PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr KALYDECO®

Ivacaftor tablets 150 mg
Ivacaftor granules 50 mg per packet, 75 mg per packet

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiator

ATC R07AX02

Distributed by:
Vertex Pharmaceuticals (Canada) Incorporated
20 Bay Street, Suite 1520
Toronto, Ontario
M5J 2N8

Date of Preparation:
November 1, 2017

Submission Control No.: 208071

Table of Contents

Pr KALYDECO®

Ivacaftor tablets 150 mg
Ivacaftor granules 50 mg per packet, 75 mg per packet

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Non-medicinal Ingredients
oral	tablet 150 mg	lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*
oral	granules 50 mg, 75 mg	lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

KALYDECO tablets (150 mg) are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.* KALYDECO tablets (150 mg) are also indicated for the treatment of cystic fibrosis (CF) in patients age 18 years and older with an *R117H* mutation in the *CFTR* gene.

KALYDECO granules (50 mg and 75 mg) are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R.*

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

Geriatrics (≥65 years of age):
The efficacy and safety of KALYDECO in patients age 65 years or older have not been evaluated.

Pediatrics (<18 years of age):
The efficacy and safety of KALYDECO in patients younger than age 2 years have not been evaluated.

CONTRAINDICATIONS
Patients who are hypersensitive to the active substance or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Effect on Liver Function Tests
Elevated transaminases (alanine transaminase [ALT] or aspartate transaminase [AST]) have been reported in patients with CF receiving KALYDECO (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Hepatic Impairment
Use of KALYDECO is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of overexposure. In such case, the starting dose of KALYDECO should be one tablet or one packet of granules once daily or less frequently and modified according to tolerability and clinical response (see **DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Concomitant Use with CYP3A Inhibitors or Inducers
Ivacaftor is a substrate of CYP3A. Medicinal products that inhibit or induce CYP3A activity may impact the pharmacokinetics of ivacaftor.

The dose of KALYDECO must be adjusted when concomitantly used with strong or moderate CYP3A inhibitors (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**).

Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in loss of KALYDECO efficacy (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, and **Drug-Herb Interactions**).

Renal

Renal Impairment
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 (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Ophthalmologic

Cataracts
Cases of non-congenital lens opacities, without impact on vision, have been reported in pediatric patients treated with KALYDECO. Although other risk factors were present in some cases, such as corticosteroid use and 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.

Special Populations

Pregnant Women
No adequate and well-controlled studies of KALYDECO have been conducted in pregnant women. Ivacaftor was not teratogenic in rats at approximately 5 times the maximum recommended human dose (MRHD) (based on summed AUCs for ivacaftor and its major metabolites at a maternal dose of 200 mg/kg/day). Ivacaftor was not teratogenic in rabbits at approximately 11 times the MRHD (based on the AUC for ivacaftor at a maternal dose of 100 mg/kg/day). Ivacaftor decreased the fertility index in female rats and the number of corpora lutea, implantations and viable embryos at 200 mg/kg/day when dams were dosed prior to and during early pregnancy (see **TOXICOLOGY**). 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 the expected benefit to the patient clearly outweighs the potential risk to the fetus.

Nursing Women
Ivacaftor is excreted into the milk of lactating female rats. Excretion of ivacaftor into human milk is probable. There are no human trials that have investigated the effects of ivacaftor on breastfed infants. The use of KALYDECO by nursing women should only be considered if the expected benefit to the patient outweighs the potential risk to the breastfed infant.

Pediatrics (<18 years of age)
The efficacy and safety of KALYDECO in patients younger than age 2 years have not been evaluated.

With regard to the *R117H* mutation in the *CFTR* gene, the efficacy of KALYDECO in patients 6 to 17 years of age has not been adequately established at this time, and the safety data are included in the safety profile of Trial 5 (see **ADVERSE REACTIONS**).

Geriatrics (≥65 years of age)
The efficacy and safety of KALYDECO in patients age 65 years or older have not been evaluated.

Monitoring and Laboratory Tests

Transaminase (ALT or AST) Elevations and Monitoring
Elevated transaminases have been reported in patients with CF receiving KALYDECO (see **ADVERSE REACTIONS**). 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 x upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO dosing.

Patients should be advised to contact their doctor immediately if they develop symptoms suggestive of increased transaminases (e.g., abdominal pain, anorexia, jaundice, dark urine, pale stools, pruritus).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety profile of KALYDECO is based on six clinical trials:

- **Trials 1 and 2:** Two 48-week, placebo-controlled clinical trials in 213 patients with CF ages 6 to 53 (109 received ivacaftor and 104 received placebo) who had a *G551D* mutation in the *CFTR* gene and who were treated with KALYDECO 150 mg orally or placebo twice daily.
- **Trial 3:** A 16-week, placebo-controlled trial in 140 patients with CF ages 12 to 52 who were homozygous for the *F508del* mutation.
- **Trial 4:** An 8-week crossover design study involving 39 patients with CF 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.
- **Trial 5:** A 24-week, placebo-controlled trial involving 69 patients with CF between the ages of 6 and 68 years with an *R117H* mutation in the *CFTR* gene.
- **Trial 6:** A 24-week, open-label trial in 34 patients with CF, 2 to less than 6 years of age with a *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 overall safety profile of KALYDECO is based on pooled data from Trials 1, 2, and 3, which included 353 patients with CF. Of these 353 patients, 221 received KALYDECO and

132 received placebo for 16 to 48 weeks. The proportion of patients who prematurely discontinued study drug due to adverse events was 2% for KALYDECO-treated patients and 5% for placebo-treated patients. 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 most common serious adverse reactions, occurring in more than one KALYDECO-treated patient, were abdominal pain, increased hepatic enzymes, and hypoglycemia, all of which occurred in less than 1% of patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials for each drug are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients with CF Over 6 Years of Age with a* G551D *Gating Mutation (Trials 1 and 2)

The incidence of adverse reactions below is based upon the pooled analyses of Trials 1 and 2. Table 1 shows adverse reactions occurring in at least 5% of KALYDECO-treated patients that also occurred with an incidence of at least 3% more than placebo.

Table 1 - Incidence of Adverse Drug Reactions in at Least 5% of KALYDECO-Treated Patients with the *G551D* Mutation in the *CFTR* Gene in the Phase 3 Trials with an Incidence of at Least 3% More than Placebo

	KALYDECO N=109 (%)	**Placebo N=104 (%)**
Infections and infestations		
Upper respiratory tract infection (URTI)	24 (22)	14 (14)
Nasopharyngitis	16 (15)	12 (12)
Rhinitis	8 (7)	4 (4)
Nervous system disorders		
Headache	26 (24)	17 (16)
Dizziness	10 (9)	1 (1)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	22 (20)	16 (15)
Oropharyngeal pain	24 (22)	19 (18)
Sinus congestion	8 (7)	4 (4)
Gastrointestinal		

Abdominal pain	17 (16)	13 (13)
Diarrhea	14 (13)	10 (10)
Skin and subcutaneous tissue disorders		
Rash	14 (13)	7 (7)
Investigations		
Bacteria in sputum	8 (7)	4 (4)

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).

