Subject: Kalydeco (ivacaftor)	Original Effective Date: 6/29/12
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Review Date(s): 12/15/2016	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of Kalydeco (ivacaftor) for the treatment of cystic fibrosis when appropriate criteria are met. The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- **Cystic fibrosis (CF)** is an autosomal recessive disease characterized by abnormal airways secretions, chronic endobronchial infection, and progressive airway obstruction.

- **Ivacaftor** potentiates the cystic fibrosis transmembrane conductance protein (CFTR), specifically G551D-CFTR, resulting in increased chloride transport on the surface of epithelial cells in multiple organs.

- **CFTR (cystic fibrosis transmembrane conductance regulator)** modulator therapies are designed to correct the function of the defective protein made by the CF gene. Because different mutations cause different defects in the protein, the medications that have been developed so far are effective only in people with specific mutations. There are currently two FDA-approved CFTR modulators:
  - ivacaftor (Kalydeco®)
  - lumacaftor/ivacaftor (Orkambi®)

- The FDA approved ivacaftor (Kalydeco) in **January of 2012** for the treatment of a rare form of CF in patients ages 6 years and older who have the specific *G551D* mutation in the CFTR gene.
  - The indication was later expanded in 2014 to include the *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, and *S549R* mutations in addition to the *G551D* mutation.
  - In late 2014, the indication was once more expanded to patients that have a *R117H* mutation in the CFTR gene.
  - In early 2015, the indication was again expanded to include those patients 2 years of age and older based on data extrapolated from efficacy in patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 2 to less than 6 years of

age. At the same time as the age expansion, a new formulation of Kalydeco was developed (oral granules in 50mg and 75mg unit-dose packets) for patients 2 to less than 6 years of age.
- In May 2017, the indication expanded to treat CF in individuals aged 2 years or older who have any one of 23 additional mutations of the CFTR gene. Total number of covered mutations to 33.
- Aug 2017: Indication expanded to include an additional five mutations (*2789+5G—> A*, *3272-26A—> G, 3849+10kbC—> T*, *711+3A—> G*, and *E831X)*. Total number of covered mutations to 38.

⌘ Ivacaftor significantly improved FEV1, increased body weight and BMI, improved respiratory symptom scores, and decreased the rate of pulmonary exacerbations compared with placebo in several studies of adults and children with cystic fibrosis; efficacy varied among different mutations (Ramsey BW et al.) In a separate study of patients with the R117H mutation, there was no significant difference in FEV1 (mean improvement compared with placebo, 2.1%), BMI, or time to first pulmonary exacerbation at 24 weeks. A study in patients homozygous for the F508del mutation found no significant difference for percent predicted FEV between ivacaftor and placebo, but there was a significant 2.9 mmol/L treatment difference in favor of ivacaftor for change in sweat chloride. Micromedex

⌘ The Cystic Fibrosis Pulmonary Guidelines strongly recommend chronic use of ivacaftor to improve lung function and quality of life and reduce exacerbations in patients with a qualifying mutation (Mogayzel PJ et al.)

CLASSIFICATION: Cystic Fibrosis Transmembrane Conductance Regulator Potentiators

FDA INDICATIONS

⌘ **Cystic fibrosis**
Orphan drug designation: Treatment of patients with cystic fibrosis

Treatment of cystic fibrosis in patients **2 years and older** who have one of **38 ivacaftor-responsive mutations** in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data

If the patient's genotype is unknown, an FDA-cleared cystic fibrosis mutation test should be used to detect the presence of a CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use.

Limitations of use: Kalydeco (ivacaftor) is not effective in patients with CF with two copies of the F508del mutation (F508del/F508del) in the CF gene.

Available as: Oral Granule: 50 mg/packet* 75 mg/packet*
**A weight-based oral granule formulation of Kalydeco (50 mg and 75 mg) may be mixed in soft foods or liquids to meet the needs of children in this new age group who may be unable to swallow a tablet.*
Oral Tablet: 150mg
FDA Approved:
- January 31, 2012: Indication for patients with CF who were aged 6 years and older and had at least 1 copy of the G551D mutation in the CTFR gene
- February 2014: Indication expanded to patients who are 6 years and older to cover eight additional CF-triggering mutations of the CFTR gene: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D.
- March 2015: Age expanded for use in children ages 2 to 5 with CF who have one of 10 mutations in the CFTR gene (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R and R117H)
- May 2017: Indication expanded to treat CF in individuals aged 2 years or older who have any one of 23 additional mutations of the CFTR gene. Total number of covered mutations to 33.
- August 2017: Indication expanded to five additional residual function mutations that result in a splicing defect in the CFTR gene. Total number of covered mutations to 38.

