09-J1000-68

Original Effective Date: 06/15/12

Reviewed: 04/10/24

Revised: 05/15/24

Next Review: 04/09/25

Subject: Ivacaftor (Kalydeco™) Oral

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Ivacaftor (Kalydeco™) was approved by the US Food and Drug Administration (FDA) on January 31, 2012 for treatment of cystic fibrosis (CF) in persons who have any of the following mutations in the CF transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H. CF is a life-threatening, multisystem genetic disorder characterized by progressive lung disease. The disorder is the result of mutations in the CFTR gene located on chromosome 7. CF is inherited as an autosomal recessive trait. In an individual with a mutated CFTR gene, the risk of developing CF is dependent upon the mutation(s) present. The most common mutation is F508del. Another well-known mutation is G551D. Since the identification of CFTR in 1989 almost 2,000 mutations have been identified.

Ivacaftor exerts its effects by increasing chloride transport by potentiating the channel-open probability (or gating) of the G55ID-CFTR protein (an epithelial cell chloride channel). It is the first drug that directly targets the defective CFTR protein instead of the cystic fibrosis symptoms. In clinical studies of ivacaftor, it was ineffective in subjects who were homozygous for the F508del mutation in the CFTR gene; as such, it should not be used in this population. Ivacaftor is FDA-approved for use in children age 12 months of age and older.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare

professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of ivacaftor (Kalydeco) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member has a diagnosis of cystic fibrosis (CF)
2. Member has a mutation on the CF transmembrane conductance regulator (CFTR) gene confirmed by an FDA-cleared cystic fibrosis mutation test that is responsive to treatment with ivacaftor per the FDA-approved label (Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0ab0c9f8-3eee-4e0f-9f3f-c1e16aaffe25) – laboratory documentation must be provided
3. Member is not homozygous for the F508del mutation on the CFTR gene
4. Use is not in combination with elexacaftor-tezacaftor-ivacaftor (Trikafta), lumacaftor-ivacaftor (Orkambi), or co-packaged tezacaftor/ivacaftor (Symdeko)
5. One of the following:
    a. Member is 1 month of age or older
    b. Member's age is within FDA approved labeling
6. The dose does not exceed:
    a. Adults and children ages 6 years and older: 150 mg twice daily
    b. Children ages 6 months to less than 6 years:
        i. Body weight 5 kg to less than 7 kg: 25 mg twice daily
        ii. Body weight 7 kg to 14 kg: 50 mg twice daily
        iii. Body weight 14 kg or greater: 75 mg twice daily
    c. Children ages 4 months to less than 6 months:
        i. Body weight 5 kg or greater: 25 mg twice daily
    d. Children ages 2 months to less than 4 months:
        i. Body weight 3 kg or greater: 13.4 mg twice daily
    e. Children ages 1 month to less than 2 months:
        i. Body weight 3 kg or greater: 5.8 mg twice daily

Duration of approval: 6 months

Continuation of ivacaftor (Kalydeco) me**ets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years **OR** the member has previously met all indication-specific initiation criteria
2. Member meets **ONE** of the following:

a. Member demonstrates a clinically meaningful response to treatment with lumacaftor/ivacaftor as indicated by any of the following:
    i. Improvement in forced expiratory volume in one second (FEV1) – documentation must be provided
    ii. Improvement in body mass index (BMI) – documentation must be provided
    iii. Reduction in pulmonary exacerbations – documentation must be provided
    iv. Improvement in quality of life as demonstrated by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score – documentation must be provided
b. Member currently demonstrates a beneficial response to treatment with ivacaftor AND has been receiving treatment for a minimum of 18 months

3. Ivacaftor is not administered in combination with elexacaftor-tezacaftor-ivacaftor (Trikafta), lumacaftor/ivacaftor (Orkambi), or co-packaged tezacaftor/ivacaftor (Symdeko)
4. Dose does not exceed:
    a. Adults and children ages 6 years and older: 150 mg twice daily
    b. Children ages 6 months to less than 6 years:
        i. Body weight 5 kg to less than 7 kg: 25 mg twice daily
        ii. Body weight 7 kg to 14 kg: 50 mg twice daily
        iii. Body weight 14 kg or greater: 75 mg twice daily
    c. Children ages 4 months to less than 6 months:
        i. Body weight 5 kg or greater: 25 mg twice daily
    d. Children ages 2 months to less than 4 months:
        i. Body weight 3 kg or greater: 13.4 mg twice daily
    e. Children ages 1 month to less than 2 months:
        i. Body weight 3 kg or greater: 5.8 mg twice daily
5. One of the following:
    a. Member is 1 month of age or older
    b. Member's age is within FDA approved labeling

