October 31, 2016

Submission Request Form for Pharmaceutical Manufacturers

FAX TO: John McCall, R.Ph.

1-888-656-6822

FROM: Vertex Pharmaceuticals

Print Form Reset Form

State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers

Fax this request to: 1-888-656-6822 ATTN: John McCall, R.Ph.

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Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for ***NEW*** information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

Contact Information

MANUFACTURER NAME: Vertex Pharmaceuticals Incorporated

DATE: 10 - 26 - 2016

PRODUCT MANAGER'S NAME:

TITLE:

ADDRESS: 50 Northern Avenue

CITY: Boston

STATE: MA

ZIP CODE: 02210

PHONE NUMBER: 877 - 634 - 8789

FAX NUMBER: 617 - 366 - 3966

PRODUCT: ORKAMBI (R) (lumacaftor/ivacaftor)

Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

Cystic Fibrosis (CF) is a rare, progressive, multisystem, life-shortening, genetic disease caused by defects in the CFTR protein, which regulates the flow of chloride and other ions across the epithelium. Defects in the CFTR protein arise from mutations in the CFTR gene that affect the quantity and/or function of cell surface CFTR protein. Although many different mutations of the CFTR gene have been recognized, F508del is the most common CF-causing mutation. The F508del homozygous patient population is typically characterized by an early, progressive clinical course with early onset of progressive lung function decline. There is no cure for CF, and current therapies for patients who are homozygous for the F508del-CFTR mutation treat the symptoms of the disease. In contrast, lumacaftor/ivacaftor combination therapy targets the underlying cause of CF in patients who are homozygous for the F508del-CFTR mutation by increasing the quantity, stability, and function of F508del-CFTR protein at the cell surface, resulting in increased chloride ion transport.

The approval of ORKAMBI was based on the results of two pivotal 24-week, Phase 3, randomized, double-blind, placebo-controlled studies (TRAFFIC and TRANSPORT) in patients with CF 12 years of age and older (listed as Trial 1 and Trial 2, respectively, in the full Prescribing Information). In both studies, the primary efficacy endpoint was change in lung function as determined by the absolute change from baseline in percent predicted FEV1 (ppFEV1) at Week 24. The primary endpoint was met in both studies. The treatment difference between ORKAMBI and placebo was 2.6 percentage points in TRAFFIC (P=0.0003) and 3 percentage points in TRANSPORT (P<0.0001). This corresponded to a mean relative treatment difference of 4.3 and 5.3%, respectively. Improvements were observed regardless of age, disease severity, sex, and geographic region.

In each study, a hierarchical testing procedure was performed for primary and key secondary endpoints compared to placebo. The treatment difference between ORKAMBI and placebo for BMI was statistically significant in TRANSPORT (P=0.0001) but not in TRAFFIC. Results for the CFQ-R Respiratory Domain score were not statistically significant for either trial. [Continues]

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Therefore, the hierarchy was broken in TRAFFIC at BMI, and in TRANSPORT at CFQ-R Respiratory domain. Additional findings, after the hierarchy was broken, include a 30% and 40% reduction in the number of pulmonary exacerbations compared to placebo in TRAFFIC and TRANSPORT, respectively. An additional post hoc pooled analysis showed a reduction in the number of pulmonary exacerbations leading to hospitalizations (61% reduction vs placebo).

The proportion of patients who prematurely discontinued study drug due to an adverse event was 5% for ORKAMBI and 2% for placebo. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients. Adverse reactions occurring in 5% or more of ORKAMBI patients that also occurred at a higher rate in patients treated with ORKAMBI than placebo included dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza.

ORKAMBI should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks and patients should be closely monitored. Serum transaminases (ALT and AST) and bilirubin should be measured before initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. Clinical experience in patients with ppFEV1 <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically. Lumacaftor is a strong inducer of CYP3A and administration may decrease systemic exposure of CYP3A substrates, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended. Hormonal contraceptives should not be relied upon as an effective method of birth control when co-adminstered with ORKAMBI. Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Co-administration with strong CYP3A inducers is not recommended. Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ORKAMBI and ivacaftor. Baseline and follow-up examinations are recommended in pediatric patients initiating ORKAMBI. See the full Prescribing Information for dose interruption guidance and additional information regarding drug-drug interactions.

PROGRESS extension trial data in patients 12 years of age and older:
Patients who completed 24 weeks of treatment in TRAFFIC or TRANSPORT could enter a 96-week Phase 3 blinded extension study (PROGRESS) in which everyone received 1 of the 2 lumacaftor/ivacaftor combination dosing regimens (i.e., resulting in up to 120 weeks of continuous treatment from start of TRAFFIC/TRANSPORT for patients that were on active drug and up to 96 weeks weeks of continuous treatment for patients that were on placebo in those trials). Results reported here are for the approved ORKAMBI regimen for patients 12 years and older (lumacaftor 400 mg/ivacaftor 250 mg q12h). The primary endpoint of the extension study was safety and tolerability. Selected secondary endpoints included absolute change from baseline in ppFEV1, absolute change from baseline in BMI, absolute change from baseline in CFQ-R Respiratory Domain, and number of pulmonary exacerbations. This study was not placebo controlled, is not included in the approved full Prescribing Information, and was not considered by the FDA in approving ORKAMBI.

The safety profile observed in PROGRESS was consistent with that seen in TRAFFIC/TRANSPORT. Serious adverse events (SAEs) reported with ORKAMBI in PROGRESS were consistent with those reported in TRAFFIC/TRANSPORT and were predominantly CF complications. The most frequently reported SAEs were pulmonary exacerbation, hemoptysis, and distal intestinal obstruction syndrome (DIOS). Three deaths occurred in PROGRESS, none of which were considered related to the study drug by investigators.

In patients receiving ORKAMBI from the beginning of TRAFFIC/TRANSPORT the mean ppFEV1 was sustained above baseline at 0.5 percentage points through Week 96. BMI continued to improve in the patients receiving ORKAMBI from the onset of TRAFFIC/TRANSPORT with a 0.96 kg/m2 improvement at week 96. ORKAMBI treatment also provided sustained reduction in pulmonary exacerbation rates up to 120 weeks, at an annualized event rate of 0.65.
[Continued]

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Published Citations (If additional space is required, use Published Citations Continuation Page).

ORKAMBI (R) (lumacaftor/ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; September 2016.

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Konstan MW, Ramsey BW, Elborn J, et al. Safety and Efficacy of Treatment with Lumacaftor in Combination with Ivacaftor in Patients with CF Homozygous for F508del-CFTR [Poster 211]. North American Cystic Fibrosis Conference. Phoenix, Arizona; 2015. Pediatric Pulmonology. 2015;50(S41):S193-S453.

Rubin JL, Pelligra CG, Ward AJ, et al. Modeling the Health Outcomes of Patients With Cystic Fibrosis who are Homozygous for the F508del-CFTR Mutation Treated With Lumacaftor and Ivacaftor Combination Therapy [Poster 236]. North American Cystic Fibrosis Conference. Phoenix, Arizona; 2015. Pediatric Pulmonology. 2015;50(S41):S193-S453.

McColley SA, Konstan MW, Ramsey BW, et al. Association Between Changes in Percent Predicted FEV1 and Incidence of Pulmonary Exacerbations, Including Those Requiring Hospitalization and/or IV Antibiotics, in Patients With CF Treated With Lumacaftor in Combination With Ivacaftor [Poster 241]. North American Cystic Fibrosis Conference. Phoenix, Arizona; 2015. Pediatric Pulmonology. 2015;50(S41):S193-S453.

De Boeck K, Elborn J, Ramsey BW, et al. Efficacy and Safety of Lumacaftor/Ivacaftor Combination Therapy in Patients With CF Homozygous for F508del-CFTR by FEV1 Subgroups [Poster 245]. North American Cystic Fibrosis Conference. Phoenix, Arizona; 2015. Pediatric Pulmonology. 2015;50(S41):S193-S453.

Elborn JS, Ramsey B, Boyle MP, et al. Lumacaftor in combination with ivacaftor in patients with cystic fibrosis who were homozygous for the F508del-CFTR mutation [poster]. European Cystic Fibrosis Conference. Brussels, Belgium; 2015.

Elborn JS, Ramsey B, Boyle MP, et al. Lumacaftor/Ivacaftor Combination Therapy in CF Patients Homozygous for F508del-CFTR With Severe Lung Dysfunction [Poster 143]. European Cystic Fibrosis Conference. Brussels, Belgium; 2015.

Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M. Results from an open-label phase 3 study evaluating the safety, tolerability, and pharmacodynamics of combination lumacaftor/ivacaftor therapy in children aged 6 through 11 years with cystic fibrosis homozygous for the F508del-CFTR mutation. 39th European Cystic Fibrosis Conference. Basel, Switzerland. 2016.

Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. Lancet Respir Med. 2014; (7):527-538.

Rowe SM, McColley SA, Rietschel E, et al. Effect of 8 Weeks of Lumacaftor in Combination With Ivacaftor in Patients With CF and Heterozygous for the F508del-CFTR Mutation. North American Conference of the Cystic Fibrosis Foundation. Atlanta, GA; 2014.

Konstan MW, McKone E, Moss R, et al. Evidence of reduction in annual rate of FEV1 decline and sustained benefits with lumacaftor and ivacaftor (LUM/IVA) in patients (pts) with CF homozygous for F508del-CFTR. NACFC. Orlando, FL. 2016: Abstract 180.

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Clinical Rationale Continuation Page (Use only if needed).

Patients in PROGRESS knew they were on active drug; these patients also may have had changes in their stable medication regimen. PROGRESS is not included in the full Prescribing Information and the FDA did not consider this data in approving ORKAMBI. PROGRESS may not meet the FDA definition of an adequate and well-controlled study due to its study design.

Data from the PROGRESS study were used to evaluate whether ORKAMBI altered the rate of change in lung function and nutritional measures compared to a matched control cohort from the US CF Foundation Patient Registry (CFFPR). Each patient treated with ORKAMBI was matched on known predictors of lung disease progression using a propensity score approach with up to 5 eligible control patients who were ≥12 years of age and homozygous for F508del. ORKAMBI-treated patients (n=455) who met the inclusion criteria were matched with 1,588 control patients. This analysis found that the annual rate of percent predicted FEV1 decline was reduced by 42% in ORKAMBI-treated patients compared with the matched control group (slope: −1.33 vs −2.29 per year, respectively; P<0.001). The annual rate of change in BMI z-score was 0.068 greater in ORKAMBI-treated patients compared with the control group (+0.028 vs −0.040 per year; P<0.001). The annual rate of change in BMI was 0.160 greater in ORKAMBI-treated patients compared with the control group (+0.259 vs +0.100 per year; P=0.002).

Because this analysis was not a randomized controlled trial, causality cannot be definitively established. In addition, rate of change estimates were based on measurements spanning different lengths of time for different patients, with more patients contributing information in the first year than in the second year. The rate of change analysis is not included in the approved full Prescribing Information and the FDA did not consider this analysis in approving ORKAMBI. This analysis may not meet the FDA definition of an adequate and well-controlled study due to reliance, in part, on data from a study that was not placebo-controlled.

809-011 ORKAMBI 6 through 11 year old trial
Safety and tolerability of ORKAMBI in 58 patients 6 through 11 with CF who are homozygous for the F508del mutation were evaluated in a Phase 3 open-label multicenter trial. The dose of lumacaftor and ivacaftor used was selected to match the exposure to the levels observed in adult patients. There were 58 patients in the study (listed as Trial 3 in the full Prescribing Information), all of whom received lumacaftor 200 mg/ivacaftor 250 mg twice daily in addition to their prescribed CF therapies. There was a 2-week washout period between the end of treatment and the start of the safety follow-up that was used to assess off-treatment effects.

The safety profile was generally similar to that in patients 12 years and older in the TRAFFIC and TRANSPORT trials. With respect to adverse events, the incidence of maximum transaminase (ALT or AST) levels >8, >5, >3x ULN was 5%, 9%, and 19%, respectively. No patients had an increase in total bilirubin levels >2x ULN. ORKAMBI dosing was maintained or successfully resumed after interruption in all eleven patients with LFT elevations, except one patient who discontinued treatment prematurely. The incidence of respiratory adverse reactions was 3% (2/58 patients). The ppFEV1, evaluated as a safety measure, improved by 2.5 percentage points at Week 24. During the washout period from Week 24 to Week 26, the change was -3.2 percentage points.

Sweat chloride, a pharmacodynamic measure, showed a reduction at Day 15 of 20.4 mmol/L that was sustained through Week 24 (mean change, decrease of 24.8 mmol/L). Following a 2-week washout period, mean sweat chloride increased by 21.3 mmol/L. Based on this data, as well as TRAFFIC/TRANSPORT, the FDA recently approved an expanded indication for ORKAMBI for 6 through 11 year old patients homozygous for the F508del mutation at a dose of 200 mg lumacaftor with 250 mg ivacaftor every 12 hours.

In summary, 24-week Phase 3 trials have shown that ORKAMBI improves outcomes across multiple clinical parameters including ppFEV1, nutritional status (BMI) and pulmonary exacerbations in patients age 12 years and older who are homozygous for the F508del-CFTR mutation. The longer-term extension data from PROGRESS demonstrates that these outcomes are sustained through up to 120 weeks of treatment. The safety profile in patients 6 through 11 years and homozygous for the F508del-CFTR mutation was consistent with the profile observed in older patients. By targeting the underlying protein defect, ORKAMBI represents a treatment advancement for people with CF who are 6 years of age and older and homozygous for the F508del-CFTR mutation; a population with high unmet medical need. Results from the rate of change analysis of patients 12 years and older suggest ORKMABI is a disease-modifying therapy.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORKAMBI safely and effectively. See full prescribing information for ORKAMBI.

ORKAMBI® (lumacaftor/ivacaftor) tablets, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	9/2016
Dosage and Administration (2)	9/2016
Warnings and Precautions, Effect on Blood Pressure (5.4)	5/2016

----------INDICATIONS AND USAGE----------

ORKAMBI is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene. (1)

Limitations of Use:
The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation. (1)

----------DOSAGE AND ADMINISTRATION----------

- Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. (2.1)
- Pediatric patients age 6 through 11 years: two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours. (2.1)
- Reduce dose in patients with moderate or severe hepatic impairment. (2.2, 8.6, 12.3)
- When initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce ORKAMBI dose for the first week of treatment. (2.3, 7.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 200 mg and ivacaftor 125 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Use in patients with advanced liver disease: ORKAMBI should be used with caution in these patients and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced. (2.2, 5.1, 6.1)
- Liver-related events: Elevated transaminases (ALT/AST) have been observed in some cases associated with elevated bilirubin. Measure serum transaminases and bilirubin before initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Interrupt dosing in patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution, consider the benefits and risks of resuming dosing. (5.2, 6.1)
- Respiratory events: Chest discomfort, dyspnea, and respiration abnormal were observed more commonly during initiation of ORKAMBI. Clinical experience in patients with percent predicted FEV_1 (ppFEV$_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. (5.3, 6.1)
- Blood pressure: Increased blood pressure has been observed in some patients. Periodically monitor blood pressure in all patients. (5.4, 6.1)
- Drug interactions: Use with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index may decrease systemic exposure of the medicinal products and co-administration is not recommended. Hormonal contraceptives should not be relied upon as an effective method of contraception and their use is associated with increased menstruation-related adverse reactions. Use with strong CYP3A inducers may diminish exposure of ivacaftor, which may diminish its effectiveness; therefore, co-administration is not recommended. (5.5, 6.1, 7, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Baseline and follow-up examinations are recommended in pediatric patients initiating ORKAMBI. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions to ORKAMBI (occurring in ≥5% of patients with CF homozygous for the *F508del* mutation in the *CFTR* gene) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

See Full Prescribing Information for a complete list. (2.3, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

Limitations of Use

The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information in Adults and Children Age 6 Years and Older

Table 1: Dosage of ORKAMBI in Patients Age 6 Years and Older

Age	ORKAMBI Dose	Total Daily Dose
6 through 11 years	Take two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food.	lumacaftor 400 mg/ivacaftor 500 mg
12 years and older	Take two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food.	lumacaftor 800 mg/ivacaftor 500 mg

Examples of appropriate fat-containing foods include eggs, avocados, nuts, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. If a patient misses a dose and remembers the missed dose within 6 hours, the patient should take the dose with fat-containing food. If more than 6 hours elapsed after the usual dosing time, the patient should skip that dose and resume the normal schedule for the following dose. A double dose should not be taken to make up for the forgotten dose *[see Clinical Pharmacology (12.3) and Patient Counseling Information (17)]*.