Black Box Warnings: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Kalydeco (ivacaftor) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. **Prescriber specialty [ONE]**

   ❒ Prescribed by, or in consultation with, a board-certified pulmonologist, cystic fibrosis specialist or physician from a CF center accredited by the Cystic Fibrosis Foundation. Submit consultation notes if applicable.
   NOTE: Consultation notes must be submitted for initial request AND at least once annually for continuation of treatment requests.

2. **Diagnosis/Indication [ONE]**
   Clinical documented diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

   ❒ Diagnosis of cystic fibrosis

   .

   ❒ ONE (1) mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data listed in Table 1 (below)
   AND
   ONE (1) of the following documentation: [ONE]

   ❍ An FDA-cleared CF mutation test (utilized to detect the presence of a CFTR mutation followed by verification with bi‑directional sequencing when recommended by the mutation test instructions)

   ❍ Member's mutation confirmed from the Cystic Fibrosis Foundation CF Patient Registry

Table 1 .*CFTR* Gene Mutations* Responsive to Kalydeco (ivacaftor)

**Mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) in vitro data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal).*

					Added August 2017
E56K	G178R	S549R	K1060T	G1244E	*2789+5G —> A*
P67L	E193K	G551D	A1067T	S1251N	3272-26A —> G
R74W	L206W	G551S	G1069R	S1255P	*3849+10kbC —> T*
D110E	R347H	D579G	R1070Q	D1270N	*711+3A —> G*
D110H	R352Q	S945L	R1070W	G1349D	E831X
R117C	A455E	S977F	F1074L		
R117H	S549N	F1052V	D1152H		

Reference: Kalydeco [prescribing information].Boston, MA: Vertex Pharmaceuticals Incorporated; May 2017.

NOTE: Kalydeco is <u>not</u> effective in patients who are homozygous for the F508del mutation in the CTFR gene and 26 other mutations are considered not responsive to ivacaftor: A46D, G85E, E92K, P205S, R334W,R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K *(Prescribing Information, May 2017)*

3. Age/Gender/Other restrictions [ALL]

❒ 2 years of age or older

The safety and efficacy of Kalydeco in patients with CF younger than 2 years of age have not been studied. The use of Kalydeco in children under the age of 2 years is not recommended

4. Step/Conservative Therapy/Other condition Requirements [ALL]

❒ Baseline liver function tests prior to initiating therapy then annually with continuation of treatment requests

Informational Note:

- *May increase hepatic transaminases. Increased monitoring may be necessary in patients with a history of elevated hepatic transaminases. Temporarily discontinue treatment if ALT or AST more than 5 times the upper limit of normal.*
- *Following resolution of transaminase elevations, consider the benefits and risks of resuming therapy.*
- *Dosage adjustment recommended in patients with moderate to severe (Child-Pugh class B or C) impairment*

❒ Baseline FEV1 within the previous 30 days: For members 6 years or older only

EXCEPTION: Prescriber submit documentation for children 6 years or older who are not able to voluntarily perform the physiological maneuvers required for the pulmonary function tests (PFTs) for Medical/Pharmacy Director review. **[MEDICAL/PHARMACY DIRECTOR REVIEW REQUIRED]**

Informational Note:

- *FEV1 was the clinical endpoint in the two pivotal studies that led to the FDA approval of ivacaftor in 2012.*
- *FEV1 in patients < 2 years is not possible. Children in this age group are not able to voluntarily perform many of the physiological maneuvers required for the pulmonary function tests used in older children and adults. FEV1 measurement is possible in patients younger than six years, however may only in specialized centers.*

❒ Members up to 17 years of age: Baseline ophthalmic examination to monitor lens opacities/cataracts

Informational Note:

- *Non-congenital lens opacities and cataracts have been reported in pediatric patients treated with ivacaftor; other risk factors were present in some cases (e.g., corticosteroid use, exposure to radiation), but a possible risk related to ivacaftor cannot be excluded.*
- *Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Kalydeco treatment*

❒ Not prescribed or intended for concurrent therapy with lumacaftor-ivacaftor (Orkambi)

5. Contraindications*/Exclusions/Discontinuations

**There are no contraindications listed in the manufacturer's labeling*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Homozygous for the F508del mutation in the CTFR gene
  - ➢ *Ivacaftor is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.*
- ❒ Hypersensitivity to Kalydeco (ivacaftor) or any of its components
- ❒ Concurrent therapy with lumacaftor-ivacaftor (Orkambi)

