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
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------
KALYDECO is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* 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 *G551D* mutation. (1)

Limitations of Use:
- Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene. (1, 14)
- KALYDECO has not been studied in other populations of patients with CF. (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, 12.3)
- Reduce dose in patients with moderate and severe hepatic impairment. (8.6, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (7.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 150 mg (3)

----------CONTRAINDICATIONS----------
- None known

----------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. 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)

----------ADVERSE REACTIONS----------
The most common adverse drug reactions to KALYDECO (occurring ≥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 150 mg twice-a-week when co-administered with strong CYP3A inhibitors (e.g., ketoconazole). Reduce KALYDECO dose to 150 mg 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 1-877-752-5933 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

Revised: [August/2012]

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 classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* 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 *G551D* mutation.

Limitations of Use

KALYDECO is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene and has not been studied in other populations of patients with CF.

2 DOSAGE AND ADMINISTRATION

2.1 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. Examples of appropriate fat-containing food include eggs, butter, peanut butter, cheese pizza, etc. [see *Clinical Pharmacology (12.3)* and *Patient Counseling Information (17.4)*].

2.2 Dosage Adjustment for Patients with Hepatic Impairment

The dose of KALYDECO should be reduced to 150 mg 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 150 mg once daily or less frequently [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*, and *Patient Counseling Information (17.3)*].

2.3 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 150 mg twice-a-week. The dose of KALYDECO should be reduced to 150 mg once daily when co-administered with moderate CYP3A inhibitors (e.g., fluconazole). Food containing grapefruit or Seville oranges should be avoided [see *Drug Interactions (7.1)*, *Clinical Pharmacology (12.3)*, and *Patient Counseling Information (17.2)*].

3 DOSAGE FORMS AND STRENGTHS

150 mg tablets.

4 CONTRAINDICATIONS

None known.

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. 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)*].

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)*].

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 placebo-controlled clinical trials conducted in 353 patients with CF who had a *G551D* mutation in the *CFTR* gene or were homozygous for the *F508del* mutation. Of the 353 patients, 50% of patients were female and 97% were Caucasian; 221 received KALYDECO and 132 received placebo from 16 to 48 weeks. Patients treated with KALYDECO were between the ages of 6 and 53 years.

In these trials, 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, which occurred more frequently in KALYDECO-treated patients included abdominal pain, increased hepatic enzymes, and hypoglycemia.

Overall, the most common adverse reactions in 221 patients with CF who had either a *G551D* mutation or were homozygous for the *F508del* mutation in the CFTR and 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 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 1 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 1: 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 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

Laboratory Abnormalities
Transaminase Elevations: During 48-week, placebo-controlled clinical studies, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 2%, 3% 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 >8x ULN. Two patients treated with KALYDECO were reported to have serious adverse reactions of elevated liver transaminases compared to none on placebo [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. Therefore, a reduction of the KALYDECO dose to 150 mg twice-a-week is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold. Therefore, a reduction of the KALYDECO dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

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)*].

Potential for ivacaftor to affect other drugs

7.3 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. Administration of KALYDECO may increase systemic exposure of drugs which are substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse events. Therefore, caution is recommended when co-administering KALYDECO with 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* mutation in the *CFTR* gene has been demonstrated in 2 placebo-controlled clinical trials. Trial 1 evaluated 161 patients with CF who were 12 years of age or older and Trial 2 evaluated 52 patients with CF who were 6 to 11 years of age [see *Clinical Studies (14.1)*].

The safety and efficacy of KALYDECO in patients with CF younger than age 6 years have not been established.

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 150 mg once daily is recommended in 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 dose of 150 mg once daily or less frequently in patients with severe hepatic impairment after weighing the risks and benefit 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 (14.2)*]. 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.

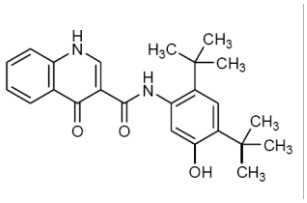
The highest single dose used in a clinical study was 800 mg in a solution formulation without any treatment-related adverse events.

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 is ivacaftor 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 tablet contains the 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.

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 G551D-CFTR protein.

In vitro, ivacaftor increased CFTR-mediated transepithelial current (I_T) in rodent cells expressing 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.

