EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Cystic Fibrosis – Trikafta™ (elexacaftor/tezacaftor/ivacaftor tablets; ivacaftor tablets, co-packaged – Vertex)

TAC APPROVAL DATE: 10/23/2019

OVERVIEW

Trikafta is a combination of ivacaftor, a cystic fibrosis transmembrane regulator (CFTR) potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients ≥ 12 years of age who have at least one F508del mutation in the CFTR gene.[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.

Elexacaftor is a new chemical entity. Ivacaftor is also available as Kalydeco® (tablets and oral granules) and as part of the co-formulated Orkambi® (lumacaftor/ivacaftor tablets and oral granules).[2,3] Tezacaftor and ivacaftor are part of the co-formulated product, Symdeko® (tezacaftor/ivacaftor tablets; ivacaftor tablets).[4]

Both elexacaftor and tezacaftor bind to different sites of 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 with either molecule alone.[1] Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of the three drugs is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

The F508del is the most common mutation found in patients with CF, in 2017 it was estimated that 25,276 patients with CF had at least one copy of the F508del mutation (85.8% of the CF population).[6]

Prevalence of F508del Mutations in Patients with CF in 2017.[6]

F508del Mutation	Percent of all Patients with CF
Homozygous F508del	45.3%
Heterozygous F508del	40.9%
Neither F508del or Unknown	13.7%

CF – Cystic fibrosis.

Clinical Efficacy

The efficacy of Trikafta in patients ≥ 12 years of age with CF was evaluated in two Phase III, double-blind, controlled trials.[1] Patients in both studies continued on their other standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an F508del mutation on one allele and a mutation on the second allele either with no CFTR protein or a CFTR protein that is not responsive to Symdeko.[1] An interim analysis was planned when ≥ 140 patients completed Week 4 and ≥ 100 patients completed Week 12. Of the 403 patients included in the interim analysis, the treatment difference between Trikafta and placebo for the mean absolute change from

baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) at Week 4 was 13.8% (95% confidence interval [CI]: 12.1, 15.4; P < 0.0001). The treatment difference between Trikafta and placebo for mean absolute change in ppFEV1 from baseline through Week 24 was 14.3% (95% CI: 12.7, 15.8; P < 0.0001).

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in patients who were homozygous for the F508del mutation (n = 107).[1] Patients received Symdeko every 12 hours during a 4-week, open-label, run-in period and were then randomized and dosed to receive Trikafta or Symdeko every 12 hours during a 4-week, double-blind, treatment period. The mean ppFEV1 at baseline, following the 4-week open-label run-in period with Symdeko was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in ppFEV1 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).

Guidelines

Guidelines from the CF Foundation (2018) provide guidance on the use of CFTR therapy in patients with CF; Trikafta is not addressed.[5]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Trikafta. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Trikafta as well as the monitoring required for adverse events and long-term efficacy, approval requires Trikafta to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Trikafta is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Cystic Fibrosis (CF).** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The patient is ≥ 12 years of age; AND
   - **B)** Trikafta is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of CF; AND
   - **C)** The patient has at least one copy of the F508del mutation in the cystic fibrosis conductance regulator gene.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Trikafta has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Cystic Fibrosis (CF), Patients with Unknown Cystic Fibrosis Transmembrane Regulator (CFTR) Gene Mutation.** An FDA-cleared CF mutation test should be used to detect the presence of the CFTR mutation prior to use of Trikafta.[1]

2. **Combination Therapy with Orkambi, Kalydeco, or Symdeko.** Trikafta contains ivacaftor which is a component of Orkambi, Kalydeco, and Symdeko. Tezacaftor, another component of Trikafta is also contained in Symdeko.

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Trikafta™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; June 2019.
2. Kalydeco™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; April 2019.
3. Orkambi™ tablets and oral granules [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; July 2019.
4. Symdeko™ tablets [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals, Inc; June 2019.
5. Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation Pulmonary Guidelines: Use of cystic fibrosis trasmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
6. CF patient registry 2017. Available at: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf. Accessed on October 22, 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	10/23/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; TAC – Therapeutic Assessment Committee.