Precautions (not an Exclusion; however if noted in member's medical record, **Peer-to-Peer or additional documentation from Prescriber may be requested) [ANY]**

- ❒ Any other mutations of the CTFR gene other than the CFTR mutations indicated (Kalydeco Prescribing Information as of August 2017)
- ❒ Concomitant Use With CYP3A Inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)
  - ➢ *Use of ivacaftor with CYP3A inducers reduces exposure and may diminish effectiveness.*

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Kalydeco (ivacaftor) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria

- ❑ If Prescriber is *not* a board-certified pulmonologist, cystic fibrosis specialist or physician from a CF center accredited by the Cystic Fibrosis Foundation: **Recent consultation notes** must be submitted for continuation of treatment requests indicating ongoing benefit from therapy.

2. Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL APPLICABLE]

Kalydeco (ivacaftor) therapy may be authorized when therapy has demonstrated efficacy as evidenced by an improvement in disease activity after initial therapy. **Documentation of disease stabilization or improvement** is required for continuation of therapy, including: **[ALL APPLICABLE]**

- ❒ Improved lung function or stable lung function: [ONE]

  - ❍ Decreased pulmonary exacerbations compared to pre-treatment baseline

  - ❍ Improvement or stabilization of lung function† compared to baseline or decrease in the rate of decline of lung function.

    †Lung function measured as FEV1, or forced expiratory volume exhaled in 1 second. Improvement in FEV1 is indicative of efficacy

- ❒ Improvement in BMI

- ❒ Liver functions tests (ALT/AST) provided with continuation of treatment request during the first year of treatment and annually thereafter.

  Monitor ALT and AST levels prior to initiation, every 3 months for the first year of treatment, and then annually. If abnormalities develop, closely monitor until resolution

- ❒ Improvement in CF respiratory symptoms† as documented by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

  †CFQ-R respiratory domain score is a measure of respiratory symptoms relevant to people with CF such as cough, sputum production, and difficulty breathing (assessed in Pivotal Trials, Study 1 and Study 2)

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Exclusions
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to Kalydeco (ivacaftor) or any of its components
  - ❍ Concurrent therapy with lumacaftor-ivacaftor (Orkambi)

- ❑ Precaution (not an Exclusion; however if noted in member's medical record, **Peer-to-Peer or additional documentation from Prescriber may be requested)** [ANY]
  - ❍ Concomitant use with a strong CYP3A inducer (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort)
  - ❍ ALT/AST greater the 5 times upper limit of normal (ULN)

    Ivacaftor therapy should be interrupted in patients with ALT or AST elevations exceeding 5 times the ULN. Following resolution of aminotransferase elevations, the benefits and risks of resuming ivacaftor therapy should be considered.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL APPLICABLE]
Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and toxicity.

- ❒ **Younger than 2 years:** Safety and efficacy have not been established
- ❒ **2 to less than 6 years:** weight-based and should be given with fat-containing food
  - ❍ Weighing 14 kg or more: 75 mg granule packet every 12 hours
  - ❍ Weighing less than 14 kg: 50 mg granule packet every 12 hours
- ❒ **Adults and pediatric patients 6 years and older:** 150 mg every 12 hours
- ❒ Dose Adjustments [AS APPLICABLE]
  - ❍ Reduce dose in patients with moderate and severe hepatic impairment
    - *mild (Child-Pugh class A): No adjustment required*
    - *moderate (Child-Pugh class B), 6 years or older: 150 mg orally once daily*
    - *moderate (Child-Pugh class B), 2 to younger than 6 years, less than 14 kg: One 50-mg packet of granules orally once daily*
    - *moderate (Child-Pugh class B), 2 to younger than 6 years, 14 kg or greater: One 75-mg packet of granules orally once daily*
    - *severe (Child-Pugh class C): 150 mg OR 1 packet of granules orally once daily or less frequently*
  - ❍ Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors

2. Authorization Limit [ALL]

- ❒ Quantity limit: Maximum dose of 150 mg twice daily; 60 tablets per 30 days
- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time
- ❒ Duration of initial authorization: 3 months
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required **every 6 months** to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

- ❒ Kalydeco (ivacaftor) is deemed 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 will not be authorized.
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy only addresses **Kalydeco (ivacaftor)** for the treatment of **cystic fibrosis** in patients who are **homozygous for the F508del mutation** when appropriate criteria are met.

All other uses of **Kalydeco (ivacaftor)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare, including but not limited to:

- ❒ Members with CF homozygous for the *F508del* mutation and 26 other mutations are considered not responsive to ivacaftor: A46D, G85E, E92K, P205S, R334W,R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K mutations in the CFTR gene do not meet the threshold of change in CFTR mediated chloride transport of at least 10% of normal over baseline.

