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) 09/2020
- Dosage and Administration (2) 09/2020

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

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or *in vitro* assay data. (12.1, 14)

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)

----------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 4 months to less than 6 months of age and 5 kg or greater: one 25 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 6 months to less than 6 years of age and weighing 5 kg to less than 7 kg: one 25 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 6 months to less than 6 years of age and weighing 7 kg to 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 6 months 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)
- Reduce dose in patients 6 months and older with moderate or severe hepatic impairment. (2.4, 8.6)
- See full prescribing information for dosage modifications due to drug interactions with KALYDECO. (2.5, 7.1)
- Not recommended in pediatric patients less than 4 months of age. (2.3, 8.4)
- Not recommended in patients 4 months to less than 6 months of age with hepatic impairment. (2.3, 8.6)

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

- Tablets: 150 mg (3)
- Oral granules: Unit-dose packets of 25 mg, 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. Interrupt dosing 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 (≥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)

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

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

CYP3A inhibitors: Reduce KALYDECO dose when co-administered with strong CYP3A inhibitors (e.g., ketoconazole) or moderate CYP3A inhibitors (e.g., fluconazole). Avoid food containing grapefruit. (2.5, 7.1)

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

Revised: 12/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data *[see Clinical Pharmacology (12.1) and Clinical Studies (14)]*.

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.

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, yogurt, breast milk or infant formula), etc. *[see Clinical Pharmacology (12.3) and Patient Counseling Information (17)]*.

2.2 Recommended Dosage in Adults and Pediatric Patients Aged 6 Years and Older

The recommended dosage of KALYDECO for adults and pediatric patients ages 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 Recommended Dosage in Pediatric Patients Aged 4 Months to Less than 6 Years

The recommended dosage of KALYDECO (oral granules) for patients ages 4 months 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 4 months to less than 6 Years

Age	Body Weight (kg)	KALYDECO Dosage	Total Daily Dose
4 months* to less than 6 months+	5 kg or greater	One 25 mg packet every 12 hours	50 mg/day
6 months or older	5 kg to less than 7 kg	One 25 mg packet every 12 hours	50 mg/day
	7 kg to 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

*KALYDECO is not recommended for use in children under 4 months of age.
+KALYDECO is not recommended for use in children aged 4 months to less than 6 months with hepatic impairment and/or taking concomitant moderate or strong CYP3A inhibitors

Instructions for Administration of Oral Granules

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, breast milk, infant formula, milk, or juice. Each dose should be administered just before or just after fat-containing food *[see Dosage and Administration (2.1)]*.

2.4 Dosage Adjustment for Patients with Hepatic Impairment Aged 6 Months and Older

The dosage of KALYDECO should be reduced to one tablet or one packet of oral granules once daily for patients aged 6 months and older with moderate hepatic impairment (Child-Pugh Class B). KALYDECO should be used with caution in patients aged 6 months and older with severe hepatic impairment (Child-Pugh Class C), at a dosage of one tablet or one packet of oral granules once daily or less frequently. Use is not recommended in patients with hepatic impairment below 6 months of age *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

2.5 Dosage Adjustment for Patients Aged 6 Months and Older Taking Drugs that are CYP3A Inhibitors

When KALYDECO is being co-administered with strong CYP3A inhibitors (e.g., ketoconazole) in patients aged 6 months or older, 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). Concomitant use of moderate or strong CYP3A inhibitors is not recommended in patients below 6 months of age. Food containing grapefruit 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, light blue, film-coated, capsule shaped tablets, with the characters "V 150" on one side and plain on the other.
Oral granules: 25 mg, 50 mg or 75 mg, white to off-white granules, 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. ALT and AST should 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, consider more frequent monitoring of liver function tests. 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 *[see Adverse Reactions (6) and Use in Specific Populations (8.6)]*.

5.2 Concomitant Use with CYP3A Inducers

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

5.3 Cataracts

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

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6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Transaminase Elevations *[see Warnings and Precautions (5.1)]*
- Cataracts *[see Warnings and Precautions (5.3)]*

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.
- An 8-week, crossover design trial (Trial 7) involving patients between the ages of 12 and 72 years who were heterozygous for the *F508del* mutation and a second *CFTR* mutation predicted to be responsive to ivacaftor. A total of 156 patients were randomized to and received KALYDECO.
- A cohort of 19 patients aged 12 months to less than 24 months, a cohort of 11 patients aged 6 months to less than 12 months, and a cohort of 6 patients aged 4 months to less than 6 months in a 24-week open-label clinical trial in patients with CF aged less than 24 months (Trial 8).