2.2 Dosage Adjustment for Patients with Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction to 2 tablets in the morning and 1 tablet in the evening is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening, or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

2.3 Dosage Adjustment for Patients Taking CYP3A Inhibitors

No dose adjustment is necessary when CYP3A inhibitors are initiated in patients already taking ORKAMBI. However, when initiating ORKAMBI in patients currently taking strong CYP3A inhibitors (e.g., itraconazole), reduce ORKAMBI dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

If ORKAMBI is interrupted for more than 1 week and then re-initiated while taking strong CYP3A inhibitors, patients should reduce ORKAMBI dose to 1 tablet daily for the first week of treatment re-initiation. Following this period, continue with the recommended daily dose.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg lumacaftor and 125 mg ivacaftor; supplied as pink, oval-shaped, film-coated, fixed-dose combination tablets containing 100 mg of lumacaftor and 125 mg of ivacaftor. Each tablet is printed with the characters "1V125" in black ink on one side and plain on the other.

Tablets: 200 mg lumacaftor and 125 mg ivacaftor; supplied as pink, oval-shaped, film-coated, fixed-dose combination tablets containing 200 mg of lumacaftor and 125 mg of ivacaftor. Each tablet is printed with the characters "2V125" in black ink on one side and plain on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Use in Patients with Advanced Liver Disease

Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported in some patients with CF while receiving ORKAMBI. Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.2 Liver-related Events

Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin.

It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve.

Dosing should be interrupted in patients with ALT or AST greater than 5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing *[see Adverse Reactions (6.1)]*.

5.3 Respiratory Events
Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy *[see Adverse Reactions (6.1)]*.

5.4 Effect on Blood Pressure
Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI *[see Adverse Reactions (6.1)]*.

5.5 Drug Interactions
Substrates of CYP3A
Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.

ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular (27% in women using hormonal contraceptives compared with 3% in women not using hormonal contraceptives). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI *[see Adverse Reactions (6.1), Drug Interactions (7.3, 7.11), and Clinical Pharmacology (12.3)]*.

Strong CYP3A Inducers
Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers (e.g., rifampin, St. John's wort [*Hypericum perforatum*]) is not recommended *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5.6 Cataracts
Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded *[see Use in Specific Populations (8.4)]*. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ORKAMBI treatment.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Use in Patients with Advanced Liver Disease *[see Warnings and Precautions (5.1)]*
- Liver-related Events *[see Warnings and Precautions (5.2)]*
- Respiratory Events *[see Warnings and Precautions (5.3)]*
- Effect on Blood Pressure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety profile of ORKAMBI is based on the pooled data from 1108 patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene and who received at least one dose of study drug in 2 double-blind, placebo-controlled, Phase 3 clinical trials, each with 24 weeks of treatment (Trials 1 and 2). Of the 1108 patients, 49% were female and 99% were Caucasian; 369 patients received ORKAMBI every 12 hours and 370 received placebo. Additional safety data in 58 patients with CF aged 6 through 11 years who are homozygous for the *F508del-CFTR* mutation were obtained from a 24-week, open-label, multicenter Phase 3 safety trial (Trial 3).

The proportion of patients who prematurely discontinued study drug due to adverse events was 5% for patients treated with ORKAMBI and 2% for patients who received placebo.

Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients.

Table 2 shows adverse reactions occurring in ≥5% of patients with CF ages 12 years and older treated with ORKAMBI who are homozygous for the *F508del* mutation in the *CFTR* gene that also occurred at a higher rate than in patients who received placebo in the two double-blind, placebo-controlled trials.

Table 2: Incidence of Adverse Drug Reactions in ≥5% of ORKAMBI-Treated Patients Ages 12 Years and Older Who are Homozygous for the *F508del* Mutation in the *CFTR* Gene in 2 Placebo-Controlled Phase 3 Clinical Trials of 24 Weeks Duration

Adverse Reaction (Preferred Term)	ORKAMBI N=369 (%)	Placebo N=370 (%)
Dyspnea	48 (13)	29 (8)
Nasopharyngitis	48 (13)	40 (11)
Nausea	46 (13)	28 (8)
Diarrhea	45 (12)	31 (8)
Upper respiratory tract infection	37 (10)	20 (5)
Fatigue	34 (9)	29 (8)

Respiration abnormal	32 (9)	22 (6)
Blood creatine phosphokinase increased	27 (7)	20 (5)
Rash	25 (7)	7 (2)
Flatulence	24 (7)	11 (3)
Rhinorrhea	21 (6)	15 (4)
Influenza	19 (5)	8 (2)

The safety profile from the 24-week, open-label, multicenter Phase 3 safety trial in 58 patients aged 6 through 11 years with CF who are homozygous for the *F508del-CFTR* mutation (Trial 3) was similar to that observed in Trials 1 and 2.

Additional information on selected adverse reactions from these trials is detailed below.

Description of Selected Adverse Drug Reactions

Liver-related Adverse Reactions

In Trials 1 and 2, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN elevations was similar between patients treated with ORKAMBI and those who received placebo. Three patients who received ORKAMBI had liver-related serious adverse reactions, including 2 reported as transaminase elevations and 1 as hepatic encephalopathy, compared to none in the placebo group. Of these three, one had elevated transaminases (>3 x ULN) associated with bilirubin elevation >2 x ULN. Following discontinuation or interruption of ORKAMBI, transaminases decreased to <3 x ULN.

Among 6 patients with pre-existing cirrhosis and/or portal hypertension who received ORKAMBI, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in one patient. The event occurred within 5 days of the start of dosing and resolved following discontinuation of ORKAMBI *[see Warnings and Precautions (5.1, 5.2)]*.

During the 24-week, open-label Phase 3 clinical trial in 58 patients aged 6 through 11 years (Trial 3), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 5%, 9%, and 19%. No patients had an increase in total bilirubin levels > 2 x ULN. Lumacaftor/ivacaftor dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except 1 patient who discontinued treatment permanently.

Respiratory Adverse Reactions

In Trials 1 and 2, the incidence of respiratory symptom-related adverse reactions (e.g., chest discomfort, dyspnea, and respiration abnormal) was more common in patients treated with ORKAMBI (22%) compared to patients who received placebo (14%). The incidence of these adverse reactions was more common in patients treated with ORKAMBI with lower pre-treatment FEV_1. In patients treated with ORKAMBI, the majority of the events began during the first week of treatment *[see Warnings and Precautions (5.3)]*.

During the 24-week, open-label Phase 3 clinical trial (Trial 3) in 58 patients aged 6 through 11 years (mean baseline $ppFEV_1$ was 91.4), the incidence of respiratory symptom-related adverse reactions was 3% (2/58).

Menstrual Abnormalities

In Trials 1 and 2, the incidence of combined menstrual abnormality adverse reactions (e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular) was more common in female patients treated with ORKAMBI (10%) compared to placebo (2%). These events occurred more frequently in the subset of female patients treated with ORKAMBI who were using hormonal contraceptives (27%) compared to those not using hormonal contraceptives (3%) *[see Warnings and Precautions (5.5) and Drug Interactions (7.11)]*.

Increased Blood Pressure

In Trials 1 and 2, adverse reactions related to increases in blood pressure (*e.g.*, hypertension, blood pressure increased) were reported in 1.1% (4/369) of patients treated with ORKAMBI and in no patients who received placebo.

The proportion of patients who experienced a systolic blood pressure value >140 mmHg or a diastolic blood pressure >90 mmHg on at least two occasions was 3.6% and 2.2% in patients treated with ORKAMBI, respectively, compared with 1.6% and 0.5% in patients who received placebo *[see Warnings and Precautions (5.4)]*.

7 DRUG INTERACTIONS

Potential for Other Drugs to Affect Lumacaftor/Ivacaftor

7.1 Inhibitors of CYP3A

Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours (the approved dose of ivacaftor monotherapy). Therefore, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI. However, when initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce the ORKAMBI dose to 1 tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose for patients aged 12 years and over; lumacaftor 100 mg/ ivacaftor 125 mg total daily dose for patients aged 6 through 11 years) for the first week of treatment to allow for the steady-state induction effect of lumacaftor. Following this period, continue with the recommended daily dose *[see Dosage and Administration (2.3)]*.

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin, clarithromycin.

No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.

7.2 Inducers of CYP3A

Co-administration of lumacaftor/ivacaftor with rifampin, a strong CYP3A inducer, had minimal effect on the exposure of lumacaftor, but decreased ivacaftor exposure (AUC) by 57%. This may reduce the effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*), is not recommended *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

No dose adjustment is recommended when used with moderate or weak CYP3A inducers.

Potential for Lumacaftor/Ivacaftor to Affect Other Drugs

7.3 CYP3A Substrates
Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%. Administration of ORKAMBI may decrease systemic exposure of medicinal products which are substrates of CYP3A, thereby decreasing the therapeutic effect of the medicinal product.

Co-administration of ORKAMBI is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]* such as:

- **Benzodiazepines**: midazolam, triazolam (consider an alternative to these benzodiazepines).
- **Immunosuppressants**: cyclosporine, everolimus, sirolimus, and tacrolimus (avoid the use of ORKAMBI).

7.4 CYP2B6 and CYP2C Substrates
In vitro studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed *in vitro*. Additionally, *in vitro* studies suggest that ivacaftor may inhibit CYP2C9. Therefore, concomitant use of ORKAMBI with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates.

7.5 Digoxin and Other P-gp Substrates
Based on *in vitro* results which showed P-gp inhibition and pregnane-X-receptor (PXR) activation, lumacaftor has the potential to both inhibit and induce P-gp. Additionally, a clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of ORKAMBI with P-gp substrates may alter the exposure of these substrates.

Monitor the serum concentration of digoxin and titrate the digoxin dose to obtain the desired clinical effect.

7.6 Anti-allergics and Systemic Corticosteroids
ORKAMBI may decrease the exposure of montelukast, which may reduce its efficacy. No dose adjustment for montelukast is recommended. Employ appropriate clinical monitoring, as is reasonable, when co-administered with ORKAMBI.

Concomitant use of ORKAMBI may reduce the exposure and effectiveness of prednisone and methylprednisolone. A higher dose of these systemic corticosteroids may be required to obtain the desired clinical effect.

7.7 Antibiotics
Concomitant use of ORKAMBI may decrease the exposure of clarithromycin, erythromycin, and telithromycin, which may reduce the effectiveness of these antibiotics. Consider an alternative to these antibiotics, such as ciprofloxacin, azithromycin, and levofloxacin.

7.8 Antifungals
Concomitant use of ORKAMBI may reduce the exposure and effectiveness of itraconazole, ketoconazole, posaconazole, and voriconazole. Concomitant use of ORKAMBI with these antifungals is not recommended. Monitor patients closely for breakthrough fungal infections if such drugs are necessary. Consider an alternative such as fluconazole.

7.9 Anti-inflammatories
Concomitant use of ORKAMBI may reduce the exposure and effectiveness of ibuprofen. A higher dose of ibuprofen may be required to obtain the desired clinical effect.

7.10 Antidepressants
Concomitant use of ORKAMBI may reduce the exposure and effectiveness of citalopram, escitalopram, and sertraline. A higher dose of these antidepressants may be required to obtain the desired clinical effect.

7.11 Hormonal Contraceptives
ORKAMBI may decrease hormonal contraceptive exposure, reducing the effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI.

Concomitant use of ORKAMBI with hormonal contraceptives increased the menstrual abnormality events *[see Adverse Reactions (6.1)]*. Avoid concomitant use unless the benefit outweighs the risks.

7.12 Oral Hypoglycemics
Concomitant use of ORKAMBI may reduce the exposure and effectiveness of repaglinide, and may alter the exposure of sulfonylurea. A dose adjustment may be required to obtain the desired clinical effect. No dose adjustment is recommended for metformin.

7.13 Proton Pump Inhibitors, H2 Blockers, Antacids
ORKAMBI may reduce the exposure and effectiveness of proton pump inhibitors such as omeprazole, esomeprazole, and lansoprazole, and may alter the exposure of ranitidine. A dose adjustment may be required to obtain the desired clinical effect. No dose adjustment is recommended for calcium carbonate antacid.

7.14 Warfarin
ORKAMBI may alter the exposure of warfarin. Monitor the international normalized ratio (INR) when warfarin co-administration with ORKAMBI is required.

7.15 Concomitant Drugs That Do Not Need Dose Adjustment
No dosage adjustment of ORKAMBI or concomitant drug is recommended when ORKAMBI is given with the following: azithromycin, aztreonam, budesonide, ceftazidime, cetirizine, ciprofloxacin, colistimethate, colistin, dornase alfa, fluticasone, ipratropium, levofloxacin, pancreatin, pancrelipase, salbutamol, salmeterol, sulfamethoxazole and trimethoprim, tiotropium, and tobramycin. Based on the metabolism and route of elimination, ORKAMBI is not expected to impact the exposure of these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited and incomplete human data from clinical trials and postmarketing reports on use of ORKAMBI or its individual components, lumacaftor or ivacaftor, in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of lumacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse effects on fetal development at doses that produced maternal exposures up to approximately 8 (rats) and 5 (rabbits) times the exposure at the maximum recommended human dose (MRHD). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse effects on fetal development at doses that produced maternal exposures up to approximately 7 (rats) and 45 (rabbits) times the exposure at the MRHD. No adverse developmental effects were observed after oral administration of either lumacaftor or ivacaftor to pregnant rats from organogenesis through lactation at doses that produced maternal exposures approximately 8 and 5 times the exposures at the MRHD, respectively (*see Data*). There are no animal reproduction studies with concomitant administration of lumacaftor and ivacaftor.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Lumacaftor

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 7-17, lumacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 8 times the MRHD (on an AUC basis at maternal oral doses up to 2000 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7-19, lumacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 5 times the MRHD (on an AUC basis at maternal oral doses up to 200 mg/kg/day). In a pre- and postnatal development study in pregnant female rats dosed from gestation day 6 through lactation day 20, lumacaftor had no effects on delivery or growth and development of offspring at exposures up to 8 times the MRHD (on an AUC basis at maternal oral doses up to 1000 mg/kg/day). Placental transfer of lumacaftor was observed in pregnant rats and rabbits.

Ivacaftor

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 7-17, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 7 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 200 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7-19, ivacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 45 times the MRHD (on an ivacaftor AUC basis at maternal oral doses up to 100 mg/kg/day). In a pre- and postnatal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 5 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 7 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at a maternal oral dose of 200 mg/kg/day). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lumacaftor or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Both lumacaftor and ivacaftor are excreted into the milk of lactating rats; however, due to species-specific differences in lactation physiology, animal lactation data may not reliably predict levels in human milk (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORKAMBI and any potential adverse effects on the breastfed child from ORKAMBI or from the underlying maternal condition.

Data

Lumacaftor

Lacteal excretion of lumacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-lumacaftor administered 9 to 11 days postpartum to lactating mothers (dams). Exposure ($AUC_{0\text{-}24h}$) values for lumacaftor in milk were approximately 40% of plasma levels.

