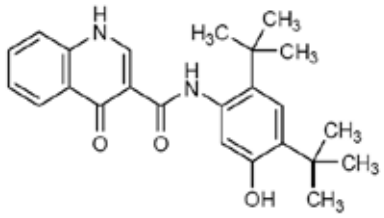
PRODUCT INFORMATION
KALYDECO™
(ivacaftor)

NAME OF THE MEDICINE

Ivacaftor is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. The empirical formula of ivacaftor is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. The pKa values of ivacaftor are 9.40 and 11.60. The log D value of ivacaftor is 5.68 at pH=7.4 and 25°C.

Its structural formula is:



CAS Number: 873054-44-5

DESCRIPTION

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

KALYDECO is available as a light blue capsule-shaped, film-coated tablet for oral administration containing 150 mg of ivacaftor. Each tablet contains the following inactive ingredients: cellulose-microcrystalline, lactose, hypromellose acetate succinate, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, magnesium stearate, carnauba wax, Opadry II complete film coating system 85F90614 Blue, OPACODE monogramming ink S-1-17823 BLACK.

PHARMACOLOGY

Mechanism of Action

Ivacaftor is a selective potentiator of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein, i.e., *in vitro* ivacaftor increases CFTR channel gating to enhance chloride transport. However, the exact mechanism leading ivacaftor to prolong the gating activity of some mutant CFTR forms has not been completely elucidated.

Pharmacodynamics

In clinical trials (Studies 1 and 2) in patients with the *G551D* mutation in one allele of the *CFTR* gene, ivacaftor led to rapid (15 days), substantial [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], and sustained (through 48 weeks) reduction in sweat chloride concentration.

Pharmacokinetics
The pharmacokinetics of ivacaftor are 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, 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
Following multiple oral dose administrations of ivacaftor, the exposure of ivacaftor generally increased with a dose from 25 mg every 12 hours to 450 mg every 12 hours. The exposure of ivacaftor increased approximately 2- to 4-fold when given with food containing fat. Therefore, ivacaftor 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.

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 (Vz/F) of ivacaftor after a single dose of 275 mg in the fed state was similar for healthy subjects and patients with CF. After oral administration of 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, the mean (±SD) apparent volume of distribution was 353 (122) L.

Metabolism
Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised 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 (88%) is eliminated in the faeces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent and minimal urinary excretion (6.6%) of ivacaftor plus metabolites. 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 the 150 mg dose was 17.3 (8.4) L/hr in healthy subjects at steady state.

Special Populations

Children and Adolescents
Based on population PK analysis, the absorption in children (2.99 h for zero-order absorption and 0.546 h^{-1} for absorption rate constant, k_a) is not different from adults. However, the predicted total body clearance was lower in children (e.g., 10 L/h for a 20 kg male) than in adults (e.g., 18.9 L/h for a 70 kg male), which resulted in a higher AUC by exposure determination from observed data in children than in adults.

Based on exposure determinations from observed data in Phase 2 and 3 studies, the 150 mg q12h dose regimen resulted in median and mean (SD) ivacaftor C_{min} of 752 and 1180 (854) ng/mL for 6-11 year old subjects, 492 and 556 (356) ng/mL for 12-17 year old subjects and 690 and 774 (468) ng/mL for the adult subjects. The corresponding AUC median and mean values were 16560 and 18200 (6547) ng*hr/mL for children 6 to 11 years old, 8122 and 8536 (3064) ng*hr/mL for adolescents 12 to 17 years old, and 8770 and 9508 (3763) ng*hr/mL for adults.

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

Renal Impairment
Pharmacokinetic studies have not been performed with ivacaftor in patients with renal impairment. In a human pharmacokinetic study, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine). There was negligible urinary excretion of ivacaftor as unchanged parent (less than 0.01% following a single oral dose of 500 mg). Therefore, no dose adjustments are recommended for mild and moderate renal impairment. However, caution is recommended when administering ivacaftor to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end stage renal disease (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Hepatic Impairment
Following a single dose of 150 mg of ivacaftor, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had similar ivacaftor C_{max} (mean (±SD) of 735 (331) ng/mL), but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ (mean (±SD) of 16800 (6140) ng*hr/mL) compared with healthy subjects matched for demographics. Simulations for predicting the steady-state exposure of ivacaftor showed that by reducing the dosage from 150 mg q12h to 150 mg once daily, subjects with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in subjects with CF. Therefore, a reduced dose of 150 mg once daily is recommended in patients with moderate hepatic impairment. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on pharmacokinetics of ivacaftor has not been studied

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15), but exposure is expected to be higher than in patients with moderate hepatic impairment. The use of KALYDECO in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 150 mg every other day. Dosing intervals should be modified according to clinical response and tolerability (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

CLINICAL TRIALS

The efficacy of KALYDECO has been evaluated in two Phase 3 randomised, double-blind, placebo-controlled, multi-centre studies of clinically stable patients with CF who had the *G551D* mutation in the *CFTR* gene on at least 1 allele and had FEV_1 (forced expiratory volume exhaled in the first second) ≥40% predicted.

Patients in both studies were randomised 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.