- ❒ Concurrent therapy with lumacaftor-ivacaftor (Orkambi)

**Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.*

Cystic fibrosis (CF) Dynamed

- CF is a serious autosomal recessive multi-organ disorder. CF is caused by mutations or variants in the CF transmembrane conductance regulator (CFTR) gene, which encodes a chloride channel. Mutations lead to disease of the exocrine gland function, resulting in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body.
  - CF is the most common fatal genetic disease in Caucasians
  - In the United States:
    - Approximately 30,000 patients of all ages have CF (Cystic Fibrosis Foundation patient registry 2015 annual data report).
    - Heterozygote frequency is approximately 1 in 20. In the U.S., prevalence is highest in Caucasians (1 case per 3,200 to 3,500 people) and lowest in Asian Americans (1 case per 31,000 people)
  - The median survival in patients with CF is 36.9 years with 80% of patients reaching adulthood. Children are anticipated to live to approximately 40 years of age with current treatments.
  - Females with CF tend to have a more rapid deterioration and earlier death compared to males with CF.
- **Diagnosis** is based on pulmonary and gastrointestinal manifestations, family history, and a positive sweat chloride test; however, newborn screening is generally provided in the U.S.
- **Treatment** is primarily dependent on the type and severity of CF symptoms, and this can differ widely from person to person
- Medication therapy for respiratory complications primarily includes antibiotics (oral, intravenous [IV], inhaled) as well as other treatments (e.g., bronchodilators, anti-inflammatory agents, and mucolytics such as dornase alfa [Pulmozyme®]) for airway clearance. Medications used to treat patients with cystic fibrosis may include the following:
  - Pancreatic enzyme supplements
  - Multivitamins (including fat-soluble vitamins)
  - Mucolytics
  - Nebulized, inhaled, oral, or intravenous antibiotics
  - Bronchodilators
  - Anti-inflammatory agents
  - Agents to treat associated conditions or complications (eg, insulin, bisphosphonates)
  - Agents devised to potentially reverse the abnormalities in chloride transport:
    CFTR potentiators are the newest class of medications available for this disease and improve chloride ion transport abnormalities. The U.S. Food and Drug Administration (FDA) approved **ivacaftor (Kalydeco) in 2012** and **lumacaftor/ivacaftor (Orkambi) in 2015**
    - Each agent is approved for differing CFTR genotypes. If a patient's genotype is unknown, an FDA-approved CF mutation test should be used to detect the presence of a CFTR mutation. This should be followed by verification if needed based on recommendations of the mutation test.
    - Use of these agents does not eliminate the need for other symptomatic and preventative therapy; rather, their treatment is intended to improve the functionality of the CFTR protein.
- Goals of CF treatment include:
  - maintaining lung function by controlling infection and clearing mucus in the airway
  - maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements
  - managing disease complications (e.g., insulin therapy in patients who develop diabetes)

CLINICAL TRIALS

Kalydeco (ivacaftor) has been studied in people with one of the following mutations in their cystic fibrosis (CF) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, G970R,* and F508del.†

*In trials, efficacy could not be established in people with the G970R mutation. KALYDECO is not indicated for people with CF who have the G970R mutation.

†Kalydeco is not effective in patients with CF with two copies of the F508del mutation (F508del/F508del) in the CF gene.

G551D MUTATION

Safety and efficacy of ivacaftor for the treatment of cystic fibrosis in patients with a G551D mutation in the CFTR gene were evaluated in 2 randomized, double-blind, placebo-controlled studies in 213 clinically stable patients with cystic fibrosis having at least one copy of the G551D mutation in the CFTR gene (PI; Ramsey BW et al.).

In G551D patients:

- **Kalydeco demonstrated significant improvements in lung function,† weight, and risk of pulmonary exacerbations through week 48, and improvements in cystic fibrosis (CF) respiratory symptoms through week 48** (Ramsey BW 2011; Davies JC 2013)
- **These beneficial effects were sustained for nearly three years** (Ramsey BW 2011; Davies JC 2013; McKone EF 2014)

◆ STRIVE [adolescent-adult study]: Evaluation of Kalydeco in patients (aged ≥12 years) with CF caused by a *G551D* mutation (Ramsey BW et al.)

The safety and efficacy of ivacaftor for the treatment of CF patients with a *G551D CFTR* mutation was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 161 patients.

Patients ≥ 12 years old (mean, 25.5 years) with CF and a FEV1 of 40% to 90% (mean, 63.6%) the predicted value were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 48 weeks in addition to their currently prescribed CF therapies (e.g., tobramycin, dornase alfa).