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

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

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

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

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

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

Adverse reactions in the 48-week clinical trials that occurred in the KALYDECO group at a frequency of 4 to 7% where rates exceeded that in the placebo group include:

Infections and infestations: rhinitis
Investigations: aspartate aminotransferase increased, bacteria in sputum, blood glucose increased, hepatic enzyme increased
Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, myalgia
Nervous system disorders: sinus headache
Respiratory, thoracic and mediastinal disorders: pharyngeal erythema, pleuritic pain, sinus congestion, wheezing
Skin and subcutaneous tissue disorders: acne

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The safety profile for the CF patients enrolled in the other clinical trials (Trials 3-8) was similar to that observed in the 48-week, placebo-controlled trials (Trials 1 and 2).

Laboratory Abnormalities

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

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

During the 24-week, open-label, clinical trial in patients aged less than 24 months (Trial 8), the incidence of patients experiencing transaminase elevations (ALT or AST) >3 , >5 , and >8 x ULN in the cohort of patients aged 12 months to less than 24 months (N=19) was 27.8% (5/18), 11.1% (2/18) and 11.1% (2/18), respectively. In the cohort of patients aged 6 months to less than 12 months (N=11) one patient (9.1%) had elevated ALT of >3 to ≤5 x ULN. In the cohort of patients aged 4 months to less than 6 months (N=6), no patients had elevated ALT or AST (> 3x ULN). No patients had elevations in total bilirubin, or discontinued ivacaftor treatment due to transaminase elevations in any cohort *[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 for patients taking concomitant strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

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 *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

Co-administration of KALYDECO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of ivacaftor. Therefore, avoid food containing grapefruit 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 CYP2C9 Substrates

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co administration of KALYDECO with warfarin is recommended. Other therapeutic products for which exposure may be increased by KALYDECO include glimepiride and glipizide; these therapeutic products should be used with caution *[see Clinical Pharmacology (12.3)]*.

7.5 CYP3A and/or P-gp Substrates

Ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with oral 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

Risk Summary

There are limited and incomplete human data from clinical trials and post marketing reports on use of KALYDECO in pregnant women. In animal reproduction studies, oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse effects on fetal development at doses that produced maternal exposures up to approximately 5 (rats) and 11 (rabbits) times the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed after oral administration of ivacaftor to pregnant rats from organogenesis through lactation at doses that produced maternal exposures approximately 3 times the exposures at the MRHD, respectively (*see Data*).

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

Data

Animal Data

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In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 7-17, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 5 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 200 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7-19, ivacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 11 times the MRHD (on an ivacaftor AUC basis at maternal oral doses up to 100 mg/kg/day). In a pre- and post-natal development study in pregnant female rats dosed from gestation day 7 through lactation day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 3 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 5 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at a maternal oral dose of 200 mg/kg/day). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

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

Data

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

8.4 Pediatric Use

The safety and effectiveness of KALYDECO for the treatment of CF have been established in pediatric patients 4 months to 17 years of age who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data *[see Clinical Pharmacology (12.1) and Clinical Studies (14)]*.

The use of KALYDECO for this indication is supported by evidence from placebo-controlled clinical trials in the following pediatric patients with CF:

- 6 to 17 years of age with a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R, or R117H* mutation in the *CFTR* gene *[see Adverse Reactions (6) and Clinical Studies (14)]*.
- 12 to 17 years of age who are heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to ivacaftor *[see Adverse Reactions (6) and Clinical Studies (14)]*.

The effectiveness of KALYDECO in patients aged 2 to less than 6 years was extrapolated from 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)]*. Safety of KALYDECO in this population was derived from a 24-week, open label, clinical trial in 34 patients ages 2 to less than 6 years (mean age 3 years) administered either 50 mg or 75 mg of ivacaftor granules twice daily (Trial 6). The type and frequency of adverse reactions in this trial were similar to those in patients 6 years and older. Transaminase elevations were more common in patients who had abnormal transaminases at baseline *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

The effectiveness of KALYDECO in patients aged 4 months to less than 24 months was extrapolated from patients 6 years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults and children 4 months to less than 24 months of age *[see Clinical Pharmacology (12.3)]*. Safety of KALYDECO in this population was derived from a cohort of 6 patients aged 4 months to less than 6 months (mean age 4.5 months at baseline), a cohort of 11 patients aged 6 months to less than 12 months (mean age 9.0 months at baseline), and a cohort of 19 patients aged 12 months to less than 24 months (mean age 15.2 months at baseline) in a 24-week, open-label clinical study, administered either 25 mg, 50 mg or 75 mg of ivacaftor granules twice daily (Trial 8). The safety profile of patients in this trial is similar to that observed in patients 2 years and older.

The safety and effectiveness of KALYDECO in patients with CF younger than 4 months of age have not been established. The use of KALYDECO in children under the age of 4 months is not recommended.

Juvenile Animal Toxicity Data

In a juvenile toxicology study in which ivacaftor was administered to rats from postnatal days 7 to 35, cataracts were observed at all dose levels, ranging from 0.1 to 0.8 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at oral doses of 10-50 mg/kg/day). This finding has not been observed in older animals.