12.2 Pharmacodynamics

Sweat Chloride Evaluation

In clinical trials in patients with the *G551D* mutation in the *CFTR* gene, KALYDECO led to statistically significant reductions in sweat chloride concentration. In two randomized, double-blind, placebo-controlled clinical trials (one in patients 12 and older and the other in patients 6-11 years of age), the 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. 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- to 4-fold when given with food containing fat. Therefore, KALYDECO should be administered with fat-containing food. Examples of fat-containing foods include eggs, butter, peanut butter, and cheese pizza. The median (range) t_{max} is approximately 4.0 (3.0; 6.0) hours in the fed state.

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.

The mean apparent volume of distribution (Vz/F) of ivacaftor after a single dose of 275 mg of KALYDECO in the fed state was similar for healthy subjects and patients with CF. 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.

Special populations

Hepatic impairment

Patients with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max}, but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Therefore, a reduced KALYDECO dose of 150 mg once daily is recommended for patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A) on 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 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 150 mg given once daily or less frequently.

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.

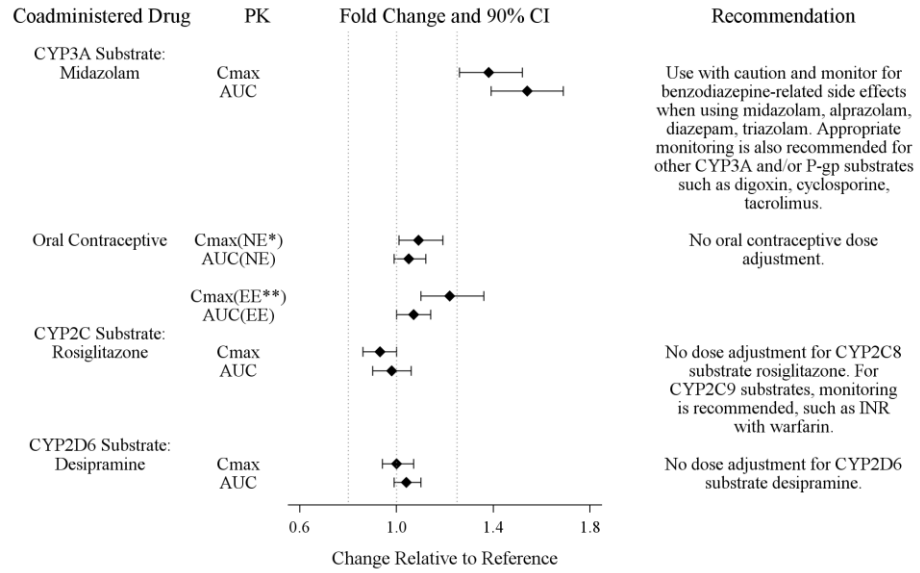
Gender
The effect of gender on KALYDECO pharmacokinetics was evaluated using population pharmacokinetics of data from clinical studies of KALYDECO. No dose adjustments are necessary based on gender.

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
In vitro studies showed that ivacaftor is a weak inhibitor of CYP3A and has potential to inhibit P-gp at therapeutic concentrations, and may also inhibit the CYP2C8 and CYP2C9 isozymes. Metabolite M1, but not M6, also has potential to inhibit CYP3A and P-gp. Ivacaftor, M1, and M6 were not inducers of CYP isozymes. Dosing recommendations for co-administered drugs following administration with KALYDECO are shown in Figure 1.

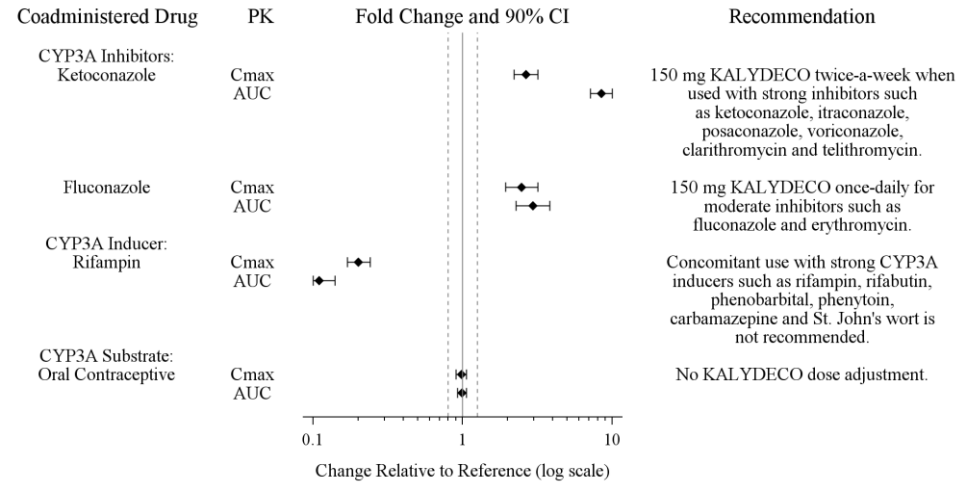
Figure 1: Impact of KALYDECO on Other Drugs



