

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

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KALYDECO® (ivacaftor) Tablets and Granules

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)*].

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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

Adverse Reaction (Preferred Term)	Incidence: Pooled 48-Week Trials	
	KALYDECO	Placebo
	N=109 n (%)	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).

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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

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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 (FEV₁) 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.

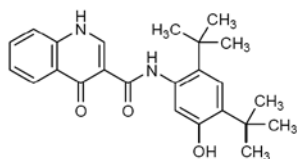
The highest single dose used in a clinical study was 800 mg in a solution formulation without any treatment-related adverse events.

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 C₂₄H₂₈N₂O₃ 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_{Cl}) in rodent cells expressing the G551D-CFTR protein following addition of a cyclic adenosine monophosphate (cAMP) agonist with an EC₅₀ of 100 ± 47 nM; however, ivacaftor did not increase I_{Cl} in the absence of cAMP agonist. Ivacaftor also increased I_{Cl} in human bronchial epithelial cells expressing G551D-CFTR protein following addition of a cAMP agonist by 10-fold with an EC₅₀ 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_{Cl}. These mutant CFTR forms included G178R-, S549N-, S549R-, G551S-, G970R-, G1244E-,

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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 (FEV₁).

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 than 12 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.

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Pediatric patients 12 to less than 18 years of age

Following oral administration of KALYDECO tablets, 150 mg every 12 hours, the mean (\pm SD) AUC_{0-∞} was 9240 (3420) ng/mL*h and is similar to the mean AUC_{0-∞} 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-∞} 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-∞} 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

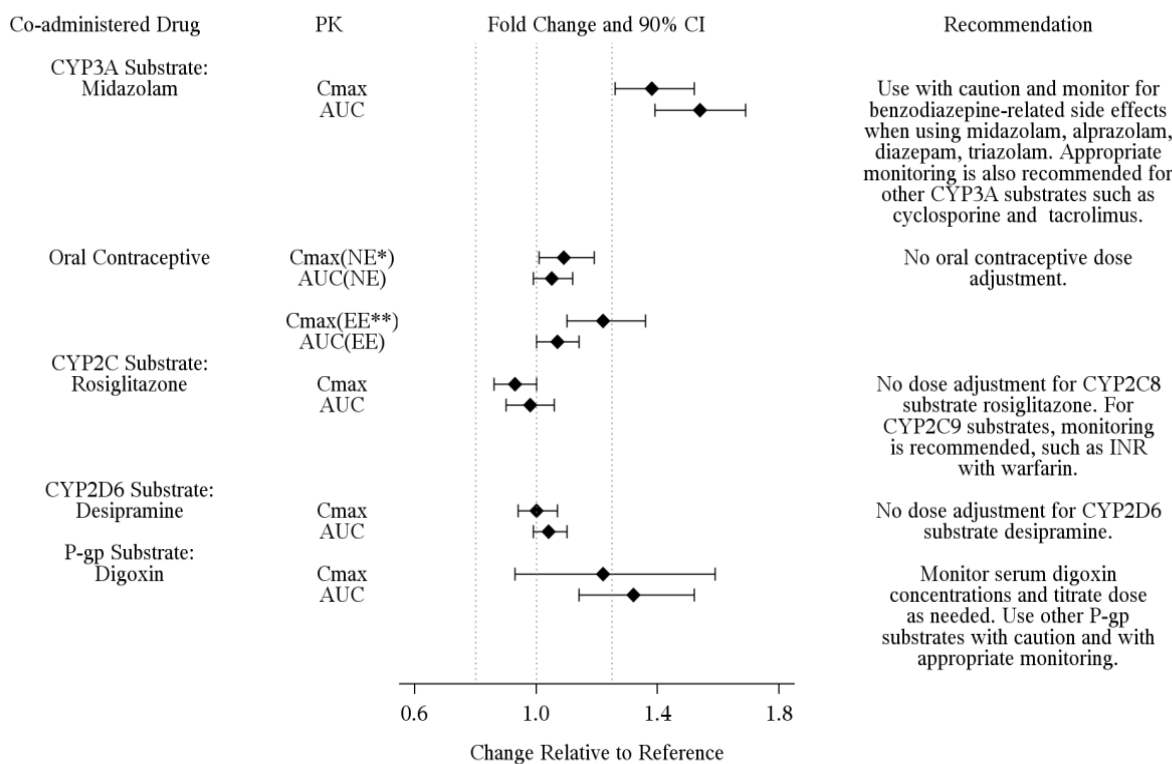
Drug interaction studies were performed with KALYDECO and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies [see *Drug Interactions (7)*].