8.5 Geriatric Use

CF is largely a disease of children and young adults. Clinical trials of 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 aged 6 months or older with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*.

A reduced dose is recommended in patients aged 6 months or older with moderate hepatic impairment (Child-Pugh Class B) *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

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 reduced dose, in patients aged 6 months or older with severe hepatic impairment after weighing the risks and benefits of treatment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

Due to variability in maturation of cytochrome (CYP) enzymes involved in ivacaftor metabolism, treatment with KALYDECO is not recommended in patients aged 4 months to less than 6 months with hepatic impairment *[see Dosage and Administration (2.3)]*.

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.

10 OVERDOSAGE

There have been no reports of overdose with KALYDECO.

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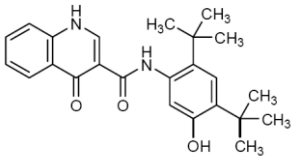
No specific antidote is available for overdose with KALYDECO. Treatment of overdose with KALYDECO consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

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



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

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

KALYDECO is also available as white to off-white granules for oral administration (sweetened but unflavored) and enclosed in a unit-dose packet containing 25 mg of ivacaftor, 50 mg of ivacaftor or 75 mg of ivacaftor. Each unit-dose packet of KALYDECO oral granules contains 25 mg of ivacaftor, 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 CFTR protein located at the cell surface. The overall level of ivacaftor-mediated CFTR chloride transport is dependent on the amount of CFTR protein at the cell surface and how responsive a particular mutant CFTR protein is to ivacaftor potentiation.

<u>CFTR Chloride Transport Assay in Fisher Rat Thyroid (FRT) cells expressing mutant CFTR</u>

The chloride transport response of mutant CFTR protein to ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Ivacaftor increased chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response. A patient must have at least one *CFTR* mutation responsive to ivacaftor to be indicated.

Note that splice site mutations cannot be studied in the FRT assay. Evidence of clinical efficacy exists for non-canonical splice mutations *2789+5G→A*, *3272-26A→G*, *3849+10kbC→T*, *711+3A→G* and *E831X* and these are listed in Table 3 below *[see also Clinical Studies (14.4)]*. The *G970R* mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface that can be potentiated by ivacaftor *[see Clinical Studies (14.2)]*.

Ivacaftor also increased chloride transport in cultured human bronchial epithelial (HBE) cells derived from CF patients who carried *F508del* on one *CFTR* allele and either *G551D* or *R117H-5T* on the second *CFTR* allele.

Table 3 lists mutations that are responsive to ivacaftor based on 1) a positive clinical response and/or 2) *in vitro* data in FRT cells indicating that ivacaftor increases chloride transport to at least 10% over baseline (% of normal).

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Table 3: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to KALYDECO				
711+3A→G *	*F311del*	*I148T*	*R75Q*	*S589N*
2789+5G→A *	*F311L*	*I175V*	*R117C* *	*S737F*
3272-26A→G *	*F508C*	*I807M*	*R117G*	*S945L* *
3849+10kbC→T *	*F508C;S1251N* †	*I1027T*	*R117H* *	*S977F* *
A120T	*F1052V*	*I1139V*	*R117L*	*S1159F*
A234D	*F1074L*	*K1060T*	*R117P*	*S1159P*
A349V	*G178E*	*L206W* *	*R170H*	*S1251N* *
A455E *	*G178R* *	*L320V*	*R347H* *	*S1255P* *
A1067T	*G194R*	*L967S*	*R347L*	*T338I*
D110E	*G314E*	*L997F*	*R352Q* *	*T1053I*
D110H	*G551D* *	*L1480P*	*R553Q*	*V232D*
D192G	*G551S* *	*M152V*	*R668C*	*V562I*
D579G *	*G576A*	*M952I*	*R792G*	*V754M*
D924N	*G970D*	*M952T*	*R933G*	*V1293G*
D1152H *	*G1069R*	*P67L* *	*R1070Q*	*W1282R*
D1270N	*G1244E* *	*Q237E*	*R1070W* *	*Y1014C*
E56K	*G1249R*	*Q237H*	*R1162L*	*Y1032C*
E193K	*G1349D* *	*Q359R*	*R1283M*	
E822K	*H939R*	*Q1291R*	*S549N* *	
E831X *	*H1375P*	*R74W*	*S549R* *	

* Clinical data exist for these mutations *[see Clinical Studies (14)]*.

† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

12.2 Pharmacodynamics

Sweat Chloride Evaluation

Changes in sweat chloride (a biomarker) response to KALYDECO were evaluated in seven clinical trials *[see Clinical Studies (14)]*. 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). The 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 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 Use in Specific Populations (8.4)]*. In a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in patients with CF age 12 years and older who were heterozygous for the *F508del* mutation and with a second *CFTR* mutation predicted to be responsive to ivacaftor (Trial 7), the treatment difference in mean change in sweat chloride from study baseline to the average of Week 4 and Week 8 of treatment for KALYDECO treated patients was -4.5 mmol/L (95% CI -6.7, -2.3). In a 24-week, open-label clinical trial in patients with CF aged less than 24 months administered either 25 mg, 50 mg or 75 mg of ivacaftor twice daily (Trial 8), the mean absolute change from baseline in sweat chloride for patients aged 12 months to less than 24 months (n=10) was -73.5 mmol/L (95% CI -86.0, -61.0) at Week 24, the mean absolute change from baseline in sweat chloride for patients aged 6 months to less than 12 months (n=6) was -58.6 mmol/L (95% CI -75.9, -41.3) at Week 24, and the mean absolute change from baseline in sweat chloride for patients aged 4 months to less than 6 months (n=3) was -50 mmol/L (95% CI -93.1, -6.9) at Week 24. *[see Use in Specific Populations (8.4)]*.

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

Cardiac Electrophysiology

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, yogurt, breast milk and infant formula), 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.

Elimination

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.

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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.

Excretion
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.

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

Table 4: Ivacaftor Exposure by Age Group, Mean (SD)

Age Group	Dose	AUC_{ss} (ng*h/mL)
4 to less than 6 months (≥5 kg)	25 mg q12h	6480 (2520) ^
6 to less than 12 months (5 kg to <7 kg) *	25 mg q12h	5360 ^
6 to less than 12 months (7 kg to <14 kg)	50 mg q12h	9390 (3120) ^
12 to less than 24 months (7 kg to <14 kg)	50 mg q12h	9050 (3050)
12 to less than 24 months (≥14 kg to <25 kg)	75 mg q12h	9600 (1800)
2 to less than 6 years (<14 kg)	50 mg q12h	10500 (4260)
2 to less than 6 years (≥14 kg to <25 kg)	75 mg q12h	11300 (3820)
6 to less than 12 years	150 mg q12h	20000 (8330)
12 to less than 18 years	150 mg q12h	9240 (3420)
Adults (≥18 years)	150 mg q12h	10700 (4100)

* Value based on data from a single patient; standard deviation not reported
^ Values based on population PK modeling incorporating data from patients 4 to < 6 months of age from Trial 8

Patients with Hepatic impairment
Adult subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had similar ivacaftor C_{max}, but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Based on simulations of these results, a reduced KALYDECO dose to one tablet or packet of granules once daily is recommended for patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. The impact of severe hepatic impairment (Child-Pugh Class C, score 10-15) on the pharmacokinetics of ivacaftor has not been studied. The magnitude of increase in exposure in these patients is unknown but is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, KALYDECO should be used with caution in patients with severe hepatic impairment at a dose of one tablet or one packet of granules given once daily or less frequently *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Patients with 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.

Male and Female Patients
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 Interaction Studies
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 2.