Description of Selected Adverse Reactions

Upper Respiratory Tract Events
During Trials 1 and 2, the incidence of several upper respiratory tract events was higher in KALYDECO-treated patients than placebo. URTI was reported in 22% of KALYDECO-treated patients compared to 14% in the placebo group. Other respiratory tract events occurring in KALYDECO-treated patients with an incidence of at least 3% more than placebo included oropharyngeal pain (22%), nasal congestion (20%), nasopharyngitis (15%), rhinitis (7%), and sinus congestion (7%). None of those events were serious and no patients in the KALYDECO-treated group discontinued treatment because of upper respiratory tract events.

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.

During Trial 6, 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 1 patient in this study (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

Ivacaftor is a sensitive CYP3A substrate. Any medicinal products that modify CYP3A activity may impact the pharmacokinetics of ivacaftor. Ivacaftor is also a weak inhibitor of CYP3A and P-gp. Administration of KALYDECO may increase systemic exposure to medicinal products that are substrates of CYP3A or P-gp, which could increase or prolong their therapeutic effect and adverse reactions. Concomitant use of KALYDECO may increase the concentrations of medicinal products that are substrates of CYP2C9. Caution is warranted when co-administration is required (see **DETAILED PHARMACOLOGY**).

Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions Between Ivacaftor and CYP3A Inhibitors

Drug	Ref	Effect	Clinical Comment
Strong CYP3A Inhibitors			
Ketoconazole	CT	↑ 8.5 × $AUC_{0-\infty}$, Substantially increased exposure	Reduction of ivacaftor dose to one tablet or one packet of granules twice a week.*
e.g., Itraconazole Posaconazole Voriconazole Clarithromycin	T	↑ $AUC_{0-\infty}$, Potential for substantially increased exposure	Reduction of ivacaftor dose to one tablet or one packet of granules twice a week.*
Moderate CYP3A Inhibitors			
Fluconazole	CT	↑ 3 × AUC_{0-12h}, Increased exposure	Reduction of ivacaftor dose to one tablet or one packet of granules once daily.*
e.g., Erythromycin	T	↑ AUC_{0-12h}, Potential for increased exposure	Reduction of ivacaftor dose to one tablet or one packet of granules once daily.*
Legend: CT = Clinical Trial; T = Theoretical * See **DOSAGE AND ADMINISTRATION** for details.			

Ciprofloxacin

Co-administration with ciprofloxacin had no effect on the exposure of ivacaftor. No dose adjustment is necessary during concomitant administration of KALYDECO with ciprofloxacin.

Inducers of CYP3A
Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, 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 (*Hypericum perforatum*), is not recommended.

Concomitant use of moderate inducers of CYP3A may decrease the exposure of ivacaftor and thus may reduce KALYDECO efficacy.

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

Potential for Ivacaftor to Affect Other Drugs

CYP3A, P-gp, or CYP2C9 Substrates
Based on pre-clinical studies, ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. In humans, 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 the weak inhibition of P-gp. 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. Use with caution and monitor for benzodiazepine-related side effects when using oral midazolam, alprazolam, diazepam, or triazolam. Use with caution and appropriate monitoring when co-administering KALYDECO with sensitive CYP3A and/or P-gp substrates such as digoxin, cyclosporine, or tacrolimus.

Ivacaftor may inhibit CYP2C9. Therefore, monitoring the international normalized ratio (INR) during co-administration with warfarin is recommended.

Drug-Food Interactions
Grapefruit juice contains one or more components that moderately inhibit CYP3A and its co-administration may increase plasma concentrations of ivacaftor. Food containing grapefruit or Seville oranges should be avoided during treatment with KALYDECO.

Drug-Herb Interactions
Co-administration of KALYDECO with herbal products that strongly induce CYP3A (e.g., St. John's wort) may decrease efficacy and is not recommended.

Drug-Lifestyle Interactions
Driving and Using Machines: Dizziness has been reported in patients receiving KALYDECO, which could influence the ability to drive or operate machines (see **ADVERSE REACTIONS**). Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

In the case of children, KALYDECO should be taken under parental or caregiver supervision. Children should be cautioned against riding bicycles or doing other activities that require them to be alert until it is known how KALYDECO will affect them.

DOSAGE AND ADMINISTRATION

Dosing Considerations

KALYDECO should only be administered to patients who have a mutation in the *CFTR* gene listed in **INDICATIONS AND CLINICAL USE**.

KALYDECO should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed before starting treatment to confirm the presence of one of the above-listed gating mutations or an *R117H* mutation in at least one allele of the *CFTR* gene.

Recommended Dose and Dosage Adjustment

KALYDECO 150 mg film-coated tablets: *Adults, adolescents and children aged 6 years and older and weighing 25 kg or more, the recommended dose of KALYDECO tablets is 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food (see Table 3).*

For oral use. Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break, or dissolve the tablet).

KALYDECO 50 mg and 75 granules in packet: *Children aged 2 years and older and weighing less than 25 kg (see Table 3).*

For oral use. The entire contents of each packet of granules should be mixed with 1 teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed. Food or liquid should be at or below room temperature. Each packet is for single use only. Once mixed, the product has been shown to be stable for 1 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 (except for grapefruit juice). Each dose should be administered just before or just after fat-containing food. If mixed with food, KALYDECO granules must not be stored for future use.

Table 3 - Dosage by Body Weight in Patients Aged 2 Years and Older		
Body Weight (kg)	**KALYDECO Dose**	**Total Daily Dose**
<14 kg	One 50 mg packet of granules taken orally every 12 hours	100 mg/day
≥14 kg to <25 kg	One 75 mg packet of granules taken orally every 12 hours	150 mg/day
≥25 kg	One 150 mg tablet taken orally every 12 hours	300 mg/day

Both tablets and granules should be taken with fat-containing food. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a typical CF diet should be given. Examples of meals that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats. Food containing grapefruit or Seville oranges should be avoided.
The efficacy and safety of KALYDECO in patients younger than age 2 years have not been evaluated.

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.