Ivacaftor

Lacteal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-ivacaftor administered 9 to 10 days postpartum to lactating mothers (dams). Exposure ($AUC_{0\text{-}24h}$) values for ivacaftor in milk were approximately 1.5 times higher than plasma levels.

8.3 Females and Males of Reproductive Potential

ORKAMBI may decrease hormonal contraceptive exposure, reducing the effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI *[see Warnings and Precautions (5.5) and Drug Interactions (7.11)]*.

8.4 Pediatric Use

The efficacy of ORKAMBI in children ages 6 through 11 years is extrapolated from efficacy in patients ages 12 years and older homozygous for the *F508del* mutation in the *CFTR* gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years *[see Clinical Pharmacology (12.3)]*.

Additional safety data were obtained from a 24-week, open-label, Phase 3 clinical trial in 58 patients aged 6 through 11 years, mean age 9 years (Trial 3). Trial 3 evaluated subjects with a screening $ppFEV_1 \geq 40$ [mean $ppFEV_1$ 91.4 at baseline (range: 55 to 122.7)]. The safety profile of ORKAMBI in children 6 through 11 years of age was similar to those in patients 12 years and older *[see Adverse Reactions (6.1)]*.

In Trial 3, spirometry ($ppFEV_1$) was assessed as a planned safety endpoint. The within-group LS mean absolute change from baseline in $ppFEV_1$ at Week 24 was 2.5 percentage points. At the Week 26 safety follow-up visit (following a planned discontinuation) $ppFEV_1$ was also assessed. The within-group LS mean absolute change in $ppFEV_1$ from Week 24 at Week 26 was -3.2 percentage points.

The safety and efficacy of ORKAMBI in patients with CF younger than age 6 years have not been established. Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded *[see Warnings and Precautions (5.6)]*.

Juvenile Animal Toxicity Data

In a juvenile toxicology study in which ivacaftor was administered to rats from postnatal days 7 to 35, cataracts were observed at all dose levels, ranging from 0.3 to 2 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at oral doses of 10-50 mg/kg/day). This finding has not been observed in older animals.

8.5 Geriatric Use
CF is largely a disease of children and young adults. Clinical trials of ORKAMBI did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction to 2 tablets in the morning and 1 tablet in the evening is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a maximum dose of 1 tablet in the morning and 1 tablet in the evening, or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

8.7 Renal Impairment
ORKAMBI has not been studied in patients with mild, moderate, or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is necessary for patients with mild and moderate renal impairment. Caution is recommended while using ORKAMBI in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease.

8.8 Patients with Severe Lung Dysfunction
The Phase 3 trials (Trials 1 and 2) included 29 patients receiving ORKAMBI with ppFEV$_1$ <40 at baseline. The treatment effect in this subgroup was comparable to that observed in patients with ppFEV$_1$ ≥40.

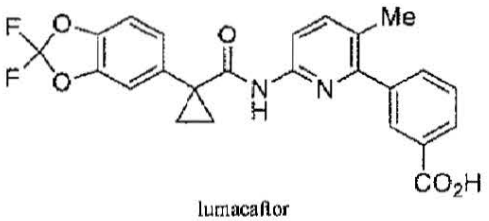
8.9 Patients After Organ Transplantation
ORKAMBI has not been studied in patients with CF who have undergone organ transplantation. Use in transplanted patients is not recommended due to potential drug-drug interactions *[see Drug Interactions (7.3)]*.

10 OVERDOSAGE
There have been no reports of overdose with ORKAMBI.

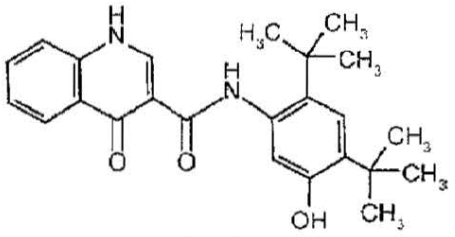
The highest repeated dose was lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h administered to 49 healthy subjects for 7 days in a trial evaluating the effect of ORKAMBI on electrocardiograms (ECGs). Adverse events reported at an increased incidence of ≥5% compared to the lumacaftor 600 mg/ivacaftor 250 mg dosing period and placebo included: headache (29%), transaminase increased (18%), and generalized rash (10%).

No specific antidote is available for overdose with ORKAMBI. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION
The active ingredients in ORKAMBI tablets are lumacaftor, which has the following chemical name: 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid, and ivacaftor, a CFTR potentiator, which has the following chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. The molecular formula for lumacaftor is $C_{24}H_{18}F_2N_2O_5$ and for ivacaftor is $C_{24}H_{28}N_2O_3$. The molecular weights for lumacaftor and ivacaftor are 452.41 and 392.49, respectively. The structural formulas are:



lumacaftor



ivacaftor

Lumacaftor is a white to off-white powder that is practically insoluble in water (0.02 mg/mL). Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 microgram/mL).

ORKAMBI is available as a pink, oval-shaped, film-coated tablet for oral administration containing 200 mg of lumacaftor and 125 mg of ivacaftor. Each ORKAMBI tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor, and the following inactive ingredients: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate. The tablet film coat contains carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

ORKAMBI is also available as a pink, oval-shaped, film-coated tablet for oral administration containing 100 mg of lumacaftor and 125 mg of ivacaftor. Each ORKAMBI tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor, and the following inactive ingredients: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate. The tablet film coat contains carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation results in protein misfolding, causing a defect in cellular processing and trafficking that targets the protein for degradation and therefore reduces the quantity of CFTR at the cell surface. The small amount of F508del-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective gating activity) compared to wild-type CFTR protein.

Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. *In vitro* studies have demonstrated that both lumacaftor and ivacaftor act directly on the CFTR protein in primary human bronchial epithelial cultures and other cell lines harboring the *F508del-CFTR* mutation to increase the quantity, stability, and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. *In vitro* responses do not necessarily correspond to *in vivo* pharmacodynamic response or clinical benefit.

12.2 Pharmacodynamics

Sweat Chloride Evaluation

Changes in sweat chloride in response to relevant doses of lumacaftor alone or in combination with ivacaftor were evaluated in a double-blind, placebo-controlled, Phase 2 clinical trial in patients with CF 18 years of age and older either homozygous or heterozygous for the *F508del* mutation. In that trial, 10 patients (homozygous for *F508del*) completed dosing with lumacaftor alone 400 mg q12h for 28 days followed by the addition of ivacaftor 250 mg q12h for an additional 28 days and 25 patients (homozygous or heterozygous for *F508del*) completed dosing with placebo. The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean change in sweat chloride from baseline to Day 28 compared to placebo was -8.2 mmol/L (95% CI -14, -2). The treatment difference between the combination of lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo evaluated as mean change in sweat chloride from baseline to Day 56 compared to placebo was -11 mmol/L (95% CI -18, -4).

Changes in sweat chloride in response to lumacaftor/ivacaftor were also evaluated in a 24-week, open-label Phase 3 clinical trial (Trial 3) in 58 patients with CF, aged 6 through 11 years (homozygous for *F508del*) who received lumacaftor 200 mg/ivacaftor 250 mg q12h for 24 weeks. Patients treated with lumacaftor/ivacaftor had a reduction in sweat chloride at Day 15 that was sustained through Week 24. The within-group LS mean absolute change from baseline in sweat chloride was -20.4 mmol/L at Day 15 and -24.8 mmol/L at Week 24. In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The within-group LS mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 21.3 mmol/L.

There was no direct correlation between decrease in sweat chloride levels and improvement in lung function ($ppFEV_1$).

Cardiac Electrophysiology

The effect of multiple doses of lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h on QTc interval was evaluated in a randomized, placebo- and active-controlled (400 mg moxifloxacin), parallel, thorough QT study in 168 healthy subjects. No meaningful changes in QTc interval were observed with either lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h dose groups. A maximum decrease in mean heart rate of up to 8 beats per minute (bpm) from baseline was observed with lumacaftor/ivacaftor treatment. In Trials 1 and 2, a similar decrease in heart rate was observed in patients during initiation of ORKAMBI (lumacaftor 400 mg/ivacaftor 250 mg q12h).

12.3 Pharmacokinetics

The exposure (AUC) of lumacaftor is approximately 2-fold higher in healthy adult volunteers compared to exposure in patients with CF. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF. After twice-daily dosing, steady-state plasma concentrations of lumacaftor and ivacaftor in healthy subjects were generally reached after approximately 7 days of treatment, with an accumulation ratio of approximately 1.9 for lumacaftor. The steady-state exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor.

Table 3: Mean (SD) Pharmacokinetic Parameters of Lumacaftor and Ivacaftor at Steady State in Subjects with CF				
	Drug	**C_{max} (µg/mL)**	**$t_{½}$* (h)**	**AUC_{0-12h} (µg·h/mL)**
Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Lumacaftor	25.0 (7.96)	25.2 (9.94)	198 (64.8)
	Ivacaftor	0.602 (0.304)	9.34 (3.81)	3.66 (2.25)
* Based on lumacaftor 200 mg q12h/ivacaftor 250 mg q12h studied in healthy subjects				

Absorption
When a single dose of lumacaftor/ivacaftor was administered with fat-containing foods, lumacaftor exposure was approximately 2 times higher and ivacaftor exposure was approximately 3 times higher than when taken in a fasting state.

Following multiple oral dose administration of lumacaftor in combination with ivacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 200 mg every 24 hours to 400 mg every 12 hours. The median (range) t_{max} of lumacaftor is approximately 4.0 hours (2.0; 9.0) in the fed state.

Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with dose from 150 mg every 12 hours to 250 mg every 12 hours. The median (range) t_{max} of ivacaftor is approximately 4.0 hours (2.0; 6.0) in the fed state.

Distribution
Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin. After oral administration of 200 mg every 24 hours for 28 days to patients with CF in a fed state, the mean (±SD) for apparent volumes of distribution was 86.0 (69.8) L.

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin.

Elimination
The half-life of lumacaftor is approximately 26 hours in patients with CF. The typical apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/hr (29.4%) for patients with CF. The half-life of ivacaftor when given with lumacaftor is approximately 9 hours in healthy subjects. The typical CL/F (CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/hr (40.5%) for patients with CF.

Metabolism
Lumacaftor is not extensively metabolized in humans with the majority of lumacaftor excreted unchanged in the feces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolized via oxidation and glucuronidation.

Ivacaftor is extensively metabolized in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans.

Excretion
Following oral administration of lumacaftor, the majority of lumacaftor (51%) is excreted unchanged in the feces. There was minimal elimination of lumacaftor and its metabolites in urine (only 8.6% of total radioactivity was recovered in the urine with 0.18% as unchanged parent).

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine).

Specific Populations
Age: Pediatric Population

The following conclusions about exposures between adults and the pediatric population are based on population pharmacokinetics (PK) analyses:

Pediatric patients 6 through 11 years of age
Following oral administration of ORKAMBI tablets, lumacaftor 200 mg/ivacaftor 250 mg every 12 hours, the mean lumacaftor (±SD) AUC_{ss} was 203 (57.4) µg/mL*h and is comparable to the mean AUC_{ss} in patients 12 years and older administered ORKAMBI tablets, lumacaftor 400 mg/ivacaftor 250 mg every 12 hours. The mean ivacaftor (±SD) AUC_{ss} was 5.26 (3.08) µg/mL*h and is comparable to the mean AUC_{ss} in patients 12 years and older administered ORKAMBI tablets, lumacaftor 400 mg/ivacaftor 250 mg every 12 hours *[see Use in Specific Populations (8.4)]*.

Pediatric patients 12 to less than 18 years of age
Following oral administration of ORKAMBI tablets, lumacaftor 400 mg/ivacaftor 250 mg every 12 hours, the mean lumacaftor (±SD) AUC_{ss} was 241 (61.4) µg/mL*h and is comparable to the mean AUC_{ss} in adult patients administered ORKAMBI tablets, lumacaftor 400 mg/ivacaftor 250 mg every 12 hours. The mean ivacaftor (±SD) AUC_{ss} was 3.90 (1.56) µg/mL*h and is comparable to the mean AUC_{ss} in adult patients administered ORKAMBI tablets, lumacaftor 400 mg/ivacaftor 250 mg every 12 hours *[see Use in Specific Populations (8.4)]*.

Sex
The pharmacokinetics of ORKAMBI was evaluated using a population PK analysis of data from clinical studies of lumacaftor given in combination with ivacaftor. Results indicate no clinically relevant difference in pharmacokinetic parameters for lumacaftor and ivacaftor between males and females.

Renal Impairment
Pharmacokinetic studies have not been performed with ORKAMBI in patients with renal impairment *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment
Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had approximately 93% higher exposures (AUC_{0-12h}) and approximately 30% higher C_{max} for both lumacaftor and ivacaftor compared with healthy subjects matched for demographics. Pharmacokinetic studies have not been conducted in patients with mild (Child-Pugh Class A, score 5 to 6) or severe hepatic impairment (Child-Pugh Class C, score 10 to 15) receiving ORKAMBI *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6), and Use in Specific Populations (8.6)]*.

Drug Interaction Studies
Drug interaction studies were performed with lumacaftor/ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies *[see Drug Interactions (7)]*.

Potential for Lumacaftor/Ivacaftor to Affect Other Drugs
Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by 80%. Ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. The net effect of lumacaftor/ivacaftor therapy is strong CYP3A induction *[see Drug Interactions (7.3)]*.

Based on *in vitro* results which showed P-gp inhibition and PXR activation, lumacaftor has the potential to both inhibit and induce P-gp. A clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of ORKAMBI with P-gp substrates may alter the exposure of these substrates *[see Drug Interactions (7.5)]*.

In vitro studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed *in vitro*. *In vitro* studies suggest that ivacaftor may inhibit CYP2C9. Therefore, concomitant use of ORKAMBI with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates *[see Drug Interactions (7.4)]*.

Potential for Other Drugs to Affect Lumacaftor/Ivacaftor
Lumacaftor exposure is not affected by concomitant CYP3A inducers or inhibitors. Exposure of ivacaftor when given in combination with lumacaftor is reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors *[see Dosage and Administration (2.3), Warnings and Precautions (5.5), and Drug Interactions (7)]*.

The effects of co-administered drugs on the exposure of lumacaftor and ivacaftor are shown in Table 4 *[see Dosage and Administration (2.3), Warnings and Precautions (5.5), and Drug Interactions (7)]*.

Table 4: Impact of Other Drugs on Lumacaftor 200 mg q12h/Ivacaftor 250 mg q12h

Co-administered Drug	Dose of Co-administered Drug	Effect on PK*	Mean Ratio (90% CI) of Lumacaftor and Ivacaftor No Effect=1.0	
			AUC	C_{max}
CYP3A inhibitor: itraconazole	200 mg once daily	↔ Lumacaftor	0.97 (0.91, 1.02)	0.99 (0.92, 1.05)
		↑ Ivacaftor	4.30† (3.78, 4.88)	3.64† (3.19, 4.17)
CYP3A inducer: rifampin	600 mg once daily	↔ Lumacaftor	0.87 (0.81, 0.93)	0.96 (0.87, 1.05)
		↓ Ivacaftor	0.43 (0.38, 0.49)	0.50 (0.43, 0.58)
Other: ciprofloxacin	750 mg q12h	↔ Lumacaftor	0.86 (0.79, 0.95)	0.88 (0.80, 0.97)
		↔ Ivacaftor	1.29 (1.12, 1.48)	1.29 (1.11, 1.49)

* ↑ = increase, ↓ = decrease, ↔ = no change.
† The net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours, the approved dose of ivacaftor monotherapy.
CI = Confidence interval, PK = Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ORKAMBI; however, studies are available for individual components, lumacaftor and ivacaftor, as described below.