Duration of approval: 1 year

NOTE: If the member's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of any mutation. Quest Diagnostics® can perform the CF mutation test. Additionally, documentation of member's mutation from the Cystic Fibrosis Foundation CF Patient Registry is acceptable in place of original laboratory documentation.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL

PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

- Adults and children ages 6 years and older: 150 mg twice daily
- Children ages 6 months to less than 6 years:
    - Body weight 5 kg to less than 7 kg: 25 mg twice daily
    - Body weight 7 kg to 14 kg: 50 mg twice daily
    - Body weight 14 kg or greater: 75 mg twice daily
- Children ages 4 months to less than 6 months:
    - Body weight 5 kg or greater: 25 mg twice daily
- Children ages 2 months to less than 4 months:
    - Body weight 3 kg or greater: 13.4 mg twice daily
- Children ages 1 month to less than 2 months:
    - Body weight 3 kg or greater: 5.8 mg twice daily

Dosage Adjustment:

- Hepatic Impairment: The dose of ivacaftor should be reduced to 150 mg once daily for persons with moderate hepatic impairment. Ivacaftor should be used with caution in persons with severe hepatic impairment at a dose of 150 mg once daily or less frequently.
- CYP3A inhibitors: When ivacaftor is being co-administered with strong CYP3A inhibitors (e.g., ketoconazole) the dose should be reduced to 150 mg twice-a-week.
- The dose of ivacaftor should be reduced to 150 mg once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Food containing grapefruit or Seville oranges should be avoided.

Drug Availability:

- Tablets: 150 mg
- Oral granules: Unit-dose packets of 5.8 mg, 13.4 mg, 25 mg, 50 mg, and 75 mg

PRECAUTIONS:

Transaminase (ALT or AST) Elevations: Elevated transaminases have been reported in persons with CF receiving ivacaftor. Transaminases (ALT and AST) should be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. If a member develops increased transaminase levels, levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in persons with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Concomitant Use with CYP3A Inducers: Use of ivacaftor with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of ivacaftor. Therefore, co-administration of ivacaftor with strong CYP3A inducers (e.g., rifampin, St. John's Wort) is not recommended.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J8499	Prescription drug, oral, non chemotherapeutic, nos

ICD-10 Diagnoses Codes That Support Medical Necessity:

E84.0	Cystic fibrosis with pulmonary manifestations
E84.11	Meconium ileus in cystic fibrosis
E84.19	Cystic fibrosis with other intestinal manifestations
E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Genetic Testing, 05-82000-28

Lumacaftor/Ivacaftor Capsule, 09-J2000-29

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 4/10/24.

GUIDELINE UPDATE INFORMATION:

06/15/12	New Medical Coverage Guideline.
06/15/13	Review and revision to guideline; consisting of revising position statement to exclude coverage for members who are homozygous for the F508del mutation and revising description section; reformatting dosage/administration and precautions section; updating references.
06/15/14	Review and revision to guideline; consisting of revising position statement and updating references.
02/15/15	Review and revision to guideline; consisting of revision of position statement
05/15/15	Revised guideline; consisting of position statement and dosing/administration, references
06/15/15	Review and revision to guideline; consisting of position statement, related guidelines, references
07/15/15	Revision to guideline; updated HCPCS code.
11/01/15	Revision: ICD-9 Codes deleted.
06/15/16	Review and revision to guideline; consisting of revising description, position statement, references.
06/15/17	Review and revision to guideline; consisting of updating references.
07/15/17	Revised position statement to include new mutations per updated FDA indication.
09/15/17	Revised position statement to include new mutations per updated FDA indication.
05/15/18	Review and revision to guideline; consisting of updating references.
11/15/18	Revision to guideline; consisting of updating position statement and dosing

05/15/19	Review and revision to guideline; consisting of updating position statement and references.
05/15/21	Review and revision to guideline; consisting of updating position statement and references.
05/15/24	Review and revision to guideline; consisting of updating position statement, dosing, and references.