Dosage Adjustment for Patients with Hepatic Impairment
The dose of KALYDECO should be reduced to one tablet or one packet of 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 starting dose of one tablet or one packet of granules every other day and modified according to tolerability and clinical response. There is no experience in the use of KALYDECO in patients with severe hepatic impairment and therefore its use is not recommended unless the benefits outweigh the risks (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors (see **DRUG INTERACTIONS**)

When KALYDECO is co-administered with strong CYP3A inhibitors (e.g., ketoconazole), the dose should be reduced as follows:

Table 4 - Dosage by Body Weight in Patients Aged 2 Years and Older, when KALYDECO is co-administered with strong CYP3A inhibitors	
Body Weight (kg)	**KALYDECO Dose**
<14 kg	One 50 mg packet of granules taken orally twice a week
≥14 kg to <25 kg	One 75 mg packet of granules taken orally twice a week
≥25 kg	One 150 mg tablet taken orally twice a week

When KALYDECO is co-administered with moderate CYP3A inhibitors (e.g., fluconazole), the dose should be reduced as follows:

Table 5 - Dosage by Body Weight in Patients Aged 2 Years and Older, when KALYDECO is co-administered with moderate CYP3A inhibitors	
Body Weight (kg)	**KALYDECO Dose**
<14 kg	One 50 mg packet of granules taken orally once daily
≥14 kg to <25 kg	One 75 mg packet of granules taken orally once daily
≥25 kg	One 150 mg tablet taken orally once daily

Missed Dose

If a dose is missed within 6 hours of the scheduled time, it should be taken as soon as possible with fat-containing food. If more than 6 hours have passed since the dose should have been taken, this dose should be skipped and the usual dosing schedule resumed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been no reports of overdose with KALYDECO.

Ivacaftor doses as high as 500 mg/kg in rats and 2000 mg/kg in mice were administered. These doses are 13- and 27-fold higher, respectively, than the intended daily therapeutic dose of 300 mg for ivacaftor for patients 6 years and older.

The highest single dose used in a clinical trial 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 electrocardiograms (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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

The *G970R* mutation has been identified as causing a splicing defect resulting in little-to-no CFTR protein at the cell surface able to be potentiated by ivacaftor.

Pharmacodynamics

Sweat Chloride Evaluation

In clinical trials in patients with the *G551D* mutation in the *CFTR* gene, KALYDECO led to statistically significant reductions in sweat chloride concentration. In two randomized, double-blind, placebo-controlled clinical trials (Trial 1 in patients 12 and older and Trial 2 in patients 6 to 11 years of age), the treatment difference (between KALYDECO and placebo) in the mean change in sweat chloride from baseline through Week 24 was -48 mmol/L (95% CI -51, -45) and -54 mmol/L (95% CI -62, -47), respectively. These changes persisted through 48 weeks.

In a clinical trial in patients with a *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R* mutation, KALYDECO led to a statistically significant reduction in sweat chloride concentration. The treatment difference in the mean change from baseline in sweat chloride was -49 mmol/L (95% CI -57, -41) through 8 weeks of treatment. In this trial, 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, Phase 3 clinical trial in 34 patients ages 2 to <6 years with the above mutations, administered either 50 mg or 75 mg of ivacaftor twice daily (Trial 6), the mean absolute change from baseline in sweat chloride was -47 mmol/L (95% CI -58, -36) at Week 24.

In a randomized, double-blind, placebo-controlled clinical trial in patients with CF who have an *R117H* mutation in the *CFTR* gene (Trial 5), the mean baseline sweat chloride for patients 18 years and older was 71 mmol/L. The treatment difference in mean change in sweat chloride from baseline through 24 weeks of treatment for patients 18 years and older was -22 mmol/L (95% CI -26, -17).

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 (CI) for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern.

Pharmacokinetics
The pharmacokinetics of ivacaftor is similar between healthy adult volunteers and patients with CF. Table 6 shows the pharmacokinetic parameters of ivacaftor in healthy subjects following a single 150 mg oral dose in the fed and fasted conditions.

Table 6 - Mean (SD) Pharmacokinetic Parameters of Ivacaftor Following a Single 150 mg Dose in Healthy Adult Subjects (N=18)

	C_{max} (ng/mL)	**$t_{½}$ (hr)**	**$AUC_{0-\infty}$ (ng*hr/mL)**	**Apparent Clearance (L/hr)**	**Apparent Volume of Distribution (L)**
Fasted	218 (110)	16.7 (4.9)	3620 (1840)	50.6 (21.8)	1230 (707)
Fed	768 (233)	12 (2.7)	10600 (5260)	17.3 (8.4)	286 (149)

Absorption
After oral administration of a single 150 mg dose to healthy volunteers in the fasted state, peak plasma concentrations occurred at approximately 4 hours (t_{max}), and the mean (SD) for $AUC_{0-\infty}$ and C_{max} were 3620 (1840) ng*hr/mL and 218 (110) ng/mL, respectively. In the same study, oral administration of a single 150 mg dose in the fed state led to a substantial increase in exposure: $AUC_{0-\infty}$ was 10600 (5260) ng*hr/mL and C_{max} was 768 (233) ng/mL; t_{max} was unchanged.

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.

The exposure of ivacaftor increased approximately 2.5- to 4-fold when given with food containing fat. Therefore, KALYDECO should be administered with fat-containing food. The median (range) t_{max} is approximately 4.0 (3.0; 6.0) hours in the fed state.

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.

The apparent volume of distribution of ivacaftor is similar in healthy subjects and patients with CF. After oral administration of 150 mg every 12 hours for 7 days to healthy volunteers in a fed state, the mean (SD) for apparent volume of distribution was 353 (122) L.

Metabolism

Ivacaftor is extensively metabolized in humans. *In vitro* and clinical studies indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately $1/6^{th}$ the potency of ivacaftor and is considered pharmacologically active. M6 has less than $1/50^{th}$ the potency of ivacaftor and is not considered pharmacologically active.

Excretion

Following oral administration, the majority of ivacaftor (88%) 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 in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The mean (SD) of CL/F for a single 150 mg dose was 17.3 (8.4) L/hr in healthy adult subjects.

Special Populations and Conditions

Pediatrics

Ivacaftor exposure in pediatric patients 2 to <6 years of age administered KALYDECO granules, 50 mg every 12 hours (weight <14 kg) or 75 mg every 12 hours (weight ≥14 kg), was similar to that observed in adults administered KALYDECO tablets, 150 mg every 12 hours. Ivacaftor exposure observed in Phase 2 and 3 studies as determined using population pharmacokinetic (PK) analysis is presented by age group (and body weight for patients less than 12 years of age) in Table 7. Exposures in 6- to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

Table 7: Mean (SD) Ivacaftor Exposure by Age Group

Age Group	Dose	$C_{min, ss}$ (ng/mL)	$AUC_{, ss}$ (ng*h/mL)
2- to 5-year-olds (<14 kg)	50 mg q12h	577 (317)	10500 (4260)
2- to 5-year-olds (≥14 kg to <25 kg)	75 mg q12h	629 (296)	11300 (3820)
6- to 11-year-olds (≥14 kg to <25 kg)	75 mg q12h	641 (329)	10760 (4470)
6- to 11-year-olds (≥25 kg)	150 mg q12h	958 (546)	15300 (7340)
12- to 17-year-olds	150 mg q12h	564 (242)	9240 (3420)
Adults (≥18 years old)	150 mg q12h	701 (317)	10700 (4100)

Gender
Population pharmacokinetic analysis of data from clinical trials of KALYDECO indicated that there was no clinically relevant effect of gender on the clearance of ivacaftor.