Use of hypertonic saline was not allowed, and those with persistent abnormal liver function or with *Burkholderia cenocepacia*, *Burkholderia dolosal*, or *Mycobacterium abscessus* in their sputum were excluded. The treatment difference between ivacaftor and placebo in mean change in FEV1 from baseline to week 24, the primary endpoint, was 10.6% ($p<0.0001$, favoring ivacaftor), and these changes persisted through the 48 weeks.

No key differences were found in subgroups. Significant differences were also found between ivacaftor and placebo at Weeks 24 and 48 in mean change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score, mean absolute change from baseline in body weight, and absolute change in sweat chloride ($p\leq0.001$ for all measures). Ivacaftor also reduced the risk of pulmonary exacerbation compared to placebo at Week 48 (hazard ratio [HR], 0.455; $p=0.001$). Adverse effects were similar between the 2 groups.

- ENVISION [child study]: Evaluation of Kalydeco in patients (aged 6–11 years) with CF caused by a G551D mutation

  A nearly identically designed trial assessed the safety and efficacy of ivacaftor for the treatment of CF patients with a *G551D CFTR* mutation was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 52 patients.41,42 Patients 6 to 11 years old (mean, 8.9 years) with CF and a FEV1 of 40% to 105% (mean, 84.2%) the predicted value were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 48 weeks in addition to their currently prescribed CF therapies. Like the former trial, use of hypertonic saline was not allowed, and those with persistent abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded. The treatment difference between ivacaftor and placebo in mean change in FEV1 from baseline to week 24, the primary endpoint, was 12.5% ($p<0.0001$, favoring ivacaftor), and these changes persisted through the 48 weeks (mean change in FEV1, 10%; $p<0.001$). No key differences were found in subgroups. Significant differences were also found between ivacaftor and placebo at Weeks 24 and 48 mean absolute change from baseline in body weight and absolute change in sweat chloride ($p<0.001$ for all measures). No significant differences were found between ivacaftor and placebo at Weeks 24 and 48 in mean change from baseline in CFQ-R respiratory domain score. Adverse effects were similar between the 2 groups. (Davies JC et al)

  In both studies, treatment with ivacaftor resulted in substantial improvement in FEV_1 (Ramsey BW et al.) The mean absolute change from baseline in percent predicted FEV_1 at 24 weeks (primary efficacy endpoint) was greater with ivacaftor than placebo by 10.6 and 12.5 percentage points in the first and second studies, respectively; these changes persisted through 48 weeks. Patients receiving ivacaftor also demonstrated improvements in secondary endpoints (e.g., risk of pulmonary exacerbations, symptoms of cystic fibrosis, and gain in body weight) (Ramsey BW et al.)

  The most common adverse reactions in patients with a *G551D* mutation in the *CFTR* gene (Trials 1 and 2) with an incidence of ≥8% and at a higher incidence for patients treated with KALYDECO (N=109) than for placebo (N=104) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.

- PERSIST: Long-term safety and efficacy of Kalydeco in patients (aged ≥6 years) with CF caused by a G551D mutation

Homozygous for the F508del-CFTR mutation

A 16-week randomized, double-blind, placebo-controlled, parallel-group trial assessing the efficacy of ivacaftor for the treatment of 140 patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene found no improvement in forced expiratory volume in 1 second (FEV1) compared to placebo.

- Age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≥40% predicted (Flume PA et al.)
- Patients were randomized 4:1 to receive Kalydeco (ivacaftor) 150 mg (n=112) every 12 hours or placebo (n=28) in addition to their prescribed CF therapies.
- The mean age of patients enrolled was 23 years and the mean baseline FEV1 was 79% predicted (range 40% to 129%)
- As in Trials 1 and 2, patients who had persistent Burkholderia cenocepacia, Burkholderia dolosa, or Mycobacterium abscessus isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was not permitted.
- The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV1.
- The treatment difference from placebo for the mean absolute change in percent predicted FEV1 through Week 16 in patients with CF homozygous for the F508del mutation in the CFTR gene was 1.72 percentage points

(1.5% and -0.2% for patients in the Kalydeco (ivacaftor) and placebo-treated groups, respectively) and did not reach statistical significance.

Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene (Flume PA et al.).