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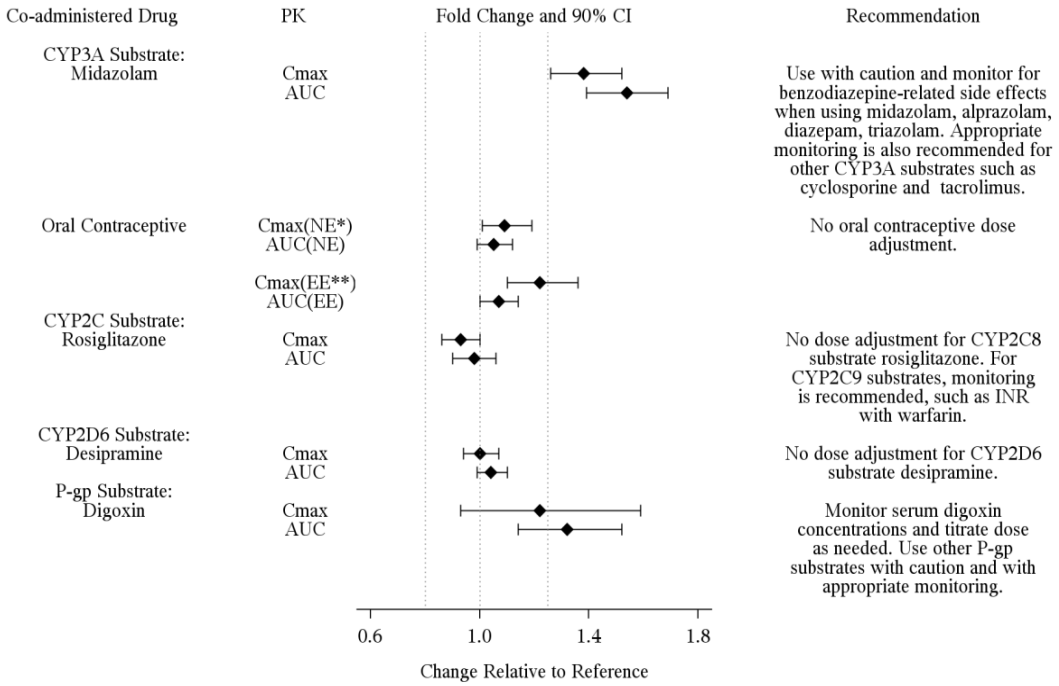
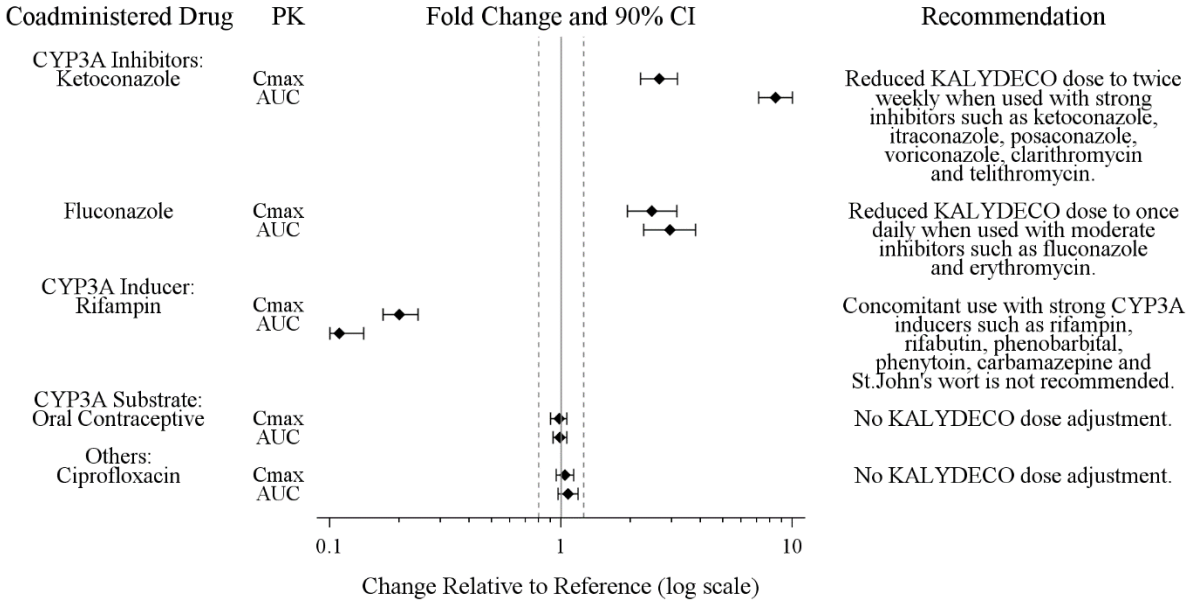
Figure 2: Impact of KALYDECO on Other Drugs



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 (2.5) and Drug Interactions (7)]*. KALYDECO dosing recommendations for co-administration with other drugs are shown in Figure 3.

Figure 3: 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 CD-1 mice and Sprague-Dawley 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 equal to 1 and 4 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

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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 (yielding exposures approximately 8 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its major 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 5 times the MRHD based on summed AUCs of ivacaftor and its major 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 (yielding exposures approximately 6 and 3 times, respectively, the MRHD based on summed AUCs of ivacaftor and its major metabolites).

14 CLINICAL STUDIES

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

Dose Ranging:

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

Efficacy:

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

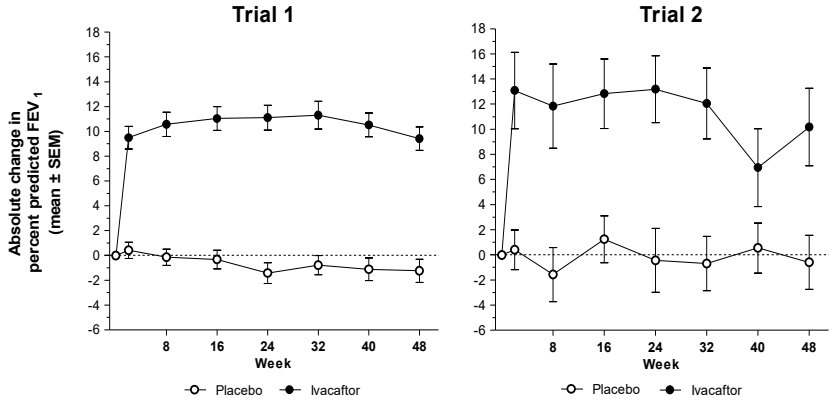
Trial 1 evaluated 161 patients with CF who were 12 years of age or older (mean age 26 years) with FEV_1 at screening between 40-90% predicted [mean FEV_1 64% predicted at baseline (range: 32% to 98%)]. Trial 2 evaluated 52 patients who were 6 to 11 years of age (mean age 9 years) with FEV_1 at screening between 40-105% predicted [mean FEV_1 84% predicted at baseline (range: 44% to 134%)]. Patients who had persistent *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal were excluded.