Hepatic Insufficiency
Adult subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max} but an approximately 2-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics. Based on these results, a reduced KALYDECO dose of 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, score 5 to 6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than 2-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 to 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 starting dose of one tablet or packet of granules every other day and modified according to tolerability and clinical response (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency
Pharmacokinetic studies have not been performed with KALYDECO in patients with renal impairment. No dose adjustments are recommended for patients with mild or moderate renal impairment because of minimal urinary excretion of ivacaftor as unchanged parent (<0.01%) and 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 (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY
Store at 20-25°C; excursions permitted to 15-30°C.

Keep out of the sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

Disposal of Unused/Expired Medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

KALYDECO (ivacaftor) tablets are supplied as light blue, capsule-shaped tablets for oral administration. Each tablet is printed with "V 150" in black ink on one side and plain on the other.

KALYDECO (ivacaftor) granules are supplied 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.

Composition

KALYDECO 150 mg tablets: Each tablet contains 150 mg of ivacaftor and the following non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, indigo carmine aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, PEG 3350, polyvinyl alcohol, sodium lauryl sulfate, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

KALYDECO granules: Each packet of granules (granules are presented as minitablets) contains 50 mg of ivacaftor or 75 mg of ivacaftor and the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate

Packaging

The following pack sizes are available:

KALYDECO 150 mg tablets:
-- Blister pack containing 56 film-coated tablets.
-- Bottle containing 60 film-coated tablets.

KALYDECO 50 mg or 75 mg granules:
-- 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)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

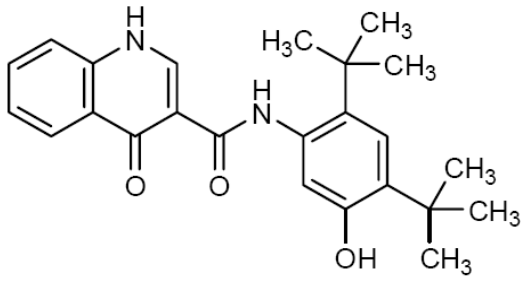
Common name: ivacaftor (INN)

Chemical name: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide or *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

Empirical formula: $C_{24}H_{28}N_2O_3$

Molecular Weight: 392.49

Structural formula:



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

CLINICAL TRIALS

Study Demographics and Trial Design

The trial design and patient demographics for the KALYDECO clinical trials are summarized in Table 8.

Table 8 - Trials 1, 2, 3, 4, 5 (KALYDECO Compared with Placebo) and Trial 6					
Study Number	**Trial Design**	**Dosage; Route of Administration; Duration**	**Number of Subjects**	**Mean Age (Range)**	**Gender**
Trial 1 (subjects with a *G551D-CFTR* mutation)	Randomized, placebo-controlled, double-blind, parallel-group, multiple-dose, multi-centered	150 mg of KALYDECO or placebo; oral; every 12 hours with food for 48 weeks	161	26 years (12 to 53 years)	Male: 48% Female: 52%
Trial 2 (subjects with a *G551D-CFTR* mutation)	Randomized, placebo-controlled, double-blind, parallel-group, multiple-dose, multi-centered	150 mg of KALYDECO or placebo; oral; every 12 hours with food for 48 weeks	52	9 years (6 to 12 years)	Male: 48% Female: 52%
Trial 3 (subjects homozygous for the *F508del-CFTR* mutation)	Randomized, placebo-controlled, double-blind, parallel-group, multiple-dose, multi-centered	150 mg of KALYDECO or placebo; oral; every 12 hours with food for 16 weeks	140	23 years (12 to 52 years)	Male: 53% Female: 47%
Trial 4 (subjects with at least one of the following non-*G551D* gating mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R*)	Randomized, placebo-controlled, double-blind, crossover, multiple-dose, multi-centered	150 mg of KALYDECO or placebo; oral; every 12 hours with food for 8 weeks	39	23 years (6 to 57 years)	Male: 56% Female: 44%
Trial 5 (subjects with an *R117H-CFTR* mutation)	Randomized, placebo-controlled, double-blind, parallel-group	150 mg of KALYDECO or placebo; oral; every 12 hours with food for 24 weeks	69	31 years (6 to 68 years)	Male: 44% Female: 56%

Trial 6 (subjects eligible for the trial had CF with a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, or *S549R* mutation in the *CFTR* gene)	Non-randomized, open-label, multiple-dose	50 mg KALYDECO granules or 75 mg KALYDECO granules according to weight; oral; every 12 hours for 24 weeks	34	2 to <6 years of age (mean age 3 years)	Male: 82% Female: 18%
The *G970R* mutation causes a splicing defect resulting in little-to-no CFTR protein at the cell surface; the resulting low level of protein can be potentiated by ivacaftor.					

Trial 1
Trial 1 evaluated 161 patients with CF and a *G551D–CFTR* mutation 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
Trial 2 evaluated 52 patients with CF and a *G551D–CFTR* mutation 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%]).

Trial 4
Trial 4 evaluated 39 patients with CF and a *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R CFTR* mutation who were 6 years of age or older (mean age 23 years) with FEV_1 ≥40% predicted at screening (mean FEV_1 78% predicted at baseline [range: 43% to 119%]).

Trial 5
Trial 5 evaluated 69 patients with CF and an *R117H* mutation 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%). In the indicated patient population, 18 years of age and older, the mean FEV_1 was 65% predicted at baseline (range: 33% to 93%).

The patients had well preserved body mass index (BMIs) (mean overall: 23.8 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 x ULN were excluded.

Study Results

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 $FEV_1 \geq 40\%$ predicted. Twenty patients with median predicted FEV_1 at baseline of 56% (range: 42% to 109%) received KALYDECO 25, 75, 150 mg or placebo every 12 hours for 14 days and 19 patients with median predicted FEV_1 at baseline of 69% (range: 40% to 122%) received KALYDECO 150 mg, 250 mg, or placebo every 12 hours for 28 days. The selection of the 150 mg every 12 hours dose was primarily based on nominal improvements in lung function (pre-dose FEV_1) and changes in pharmacodynamic parameters (sweat chloride and nasal potential difference). The twice-daily dosing regimen was primarily based on an apparent terminal plasma half-life of approximately 12 hours. Selection of the 150 mg dose of KALYDECO for children 6 to 11 years of age was based on achievement of comparable pharmacokinetics for the key pharmacokinetic parameter as those observed for adult patients.