⌘ **NON-G551D MUTATIONS** (9 Additional Mutations: *G1244E, G1349D, G178R, G551S, G970R,* S1251N, S1255P, S549N,* or *S549R)*

◆ KONNECTION: Kalydeco in patients with CF caused by specific non-G551D mutations

Study Design: A 2-part, randomized, double-blind, placebo-controlled crossover trial assessed the efficacy and safety of ivacaftor in CF patients ≥ 6 years old (mean, 23 years) with a *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R CFTR* mutation (n=39 (De Boeck K et al. 2014)

- Part 1: 8-week crossover study
  Patients were randomized (1:1 ratio) to receive either Kalydeco 150 mg or placebo twice daily for 8 weeks, followed by a 4- to 8-week washout period, and then an 8-week crossover treatment.
- Part 2: 16-week open-label extension study
  All patients received Kalydeco for 16 weeks. Patients completing treatment sequence 1 (n=18) received 16 weeks continuous treatment; those completing treatment sequence 2 (n=18) received 24 weeks continuous treatment.

Subjects

- All baseline characteristics were similar between treatment sequences and similar to G551D patient populations
- Patients with a FEV1 ≥ 40% at screening (mean, 78%) were randomized 1:1 to ivacaftor 150 mg orally every 12 hours with fat-containing food or placebo for 8 weeks in addition to their currently prescribed CF therapies. Patients then received the opposite therapy for a second 8 weeks following a 4- to 8-week washout period. A 16-week open label extension trial followed (part 2).
- Use of inhaled hypertonic saline was not allowed, and those with abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded.

Endpoints

- Primary endpoint: Absolute change from baseline in percent of predicted FEV_1 ($ppFEV_1$) through 8 weeks (Part 1) and 24 weeks (Part 2) of treatment
- Secondary endpoints included:
  - Absolute change from baseline in body mass index (BMI) at 8 and 24 weeks
  - Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score through 8 and 24 weeks

Result: Efficacy varied among the different mutations and was not established in patients with a *G970R CFTR* mutation; ivacaftor is not approved in patients with this mutation.

- **Based on clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the G970R mutation could not be established.**

***Note: Kalydeco is not indicated for patients with a G970R mutation. Clinical efficacy in patients with the G970R mutation of the CFTR gene has not been established.**

⌘ R117H MUTATION

- KONDUCT: Safety and efficacy of Kalydeco in patients (aged ≥6 years) with CF caused by a R117H mutation
  Study of Ivacaftor in Subjects with Cystic Fibrosis (CF) Who Have the R117H-CF Transmembrane Conductance Regulator (CFTR) Mutation (Moss RB 2015)
  - The safety and efficacy of ivacaftor for the treatment of CF patients with a *R117H CFTR* mutation was evaluated in a phase 3, randomized, double-blind, placebo-controlled clinical trial in 69 patients age 6 years and older. Subjects were given Kalydeco (ivacaftor) or placebo every 12 hours with fat-containing food for 24 weeks
  - Patients ≥ 6 years old (mean, 31 years) with CF and a FEV1 of 40% to 90% the predicted value in those ≥ 12 years old or a FEV1 of 40% to 105% the predicted value in those 6 to 11 years old (mean, 73%) were randomized 1:1 to either 150 mg oral ivacaftor or placebo every 12 hours with fat containing food for 24 weeks in addition to their currently prescribed CF therapies.
  - Patients with persistent abnormal liver function or with *B. cenocepacia*, *B. dolosal*, or *M. abscessus* in their sputum were excluded.
  - Results
    - The treatment difference between ivacaftor and placebo in mean change in FEV1 from baseline to week 24, the primary endpoint, was 2.1% (p=not significant [NS])
    - Statistically significant differences were found between ivacaftor and placebo at Week 24 in mean change from baseline in CFQ-R respiratory domain score (mean difference, 8.4; 95% CI, 2.2 to 14.6) and absolute change in sweat chloride (mean difference, -24 mmol/L; 95% CI, -28 to -19.9)
    - No significant difference was found in change in BMI (0.3 kg/m2; p=NS) or time to first pulmonary exacerbation (hazard ratio [HR], 0.93; p=NS)

Reference: ClinicalTrials.gov. NCT01614457. Available at: https://clinicaltrials.gov/ct2/show/NCT01614457?term=ivacaftor+R117H&rank=1. Accessed July 2017

⌘ AGES 2 TO < 6 YEARS

KIWI: Evaluation of safety and efficacy of Kalydeco granules in patients with CF aged 2 to < 6 years
Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study (Davies JC et al. 2016)