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

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

In both studies, treatment with KALYDECO resulted in a significant improvement in FEV_1. The treatment difference between KALYDECO and placebo for the mean absolute change in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points (P<0.0001) in Trial 1 and 12.5 percentage points (P<0.0001) in Trial 2 (Figure 4). These changes persisted through 48 weeks. Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, and geographic region.

Figure 4: Mean Absolute Change from Baseline in Percent Predicted FEV_1 *



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

Other efficacy variables included absolute change from baseline in sweat chloride *[see Clinical Pharmacology (12.2)]*, time to first pulmonary exacerbation (Trial 1 only), absolute change from baseline in weight, and improvement from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory domain score, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing. For the purpose of the study, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with KALYDECO demonstrated statistically significant improvements in risk of pulmonary exacerbations, CF symptoms (in Trial 1 only), and gain in body weight (Table 5). 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.

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Table 5: Effect of KALYDECO on Other Efficacy Endpoints in Trials 1 and 2

Endpoint	Trial 1 Treatment difference * (95% CI)	Trial 1 *P* value	Trial 2 Treatment difference * (95% CI)	Trial 2 *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 †	0.0016	NA	NA
Through Week 48	0.46 †	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
* Treatment difference = effect of KALYDECO – effect of Placebo
† Hazard ratio for time to first pulmonary exacerbation

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

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

Patients were 6 years of age or older (mean age 23 years) with FEV_1 ≥40% at screening [mean FEV_1 at baseline 78% predicted (range: 43% to 119%)]. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal at screening were excluded.

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

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 8 weeks of treatment. Other efficacy variables included absolute change from baseline in sweat chloride through 8 weeks of treatment *[see Clinical Pharmacology (12.2)]*, absolute change from baseline in body mass index (BMI) at 8 weeks of treatment (including body weight at 8 weeks), and improvement in CFQ-R respiratory domain score through 8 weeks of treatment. For the overall population of the 9 mutations studied, treatment with KALYDECO compared to placebo resulted in significant improvement in percent predicted FEV_1 [10.7 through Week 8 (P<0.0001)], BMI [0.66 kg/m^2 at Week 8 (P<0.0001)], and CFQ-R respiratory domain score [9.6 through Week 8 (P=0.0004)]; however, there was a high degree of variability of efficacy responses among the 9 mutations (Table 6).

Table 6: Effect of KALYDECO for Efficacy Variables in the Overall Populations and for Specific *CFTR* Mutations

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

* n=36 for the analysis of absolute change in sweat chloride.

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Table 6: 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

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

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

The efficacy and safety of KALYDECO in patients with CF who have an *R117H* mutation in the *CFTR* gene were evaluated in a randomized, double-blind, placebo-controlled, parallel-group clinical trial (Trial 5). Fifty-nine of 69 patients completed 24 weeks of treatment. Two patients discontinued and 8 patients did not complete treatment due to study termination. Trial 5 evaluated 69 clinically stable patients with CF who were 6 years of age or older (mean age 31 years). Patients who were 12 years and older had FEV_1 at screening between 40-90% predicted, and patients who were 6-11 years of age had FEV_1 at screening between 40-105% predicted. The overall mean FEV_1 was 73% predicted at baseline (range: 33% to 106%). The patients had well preserved BMIs (mean overall: 23.76 kg/m^2) and a high proportion were pancreatic sufficient as assessed by a low rate of pancreatic enzyme replacement therapy use (pancreatin: 11.6%; pancrelipase: 5.8%). Patients who had persistent *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening, and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the ULN, were excluded.

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

The primary efficacy endpoint was improvement in lung function as determined by the mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment. The treatment difference for absolute change in percent predicted FEV_1 through Week 24 was 2.1 percentage points (analysis conducted with the full analysis set which included all 69 patients) and did not reach statistical significance (Table 7).

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 7), absolute change in body mass index (BMI) at Week 24, and time to first pulmonary exacerbation. The overall treatment difference for the absolute change from baseline in BMI at Week 24 was 0.3 kg/m^2 and the calculated hazard ratio for time to first pulmonary exacerbation was 0.93, which were not statistically significant.

Statistically significant improvements in clinical efficacy (FEV_1, CFQ-R respiratory domain) were seen in several subgroup analyses and decreases in sweat chloride were observed in all subgroups. The mean baseline sweat chloride for all patients was 70 mmol/L. Subgroups analyzed included those based on age, lung function, and poly-T status (Table 7).