Lumacaftor
A two-year study in Sprague-Dawley rats and a 26-week study in transgenic Tg.rasH2 mice were conducted to assess carcinogenic potential of lumacaftor. No evidence of tumorigenicity was observed in rats at lumacaftor oral doses up to 1000 mg/kg/day (approximately 5 and 13 times the MRHD on a lumacaftor AUC basis in males and females, respectively). No evidence of tumorigenicity was observed in Tg.rasH2 mice at lumacaftor oral doses up to 1500 and 2000 mg/kg/day in female and male mice, respectively. Lumacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Lumacaftor had no effects on fertility and reproductive performance indices in male and female rats at an oral dose of 1000 mg/kg/day (approximately 3 and 8 times, respectively, the MRHD on a lumacaftor AUC basis).

Ivacaftor
Two-year studies were conducted in mice and rats to assess carcinogenic potential of ivacaftor. No evidence of tumorigenicity was observed in mice and rats at ivacaftor oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 3 and 10 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (approximately 15 and 7 times the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 7 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at an oral dose of ≤100 mg/kg/day (approximately 8 and 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

14 CLINICAL STUDIES

Dose Ranging
Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, multiple-cohort trial which included 97 Caucasian patients with CF (homozygous for the *F508del* mutation) 18 years of age and older with a screening ppFEV$_1$ ≥40. In the trial, 76 patients (homozygous for the *F508del* mutation) were randomized to receive lumacaftor alone at once-daily doses of 200 mg, 400 mg, or 600 mg or 400 mg q12h for 28 days followed by the addition of ivacaftor 250 mg q12h and 27 patients (homozygous or heterozygous for the *F508del* mutation) received placebo. During the initial 28-day lumacaftor monotherapy period, treatment with lumacaftor demonstrated a dose-dependent decrease in ppFEV$_1$ compared to placebo. Changes from Day 1 at Day 28 in ppFEV$_1$ compared to placebo were 0.24, -1.4, -2.7, and -4.6 for the 200 mg once daily, 400 mg once daily, 600 mg once daily, and 400 mg q12h lumacaftor doses, respectively. Following the addition of ivacaftor 250 mg q12h, the changes from Day 1 at Day 56 in ppFEV$_1$ compared to placebo were 3.8, 2.7, 5.6, and 4.2, respectively.

Sweat chloride was also assessed in this trial. Following the initial 28 days of lumacaftor monotherapy, the changes from Day 1 at Day 28 in sweat chloride compared to placebo were -4.9, -8.3, -6.1, and -8.2 mmol/L for the 200 mg once daily, 400 mg once daily, 600 mg once daily, and 400 mg q12h lumacaftor doses, respectively. Following the addition of ivacaftor 250 mg q12h, the changes from Day 1 at Day 56 in sweat chloride compared to placebo were -5.0, -9.8, -9.5, and -11 mmol/L, respectively.

These data supported the evaluation of lumacaftor 400 mg/ivacaftor 250 mg q12h (ORKAMBI) and lumacaftor 600 mg once daily/ivacaftor 250 mg q12h in the confirmatory trials.

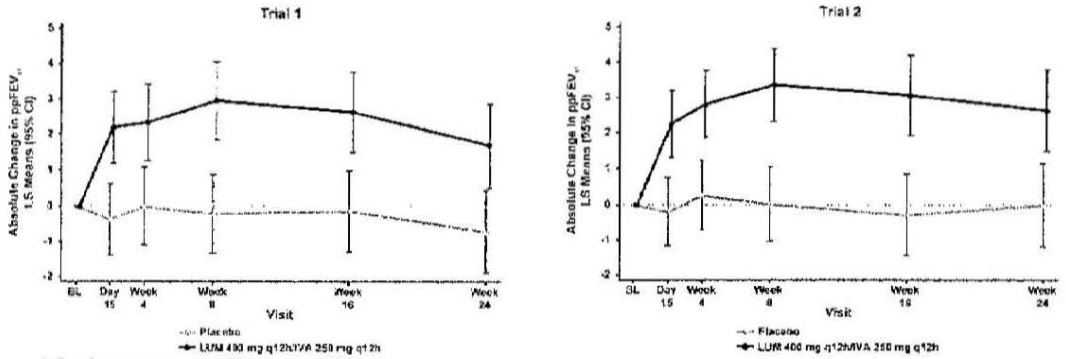
Confirmatory
The efficacy of ORKAMBI in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials (Trials 1 and 2) in 1108 clinically stable patients with CF of whom 369 patients received ORKAMBI twice daily.

Trial 1 evaluated 549 patients with CF who were aged 12 years and older (mean age 25.1 years) with ppFEV$_1$ at screening between 40-90 [mean ppFEV$_1$ 60.7 at baseline (range: 31.1 to 94.0)]. Trial 2 evaluated 559 patients aged 12 years and older (mean age 25.0 years) with ppFEV$_1$ at screening between 40-90 [mean ppFEV$_1$ 60.5 at baseline (range: 31.3 to 99.8)]. Patients with a history of colonization with organisms such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x the ULN or total bilirubin ≥2 x the ULN) were excluded.

Patients in both trials were randomized 1:1:1 to receive either ORKAMBI (lumacaftor 400 mg q12h/ivacaftor 250 mg q12h; or lumacaftor 600 mg once daily/ivacaftor 250 mg q12h) or placebo. Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline).

The primary efficacy endpoint in both trials was change in lung function as determined by absolute change from baseline in ppFEV$_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with ORKAMBI resulted in a statistically significant improvement in ppFEV$_1$. The treatment difference between ORKAMBI and placebo for the mean absolute change in ppFEV$_1$ from baseline at Week 24 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.0001). These changes persisted throughout the 24-week treatment period (Figure 1). Improvements in ppFEV$_1$ were observed regardless of age, disease severity, sex, and geographic region.

Figure 1. Absolute Change From Baseline at Each Visit in Percent Predicted FEV_1 in Trial 1 and Trial 2.



LS = least squares; q12h = every 12 hours

Key secondary efficacy variables included relative change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score at Week 24, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing; proportion of patients achieving ≥5% relative change from baseline in $ppFEV_1$ using the average of Week 16 and Week 24; and number of pulmonary exacerbations through Week 24. For the purposes of these trials, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.

Table 5: Summary of Other Efficacy Endpoints in Trials 1 and 2*

		Trial 1		Trial 2	
		Placebo (n=184)	**ORKAMBI LUM 400 mg q12h/IVA 250 mg q12h (n=182)**	**Placebo (n=187)**	**ORKAMBI LUM 400 mg q12h/IVA 250 mg q12h (n=187)**
Relative change in $ppFEV_1$ at Week 24† (%)	Treatment difference (95% CI)	–	4.3 (1.9, 6.8) P=0.0006‡	–	5.3 (2.7, 7.8) P<0.0001‡
Absolute change in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI)	–	0.1 (-0.1, 0.3)	–	0.4 (0.2, 0.5) P=0.0001‡
Absolute change in CFQ-R Respiratory Domain Score (Points) at Week 24	Treatment difference (95% CI)	–	1.5 (-1.7, 4.7)	–	2.9 (-0.3, 6.0)
Proportion of patients with ≥5% relative change in $ppFEV_1$ at Week 24†	%	22%	37%	23%	41%
	Odds ratio (95% CI)	–	2.1 (1.3, 3.3)	–	2.4 (1.5, 3.7)
Number of pulmonary exacerbations through Week 24	# of events (rate per 48 weeks)	112 (1.1)	73 (0.7)	139 (1.2)	79 (0.7)
	Rate ratio (95% CI)	–	0.7 (0.5, 0.9)	–	0.6 (0.4, 0.8)

* In each trial, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.0250$ and all previous tests also meeting this level of significance was required for statistical significance.
† Assessed as the average of the treatment effects at Week 16 and Week 24.
‡ Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures considered not statistically significant.

16 HOW SUPPLIED/STORAGE AND HANDLING

ORKAMBI (lumacaftor 200 mg/ivacaftor 125 mg) is supplied as pink, oval-shaped tablets; each tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor, printed with "2V125" in black ink on one side and plain on the other, and is packaged as follows:

112-count tablet box containing a 4-week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip). **NDC** 51167-809-01

ORKAMBI (lumacaftor 100 mg/ivacaftor 125 mg) is supplied as pink, oval-shaped tablets; each tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor, printed with "1V125" in black ink on one side and plain on the other, and is packaged as follows:

112–count tablet box containing a 4-week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip). NDC 51167-700-02

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advanced Liver Disease

Inform patients that worsening of liver function in patients with advanced liver disease occurred in some patients treated with ORKAMBI. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Abnormalities in Liver Function and Testing

Inform patients that abnormalities in liver function have occurred in patients treated with ORKAMBI. Blood tests to measure transaminases (ALT and AST) and bilirubin will be performed prior to initiating ORKAMBI, every 3 months during the first year of therapy, and annually thereafter *[see Warnings and Precautions (5.2)]*.

Respiratory Events

Inform patients that chest discomfort, dyspnea, and respiration abnormal were more common during initiation of ORKAMBI therapy. Additional monitoring of patients with ppFEV$_1$ <40 is recommended during initiation of therapy *[see Warnings and Precautions (5.3)]*.

Effect on Blood Pressure

Inform patients that increased blood pressure has been observed in some patients treated with ORKAMBI and that periodic monitoring of their blood pressure during treatment is recommended *[see Warnings and Precautions (5.4)]*.

Drug Interactions with CYP3A Inhibitors and Inducers

Ask patients to tell you all the medications they are taking, including any herbal supplements or vitamins. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended *[see Warnings and Precautions (5.5), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Instruct patients on alternative methods of birth control because hormonal contraceptives should not be relied upon as an effective method of contraception and there is an increased incidence of menstruation-related adverse reactions when co-administered with ORKAMBI *[see Warnings and Precautions (5.5), Adverse Reactions (6.1), and Drug Interactions (7.11)]*.

When initiating ORKAMBI in patients taking strong CYP3A inhibitors (e.g., itraconazole), instruct the patient to reduce the dose of ORKAMBI to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose *[see Dosage and Administration (2.3), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Patients should be instructed to tell their doctor if they stop ORKAMBI for more than 1 week while they are also taking a strong CYP3A inhibitor because the dose of ORKAMBI would need to be reduced upon re-initiation. The dose of ORKAMBI should be reduced to 1 tablet daily for the first week upon treatment re-initiation. Following this period, continue with the recommended daily dose *[see Dosage and Administration (2.3), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Use in Patients with Hepatic Impairment

Inform patients with moderate hepatic impairment (Child-Pugh Class B) to reduce the dose of ORKAMBI to 2 tablets in the morning and 1 tablet in the evening.

If initiating ORKAMBI in a patient with severe hepatic impairment, after weighing the risks and benefits of treatment, instruct the patient to take a maximum dose of 1 tablet every 12 hours, or less *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

Administration

Inform patients that ORKAMBI is best absorbed by the body when taken with fat-containing food. A typical CF diet will satisfy this requirement. Examples of fat-containing foods include eggs, avocados, nuts, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

Inform patients that if a dose is missed and they remember the missed dose within 6 hours, the patients should take the dose with fat-containing food. If more than 6 hours elapsed after the usual dosing time, the patients should skip that dose and resume the normal schedule for the following dose. Patients should be informed not to take a double dose to make up for the forgotten dose *[see Dosage and Administration (2.1)]*.

Cataracts

Inform patients that abnormalities of the eye lens (cataract) have been noted in some children and adolescents receiving ORKAMBI and ivacaftor, a component of ORKAMBI. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ORKAMBI treatment *[see Warnings and Precautions (5.6)]*.

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

104508-02

Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION
ORKAMBI (or-KAM-bee)
(Lumacaftor/Ivacaftor)
Film-Coated Tablets

What is ORKAMBI?

ORKAMBI is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have two copies of the *F508del* mutation (*F508del/F508del*) in their *CFTR* gene.

ORKAMBI should not be used in patients other than those who have two copies of the *F508del* mutation in their *CFTR* gene.

It is not known if ORKAMBI is safe and effective in children under 6 years of age.

Who should not take ORKAMBI?

Do not take ORKAMBI if you take certain medicines or herbal supplements such as:

- antibiotics: rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medications: phenobarbital, carbamazepine (Tegretol®, Carbatrol®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- sedatives/anxiolytics: triazolam (Halcion®) or midazolam (Dormicum®, Hypnovel®, and Versed®)
- immunosuppressant medicines: everolimus (Zortress®), sirolimus (Rapamune®), or tacrolimus (Astagraf XL®, Envarsus® XR, Prograf®, Protopic®)
- St. John's wort (*Hypericum perforatum*)

Talk to your doctor before taking ORKAMBI if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking ORKAMBI?

Before you take ORKAMBI, tell your doctor if you:

- have or have had liver problems
- have had an organ transplant
- have kidney problems
- are using birth control (hormonal contraceptives, including oral, injectable, transdermal, or implantable forms). Hormonal contraceptives should not be used as a method of birth control when taking ORKAMBI. Talk to your doctor about the best birth-control method you should use while taking ORKAMBI.
- are pregnant or plan to become pregnant. It is not known if ORKAMBI will harm your unborn baby. You and your doctor should decide if you will take ORKAMBI while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if ORKAMBI passes into your breast milk. You and your doctor should decide if you will take ORKAMBI while you are breastfeeding.

ORKAMBI may affect the way other medicines work, and other medicines may affect how ORKAMBI works.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements, because the dose of ORKAMBI may need to be adjusted when taken with certain medications.
Ask your doctor or pharmacist for a list of these medicines if you are not sure.
Especially tell your doctor if you take:

- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), or voriconazole (e.g., Vfend®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ORKAMBI?

- Take ORKAMBI exactly as your doctor tells you to take it.
- Always take ORKAMBI tablets with fat-containing foods such as eggs, avocados, nuts, butter, peanut butter, cheese pizza, whole-milk dairy products, (such as whole milk, cheese, and yogurt), etc.
- Take your doses of ORKAMBI **12** hours apart.
- Each ORKAMBI box contains 4 weekly cartons.
- Each carton contains 7 daily blister strips.

- Each blister strip contains 4 tablets so you can take 2 tablets for the morning and 2 tablets for the evening.
- You may cut along the dotted line to separate your morning dose from your evening dose.
- In the morning, unpeel the paper backing from a blister strip (do not push tablet through backing) to remove 2 ORKAMBI tablets and take them with fat-containing food.
- In the evening, 12 hours later, open another blister strip (do not push tablet through backing) to remove 2 ORKAMBI tablets and take them with fat-containing food.
- If you miss a dose **within 6 hours** of when you usually take it, take your dose with fat-containing food as soon as possible.
- If you miss a dose and it is **more than 6 hours** after the time you usually take it, **skip that dose only** and take the next dose when you usually take it. Do **not** take 2 doses at the same time to make up for your missed dose.
- Tell your doctor if you stop ORKAMBI for more than 1 week. Your doctor may need to change your dose of ORKAMBI or other medicines you take.

What should I avoid while taking ORKAMBI?

It is unknown if ORKAMBI causes dizziness. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how ORKAMBI affects you.

What are the possible side effects of ORKAMBI?

ORKAMBI can cause serious side effects.

High liver enzymes in the blood, which can be a sign of liver injury, have been reported in patients receiving ORKAMBI. Your doctor will do blood tests to check your liver:

- before you start ORKAMBI
- every 3 months during your first year of taking ORKAMBI
- every year while you are taking ORKAMBI

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- loss of appetite
- dark, amber-colored urine
- yellowing of your skin or the white part of your eyes
- nausea or vomiting
- confusion

Respiratory events such as shortness of breath or chest tightness were observed in patients when starting ORKAMBI. If you have poor lung function, your doctor may monitor you more closely when you start ORKAMBI.

An increase in blood pressure has been seen in some patients treated with ORKAMBI. Your doctor should monitor your blood pressure during treatment with ORKAMBI.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving ORKAMBI and ivacaftor, a component of ORKAMBI. If you are a child or adolescent, your doctor should perform eye examinations prior to and during treatment with ORKAMBI to look for cataracts.

