patients aged 6 to less than 12 years was extrapolated from patients age 12 years and older with support from population pharmacokinetic analyses showing similar tezacaftor and ivacaftor exposure levels in patients age 6 to less than 12 years and in patients age 12



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years and older. Safety of Symdeko in this population was derived from a 240 week, open-label, clinical trial in 70 patients age 6 to less than 12 years administered either tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 75 mg or tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg, 12 hours apart. The safety profile for patients in this trial was similar to that observed in Trials 1 and 3.

References

1. Symdeko [package insert]. Vertex Pharmaceuticals. Boston, MA. August 2021.
2. Symdeko prior authorization document. Express Scripts.
3. UpToDate. Cystic fibrosis: Overview of the treatment of lung disease.

Policy History

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| 05/03/2018 | Medical Policy Committee review |
| 05/16/2018 | Medical Policy Implementation Committee approval. New policy. |
| 05/02/2019 | Medical Policy Committee review |
| 05/15/2019 | Medical Policy Implementation Committee approval. No change to coverage. |
| 12/05/2019 | Medical Policy Committee review |
| 12/11/2019 | Medical Policy Implementation Committee approval. Updated criteria and background information to reflect FDA approval for patients aged 6-11 years. Added Trikafta as a drug that should not be combined with Symdeko. |
| 12/03/2020 | Medical Policy Committee review |
| 12/09/2020 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/02/2021 | Medical Policy Committee review |
| 12/08/2021 | Medical Policy Implementation Committee approval. Updated criteria and background information to include newly approved mutations. |
| 12/01/2022 | Medical Policy Committee review |
| 12/14/2022 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/07/2023 | Medical Policy Committee review |
| 12/13/2023 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 12/05/2024 | Medical Policy Committee review |
| 12/11/2024 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

Next Scheduled Review Date: 12/2025



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*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.