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). KALYDECO dosing recommendations for co-administration with CYP3A inhibitors or inducers 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, and 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 and 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, cross-over trial in 39 adult (mean age 31 years) Caucasian patients with CF who had $FEV_1 \geq 40\%$ 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. Selection of the 150 mg dose of KALYDECO for children 6 to 11 years of age was based on achievement of comparable pharmacokinetics as those observed for adult patients.

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.

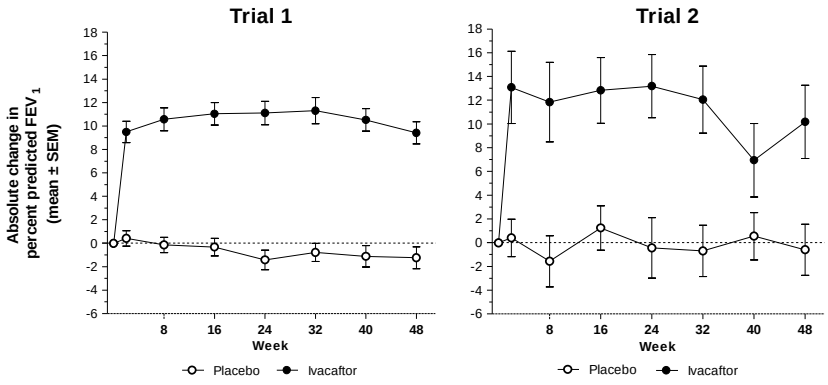
Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with baseline FEV_1 between 40-90% predicted [mean FEV_1 64% predicted (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with baseline FEV_1 between 40-105% predicted [mean FEV_1 84% predicted (range: 44% to 134%)]. Patients who had persistent *Burkholderia cenocepacia*, *dolosa*, or *Mycobacterium abcessus* 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 in sweat chloride from baseline to week 24 [discussed in *Clinical Pharmacology (12.2)*], time to first pulmonary exacerbation through week 48 (Trial 1 only), absolute change in weight from baseline to week 48, and improvement in cystic fibrosis symptoms including relevant respiratory symptoms 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 2). Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, was consistent with absolute change from baseline in weight.

Table 2: 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 CF symptom 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

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 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 twelve 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, dolosa*, or *Mycobacterium abcessus* 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

KALYDECO™ (ivacaftor) is 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

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

17 PATIENT COUNSELING INFORMATION

17.1 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 [see *Warnings and Precautions (5.1)*].

17.2 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 150 mg twice-a-week is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Dose reduction to 150 mg 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)*].

17.3 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 to 9) to 150 mg 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 150 mg 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 *Clinical Pharmacology (12.3)*].

17.4 Take with Fat-containing Food

Inform your patients that KALYDECO is best absorbed by the body when taken with fatty food. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, etc.

Manufactured for
Vertex Pharmaceuticals Incorporated
Cambridge, MA 02139

69264-01
Revised August 2012

Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION

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

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 6 years and older who have a certain mutation in their CF gene called the *G551D* mutation.

KALYDECO is not for use in people with CF due to other mutations in the CF gene. It 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 6 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.
- Always take KALYDECO with fatty food. Examples of fat-containing food include eggs, butter, peanut butter, cheese pizza, etc.

Your doses of KALYDECO should be taken 12 hours apart.

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

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

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 68ºF to 77ºF (20ºC to 25ºC).
- 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 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: 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.

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

VERTEX
Manufactured for:
Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139

Approved August 2012

69264-01