The most common side effects of ORKAMBI include:

- shortness of breath and/or chest tightness
- upper respiratory tract infection (common cold), including sore throat, stuffy or runny nose
- gastrointestinal symptoms, including nausea, diarrhea, or gas
- rash
- fatigue
- flu or flu-like symptoms
- increase in muscle enzyme levels
- irregular, missed, or abnormal periods (menses) and increase in the amount of menstrual bleeding

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ORKAMBI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ORKAMBI?

- Store ORKAMBI at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not use ORKAMBI after the expiration date on the package.

Keep ORKAMBI and all medicines out of the reach of children.

General information about the safe and effective use of ORKAMBI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ORKAMBI for a condition for which it was not prescribed. Do not give ORKAMBI to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about ORKAMBI. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ORKAMBI that is written for health professionals.

For more information, go to www.orkambi.com or call 1-877-752-5933.

What are the ingredients in ORKAMBI?

Active ingredients: lumacaftor and ivacaftor
Inactive ingredients: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate.

The tablet film coat contains: carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

The printing ink contains: ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

VERTEX

Manufactured for: Vertex Pharmaceuticals Incorporated; 50 Northern Avenue, Boston, MA 02210

104508-02
This Patient Information has been approved by the U.S. Food and Drug Administration. Approved September 2016

Print Form Reset Form

State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers

Fax this request to: 1-888-656-6822 ATTN: John McCall, R.Ph.

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Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for *NEW* information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

Contact Information

MANUFACTURER NAME: Vertex Pharmaceuticals Incorporated

DATE: 10 - 26 - 2016

PRODUCT MANAGER'S NAME:

TITLE:

ADDRESS: 50 Northern Avenue

CITY: Boston

STATE: MA

ZIP CODE: 02210

PHONE NUMBER: 877 - 634 - 8789

FAX NUMBER: - -

PRODUCT: KALYDECO (R) (ivacaftor)

Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

KALYDECO (R) (ivacaftor) is the first and only therapy that targets the underlying cause of cystic fibrosis (CF) in patients 2 and older who have one of the [10] indicated mutations. CF is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. KALYDECO facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.

KALYDECO was first approved in January 2012 for the treatment of CF in patients age 6 years and older who have a G551D mutation on their CFTR gene. In 2014, the indication was expanded to include the treatment of CF in patients age 6 years and older with one of 9 additional mutations as outlined in the prescribing information (G1244E, G1349D, G178R, G551S, S1251N, S1225P, S549N, S549R, or R117H). Most recently (March 2015), KALYDECO was approved for the treatment of CF in patients age 2 years and older who have at least one of the 10 CFTR gene mutations outlined in the prescribing information. KALYDECO is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene. A safe and efficacious dose of KALYDECO for patients less than 2 years of age has not been established. The use of KALYDECO in children under the age of 2 years is not recommended. Below is a summary of selected data that has not been previously shared with the committee.

PERSIST was a 96-week open-label extension study in 192 patients who rolled over from the 48-week phase 3 pivotal studies of KALYDECO in patients ages 6 and older with a G551D mutation. The primary endpoint was safety and results showed that KALYDECO was generally well tolerated and had a safety profile consistent with that seen in the phase 3 studies.

A post-hoc analysis of the rate of change in lung function and nutritional measures was also conducted to compare outcomes in patients with CF with a G551D mutation receiving ivacaftor to a propensity score matched cohort of patients US CFF Patient Registry who were homozygous for the F508del mutation and did not receive ivacaftor for up to three years by Sawicki et al. Propensity scoring is a statistical matching technique used in observational research that attempts to balance the study groups to

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Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

make them as similar as possible. Eligible patients had a minimum of three FEV1 measures spanning ≥6 months after 30 days on ivacaftor treatment. Eligible control patients were enrolled in the CFF Patient Registry in 2010, were aged ≥6 years and homozygous for the F508del mutation, had sweat chloride concentrations >40 mmol/L, had no evidence in the registry of death, lung transplant, or pregnancy through the end of 2010, and were clinically stable based on care episode, medication, and spirometry data. The choice of comparator groups was made to represent the most common genotype in the CF population in order to ensure there would be a sufficient number of patients to serve as matched comparators. Prior analyses of patient registry data also indicated that patients with G551D mutations have similar clinical characteristics, including sweat chloride and pulmonary function, to those with homozygous F508del mutations.

Five patients homozygous for F508del were matched to each G551D ivacaftor patient using a propensity score, which takes into account several factors for which previous studies have suggested an association with FEV1 decline including spirometry measurements, age, gender, nutritional parameters, bacteriology, sweat chloride values, use of inhaled antibiotics and other therapies, and the presence of CF-related diabetes. Measured outcomes included the annualized mean rate of change in percent predicted FEV1, weight-for-age, and BMI-for-age z-scores.

There are limitations with this type of approach. Studying patients with differing genotypes, geography of patients, differences in unmeasured characteristics, differing amounts of data contributed to the analysis by patients, and rates of clinical trial participation may have affected the results. Not all variables affecting lung function decline may have been captured in propensity score matching. Causality is not definitely established and the model assumes the rate of lung function decline is constant over the observation period for each individual.

In total, 189 G551D patients who received ivacaftor for up to 144 weeks and 886 matched control patients homozygous for F508del were included in the analysis. There were no statistically significant differences between the 2 groups in the variables used for the propensity scores. The estimated annualized rate of decline in percent predicted FEV1 in ivacaftor-treated G551D patients was −0.91 (SE=0.34) vs. −1.72 (SE=0.16) in the F508del homozygous control group. The difference in slope of 0.80 (95% CI: 0.06, 1.55) percentage points per year represents an approximately 47% reduction in the annualized rate of decline in percent predicted FEV1 with ivacaftor treatment (P=0.03). Estimates of average annual rate of decline were based on lung function measurements spanning different lengths of time for different patients, with more patients contributing information about th erate of decline in the earlier years than in the subsequent years.

There were no statistically significant differencess in the rate of change between the G551D patients and the matched controls for either WFA or BMI-for-age z score, suggesting that the initial treatment effect was maintained for up to 3 years.

The overall safety profile of KALYDECO (ivacafor) is based on pooled data from three placebo-controlled trials conducted in 353 patients with CF who had a G551D mutation or were homozygous for the F508del mutation. In these trials, the proportion of patients who prematurely discontinued study drug due to adverse reactions was 2% for patients treated with KALYDECO and 5% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently included abdominal pain, increased hepatic enzymes, and hypoglycemia. In phase 3 trials of CF patients with a G551D mutation, the most common adverse events occurring in 8% or more in patients treated with KALYDECO and higher than in patients receiving placebo were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea and dizziness. The safety profile for the 39 patients with CF with one of the 9 non-G551D mutations enrolled in the 8-week crossover trial, for the 69 patients with CF with an R117H mutation enrolled in the 24-week placebo-controlled trial, and for the 34 patients ages 2 to less than 6 years in the 24-week, open-label clinical trial were similar to that observed in the 48-week placebo-controlled trials.

There are no known contraindications to KALYDECO. Elevated transaminases have been reported in patients with CF receiving KALYDECO. Therefore, it is recommended that ALT and AST be assessed prior to initiating therapy, every 3 months during the first year of treatment, and annually thereafter. Transaminase elevations were more common in patients with a history of transaminas

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Published Citations (If additional space is required, use Published Citations Continuation Page).

KALYDECO (R) (ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; March 2015.

Phase 3:
Rosenfeld M, Robertson S, Green Y, et al. An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2 to 5 years with cystic fibrosis and a CFTR gating mutation: The KIWI study. J Cystic Fibros. June 2015; 14(Suppl 1):S2.

Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med. 2015. Published online June 10, 2015.

De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J Cyst Fibros. 2014;13:674-80.

McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a Phase 3, open-label extension study (PERSIST). Lancet Respir Med. 2014;2:902-10.

Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med. 2013;187:1219-25.

Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365:1663-72.

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Sagel SD, Heltshe SL, Khan U, et al. Effect of ivacaftor in R117H patients following FDA approval: early results of the G551D observational-expanded and extended (GOAL-E2) study. Ped Pulm. 2015;50(S41):275-76. Presented at the North American Cystic Fibrosis Conference 2015.

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Barry PJ, Plant BJ, Simmonds NJ, et al. Ivacaftor decreases mortality in G551D patients with severe lung disease. Ped Pulm. 2015; 50(S41):261. Presented at the North American Cystic Fibrosis Conference 2015.

Sawicki GS, et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and CF patient registry data. Am J Respir Crit Care Med. 2015;192(7):836-842.

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Taylor-Cousar J, Niknian M, Gilmartin G, et al. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: Safety and efficacy in an expanded access program in the United States. J Cyst Fibros. 2015. Corrected proof published online February 11, 2015.

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ACTION TO BE TAKEN: **DATE:** ☐☐ - ☐☐ - ☐☐☐☐

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Clinical Rationale Continuation Page (Use only if needed).

elevations. In patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. Dosing should be interrupted in a patient whose ALT or AST is greater than 5 times the upper limit of normal and consideration given to the benefits and risks of resuming KALYDECO therapy. Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Therefore, co-administration of KALYDECO with stron CYP3A inducers is not recommended. Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

In summary, KALYDECO was the first drug that targets the underlying cause of CF. Most available therapies treat the symptoms or manifestations of the disease.

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Public Citations Continuation Page (Use only if needed).

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Barry PJ, Plant BJ, Nair A, et al. Effects of ivacaftor in cystic fibrosis patients carrying the G551D mutation with severe lung disease. Chest. 2014;146(1):152-8

Hebestreit, H. Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation. J Cyst Fibros. 2013; 12(6):599-603.

Heltshe SL, Mayer-Hamblett N, Burns JL, et al. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clin Infect Dis. 2015;60(5):703-712.

Borowitz D, et al. Nutritional status outcomes in patients with CF and the G551D mutation before and after CFTR modulation. Dig Dis Sci. 2015;Aug 7. [Epub ahead of print]

Konstan MW, Plant BJ, Elborn JS, et al. Efficacy response in CF patients treated with ivacaftor: Post-hoc analysis. Pediatr Pulmonol. 2015;50:447-55.

Quittner A, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE clinical study. Health Qual Life Outcomes 2015;13:93.

Davies JC, Sheridan H, Bell N, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013;1:630-8.

Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med. 2010;363:1991-2003.

Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest. 2012;142:718-24.

Magellan HEALTH

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KALYDECO safely and effectively. See full prescribing information for KALYDECO.

KALYDECO® (ivacaftor) tablets, for oral use
KALYDECO® (ivacaftor) oral granules
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

• Indications and Usage (1)	03/2015
• Dosage and Administration (2)	03/2015
• Warnings and Precautions (5.1, 5.3)	03/2015

INDICATIONS AND USAGE

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.*

KALYDECO is indicated for the treatment of CF in patients age 2 years and older who have an *R117H* mutation in the *CFTR* gene.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. (1)

Limitations of Use:

- Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene. (1, 14)

DOSAGE AND ADMINISTRATION

- Adults and pediatric patients age 6 years and older: one 150 mg tablet taken orally every 12 hours with fat-containing food. (2.2, 12.3)
- Pediatric patients 2 to less than 6 years of age and less than 14 kg: one 50 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. (2.3, 12.3)
- Pediatric patients 2 to less than 6 years of age and 14 kg or greater: one 75 mg packet mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. (2.3, 12.3)
- Pediatric patients less than 2 years of age: not recommended. (2.4, 8.4)
- Reduce dose in patients with moderate and severe hepatic impairment. (2.5, 8.6, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (2.6, 7.1, 12.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 150 mg (3)
- Oral granules: Unit-dose packets of 50 mg and 75 mg (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Elevated transaminases (ALT or AST): Transaminases (ALT and AST) should be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients 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 KALYDECO dosing. (5.1, 6)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) substantially decreases exposure of ivacaftor, which may diminish effectiveness. Therefore, co-administration is not recommended. (5.2, 7.2, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up examinations are recommended in pediatric patients initiating KALYDECO treatment. (5.3)

ADVERSE REACTIONS

The most common adverse drug reactions to KALYDECO (occurring in ≥8% of patients with CF who have a *G551D* mutation in the *CFTR* gene) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness. (6.1)

DRUG INTERACTIONS

CYP3A inhibitors: Reduce KALYDECO dose to one tablet or one packet of granules twice a week when co-administered with strong CYP3A inhibitors (e.g., ketoconazole). Reduce KALYDECO dose to one tablet or one packet of granules once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Avoid food containing grapefruit or Seville oranges. (7.1, 12.3)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.*

KALYDECO is indicated for the treatment of CF in patients age 2 years and older who have an *R117H* mutation in the *CFTR* gene.

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

Limitations of Use

KALYDECO is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

KALYDECO should be taken with fat-containing food. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. [*see Clinical Pharmacology (12.3) and Patient Counseling Information (17)*].

2.2 Dosing Information in Adults and Children Ages 6 Years and Older

The recommended dose of KALYDECO for both adults and pediatric patients age 6 years and older is one 150 mg tablet taken orally every 12 hours (300 mg total daily dose) with fat-containing food [*see Dosage and Administration (2.1)*].

2.3 Dosing Information in Pediatric Patients Ages 2 to less than 6 Years

The recommended dose of KALYDECO (oral granules) for patients ages 2 to less than 6 years is weight-based according to Table 1.

Table 1: Dosage of KALYDECO Oral Granules by Body Weight in Pediatric Patients Ages 2 to less than 6 Years

Body Weight (kg)	KALYDECO Dose	Total Daily Dose
Less than 14 kg	One 50 mg packet every 12 hours	100 mg/day
14 kg or greater	One 75 mg packet every 12 hours	150 mg/day

The entire contents of each packet of oral granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed. Food or liquid should be at or below room temperature. Once mixed, the product has been shown to be stable for one hour, and therefore should be consumed during this period. Some examples of soft foods or liquids may include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice. Each dose should be administered just before or just after fat-containing food [*see Dosage and Administration (2.1)*].

2.4 Dosing Information in Pediatric Patients less than 2 Years

A safe and efficacious dose of KALYDECO for pediatric patients less than 2 years of age has not been established. The use of KALYDECO (oral granules) in children under the age of 2 years is not recommended.

2.5 Dosage Adjustment for Patients with Hepatic Impairment

The dose of KALYDECO should be reduced to one tablet or one packet of oral granules once daily for patients with moderate hepatic impairment (Child-Pugh Class B). KALYDECO should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C) at a dose of one tablet or one packet of oral granules once daily or less frequently [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3),* and *Patient Counseling Information (17)*].

2.6 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

When KALYDECO is being co-administered with strong CYP3A inhibitors (e.g., ketoconazole), the dose should be reduced to one tablet or one packet of oral granules twice a week. The dose of KALYDECO should be reduced to one tablet or one packet of granules once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Food containing grapefruit or Seville oranges should be avoided [*see Drug Interactions (7.1), Clinical Pharmacology (12.3), and Patient Counseling Information (17)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg; supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" on one side and plain on the other

Oral granules: Unit-dose packets containing 50 mg or 75 mg per packet; supplied as small, white to off-white granules and enclosed in unit-dose packets

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Transaminase (ALT or AST) Elevations

Elevated transaminases have been reported in patients with CF receiving KALYDECO. It is recommended that ALT and AST be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients 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 KALYDECO dosing [see *Adverse Reactions (6) and Use in Specific Populations (8.6)*].

5.2 Concomitant Use with CYP3A Inducers

Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Therefore, co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

5.3 Cataracts
Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Although other risk factors were present in some cases (such as corticosteroid use and/or exposure to radiation), a possible risk attributable to KALYDECO cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating KALYDECO treatment.