Table 7: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) and in Relevant Subgroups Through 24 Weeks

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

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Table 7: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) and in Relevant Subgroups Through 24 Weeks										
		Absolute Change through Week 24 *- All Randomized Patients								
>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 with CF Heterozygous for the *F508del* Mutation and a Second Mutation Predicted to be Responsive to ivacaftor

The efficacy and safety of KALYDECO and an ivacaftor-containing combination product in 246 patients with CF was evaluated in a randomized, double−blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover design clinical trial (Trial 7). Mutations predicted to be responsive to ivacaftor were selected for the study based on the clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and *in vitro* responsiveness to ivacaftor.

Eligible patients were heterozygous for the *F508del* mutation with a second mutation predicted to be responsive to ivacaftor. Of the 244 patients included in the efficacy analysis, who were randomized and dosed, 146 patients had a splice mutation and 98 patients had a missense mutation, as the second allele. 156 patients received KALYDECO and 161 patients received placebo. Patients were aged 12 years and older (mean age 35 years [range 12-72]) and had a percent predicted FEV_1 at screening between 40-90 [mean $ppFEV_1$ at study baseline 62 (range: 35 to 94)]. Patients with evidence of colonization with organisms associated with a more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus*) and those with abnormal liver function at screening were excluded. Abnormal liver function was defined as 2 or more liver function tests (ALT, AST, ALP, GGT) ≥3 times the upper limit of normal or total bilirubin ≥2 times the upper limit of normal, or a single increase in ALT/AST ≥5 times the upper limit of normal.

The primary efficacy endpoint was the mean absolute change from study baseline in percent predicted FEV_1 averaged at Weeks 4 and 8 of treatment. The key secondary efficacy endpoint was absolute change in CFQ-R respiratory domain score from study baseline averaged at Weeks 4 and 8 of treatment. For the overall population, treatment with KALYDECO compared to placebo resulted in significant improvement in $ppFEV_1$ [4.7 percent points from study baseline to average of Week 4 and Week 8 (P<0.0001)] and CFQ-R respiratory domain score [9.7 points from study baseline to average of Week 4 and Week 8 (P<0.0001)]. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (Table 8).

Table 8: Effect of KALYDECO for Efficacy Variables			
Mutation (n)	**Absolute Change in percent predicted FEV_1 *†**	**Absolute Change in CFQ-R Respiratory Domain Score (Points) *±**	**Absolute Change in Sweat Chloride (mmol/L) *±**
Splice mutations (n=94 for IVA and n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for KALYDECO vs. placebo-treated patients:			
	5.4 (4.1, 6.8)	8.5 (5.3, 11.7)	-2.4 (-5.0, 0.3)
By individual splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for KALYDECO-treated patients			
2789+5G→A (28)	5.1 (-7.1, 17.0)	8.6 (-5.6, 27.8)	0.4 (-7.5, 8.8)
3272-26A→G (23)	3.5 (-9.1, 16.0)	8.0 (-11.1, 27.8)	-2.3 (-25.0, 11.8)
3849+10kbC→T (40)	5.1 (-6.8, 16.2)	7.5 (-30.6, 55.6)	-4.6 (-80.5, 23.0)
711+3A→G (2)	9.2 (8.9, 9.6)	-8.3 (-13.9, -2.8)	-9.9 (-13.5, -6.3)
E831X (1)	7.1 (7.1, 7.1)	0.0 (0.0, 0.0)	-7.8 (-7.8, -7.8)
Missense mutations (n=62 for IVA and n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for KALYDECO vs. placebo-treated patients:			
	3.6 (1.9, 5.2)	11.5 (7.5, 15.4)	-7.8 (-11.2, -4.5)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for KALYDECO-treated patients			
D579G (2)	13.3 (12.4, 14.1)	15.3 (-2.8, 33.3)	-30.8 (-36.0, -25.5)
D1152H (15)	2.4 (-5.0, 10.2)	13.7 (-16.7, 50.0)	-4.8 (-22.0, 3.0)
A455E (14)	3.7 (-6.6, 19.7)	6.8 (-13.9, 33.3)	7.5 (-16.8, 16.0)
L206W (2)	4.2 (2.5, 5.9)	12.5 (-5.6, 30.6)	3.9 (-8.3, 16.0)
P67L (12)	4.3 (-2.5, 25.7)	10.8 (-12.5, 36.1)	-10.5 (-34.8, 9.8)
R1070W (1)	2.9 (2.9, 2.9)	44.4 (44.4, 44.4)	0.3 (0.3, 0.3)
R117C (1)	3.5 (3.5, 3.5)	22.2 (22.2, 22.2)	-36.0 (-36.0, -36.0)
R347H (3)	2.5 (-0.6, 6.9)	6.5 (5.6, 8.3)	-19.2 (-25.8, -7.0)
R352Q (2)	4.4 (3.5, 5.3)	9.7 (8.3, 11.1)	-21.9 (-45.5, 1.8)
S945L (9)	8.8 (-0.2, 20.5)	10.6 (-25.0, 27.8)	-30.8 (-50.8, -17.3)
S977F (1)	4.3 (4.3, 4.3)	-2.8 (-2.8, -2.8)	-19.5 (-19.5, -19.5)
* Average of Week 4 and 8 values † Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis. ± Absolute change in CFQ-R respiratory domain score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.			