- Efficacy of ivacaftor in patients 2 to 5 years of age is extrapolated from efficacy in patients ≥ 6 years of age with support from pharmacokinetic studies demonstrating similar drug exposure in these populations
- In this open-label safety study, 34 children age 2 to less than 6 years of age were given Kalydeco (ivacaftor) oral granules (50 mg or 75 mg) every 12 hours with fat-containing food for 24 weeks. Patients with the following mutations were eligible for this study: ***G551D, G1244E, G1349D, G178R, G551S, G970R,* S1251N, S1255P, S549N***, or ***S549R*** mutation in the CFTR gene**.** A total of 32 patients (of the 34 enrolled) had the ***G551D*** mutation and 2 had the ***S549N*** mutation. Safety and tolerability was the main endpoint, or measure, of the pediatric clinical study (Study 6). **The type and frequency of adverse reactions in this trial were comparable to those in patients ≥ 6 years.** Transaminase elevations were more common in patients who had abnormal transaminases at baseline.
- Study design
  An open-label, single-arm, two-part, 24-week Phase III trial (n=34) in patients aged 2 to <6 years weighing ≥8 kg with CF and one of the following mutations on at least one allele: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*
  - Part A: Assessed pharmacokinetic effects and short-term safety over four days (n=9)
  - Part B: Assessed safety and efficacy over 24 weeks (n=34)
  - Patients enrolled in Part A could enroll in Part B
  - Kalydeco granules dosing was based on weight:
    - Patients <14 kg received 50 mg every 12 hours (n=10)

- Patients ≥14 kg received 75 mg every 12 hours (n=24)
- All pre-study CF medications were continued

- Endpoints
  - Primary endpoint: Pharmacokinetics and safety of Kalydeco evaluated through week 24
  - Secondary endpoints evaluated at 24 weeks of treatment included absolute change from baseline in:
    - Sweat chloride concentration
    - Body weight, body mass index (BMI), and stature (height z-scores)
  - Exploratory post-hoc outcomes included changes in:
    - Faecal elastase-1 (FE-1) (measure of pancreatic function)
    - FEV_1 (in children aged ≥3 years)

◆ **Results**

- Safety **Kalydeco was well tolerated in patients aged 2 to < 6 years**
  33 (97%) of 34 patients had at least one adverse event (AE) (Part B)
  - The most common AEs were respiratory or gastrointestinal in nature
  - Most AEs were mild or moderate in severity

  The incidence of patients experiencing transaminase elevations (ALT or AST) >3 x the upper limit of normal (ULN) was 14.7% (5/34)
  - All five patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of dosing with Kalydeco granules in four patients
  - Kalydeco was permanently discontinued in one patient
  - All five patients had a history of raised transaminase concentrations and had elevated liver function tests (LFTs; >2 x ULN to <3 x ULN) at baseline (screening exclusion criteria: ≥3 x ULN)
- Pharmacokinetics **The pharmacokinetic effects of Kalydeco granules in patients aged 2 to <6 years suggest that exposure is similar to that reported in adults.**
- Sweat Chloride **Significant reduction in sweat chloride that is comparable to that reported in a Phase III trial of patients aged 6–11 years**[Ramsey BW et al. 2011]
  - Mean absolute change from baseline in sweat chloride through week 24: -47 mmol/L (P<0·0001)
  - In the Phase III ENVISION trial, mean absolute change in sweat chloride concentration in patients aged 6–11 years at week 24: -54 mmol/L [Ramsey BW et al. 2011]
- Growth measures **Improvements in growth measures that are comparable to that reported in a Phase III trial of patients aged 6–11 years:**[Ramsey BW et al. 2011]
  - Mean overall absolute change from baseline in BMI at week 24: 0.32 kg/m^2
  - Mean overall BMI-for-age z-score: 0.37
  - In the Phase III ENVISION trial, mean absolute change in BMI-for-age z-score in patients aged 6–11 years at week 24: 0.34 [Ramsey BW et al. 2011]

SYSTEMATIC REVIEWS

- **Cochrane Database of Systematic Reviews**
  - Ivacaftor may improve respiratory-related quality of life and lung function in patients with CF and CFTR mutation G551D
    Based on Cochrane review with limited evidence:
    - Systematic review of 4 randomized trials evaluating CFTR potentiators in 378 patients with CF (Patel S et al. 2015)
    - 3 trials compared ivacaftor to placebo in patients with G551D mutation on ≥ 1 *CFTR* allele
      - ivacaftor significantly improved quality of life for respiratory subdomain in 1 trial with 167 patients (summarized below)
      - ivacaftor significantly improved forced expiratory volume at one second (FEV_1) in 2 trials with 219 patients
      - dizziness in 12% with ivacaftor vs. 1.3% (p = 0.026, NNH 9) in 1 trial with 167 patients
    - 1 trial compared ivacaftor vs. placebo in 140 patients homozygous for Delta F508 mutation, no significant difference in FEV_1 or quality of life for respiratory subdomain
    - No survival data or deaths reported by trials
    - Per Dynamed: 'Level 2 (mid-level) Evidence: Representing research results addressing clinical outcomes, and using some method of scientific investigation, but not meeting the quality criteria to achieve Level 1 evidence labeling.'