6 ADVERSE REACTIONS
The following adverse reaction is discussed in greater detail in other sections of the label:
- Transaminase Elevations [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of KALYDECO is based on pooled data from three placebo-controlled clinical trials conducted in 353 patients 6 years of age and older with CF who had a *G551D* mutation in the *CFTR* gene (Trials 1 and 2) or were homozygous for the *F508del* mutation (Trial 3). In addition, the following clinical trials have also been conducted [*see Clinical Pharmacology (12)* and *Clinical Studies (14)*]:
- An 8-week crossover design trial (Trial 4) involving 39 patients between the ages of 6 and 57 years with a *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutation in the *CFTR* gene.
- A 24-week placebo-controlled trial (Trial 5) involving 69 patients between the ages of 6 and 68 years with an *R117H* mutation in the *CFTR* gene.
- A 24-week open-label trial (Trial 6) in 34 patients 2 to less than 6 years of age. Patients eligible for Trial 6 were those with the *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutation in the *CFTR* gene. Of 34 patients enrolled, 32 had the *G551D* mutation and 2 had the *S549N* mutation.

Of the 353 patients included in the pooled analyses of patients with CF who had either a *G551D* mutation or were homozygous for the *F508del* mutation in the *CFTR* gene, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO, and 132 received placebo from 16 to 48 weeks.

The proportion of patients who prematurely discontinued study drug due to adverse reactions was 2% for KALYDECO-treated patients and 5% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in KALYDECO-treated patients included abdominal pain, increased hepatic enzymes, and hypoglycemia.

The most common adverse reactions in the 221 patients treated with KALYDECO were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%).

The incidence of adverse reactions below is based upon two double-blind, placebo-controlled, 48-week clinical trials (Trials 1 and 2) in a total of 213 patients with CF ages 6 to 53 who have a *G551D* mutation in the *CFTR* gene and who were treated with KALYDECO 150 mg orally or placebo twice daily. Table 2 shows adverse reactions occurring in ≥8% of KALYDECO-treated patients with CF who have a *G551D* mutation in the *CFTR* gene that also occurred at a higher rate than in the placebo-treated patients in the two double-blind, placebo-controlled trials.

Table 2: Incidence of Adverse Drug Reactions in ≥8% of KALYDECO-Treated Patients with a *G551D* Mutation in the *CFTR* Gene and Greater than Placebo in 2 Placebo-Controlled Phase 3 Clinical Trials of 48 Weeks Duration

	Incidence: Pooled 48-Week Trials	
Adverse Reaction (Preferred Term)	**KALYDECO N=109 n (%)**	**Placebo N=104 n (%)**
Headache	26 (24)	17 (16)
Oropharyngeal pain	24 (22)	19 (18)
Upper respiratory tract infection	24 (22)	14 (14)
Nasal congestion	22 (20)	16 (15)
Abdominal pain	17 (16)	13 (13)
Nasopharyngitis	16 (15)	12 (12)
Diarrhea	14 (13)	10 (10)
Rash	14 (13)	7 (7)
Nausea	13 (12)	11 (11)
Dizziness	10 (9)	1 (1)

Adverse reactions in the 48-week clinical trials that occurred in the KALYDECO group at a frequency of 4 to 7% where rates exceeded that in the placebo group include:
Infections and infestations: rhinitis
Investigations: aspartate aminotransferase increased, bacteria in sputum, blood glucose increased, hepatic enzyme increased
Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, myalgia
Nervous system disorders: sinus headache
Respiratory, thoracic and mediastinal disorders: pharyngeal erythema, pleuritic pain, sinus congestion, wheezing
Skin and subcutaneous tissue disorders: acne

The safety profile for the CF patients enrolled in the other clinical trials (Trials 3-6) was similar to that observed in the 48-week, placebo-controlled trials (Trials 1 and 2).

Laboratory Abnormalities

Transaminase Elevations: In Trials 1, 2, and 3 the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN was 2%, 2%, and 6% in KALYDECO-treated patients and 2%, 2%, and 8% in placebo-treated patients, respectively. Two patients (2%) on placebo and 1 patient (0.5%) on KALYDECO permanently discontinued treatment for elevated transaminases, all >8 x ULN. Two patients treated with KALYDECO were reported to have serious adverse reactions of elevated liver transaminases compared to none on placebo. Transaminase elevations were more common in patients with a history of transaminase elevations [*see Warnings and Precautions (5.1)*].

During the 24-week, open-label, clinical trial in 34 patients ages 2 to less than 6 years (Trial 6), where patients received either 50 mg (less than 14 kg) or 75 mg (14 kg or greater) ivacaftor granules twice daily, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of KALYDECO dosing. Transaminase elevations were more common in patients who had abnormal transaminases at baseline. KALYDECO was permanently discontinued in one patient [*see Warnings and Precautions (5.1)*].

7 DRUG INTERACTIONS

Potential for other drugs to affect ivacaftor

7.1 Inhibitors of CYP3A

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, significantly increased ivacaftor exposure [measured as area under the curve (AUC)] by 8.5-fold. Based on simulations of these results, a reduction of the KALYDECO dose is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin, as follows: in patients 6 years and older reduce dose to one 150 mg tablet twice a week; in patients 2 to less than 6 years with body weight less than 14 kg, reduce dose to one 50 mg packet of granules twice a week; and in patients 2 to less than 6 years with body weight 14 kg or greater, reduce dose to one 75 mg packet of granules twice a week.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold. Therefore, a reduction of the KALYDECO dose is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin, as follows: in patients 6 years and older reduce dose to one 150 mg tablet once daily; in patients 2 to less than 6 years with body weight less than 14 kg, reduce dose to one 50 mg packet of granules once daily; and in patients 2 to less than 6 years with body weight 14 kg or greater, reduce dose to one 75 mg packet of granules once daily.

Co-administration of KALYDECO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor. Therefore, food containing grapefruit or Seville oranges should be avoided during treatment with KALYDECO [*see Clinical Pharmacology (12.3)*].

7.2 Inducers of CYP3A

Co-administration with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (AUC) by approximately 9-fold. Therefore, co-administration with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort is not recommended [*see Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

7.3 Ciprofloxacin

Co-administration of KALYDECO with ciprofloxacin had no effect on the exposure of ivacaftor. Therefore, no dose adjustment is necessary during concomitant administration of KALYDECO with ciprofloxacin [*see Clinical Pharmacology (12.3)*].

Potential for ivacaftor to affect other drugs

7.4 CYP3A and/or P-gp Substrates

Ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor. Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of KALYDECO may increase systemic exposure of drugs that are substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse events. Therefore, caution and appropriate monitoring are recommended when co-administering KALYDECO with sensitive CYP3A and/or P-gp substrates, such as digoxin, cyclosporine, and tacrolimus [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category B. There are no adequate and well-controlled studies of KALYDECO in pregnant women. Ivacaftor was not teratogenic in rats at approximately 6 times the maximum recommended human dose (MRHD) (based on summed AUCs for ivacaftor and its metabolites at a maternal dose of 200 mg/kg/day). Ivacaftor was not teratogenic in rabbits at approximately 12 times the MRHD (on an ivacaftor AUC basis at a maternal dose of 100 mg/kg/day, respectively). Placental transfer of ivacaftor was observed in pregnant rats and rabbits. Because animal reproduction studies are not always predictive of human response, KALYDECO should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Ivacaftor is excreted into the milk of lactating female rats. Excretion of ivacaftor into human milk is probable. There are no human studies that have investigated the effects of ivacaftor on breast-fed infants. Caution should be exercised when KALYDECO is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of KALYDECO in patients 6 to 17 years of age with CF who have a *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, or *S549R* mutation in the *CFTR* gene have been demonstrated [*see Adverse Reactions (6) and Clinical Studies (14)*].

The safety and efficacy of KALYDECO in patients 6 to 17 years of age with CF who have an *R117H* mutation in the *CFTR* gene have been demonstrated [see *Adverse Reactions (6) and Clinical Studies (14)*].

The efficacy of KALYDECO in children 2 to less than 6 years of age is 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 [see *Clinical Pharmacology (12.3)*].

The safety of KALYDECO in children 2 to less than 6 years of age (mean age 3 years) is derived from a 24-week, open-label, clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor granules twice daily (Trial 6). Eligible patients were those with the *G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N*, or *S549R* mutation in the *CFTR* gene. Of 34 patients enrolled, 32 had the *G551D* mutation and 2 had the *S549N* mutation. The type and frequency of adverse reactions in this trial were similar to those in patients 6 years and older. Transaminase elevations were more common in patients who

had abnormal transaminases at baseline. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

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.

8.5 Geriatric Use

CF is largely a disease of children and young adults. Clinical trials of KALYDECO did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of KALYDECO is recommended in patients with moderate hepatic impairment (Child-Pugh Class B), as follows: in patients 6 years and older, one 150 mg tablet once daily; in patients 2 to less than 6 years with body weight less than 14 kg, one 50 mg packet of granules once daily; and in patients 2 to less than 6 years with body weight 14 kg or greater, one 75 mg packet of granules once daily. Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a dose of one tablet or one packet of granules once daily or less frequently in patients with severe hepatic impairment after weighing the risks and benefits of treatment [*see Pharmacokinetics (12.3)*].

8.7 Renal Impairment

KALYDECO has not been studied in patients with mild, moderate, or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is necessary for patients with mild to moderate renal impairment; however, caution is recommended while using KALYDECO in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease.

8.8 Patients with CF who are Homozygous for the *F508del* Mutation in the *CFTR* Gene

Efficacy results from a double-blind, placebo-controlled trial in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene showed no statistically significant difference in forced expiratory volume exhaled in one second (FEV_1) over 16 weeks of KALYDECO treatment compared to placebo [*see Clinical Studies (14.4)*]. Therefore, KALYDECO should not be used in patients homozygous for the *F508del* mutation in the *CFTR* gene.

10 OVERDOSAGE

There have been no reports of overdose with KALYDECO.

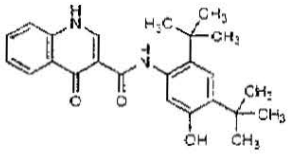
The highest single dose used in a clinical study was 800 mg in a solution formulation without any treatment-related adverse events.

The highest repeated dose was 450 mg (in a tablet formulation) every 12 hours for 4.5 days (9 doses) in a trial evaluating the effect of KALYDECO on ECGs in healthy subjects. Adverse events reported at a higher incidence compared to placebo included dizziness and diarrhea.

No specific antidote is available for overdose with KALYDECO. Treatment of overdose with KALYDECO consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

The active ingredient in KALYDECO tablets and oral granules is ivacaftor, a cystic fibrosis transmembrane conductance regulator potentiator, which has the following chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 microgram/mL).

KALYDECO is available as a light blue, capsule-shaped, film-coated tablet for oral administration containing 150 mg of ivacaftor. Each KALYDECO tablet contains 150 mg of ivacaftor and the following inactive ingredients colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

KALYDECO is also available as white to off-white granules for oral administration (sweetened but unflavored) and enclosed in a unit-dose packet containing 50 mg of ivacaftor or 75 mg of ivacaftor. Each unit-dose packet of KALYDECO oral granules contains 50 mg of ivacaftor or 75 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ivacaftor is a potentiator of the CFTR protein. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.

In vitro, ivacaftor increased CFTR-mediated transepithelial current (I_T) in rodent cells expressing the G551D-CFTR protein following addition of a cyclic adenosine monophosphate (cAMP) agonist with an EC_{50} of 100 ± 47 nM; however, ivacaftor did not increase I_T in the absence of cAMP agonist. Ivacaftor also increased I_T in human bronchial epithelial cells expressing G551D-CFTR protein following addition of a cAMP agonist by 10-fold with an EC_{50} of 236 ± 200 nM. Ivacaftor increased the open probability of G551D-CFTR protein in single channel patch clamp experiments using membrane patches from rodent cells expressing G551D-CFTR protein by 6-fold versus untreated cells after addition of PKA and ATP. In addition to G551D-CFTR, ivacaftor increased the channel-open probability of other mutant CFTR forms expressed in rodent cells, resulting in enhanced CFTR-mediated I_T. These mutant CFTR forms included G178R-, S549N-, S549R-, G551S-, G970R-, G1244E-,

S1251N-, S1255P-, and G1349D-CFTR. Ivacaftor also potentiated the channel-open probability of R117H-CFTR, which has low channel-open probability (gating) and reduced channel current amplitude (conductance) compared to normal CFTR. In vitro responses do not necessarily correspond to in vivo pharmacodynamic response or clinical benefit.

12.2 Pharmacodynamics

Sweat Chloride Evaluation

Changes in sweat chloride response to KALYDECO were evaluated in six clinical trials. In two randomized, double-blind, placebo-controlled clinical trials in patients with a *G551D* mutation in the *CFTR* gene, one in patients 12 and older (Trial 1) and the other in patients 6-11 years of age (Trial 2), the treatment difference (between KALYDECO and placebo) in mean change in sweat chloride from baseline through Week 24 was -48 mmol/L (95% CI -51, -45) and -54 mmol/L (95% CI -62, -47), respectively. These changes persisted through 48 weeks. In a 16-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial in patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene (Trial 3), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -3 mmol/L (95% CI -6, -0.2). In a two-part, randomized, double-blind, placebo-controlled, crossover clinical trial in patients with CF who had a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene (Trial 4), the treatment difference in mean change in sweat chloride from baseline through 8 weeks of treatment was -49 mmol/L (95% CI -57, -41). In Trial 4, mean changes in sweat chloride for the mutations for which KALYDECO is indicated ranged from -51 to -8, whereas the range for individual subjects with the *G970R* mutation was -1 to -11 mmol/L. In a randomized, double-blind, placebo-controlled clinical trial in patients with CF who had an *R117H* mutation in the *CFTR* gene (Trial 5), the mean baseline sweat chloride for all patients was 70 mmol/L. The treatment difference in mean change in sweat chloride from baseline through 24 weeks of treatment was -24 mmol/L (95% CI -28, -20) [*see Clinical Studies (14)*]. In an open-label clinical trial in 34 patients ages 2 to less than 6 years administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 6), the mean absolute change from baseline in sweat chloride through 24 weeks of treatment was -45 mmol/L (95% CI -53, -38) [*see Pediatric Use (8.4)*].

There was no direct correlation between decrease in sweat chloride levels and improvement in lung function (FEV_1).

ECG Evaluation

The effect of multiple doses of ivacaftor 150 mg and 450 mg twice daily on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 72 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern.

12.3 Pharmacokinetics

The pharmacokinetics of ivacaftor is similar between healthy adult volunteers and patients with CF.

After oral administration of a single 150 mg dose to healthy volunteers in a fed state, peak plasma concentrations (T_{max}) occurred at approximately 4 hours, and the mean (±SD) for AUC and C_{max} were 10600 (5260) ng*hr/mL and 768 (233) ng/mL, respectively.

After every 12-hour dosing, steady-state plasma concentrations of ivacaftor were reached by days 3 to 5, with an accumulation ratio ranging from 2.2 to 2.9.

Absorption

The exposure of ivacaftor increased approximately 2.5- to 4-fold when given with food that contains fat. Therefore, KALYDECO should be administered with fat-containing food. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. The median (range) T_{max} is approximately 4.0 (3.0, 6.0) hours in the fed state.

KALYDECO granules (2 x 75 mg) had similar bioavailability as the 150 mg tablet when given with fat-containing food in adult subjects. The effect of food on ivacaftor absorption is similar for KALYDECO granules and the 150 mg tablet formulation.

Distribution

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

After oral administration of 150 mg every 12 hours for 7 days to healthy volunteers in a fed state, the mean (±SD) for apparent volume of distribution was 353 (122) L.

Metabolism

Ivacaftor is extensively metabolized in humans. In vitro and clinical studies indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.