In an analysis of BMI at Week 8, an exploratory end-point, patients treated with KALYDECO had a mean improvement of 0.28 kg/m^2 [95% CI (0.14, 0.43)], 0.24 kg/m^2 [95% CI (0.06, 0.43)], and 0.35 kg/m^2 [95% CI (0.12, 0.58)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

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

Trial 3 was a 16-week, randomized, double-blind, placebo-controlled, parallel-group trial in 140 patients with CF age 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who had FEV_1 ≥40% predicted. Patients were randomized 4:1 to receive KALYDECO 150 mg (n=112) every 12 hours or placebo (n=28) in addition to their prescribed CF therapies. The mean age of patients enrolled was 23 years and the mean baseline FEV_1 was 79% predicted (range 40%

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

The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV_1. The treatment difference from placebo for the mean absolute change in percent predicted FEV_1 through Week 16 in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene was 1.72 percentage points (1.5% and -0.2% for patients in the KALYDECO and placebo-treated groups, respectively) and did not reach statistical significance (Table 9).

Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 16, change in cystic fibrosis respiratory symptoms through Week 16 as assessed by the CFQ-R respiratory domain score (Table 9), change in weight through Week 16, and rate of pulmonary exacerbation. The overall treatment difference for change from baseline in weight through Week 16 was -0.16 kg (95% CI -1.06, 0.74); the rate ratio for pulmonary exacerbation was 0.677 (95% CI 0.33, 1.37).

Table 9: Effect of KALYDECO on Overall Population (Percent Predicted FEV_1, CFQ-R Respiratory Domain Score, and Sweat Chloride) Through 16 Weeks

		Absolute Change through Week 16 *- Full Analysis Set								
		% 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)
F508del homozygous										
	Placebo	28	-0.2	1.72	28	-1.44	1.3	28	0.13	-2.9
	KALYDECO	111	1.5	(-0.6, 4.1)	111	-0.12	(-2.9, 5.6)	109	-2.74	(-5.6, -0.2)

* MMRM analysis with fixed effects for treatment, age week, baseline value, treatment by week, and subject as a random effect

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

56-count carton (contains 56 unit-dose packets of 25 mg ivacaftor per packet) **NDC** 51167-600-01
56-count carton (contains 56 unit-dose packets of 50 mg ivacaftor per packet) **NDC** 51167-300-01
56-count carton (contains 56 unit-dose packets of 75 mg ivacaftor per packet) **NDC** 51167-400-01

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

17 PATIENT COUNSELING INFORMATION

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

Transaminase (ALT or AST) Elevations and Monitoring

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

Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of KALYDECO with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the therapeutic effectiveness of KALYDECO. Dose reduction is recommended when patients aged 6 months and older are taking concomitant strong CYP3A inhibitors, such as ketoconazole, or moderate CYP3A inhibitors, such as fluconazole *[see Dosage and Administration (2.5), Drug Interactions (7.1)]*. Treatment with KALYDECO is not recommended in patients aged 4 months to less than 6 months who are taking concomitant moderate or strong CYP3A inhibitors. Food containing grapefruit 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 aged 6 months and older 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 aged 6 months and older with severe hepatic impairment at a reduced dose *[see Dosage and Administration (2.4)]*. Treatment with KALYDECO is not recommended in patients aged 4 months to less than 6 months with any signs of hepatic impairment. 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 tablet 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, yogurt, breast milk and infant forumla), etc.

KALYDECO® (ivacaftor) oral granules 25 mg, 50 mg or 75 mg

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

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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 healthcare provider if they have questions.

Cataracts

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

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
Boston, MA 02210

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Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION

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

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

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have at least one mutation in their CF gene that is responsive to KALYDECO.

Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if KALYDECO is safe and effective in children under 4 months 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
- 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®)

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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 4 months 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, breast milk, infant formula, 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, yogurt, breast milk and infant formula.

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 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

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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 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 the safe and effective use of KALYDECO

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

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

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

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What are the ingredients in KALYDECO?

Active ingredient: ivacaftor
Inactive ingredients:
KALYDECO Tablets are light blue, film-coated, capsule-shaped tablets for oral administration and contain 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 Oral Granules are white to off-white granules for oral administration (sweetened but unflavored) and contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

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

VERTEX
Manufactured for:
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