CLINICAL PRACTICE GUIDELINES

- **Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health (2013)**

The Cystic Fibrosis Foundation (CFF) published guidelines on chronic medications for the maintenance of lung health in CF patients in 2013 (Mogayzel Jr PJ et al.)

NOTE: The CFF published guidelines prior to the approval of expanded indications for ivacaftor (e.g., patients ≥ 2 years of age, other mutations). Similarly, lumacaftor/ivacaftor was not approved in 2013.

- The CFF recommends inhaled treatments (e.g., tobramycin, dornase alfa, hypertonic saline, corticosteroids) and oral treatments (e.g., antibiotics, corticosteroids) for treatment of symptoms, exacerbations, and/or infections in patients with CF.
- In this publication, the CFF added the recommendation of chronic treatment with ivacaftor for individuals 6 years of age and older with at least one *G551D CFTR* mutation to improve lung function and quality of life and to reduce exacerbations (Recommendation: A).
- The CFF has also published guidelines on newborn screening, diagnosis, nutritional care, gastrointestinal (GI) related issues, other respiratory care, infection control, and general clinical care by age group (e.g., infants, preschool-aged children, and adults). [CF Clinical Care Guidelines]
- Only ivacaftor has been addressed for the treatment of preschool-aged children and is currently FDA-approved in this population. [Clinical Practice Guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics]
  - CFF recommends use of ivacaftor in preschoolers with specific gating mutations (e.g., *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, and *S549R*) and *R117H* mutations.
  - Other treatments recommended in this age group for select individuals include oral, intravenous, and/or inhaled antibiotics for exacerbations, hypertonic saline, dornase alfa, and inhaled antipseudomonal antibiotics.
  - **Neither agent in this class is approved for the treatment of infants with CF.**

Hayes

At the time of this writing in June 2017, no Hayes Directory report or Hayes Rating were found regarding Kalydeco (ivacaftor) in the treatment of cystic fibrosis.

There is a Hayes Prognosis overview was published on February 2012 regarding ivacaftor (Kalydeco). This report was archived on Aug 25, 2012 and noted by Hayes as "Technology is too mature for scope of product."

DEFINITIONS

N/A

APPENDIX

APPENDIX 1: Study Measure(s)

Studies of CFTR modifier medications use a variety of different outcome measures, including: sweat chloride, nasal potential difference (NPD), and the Cystic Fibrosis Questionnaire– Revised (CFQ-R).

- Sweat chloride test: Measures the chloride content of the patient's sweat as an indicator of CFTR function. A sweat chloride value of more than 60 mmol/L is diagnostic for CF. A decrease in sweat chloride to non-CF values may correlate with clinical changes, such as lung function. However, changes in which the sweat chloride value remains greater than 60 mmol/L have not been correlated with clinical outcomes.

- Nasal potential difference (NPD): Testing is performed by running different solutions through the patient's nose; voltage measurements from these solutions are used to detect changes in CFTR function. Increases in CFTR function may result in clinical changes in CF patients, although a direct correlation has not been established.

- **Cystic Fibrosis Questionnaire-Revised (CFQ-R):** The CFQ-R measures the overall health, daily life, perceived well-being, and symptoms in patients with CF and may be self-administered, proxy-administered, or done via an interview for children.

  Three versions are available: 1 for individuals ≥ 14 years old and 2 for children ages 6 to 13 years (1 for parents and 1 for the child). Each version varies slightly in item numbers (range 35 to 50), but all have 9 quality of life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, health perceptions) and 3 symptom scales (respiratory, digestive, and weight). Each component is scored on a 4-point Likert scale with a total score ranging from 0 to 100 (higher scores indicating better health).

  Reference: Cystic Fibrosis Questionnaire-Revised. Available at: http://qol.thoracic.org/sections/instruments/ae/pages/cfq-cfq-r.html. Accessed July 2017

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10	Description [For dates of service on or after 10/01/2015]
E84.9	Cystic fibrosis, unspecified (for code 277.00)
E84.11	Meconium ileus in cystic fibrosis (for code 277.01)
E84.0	Cystic fibrosis with pulmonary manifestations (for code 277.02)
E84.19	Cystic fibrosis with other intestinal manifestations (for code 277.03)
E84.8	Cystic fibrosis with other manifestations (for code 277.09)

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