Elimination

Following oral administration, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose. The mean apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The CL/F (SD) for the 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.

Specific populations

Pediatric patients

The following conclusions about exposures between adults and the pediatric population are based on population PK analyses:

Pediatric patients 2 to less than 6 years of age who weigh less than 14 kg

Following oral administration of KALYDECO granules, 50 mg every 12 hours, the mean (±SD) steady state AUC (AUC_{ss}) was 10500 (4260) ng/mL*h and is similar to the mean AUC_{ss} of 10700 (4100) ng/mL*h in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 2 to less than 6 years of age who weigh 14 kg or greater

Following oral administration of KALYDECO granules, 75 mg every 12 hours, the mean (±SD) AUC (AUC_{ss}) was 11300 (3820) ng/mL*h and is similar to the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 6 to less than12 years of age

Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUC_{ss} was 20000 (8330) ng/mL*h and is 87% higher than the mean AUC in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Pediatric patients 12 to less than 18 years of age
Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (±SD) AUC_{∞} was 9240 (3420) ng/mL*h and is similar to the mean AUC_{∞} in adult patients administered KALYDECO tablets, 150 mg every 12 hours.

Hepatic impairment
Adult subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 -9) had similar ivacaftor C_{max}, but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Based on simulations of these results, a reduced KALYDECO dose to one tablet or packet of granules once daily is recommended for patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. The impact of severe hepatic impairment (Child-Pugh Class C, score 10-15) on the pharmacokinetics of ivacaftor has not been studied. The magnitude of increase in exposure in these patients is unknown, but is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of one tablet or one packet of granules given once daily or less frequently [*see Dosage and Administration (2.5)* and *Use in Specific Populations (8.6)*].

Renal impairment
KALYDECO has not been studied in patients with mild, moderate, or severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or in patients with end-stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients because of minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine in a human PK study); however, caution is recommended when administering KALYDECO to patients with severe renal impairment or end-stage renal disease.

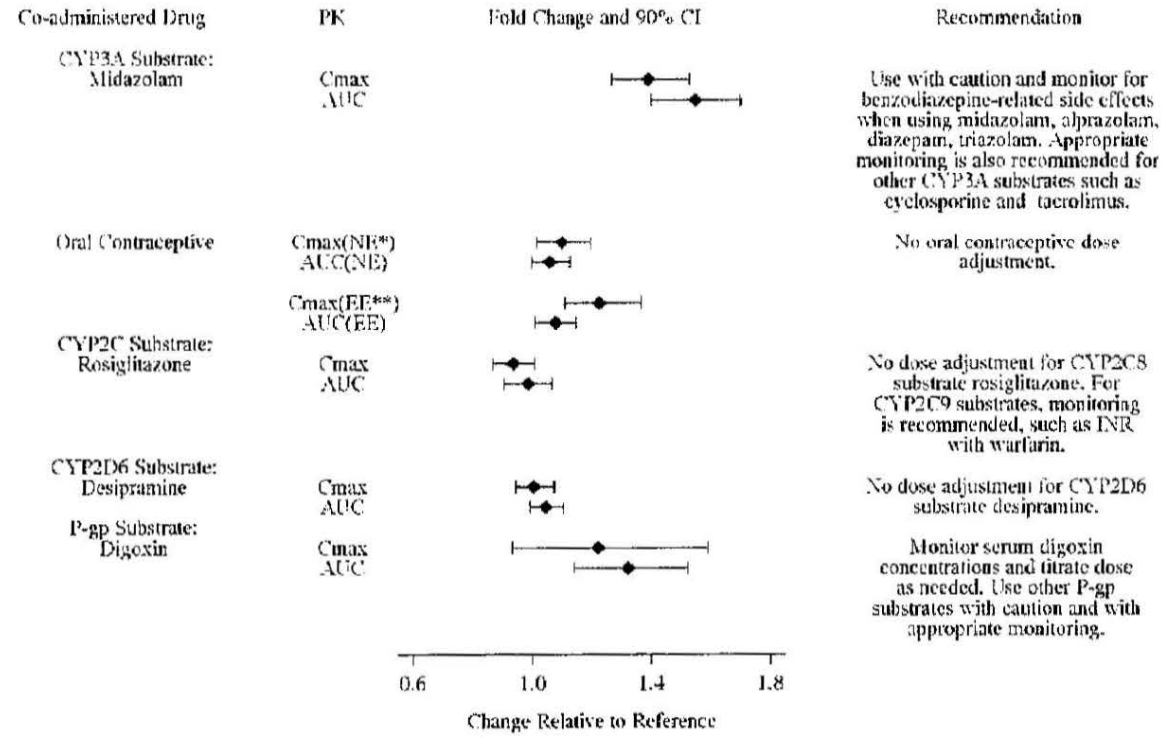
Gender
The effect of gender on KALYDECO pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of KALYDECO. No dose adjustments are necessary based on gender.

Drug Interactions
Drug interaction studies were performed with KALYDECO and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies [*see Drug Interactions (7)*].

Dosing recommendations based on clinical studies or potential drug interactions with KALYDECO are presented below.

Potential for Ivacaftor to Affect Other Drugs
Based on in vitro results, ivacaftor and metabolite M1 have the potential to inhibit CYP3A and P-gp. Clinical studies showed that KALYDECO is a weak inhibitor of CYP3A and P-gp, but not an inhibitor of CYP2C8. In vitro studies suggest that ivacaftor and M1 may inhibit CYP2C9. In vitro, ivacaftor, M1, and M6 were not inducers of CYP isozymes. Dosing recommendations for co-administered drugs with KALYDECO are shown in Figure 1.

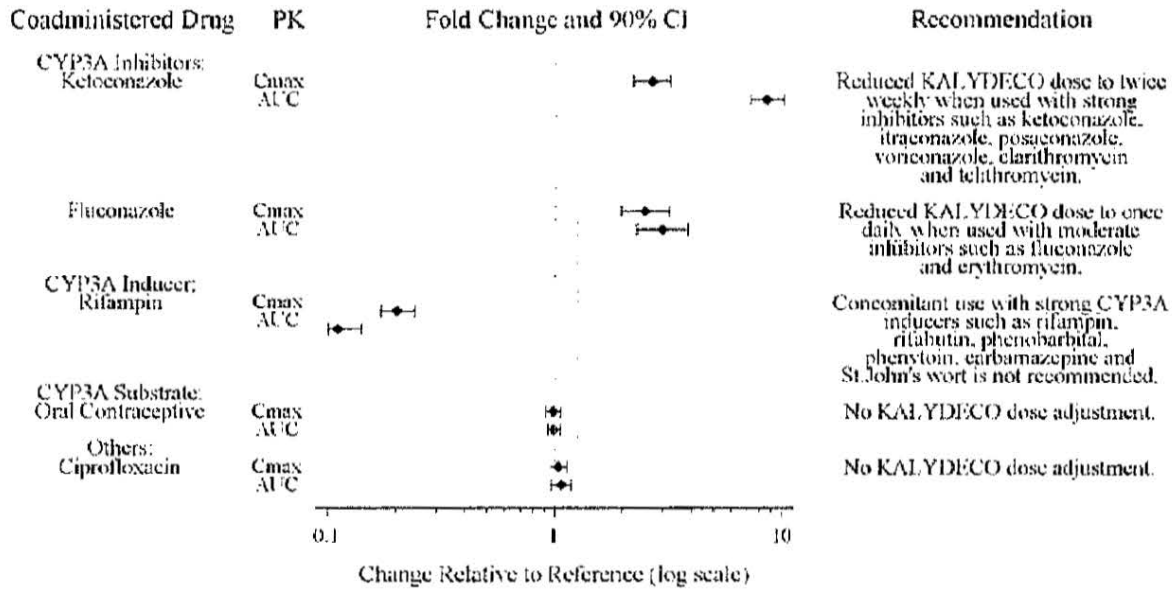
Figure 1: Impact of KALYDECO on Other Drugs



Note: The data obtained with substrates but without co-administration of KALYDECO are used as reference.
*NE: Norethindrone; **EE: Ethinyl Estradiol
The vertical lines are at 0.8, 1.0, and 1.25, respectively.

Potential for Other Drugs to Affect Ivacaftor
In vitro studies showed that ivacaftor and metabolite M1 were substrates of CYP3A enzymes (i.e., CYP3A4 and CYP3A5). Exposure to ivacaftor is reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors [*see Dosage and Administration (2.6) and Drug Interactions (7)*]. KALYDECO dosing recommendations for co-administration with other drugs are shown in Figure 2.

Figure 2: Impact of Other Drugs on KALYDECO



Note: The data obtained for KALYDECO without co-administration of inducers or inhibitors are used as reference. The vertical lines are at 0.8, 1.0 and 1.25, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year studies were conducted in mice and rats to assess carcinogenic potential of KALYDECO. No evidence of tumorigenicity was observed in mice or rats at ivacaftor oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 3 to 5 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 5 and 6 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 6 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 3 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

13.2 Animal Toxicology and/or Pharmacology

Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal day 7-35 at dose levels of 10 mg/kg/day and higher (approximately 0.12 times the MRHD based on summed AUCs of ivacaftor and its metabolites). This finding has not been observed in older animals.

14 CLINICAL STUDIES

14.1 Trials in Patients with CF who have a *G551D* Mutation in the *CFTR* Gene

Dose Ranging:

Dose ranging for the clinical program consisted primarily of one double-blind, placebo-controlled, crossover trial in 39 adult (mean age 31 years) Caucasian patients with CF who had FEV_1 ≥40% predicted. Twenty patients with median predicted FEV_1 at baseline of 56% (range: 42% to 109%) received KALYDECO 25, 75, 150 mg or placebo every 12 hours for 14 days and 19 patients with median predicted FEV_1 at baseline of 69% (range: 40% to 122%) received KALYDECO 150, 250 mg or placebo every 12 hours for 28 days. The selection of the 150 mg every 12 hours dose was primarily based on nominal improvements in lung function (pre-dose FEV_1) and changes in pharmacodynamic parameters (sweat chloride and nasal potential difference). The twice-daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours.

Efficacy:

The efficacy of KALYDECO in patients with CF who have a *G551D* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF (109 receiving KALYDECO 150 mg twice daily). All eligible patients from these trials were rolled over into an open-label extension study.

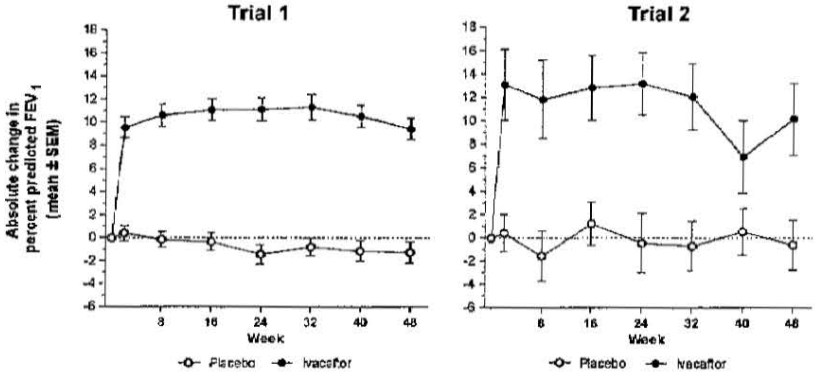
Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with FEV_1 at screening between 40-90% predicted [mean FEV_1 64% predicted at baseline (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with FEV_1 at screening between 40-105% predicted [mean FEV_1 84% predicted at baseline (range: 44% to 134%)]. 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.

Patients in both trials were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV_1 through 24 weeks of treatment.

In both studies, treatment with KALYDECO resulted in a significant improvement in FEV_1. The treatment difference between KALYDECO and placebo for the mean absolute change in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points ($P < 0.0001$) in Trial 1 and 12.5 percentage points ($P < 0.0001$) in Trial 2 (Figure 3). These changes persisted through 48 weeks. Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, and geographic region.

Figure 3: Mean Absolute Change from Baseline in Percent Predicted FEV_1 *



*Primary endpoint was assessed at the 24-week time point.

Other efficacy variables included absolute change from baseline in sweat chloride [*see Clinical Pharmacology (12.2)*], time to first pulmonary exacerbation (Trial 1 only), absolute change from baseline in weight, and improvement from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing. For the purpose of the study, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with KALYDECO demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight (Table 3). Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, were consistent with absolute change from baseline in weight.

Table 3: Effect of KALYDECO on Other Efficacy Endpoints in Trials 1 and 2

	Trial 1		Trial 2	
Endpoint	**Treatment difference[a] (95% CI)**	***P* value**	**Treatment difference[a] (95% CI)**	***P* value**
Mean absolute change from baseline in CFQ-R respiratory domain score (points)				
Through Week 24	8.1 (4.7, 11.4)	<0.0001	6.1 (-1.4, 13.5)	0.1092
Through Week 48	8.6 (5.3, 11.9)	<0.0001	5.1 (-1.6, 11.8)	0.1354
Relative risk of pulmonary exacerbation				
Through Week 24	0.40[b]	0.0016	NA	NA
Through Week 48	0.46[b]	0.0012	NA	NA
Mean absolute change from baseline in body weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002
Absolute change in sweat chloride (mmol/L)				
Through Week 24	-48 (-51, -45)	<0.0001	-54 (-62, -47)	<0.0001
Through Week 48	-48 (-51, -45)	<0.0001	-53 (-61, -46)	<0.0001

CI: confidence interval; NA: not analyzed due to low incidence of events
[a] Treatment difference = effect of KALYDECO – effect of Placebo
[b] Hazard ratio for time to first pulmonary exacerbation

14.2 Trial in Patients with a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* Mutation in the *CFTR* Gene

The efficacy and safety of KALYDECO in patients with CF who have a *G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N,* or *S549R* mutation in the *CFTR* gene were evaluated in a two-part, randomized, double-blind, placebo-controlled, crossover design clinical trial in 39 patients with CF (Trial 4). Patients who completed Part 1 of this trial continued into the 16-week open-label Part 2 of the study. The mutations studied were *G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P,* and *G1349D*. See *Clinical Studies (14.1)* for efficacy in patients with a *G551D* mutation.

Patients were 6 years of age or older (mean age 23 years) with FEV_1 ≥40% at screening [mean FEV_1 at baseline 78% predicted (range: 43% to 119%)]. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa,* or *Mycobacterium abscessus* 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 at screening were excluded.

Patients were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 8 weeks in addition to their prescribed CF therapies during the first treatment period and crossed over to the other treatment for the second 8 weeks. The two 8-week treatment periods were separated by a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 8 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride through 8 weeks of treatment [*see Clinical Pharmacology (12.2)*], absolute change from baseline in body mass index (BMI) at 8 weeks of treatment (including body weight at 8 weeks), and improvement in CFQ-R respiratory domain score through 8 weeks of treatment. For the overall population of the 9 mutations studied, treatment with KALYDECO compared to placebo resulted in significant improvement in percent predicted FEV_1 [10.7 through Week 8 ($P<0.0001$)], BMI [0.66 kg/m^2 at Week 8 ($P<0.0001$)], and CFQ-R respiratory domain score [9.6 through Week 8 ($P=0.0004$)]; however, there was a high degree of variability of efficacy responses among the 9 mutations (Table 4). Based on clinical and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established [*see Clinical Pharmacology (12.2)*].