Efficacy

The efficacy of KALYDECO in patients with CF who have a *G551D* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled Phase 3 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.

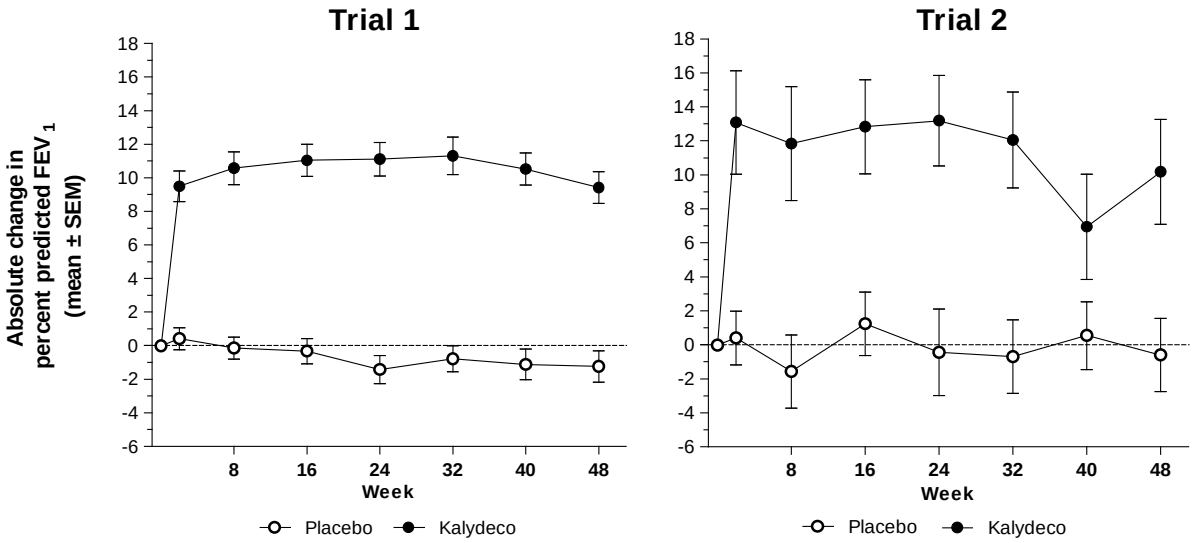
Patients who had persistent *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* isolated from sputum at screening and those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 x ULN were excluded.

Patients in both trials were randomized in a 1:1 ratio 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 trials 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 trials, 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 1). These changes persisted through 48 weeks. Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, and geographic region.

*Figure 1. Mean absolute change from baseline in percent predicted FEV_1**



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

Other Clinical Endpoints

Other efficacy variables included absolute change in sweat chloride from baseline to Week 24, absolute change in weight from baseline to Week 48, and absolute change in pooled (adult and child versions) Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline to Week 24 (the CFQ-R is a disease-specific, patient-reported, health-related, quality-of-life measure for cystic fibrosis consisting of generic and CF-specific scales). The respiratory domain was used as an assessment tool for clinically relevant respiratory symptoms such as cough, wheezing, congestion, sputum production, and difficulty breathing. Time to first pulmonary exacerbation through Week 48 was also assessed in Trial 1. For the purpose of the trial, 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 sinopulmonary 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 9). Weight data, when expressed as body mass index normalized for age and sex in patients <20 years of age, was consistent with absolute change from baseline in weight.

Table 9 - Effect of KALYDECO on Other Efficacy Endpoints in Trials 1 and 2				
	Trial 1		Trial 2	
Endpoint	Treatment difference[a] (95% CI)	*P* value	Treatment difference[a] (95% CI)	*P* value
Mean absolute change from baseline in CF symptom score (points)[b]				
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
Mean absolute change from baseline in sweat chloride (mmol/L)				
Through Week 24	-47.9 (-51.3, -44.5)	<0.0001	-54.3 (-61.8, -46.8)	<0.0001
Through Week 48	-48.1 (-51.5, -44.7)	<0.0001	-53.5 (-60.9, -46.0)	<0.0001
Relative risk of pulmonary exacerbation				
Through Week 24	0.40[c]	0.0016	NA	NA
Through Week 48	0.46[c]	0.0012	NA	NA
Mean absolute change from baseline in body weight (kg)				
At Week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
At Week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002

CI: confidence interval; NA: not analyzed due to low incidence of events
[a] Treatment difference = effect of KALYDECO – effect of Placebo
[b] Evaluated using the Cystic Fibrosis Questionnaire-Revised (CFQ-R)
[c] Hazard ratio for time to first pulmonary exacerbation

Trial 3

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. The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline through Week 16 in percent predicted FEV_1. Treatment with KALYDECO resulted in no improvement in FEV_1 relative to placebo. There were also 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).

Trial 4

Trial 4 was a Phase 3, two-part, randomized, double-blind, placebo-controlled, crossover trial (Part 1) with an open-label extension period (Part 2) to evaluate the efficacy and safety of ivacaftor in patients with CF who have a non-*G551D* gating mutation in the *CFTR* gene

(*G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *G970R*). Patients who completed Part 1 continued into the 16-week open-label Part 2 of the trial.

Trial 4 evaluated 39 patients with CF who were 6 years of age or older (mean age 23 years) with baseline FEV_1 ≥40% predicted (mean FEV_1 78% predicted [range: 43% to 119%]).

In Part 1, patients were randomized 1:1 to receive either 150 mg of ivacaftor 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. 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. The treatment difference between ivacaftor and placebo was 10.7 percentage points (P<0.0001). Improvements in percent predicted FEV_1 were observed regardless of age, disease severity, sex, geographic region, and *Pseudomonas aeruginosa* infection status at baseline. In this study, statistically significant improvement in FEV_1 was seen at Day 15 and durable through 8 weeks.

Treatment with ivacaftor resulted in consistent and statistically significant treatment effects across the secondary endpoints of absolute change from baseline in BMI and BMI-for-age z-score (0.7 kg/m^2; P<0.0001 and 0.3 points; P=0.0010, respectively), and CFQ-R respiratory domain score (9.6 points; P=0.0004) when compared to placebo. Together, these results demonstrate the positive effects of ivacaftor treatment on pulmonary and extrapulmonary measures.

Based on clinical (percent predicted FEV_1) and pharmacodynamic (sweat chloride, see Pharmacodynamics) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established. The *G970R* mutation has been identified as causing a splicing defect resulting in little-to-no CFTR protein at the cell surface able to be potentiated by ivacaftor.