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

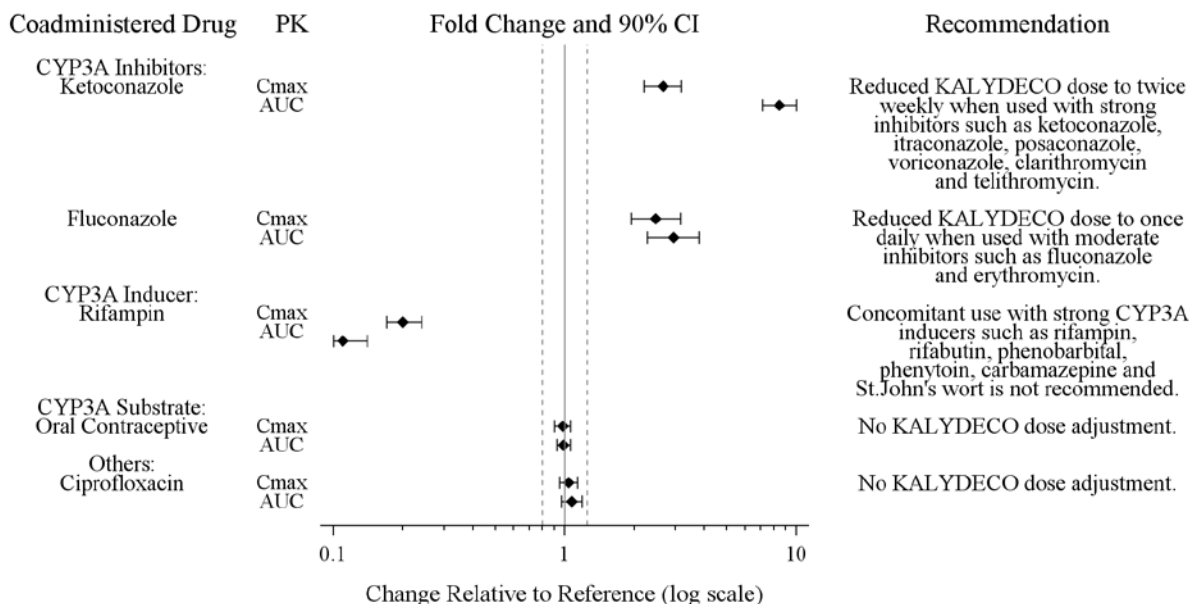
The vertical lines are at 0.8, 1.0, and 1.25, respectively.

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.

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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 FEV₁ ≥40% predicted. Twenty patients with median predicted FEV₁ 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 FEV₁ 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 FEV₁) 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 FEV₁ at screening between 40-90% predicted [mean FEV₁ 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 FEV₁ at screening between 40-105% predicted [mean FEV₁ 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.

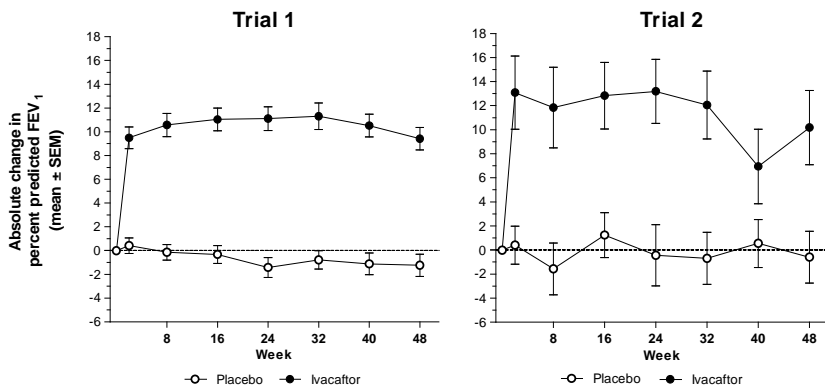
Patients in both trials were randomized 1:1 to receive either 150 mg of KALYDECO or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic saline was not permitted.

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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 FEV₁ through 24 weeks of treatment.

In both studies, treatment with KALYDECO resulted in a significant improvement in FEV₁. The treatment difference between KALYDECO and placebo for the mean absolute change in percent predicted FEV₁ 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 FEV₁ were observed regardless of age, disease severity, sex, and geographic region.

Figure 3: Mean Absolute Change from Baseline in Percent Predicted FEV₁ *



*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

Endpoint	Trial 1		Trial 2	
	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 FEV₁ ≥40% at screening [mean FEV₁ 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.

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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 FEV₁ 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 FEV₁ [10.7 through Week 8 ($P < 0.0001$)], BMI [0.66 kg/m² 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**:						
<i>G1244E</i> (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)
<i>G1349D</i> (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)
<i>G178R</i> (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)
<i>G551S</i> (2)	0 (-5, 5)	0.3 (-5, 6)	3 ^{††}	0.16 ^{††}	16.7 ^{††}	-68 ^{††}
<i>G970R</i> (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)
<i>S1251N</i> (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)
<i>S1255P</i> (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)
<i>S549N</i> (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)
<i>S549R</i> (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 FEV₁ at screening between 40-90% predicted, and patients who were 6-11 years of age had FEV₁ at screening between 40-105% predicted. The overall mean FEV₁ was 73% predicted at baseline (range: 33% to 106%). The patients had well preserved BMIs (mean overall: 23.76 kg/m²) 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 FEV₁ through 24 weeks of treatment. The treatment difference for absolute change in percent predicted FEV₁ 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/m² 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 (FEV₁, 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).

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Table 5: Effect of KALYDECO on Overall Population (Percent Predicted FEV₁, 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 FEV₁ % 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 FEV₁ ≥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 FEV₁ was 79% predicted (range 40% to 129%). As in Trials 1 and 2, patients who had persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded. The use of inhaled hypertonic saline was not permitted.

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV₁. Treatment with KALYDECO resulted in no improvement in FEV₁ 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 FEV₁ 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)
60-count bottle

NDC 51167-200-01
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)
56-count carton (contains 56 unit-dose packets of 75 mg ivacaftor per packet)

NDC 51167-300-01
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).

KALYDECO® (ivacaftor) Tablets and Oral Granules

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 pureed 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)].



Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

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Revised March 2015

KALYDECO® (ivacaftor) Tablets and Oral Granules

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:

KALYDECO® (ivacaftor) Tablets and Oral Granules

- 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

KALYDECO® (ivacaftor) Tablets and Oral Granules

- 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.

KALYDECO® (ivacaftor) Tablets and Oral Granules

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.



Manufactured for:
Vertex Pharmaceuticals Incorporated
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Boston, MA 02210

Approved March 2015

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