Table 4: Effect of KALYDECO for Efficacy Variables in the Overall Populations and for Specific *CFTR* Mutations

Mutation (n)	Absolute change in percent predicted FEV_1			BMI (kg/m^2)	CFQ-R Respiratory Domain Score (Points)	Absolute Change in Sweat Chloride (mmol/L)
	At Week 2	At Week 4	At Week 8	At Week 8	At Week 8	At Week 8
All patients (n=39) Results shown as mean (95% CI) change from baseline KALYDECO vs. placebo-treated patients:						
	8.3 (4.5, 12.1)	10.0 (6.2, 13.8)	13.8 (9.9, 17.6)	0.66† (0.34, 0.99)	12.8 (6.7, 18.9)	-50 (-58, -41)*
Patients grouped under mutation types (n) Results shown as mean (minimum, maximum) for change from baseline for KALYDECO-treated patients**:						
G1244E (5)	11 (-5, 25)	6 (-5, 13)	8 (-1, 18)	0.63 (0.34, 1.32)	3.3 (-27.8, 22.2)	-55 (-75, -34)
G1349D (2)	19 (5, 33)	18 (2, 35)	20 (3, 36)	1.15 (1.07, 1.22)	16.7 (-11.1, 44.4)	-80 (-82, -79)
G178R (5)	7 (1, 17)	10 (-2, 21)	8 (-1, 18)	0.85 (0.33, 1.46)	20.0 (5.6, 50.0)	-53 (-65, -35)
G551S (2)	0 (-5, 5)	0.3 (-5, 6)	3††	0.16††	16.7††	-68††
G970R (4)	7 (1, 13)	7 (1, 14)	3 (-1, 5)	0.48 (-0.38, 1.75)	1.4 (-16.7, 16.7)	-6 (-16, -2)
S1251N (8)	2 (-23, 20)	8 (-13, 26)	9 (-20, 21)	0.73 (0.08, 1.83)	23.3 (5.6, 50.0)	-54 (-84, -7)
S1255P (2)	11 (8, 14)	9 (5, 13)	3 (-1, 8)	1.62 (1.39, 1.84)	8.3 (5.6, 11.1)	-78 (-82, -74)
S549N (6)	11 (5, 16)	8 (-9, 19)	11 (-2, 20)	0.79 (0.00, 1.91)	8.8 (-8.3, 27.8)	-74 (-93, -53)
S549R (4)	3 (-4, 8)	4 (-4, 10)	5 (-3, 13)	0.53 (0.33, 0.80)	6.9 (0.0, 11.1)	-61††† (-71, -54)

* n=36 for the analysis of absolute change in sweat chloride.
** Statistical testing was not performed due to small numbers for individual mutations.
† Result for weight gain as a component of body mass index was consistent with BMI.
†† Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point.
††† n=3 for the analysis of absolute change in sweat chloride.

14.3 Trial in Patients with CF who have an *R117H* Mutation in the *CFTR* Gene

The efficacy and safety of KALYDECO in patients with CF who have an *R117H* mutation in the *CFTR* gene were evaluated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial (Trial 5). Fifty-nine of 69 patients completed 24 weeks of treatment. Two patients discontinued and 8 patients did not complete treatment due to study termination. Trial 5 evaluated 69 clinically stable patients with CF who were 6 years of age or older (mean age 31 years). Patients who were 12 years and older had FEV_1 at screening between 40-90% predicted, and patients who were 6-11 years of age had FEV_1 at screening between 40-105% predicted. The overall mean FEV_1 was 73% predicted at baseline (range: 33% to 106%). The patients had well preserved BMIs (mean overall: 23.76 kg/m^2) and a high proportion were pancreatic sufficient as assessed by a low rate of pancreatic enzyme replacement therapy use (pancreatin: 11.6%; pancrelipase: 5.8%). 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 ULN, were excluded.

Patients were randomized 1:1 to receive either 150 mg of KALYDECO (n=34) or placebo (n=35) every 12 hours with food containing fat for 24 weeks in addition to their prescribed CF therapies.

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment. The treatment difference for absolute change in percent predicted FEV_1 through Week 24 was 2.1 percentage points (analysis conducted with the full analysis set which included all 69 patients), and did not reach statistical significance (Table 5).

Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 24, improvement in cystic fibrosis respiratory symptoms through Week 24 as assessed by the CFQ-R respiratory domain score (Table 5), absolute change in body mass index (BMI) at Week 24, and time to first pulmonary exacerbation. The overall treatment difference for the absolute change from baseline in BMI at Week 24 was 0.3 kg/m^2 and the calculated hazard ratio for time to first pulmonary exacerbation was 0.93, which were not statistically significant.

Statistically significant improvements in clinical efficacy (FEV_1, CFQ-R respiratory domain) were seen in several subgroup analyses, and decreases in sweat chloride were observed in all subgroups. Subgroups analyzed included those based on age, lung function, and poly-T status (Table 5).

Table 5: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) and in Relevant Subgroups Through 24 Weeks

		Absolute Change through Week 24*- All Randomized Patients								
		% Predicted FEV_1 (Percentage Points)			CFQ-R Respiratory Domain Score (Points)			Sweat Chloride (mmol/L)		
Subgroup Parameter	Study Drug	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)	n	Mean	Treatment Difference (95% CI)
R117H–All Patients										
	Placebo	35	0.5	2.1	34	-0.8	8.4	35	-2.3	-24.0
	Kalydeco	34	2.6	(-1.1, 5.4)	33	7.6	(2.2, 14.6)	32	-26.3	(-28.0, -19.9)
Subgroup by Age										
6-11	Placebo	8	3.5	-6.3	7	-1.6	-6.1	8	1.0	-27.6
	Kalydeco	9	-2.8	(-12.0, -0.7)	8	-7.7	(-15.7, 3.4)	8	-26.6	(-37.2, -18.1)
12-17	Placebo	1			1			1		
	Kalydeco	1	---	---	1	---	---	1	---	---
≥18	Placebo	26	-0.5	5.0	26	-0.5	12.6	26	-4.0	-21.9
	Kalydeco	24	4.5	(1.1, 8.8)	24	12.2	(5.0, 20.3)	23	-25.9	(-26.5, -17.3)
Subgroup by Poly-T Status†										
5T	Placebo	24	0.7	5.3	24	-0.6	15.3	24	-4.6	-24.2
	Kalydeco	14	6.0	(1.3, 9.3)	14	14.7	(7.7, 23.0)	13	-28.7	(-30.2, -18.2)
7T	Placebo	5	-0.9	0.2	5	-6.0	5.2	5	3.9	-24.1
	Kalydeco	11	-0.7	(-8.1, 8.5)	11	-0.7	(-13.0, 23.4)	10	-20.2	(-33.9, -14.3)
Subgroup by Baseline FEV_1 % Predicted										
<70%	Placebo	15	0.4	4.0	15	3.0	11.4	15	-3.8	-25.5
	Kalydeco	13	4.5	(-2.1, 10.1)	13	14.4	(1.2, 21.6)	12	-29.3	(-31.8, -19.3)
70-90%	Placebo	14	0.2	2.6	13	-3.6	8.8	14	-3.1	-20.0
	Kalydeco	14	2.8	(-2.3, 7.5)	14	5.2	(-2.6, 20.2)	14	-23.0	(-26.9, -12.9)
>90%	Placebo	6	2.2	-4.3	6	-2.5	-0.7	6	1.0	-26.8
	Kalydeco	7	-2.1	(-9.9, 1.3)	6	-3.2	(-10.4, 9.0)	6	-25.9	(-39.5, -14.1)

* MMRM analysis with fixed effects for treatment, age, week, baseline value, treatment by week, and subject as a random effect
† (n=54) Poly-T status confirmed by genotyping

14.4 Trial in Patients Homozygous for the *F508del* Mutation in the *CFTR* Gene

Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who had FEV_1 ≥40% predicted. Patients were randomized 4:1 to receive KALYDECO 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 FEV_1 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 FEV_1. Treatment with KALYDECO resulted in no improvement in FEV_1 relative to placebo in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene [mean absolute change from baseline through Week 16 in percent predicted FEV_1 was 1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively (P=0.15)]. There were no meaningful differences between patients treated with KALYDECO compared to placebo for secondary endpoints (change in CF symptoms, change in weight, or change in sweat chloride concentration [*see Pharmacodynamics (12.2)*]).

16 HOW SUPPLIED/STORAGE AND HANDLING

KALYDECO (ivacaftor) tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" on one side and plain on the other, and is packaged as follows:

56-count carton (contains 4 individual blister cards of 14 tablets per card)	**NDC** 51167-200-01
60-count bottle	**NDC** 51167-200-02

KALYDECO (ivacaftor) oral granules are supplied as small, white to off-white granules and enclosed in unit-dose packets as follows:

56-count carton (contains 56 unit-dose packets of 50 mg ivacaftor per packet)	**NDC** 51167-300-01
56-count carton (contains 56 unit-dose packets of 75 mg ivacaftor per packet)	**NDC** 51167-400-01

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Transaminase (ALT or AST) Elevations and Monitoring

Inform patients that elevation in liver tests have occurred in patients treated with KALYDECO. Liver function tests will be performed prior to initiating KALYDECO, every 3 months during the first year of treatment and annually thereafter. More frequent monitoring of liver function tests should be considered in patients with a history of transaminase elevations [*see Warnings and Precautions (5.1)*].

Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the therapeutic effectiveness of KALYDECO. Reduction of the dose of KALYDECO to one tablet or one packet of granules twice a week is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Dose reduction to one tablet or one packet of granules once daily is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Food containing grapefruit or Seville oranges should be avoided [*see Drug Interactions (7.1, 7.2) and Clinical Pharmacology (12.3)*].

Use in Patients with Hepatic Impairment

Inquire and/or assess whether patients have liver impairment. Reduce the dose of KALYDECO in patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) to one tablet or one packet of granules once daily. KALYDECO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15); however, exposure is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of one tablet or one packet of granules given once daily or less frequently. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6) [*see Use in Specific Populations (8.6)*].

Administration

KALYDECO® (ivacaftor) tablets 150 mg

Inform patients that KALYDECO is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt),etc.

KALYDECO® (ivacaftor) oral granules 50 mg or 75 mg

Inform patients and caregivers that KALYDECO oral granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed to ensure delivery of the entire dose. Food or liquid should be at or below room temperature. Once mixed, the product has been shown to be stable for one hour, and therefore should be consumed during this period. Some examples of appropriate soft foods or liquids may include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice.

Inform patients and caregivers that KALYDECO is best absorbed by the body when taken with food that contains fat; therefore, KALYDECO oral granules should be taken just before or just after consuming food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc.

Patients should be informed about what to do in the event they miss a dose of KALYDECO:

- In case a dose of KALYDECO is missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of KALYDECO with fat-containing food as soon as possible.
- If more than 6 hours have passed since KALYDECO is usually taken, the missed dose should NOT be taken and the patient should resume the usual dosing schedule.
- Patients should be advised to contact their health care provider if they have questions.

Cataracts

Inform patients that abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. Baseline and follow-up ophthalmological examinations should be performed in pediatric patients initiating KALYDECO treatment [*see Warnings and Precautions (5.3)*].

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

69264-07
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Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION

KALYDECO (kuh-LYE-deh-koh)
(ivacaftor)
Film-Coated Tablets and Oral Granules

Read this Patient Information before you start taking KALYDECO and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in their CF gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, or *S549R*.

KALYDECO is used for the treatment of CF in patients age 2 years and older who have an *R117H* mutation in their CF gene.

KALYDECO is not for use in people with CF due to other mutations in the CF gene. KALYDECO is not effective in CF patients with two copies of the *F508del* mutation (*F508del/F508del*) in the CF gene.

It is not known if KALYDECO is safe and effective in children under 2 years of age.

Who should not take KALYDECO?

Do not take KALYDECO if you take certain medicines or herbal supplements such as:

- the antibiotics rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medications such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, Equetro®) or phenytoin (Dilantin®, Phenytek®)
- St. John's wort

Talk to your doctor before taking KALYDECO if you take any of the medicines or supplements listed above.

What should I tell my doctor before taking KALYDECO?

Before you take KALYDECO, tell your doctor if you:

- have liver or kidney problems
- drink grapefruit juice, or eat grapefruit or Seville oranges
- are pregnant or plan to become pregnant. It is not known if KALYDECO will harm your unborn baby. You and your doctor should decide if you will take KALYDECO while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if KALYDECO passes into your breast milk. You and your doctor should decide if you will take KALYDECO while you are breastfeeding.

KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements, as the dose of KALYDECO may need to be adjusted when taken with certain medications.

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Especially tell your doctor if you take:

- antifungal medications such as ketoconazole (e.g., Nizoral®), itraconazole (e.g., Sporanox®), posaconazole (e.g., Noxafil®), voriconazole (e.g., Vfend®), or fluconazole (e.g., Diflucan®)
- antibiotics such as telithromycin (e.g., Ketek®), clarithromycin (e.g., Biaxin®), or erythromycin (e.g., Ery-Tab®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take KALYDECO?

- Take KALYDECO exactly as your doctor tells you to take it.
- Take your doses of KALYDECO 12 hours apart.
- If you miss a dose of KALYDECO and it is **within 6 hours** of when you usually take it, take your dose of KALYDECO as prescribed with fat-containing food as soon as possible.
- If you miss a dose of KALYDECO and it is **more than 6 hours** after the time you usually take it, **skip that dose only** and take the next dose when you usually take it. Do **not** take 2 doses at the same time to make up for your missed dose.

KALYDECO Tablets (ages 6 years and older):

- Always take KALYDECO Tablets with food that contains fat. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, and whole-milk dairy products such as whole milk, cheese, and yogurt.
- Each KALYDECO box contains 4 individual blister cards.
- Each blister card contains 14 pills—7 morning doses and 7 evening doses.
- In the morning, unpeel the paper backing from a blister card to remove 1 KALYDECO tablet and take it with food that contains fat.
- In the evening, 12 hours later, open another blister card to remove 1 KALYDECO tablet and take it with food that contains fat.
- You may cut along the dotted line to separate your doses from the blister card.

KALYDECO Oral Granules (ages 2 to under 6 years old):

- Hold the packet with cut line on top.
- Shake the packet gently to settle the KALYDECO granules.
- Tear or cut packet open along cut line.
- Carefully pour all of the KALYDECO granules in the packet into 1 teaspoon of soft food or liquid. Food or liquid should be at or below room temperature. Some examples of soft foods or liquids include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice.
- Mix the KALYDECO granules with food or liquid.
- After mixing, give KALYDECO within 1 hour. Make sure all medicine is taken.
- Give a child fat-containing food just before or just after the KALYDECO granules dose. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, and whole-milk dairy products such as whole milk, cheese, and yogurt.

What should I avoid while taking KALYDECO?

- KALYDECO can cause dizziness in some people who take it. Do not drive a car, use machinery or do anything that needs you to be alert until you know how KALYDECO affects you.
- You should avoid food containing grapefruit or Seville oranges while you are taking KALYDECO.

What are the possible side effects of KALYDECO?

KALYDECO can cause serious side effects.

High liver enzymes in the blood have been reported in patients receiving KALYDECO. Your doctor will do blood tests to check your liver:

- before you start KALYDECO

- every 3 months during your first year of taking KALYDECO
- every year while you are taking KALYDECO

For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often.

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO.

Your doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts.

The most common side effects of KALYDECO include:

- headache
- upper respiratory tract infection (common cold), including:
  - sore throat
  - nasal or sinus congestion
  - runny nose
- stomach (abdominal) pain
- diarrhea
- rash
- nausea
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of KALYDECO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KALYDECO?

- Store KALYDECO at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not use KALYDECO after the expiration date on the package.

Keep KALYDECO and all medicines out of the reach of children.

General information about the safe and effective use of KALYDECO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KALYDECO for a condition for which it was not prescribed. Do not give KALYDECO to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about KALYDECO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALYDECO that is written for health professionals.

For more information, go to www.kalydeco.com or call 1-877-752-5933.

What are the ingredients in KALYDECO?

Active ingredient: ivacaftor
Inactive ingredients:
KALYDECO Tablets: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

The tablet film coat contains: carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide.

The printing ink contains: ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

KALYDECO Oral Granules are white to off-white granules for oral administration (sweetened but unflavored) and contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

VERTEX
Manufactured for:
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

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