Trial 5

Trial 5 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group clinical trial to evaluate the efficacy and safety of ivacaftor in 69 patients 6 years of age and older with an *R117H* mutation in the *CFTR* gene. All eligible patients from this trial were rolled over into an open-label extension study.

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, which did not reach statistical significance (*P*=0.1979).

Subgroup analysis according to age group was pre-specified in this study protocol.

Subgroup Analysis of Patients less than 18 Years of Age
Efficacy with respect to mean FEV_1 has not been adequately established at this time.

Subgroup Analysis of Patients 18 Years of Age and Older
Treatment with ivacaftor (n=24) resulted in a significant improvement in absolute change in percent predicted FEV_1 through Week 24 compared to placebo (n=26), with a treatment difference of 5.0 percentage points (*P*=0.0119).

Other efficacy variables that were analyzed included absolute change in sweat chloride from baseline through Week 24, absolute change in BMI at Week 24, and improvement in cystic fibrosis symptoms through Week 24 as assessed by the CFQ-R respiratory domain score. The treatment difference for the absolute change from baseline in BMI was 0.31 kg/m^2 (95% CI -1.9, 2.5). The treatment difference in CFQ-R respiratory domain score through Week 24 was 12.6 points (95% CI 5.0, 20.3).

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

Ivacaftor potentiated chloride transport of G551D-CFTR protein *in vitro*, in both recombinant rodent cells carrying this mutation and in human bronchial epithelial (HBE) cells isolated from the bronchi of a patient with CF carrying both the *G551D* and *F508del* mutations. In the *G551D-CFTR* recombinant rodent cells, ivacaftor treatment resulted in a 55-fold increase over baseline chloride transport.

The pharmacological activity of the major circulating metabolites of ivacaftor in humans, M1 (hydroxymethyl-ivacaftor) and M6 (ivacaftor carboxylate), was tested in cultured *G551D/F508del*-HBE (Ussing chamber studies). The M1 metabolite potentiated CFTR-mediated chloride transport with approximately $1/6^{th}$ the potency of ivacaftor and is considered pharmacologically active. The M6 metabolite showed $<1/50^{th}$ the potency of ivacaftor *in vitro* and is not considered to be pharmacologically active.

Safety Pharmacology

Ivacaftor was evaluated *in vitro* for off-target effects on a wide variety of receptors and enzymes in radioligand binding assays, as well as for interactions with a variety of ion channels. Ivacaftor did not potently bind to or alter the function of these targets, indicating a low potential for off-target effects. In electrophysiological studies, ivacaftor inhibited only $Ca_V1.2$ (IC_{50} = 1.3 μM) and $K_V1.5$ (IC_{50} = 3.4 μM) with moderate potency and had little or

no measurable activity (IC_{50} >10 μM) on the other sodium, calcium, and potassium channels tested.

Ivacaftor produced concentration-dependent inhibition of hERG (human ether-à-go-go related gene) tail currents, with an IC_{15} of 5.5 μM. However, no ivacaftor-related QT-prolongation was observed in a dog telemetry study at single doses up to 60 mg/kg or in ECG measurements from repeat-dose studies in dogs up to 1 year at 60 mg/kg/day. Ivacaftor produced a dose-related but transient increase in the blood pressure parameters in dogs at single oral doses up to 60 mg/kg.

Oral administration of ivacaftor did not cause adverse effects on the CNS or respiratory system in rats at single oral doses of up to 1000 mg/kg. Ivacaftor did not cause adverse effects on the cardiovascular system in telemetry studies at single oral doses up to 100 mg/kg in rats and 60 mg/kg in dogs. Ivacaftor produced an inhibition of gastric emptying and gastrointestinal transit in rats at single oral doses of 500 and 1000 mg/kg.

Pharmacokinetics

The findings from *in vivo* absorption, distribution, metabolism, and elimination studies in the mouse, rat, rabbit, and dog showed that ivacaftor was rapidly absorbed following oral administration of aqueous suspensions with the extent of absorption ranging from 30% to 100%. Apparent permeability of ivacaftor *in vitro*, using a Caco-2 cell-based assay, was high, which suggests that human intestinal absorption will be high following oral administration. Bi-directional transport studies conducted in Madin-Darby canine kidney (MDCK) cells with stably transfected human multi-drug resistance protein 1 (MDR1, also known as p-glycoprotein or P-gp) demonstrated that ivacaftor is not a P-gp efflux substrate. *In vitro* studies with recombinant Caco-2 and MDCK-MDR-1 cells also showed that ivacaftor and its metabolite M6 are not substrates of P-gp, while its metabolite M1 is a P-gp substrate. However, ivacaftor and M1 were shown to inhibit digoxin transport *in vitro*, indicating inhibition of P-gp *in vitro*.

Systemic exposure to ivacaftor tended to increase during repeat oral dosing at toxicological dose levels to mice, rats, rabbits, and dogs, possibly due to accumulation in plasma, and time to peak plasma concentrations (t_{max}) increased with increasing dose levels. In addition, systemic exposure to ivacaftor's major metabolites (data not shown) was higher for M1 than for M6 for all 3 species measured (mice, rats, and dogs); however, M1 and M6 exposures were less than ivacaftor in these species.

In vitro protein binding of ivacaftor and metabolites M1 and M6 was high (>98%) *in vitro* in mouse, rat, dog, and human plasma and to isolated human plasma protein components. *In vivo*, ivacaftor did not bind to melanin-containing tissues. Placental transfer of ^{14}C-labelled ivacaftor after a single oral dose to pregnant rats and rabbits occurred, but the exposures to ivacaftor in fetuses were low and variable. ^{14}C-labelled ivacaftor accumulated in the milk of lactating rats.

Ivacaftor was excreted predominately in the feces of all species evaluated.

In vitro inhibition studies suggested that ivacaftor and M1 may have a drug-drug interaction potential through inhibition of CYP2C8, CYP2C9, CYP3A, and P-gp.

TOXICOLOGY

The toxicity of ivacaftor was evaluated in acute, repeat-dose, genetic, carcinogenicity, developmental and reproductive, local tolerance, and other toxicity studies.

Acute Toxicity

Ivacaftor demonstrated a low potential for acute toxicity from high single doses in both mice, (maximum tolerated dose [MTD] = 2000 mg/kg) and rats (MTD = 500 mg/kg). No ivacaftor-related adverse effects were seen at levels that represent 13 to 27 times the maximum recommended human dose (MRHD) on a mg/kg basis (assuming a 50 kg human).

Repeat-dose Toxicity

Ivacaftor was tested in repeat-dose studies of up to 3 months' duration in mice, 6 months' duration in rats, and 12 months' duration in dogs. The only target organ of toxicity identified for ivacaftor was the liver of mice and rats. Clinical chemistry and/or morphological evidence of hepatotoxicity was observed at high dosages in mice (≥600 mg/kg/day in a 3-month study) and rats (≥200 mg/kg/day in the 3-month study and ≥100 mg/kg/day in the 6-month study). In mice, the main clinical pathology changes at the end of 3 months of dosing were elevated alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum electrolytes relative to the control group, and lower cholesterol and glucose, which was accompanied by minimal foci of hepatocellular necrosis in only a few of the animals. The main ivacaftor-related clinical pathology changes in rats (relative to the control group) included prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT); increases in ALT, gamma-glutamyltransferase (GGT), total protein, and blood urea nitrogen (BUN); serum electrolyte changes; and lower bicarbonate. Dose-related elevations in liver weights were accompanied by histopathological findings of centrilobular hepatocellular necrosis with acute/subacute inflammation in a few rats and mixed inflammatory cells occasionally seen in the liver. The hepatic enzyme elevations were typically less than 3-fold greater than normal.

Occasional instances of atrioventricular (AV) block occurred in dogs in repeat-dose studies. AV block is a well-documented background finding in this species. In addition, a slight increase in the incidence of supraventricular premature complex (SVPC) runs was observed in the chronic (12-month) study. The SVPC runs, which occurred in only 3 out of 40 dogs in this study, consisted of multiple events within a single electrocardiogram (ECG) recording at dosages ≥30 mg/kg/day and were reversible following a 28-day recovery period. All other ECG parameters were normal in all groups and the SVPC runs were not accompanied by morphological changes in the heart or changes in the health status of these dogs.

In the chronic toxicity studies, summed exposures to ivacaftor and its major metabolites at the no observed adverse effect level (NOAEL) in rats (50 mg/kg/day) and dogs

(60 mg/kg/day) were at least 4.4- to 5.2- and 2.5- to 3.4-fold higher than the estimated steady-state summed $AUC_{0\text{-}24hr}$ (117.8 μg·hr/mL) at the recommended human therapeutic dosage, respectively (exposures were obtained by non-compartmental analysis (NCA) from sparse PK samples collected in Trial 4).

Genotoxicity

Ivacaftor was shown to be non-mutagenic and non-clastogenic in the following standard *in vitro* and *in vivo* genotoxicity tests: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Carcinogenicity

Two-year studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4- to 7-fold higher than the plasma levels measured in humans following ivacaftor therapy and at least 1.2- to 2.4-fold higher with respect to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 16- to 29-fold higher than the plasma levels measured in humans following ivacaftor therapy, and 6- to 9-fold higher with respect to the summed AUCs for ivacaftor and its major metabolites (exposures were obtained by non-compartmental analysis (NCA) from sparse PK samples collected in Trial 4).

Developmental and Reproductive Toxicity

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 maximum recommended human dose (MRHD) based on the summed AUC of ivacaftor and its major metabolites; exposures were obtained by non-compartmental analysis (NCA) from sparse PK samples collected in Trial 4). Decreased weight of seminal vesicles in males and increases in prolonged diestrus in females were observed at 200 mg/kg/day. Ivacaftor decreased the fertility index in female rats and the number of corpora lutea, implantations, and viable embryos at 200 mg/kg/day when dams were dosed prior to and during early pregnancy. 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 the summed AUCs of ivacaftor and its major metabolites). Ivacaftor was not teratogenic when dosed orally up to 200 mg/kg/day to pregnant rats and up to 100 mg/kg/day to pregnant rabbits during the organogenesis stage of fetal development, and did not cause developmental defects (learning and memory, reproductive capacity) in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning. M1 and M6 were not directly quantitated in the developmental and reproductive toxicity studies.

Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal Day 7 to 35 at dose levels of 10 mg/kg/day and higher (approximately 0.17 and 0.27 times the MRHD based on summed AUCs of ivacaftor and its metabolites in males and females, respectively);

exposures were obtained by non-compartmental analysis (NCA) from sparse PK samples collected in Trial 4). This finding was not observed in older animals. The significance of these findings for humans is unknown.

Other Toxicity

Ivacaftor was not irritating to skin after topical administration to rabbits. Ivacaftor was classified as a non-irritant to eyes when tested *in vitro* on isolated bovine corneas (bovine corneal opacity and permeability assay). In a murine local lymph node assay, ivacaftor had no effects on the proliferative response of lymph node cells from the draining auricular lymph nodes, demonstrating that ivacaftor does not show the potential to induce skin sensitization.

REFERENCES

1. Ramsey B, Davies J, McElvaney G, Tullis E, Bell S, Dřevínek P, Griese M, McKone E, Wainwright C, Konstan M, Moss R, Ratjen F, Sermet-Gaudelus I, Rowe S, Dong Q, Rodriguez S, Yen K, Ordoñez C, Elborn S; for the VX08-770-102 Study Group. A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation. N Engl J Med. 2011 Nov 3; 365(18):1663-72.
2. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordoñez C, Geller DE, for the VX08-770-104 Study Group. Ivacaftor in Subjects with Cystic Fibrosis who are Homozygous for the *F508del-CFTR* Mutation. Chest. 2012;142(3):718-24.
3. Accurso F, Rowe S, Clancy JP, Boyle M, Dunitz J, Durie P, Sagel S, Hornick D, Konstan M, Donaldson S, Moss R, Pilewski J, Rubenstein R, Uluer A, Aitken M, Freedman S, Rose L, Mayer-Hamblett N, Dong Q, Zha J, Stone A, Olson E, Ordoñez C, Campbell P, Ashlock M, Ramsey B, Effect of VX-770 in persons with Cystic Fibrosis and the G551D-*CFTR* Mutation. N Engl J Med 2010 Nov 18; 363(21):1991-2003.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr KALYDECO®
Ivacaftor tablets
Ivacaftor granules

Read this carefully before you/your child start taking **KALYDECO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug.

Remember, this does not take the place of your/your child's doctor's instructions. Talk to your healthcare professional about your/your child's medical condition and treatment and ask if there is any new information about **KALYDECO**.

What is KALYDECO used for?

KALYDECO tablets (150 mg) are for the treatment of cystic fibrosis (CF):

- in patients age 6 years and older and weighing 25 kg or more who have one of the following mutations in their CF gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.
- in patients age 18 years and older who have an R117H mutation in their CF gene.

KALYDECO granules (50 mg and 75 mg) are for the treatment of children with cystic fibrosis (CF):

- in patients age 2 years and older and weighing less than 25 kg who have one of the following mutations in their CF gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.

KALYDECO is not for use in people with CF with two copies of the *F508del* mutation.

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

How does KALYDECO work?

KALYDECO belongs to a group of medicines called "*cystic fibrosis transmembrane conductance regulator (CFTR) potentiators.*" The CFTR protein is a channel at the surface of the cell that allows the movement of particles such as chloride in and out of the cell, contributing to salt and water balance. KALYDECO helps this CFTR protein channel open more often allowing more chloride to pass through.

KALYDECO comes in the following dosage forms:
Tablets: 150 mg
Granules: 50 mg and 75 mg

What are the ingredients in KALYDECO?

Medicinal ingredients: ivacaftor

Non-medicinal ingredients in 150 mg tablets:
carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, indigo carmine aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, PEG 3350, polyvinyl alcohol, sodium lauryl sulfate, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

Non-medicinal ingredients in 50 mg and 75 mg granules:
colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate.

Do not use KALYDECO if:
You are allergic to ivacaftor or any of the non-medicinal ingredients.

To help avoid side effects and ensure correct use, talk to your healthcare professional before you take KALYDECO. Talk about any health conditions or problems you may have, including if you:

- have kidney or liver disease.
- have a problem with the lens of your eye (cataract). Your doctor may recommend eye exams before and after your treatment with KALYDECO.
- 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.

Other warnings you should know about:

Driving and using machines: You may get dizzy when you take KALYDECO. Wait to see how you feel after taking KALYDECO before you drive or use machines. **For children**: you or your child's caregiver should supervise your child when they take KALYDECO. Wait to see if your child is dizzy after taking KALYDECO before they ride their bikes or do anything else that needs their full attention.

Abnormal blood test results:
KALYDECO can cause abnormal blood test results. Your doctor will decide if blood tests are needed.

If you have had high liver enzymes in the past, your doctor may order blood tests to check your liver more often.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KALYDECO:

- antifungal medicines, such as ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole
- antibiotics used for the treatment of bacterial infection, such as clarithromycin, erythromycin, rifampin, rifabutin
- phenobarbital, carbamazepine, phenytoin used for the treatment of epileptic seizures
- oral midazolam, alprazolam, diazepam, triazolam used for the treatment of anxiety, insomnia, agitation, etc.
- digoxin is used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation
- cyclosporine, tacrolimus are used after an organ transplantation
- warfarin is an anticoagulant used to prevent heart attacks, stroke, and blood clots
- St. John's wort (*Hypericum perforatum*) is an herbal medicine
- grapefruit juice, grapefruit, and Seville oranges

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

How to take KALYDECO:

- Always take KALYDECO exactly how your doctor tells you.
- Take your doses of KALYDECO 12 hours apart.
- Even if you feel well, keep taking KALYDECO exactly how your doctor tells you.
- Check with your doctor if you are not sure about your dose.
- Do not change the dose or stop taking the medicine without first talking to your doctor.
- Your doctor may need to adjust your dose if you have liver disease or if you are taking medications that may interact with KALYDECO.

KALYDECO Tablets (for patients aged 6 years and older and weighing 25 kg or more):
One tablet every 12 hours by mouth with fat-containing food (see below). Do not crush or chew the tablet. Swallow the tablet whole.

- Each KALYDECO box contains 4 individual blister cards.
- There are 7 days of tablets for each blister card. Each blister card contains 14 tablets - 7 morning doses and 7 evening doses.
- You may cut along the dotted line to separate your doses from the blister card.
- **Morning Dose**: unpeel the paper backing from a blister card. Do not push the tablet through the paper backing because the tablets could break. Remove one KALYDECO tablet and swallow it whole with food that contains fat.

- **Evening Dose**: 12 hours after your first dose, unpeel the paper backing from another blister card to remove one KALYDECO tablet and swallow it whole with food that contains fat.

KALYDECO Granules (for children aged 2 years and older and weighing less than 25 kg): Your doctor will prescribe the appropriate amount based on weight. The usual dose is to take 1 packet of granules every 12 hours with fat-containing food.

How to prepare the granules:

- Each KALYDECO box contains 4 individual wallets.
- There are 7 days of granules in each wallet. Each wallet contains 14 packets of granules - 7 morning doses and 7 evening doses.
- Finish all doses from one wallet before starting a new one.
- **Morning Dose:** Remove the first dose from the wallet.
- 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. Each packet is for single use only. Some examples of soft foods or liquids include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice (except for grapefruit juice).
- Mix the KALYDECO granules with food or liquid.
- **After mixing, give KALYDECO within 1 hour. Make sure all medicine is taken. This is very important for KALYDECO to work properly and be effective.**
- If mixed with food, KALYDECO granules must not be stored for future use.
- **Evening Dose:** This dose should be taken 12 hours after your **Morning Dose.** Follow the same steps listed above under **Morning Dose**.

KALYDECO should always be taken with a fat-containing food:

- Taking KALYDECO with fat-containing food is important to get the right amount of medicine in your body.
- Each dose should be taken just before or just after fat-containing food.
- Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a typical CF diet should be given.
- Examples of meals that contain fat:
  - meals prepared with butter or oils
  - meals that have eggs, nuts, whole-milk dairy products (such as whole milk, cheese, and yogurt) or meats.

Overdose:

If you think you have taken too much KALYDECO, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- 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.

Refilling your prescription:
Remember to get a new prescription from your doctor or a refill from your pharmacy before all your tablets or granules are taken.

What are possible side effects from using KALYDECO?
These are not all the possible side effects you may feel when taking KALYDECO. If you experience any side effects not listed here, contact your healthcare professional.

- Diarrhea
- Nausea
- Stomach (abdominal) pain

- Common cold
- Runny nose
- Upper respiratory tract infection
- Changes in the type of bacteria in your sputum

- Headache
- Dizziness

- Nasal congestion
- Sinus congestion
- Sore throat

- Rash

- Joint pain

Serious Side Effects and What to do About Them			
Symptom/Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Liver disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, pale stools, itchy skin		√	
Abdominal pain (stomach)	√		
Low blood sugar (glucose)	√		
UNKNOWN **Allergic reaction:** rash; hives; swelling of the face, lips, tongue or throat; difficulty swallowing or breathing			√

If you have other symptoms or side effects that are not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to: 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada,
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at 20-25°C; short periods to 15-30°C are permitted.

Keep out of reach and sight of children.

You may need to read this leaflet again. Please do not throw this away.

If you want more information about KALYDECO:

- talk to your healthcare professional.
- find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://www.hc-sc.gc.ca/index-eng.php); the manufacturer's website, http://www.vrtx.ca; or by calling: 1-877-634-VRTX (8789).

This leaflet was prepared by Vertex Pharmaceuticals (Canada) Incorporated.

Last Revised: November 1, 2017