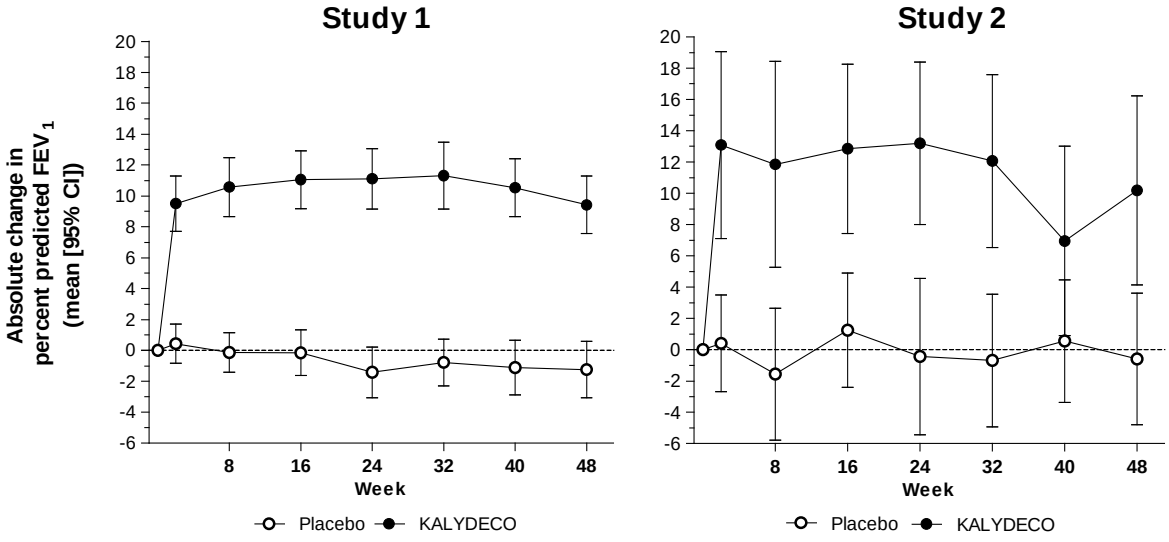
Study 1 evaluated 161 patients who were 12 years of age or older; 122 (75.8%) of patients had the *F508del* mutation in the second allele. At the start of the study, patients in the placebo group used some medicinal products at a higher frequency than the ivacaftor group. These medications included dornase alfa (73.1% versus 65.1%), salbutamol (53.8% versus 42.2%), tobramycin (44.9% versus 33.7%), and salmeterol/fluticasone (41.0% versus 27.7%). At baseline, mean predicted FEV_1 was 63.6% (range: 31.6% to 98.2%), and mean age was 26 years (range: 12 to 53 years).

Study 2 evaluated 52 patients who were 6 to 11 years of age at screening; mean (SD) body weight was 30.9 (8.63) kg; 42 (80.8%) of patients had the *F508del* mutation in the second allele. At baseline, mean predicted FEV_1 was 84.2% (range: 44.0% to 133.8%), and mean age was 9 years (range: 6 to 12 years); 8 (30.8%) of patients in the placebo group and 4 (15.4%) of patients in the ivacaftor group had an FEV_1 less than 70% predicted at baseline.

The primary efficacy endpoint in both studies was the mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment.

The treatment difference between ivacaftor and placebo for the mean absolute change (95% CI) in percent predicted FEV_1 from baseline through Week 24 was 10.6 percentage points (8.6; 12.6) in study 1 and 12.5 percentage points (6.6; 18.3) in study 2 (Figure 1). The treatment difference between ivacaftor and placebo for the mean relative change (95% CI) in percent predicted FEV_1 from baseline through Week 24 was 17.1% (13.9, 20.2) in study 1 and 15.8% (8.4, 23.2) in study 2. The mean change from baseline through Week 24 in FEV_1 (L) was 0.37 L in the ivacaftor group and 0.01 L in the placebo group in study 1 and 0.30 L in the ivacaftor group and 0.07 L in the placebo group in study 2. In both studies, improvements in FEV_1 were rapid in onset (Day 15) and durable through 48 weeks.

Figure 1 Mean Absolute Change from Baseline in Percent Predicted FEV_1



FEV_1 results at 24 and 48 weeks by age subgroups are shown in Table 1.

Table 1. Mean Absolute Change from Baseline in Percent Predicted FEV_1 by MMRM

Subgroup Age (years)	Study	Through Week 24 percentage points (95% CI)	Through Week 48 percentage points (95% CI)
6 to 11	2	12.5 (6.6, 18.3)	10.0 (4.5, 15.5)
12 to 17	1	11.9 (5.9, 17.9)	11.4 (5.4, 17.4)
≥18	1	9.9 (7.8, 12.0)	9.9 (7.7, 12.0)

CI: confidence interval; FEV_1: forced expiratory volume in 1 second;
MMRM: mixed-effects model for repeated measures

The results on clinically relevant secondary endpoints are shown in Table 2.

Table 2. Effect of ivacaftor on other efficacy endpoints in studies 1 and 2

	Study 1		Study 2	
Endpoint	**Treatment difference[a] (95% CI)**	***P* value**	**Treatment difference[a] (95% CI)**	***P* value**
Mean absolute change from baseline in CFQ-R[b] respiratory domain score (points)[c]				
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[d]	0.0016	NA	NA
Through Week 48	0.46[d]	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
Mean absolute change from baseline in BMI (kg/m^2)				
At Week 24	0.94 (0.62, 1.26)	<0.0001	0.81 (0.34, 1.28)	0.0008
At Week 48	0.93 (0.48, 1.38)	<0.0001	1.09 (0.51, 1.67)	0.0003
Mean change from baseline in *z*-scores				
Weight-for-age z-score at Week 48[e]	0.33 (0.04, 0.62)	0.0260	0.39 (0.24, 0.53)	<0.0001
BMI-for-age z-score at Week 48[e]	0.33 (0.002, 0.65)	0.0490	0.45 (0.26, 0.65)	<0.0001

CI: confidence interval; NA: not analyzed due to low incidence of events

[a] Treatment difference = effect of ivacaftor – effect of placebo

[b] CFQ-R: Cystic Fibrosis Questionnaire-Revised is a disease-specific, health-related quality-of-life measure for CF.

[c] Study 1 data were pooled from CFQ-R for adults/adolescents and CFQ-R for children 12 to 13 years of age; Study 2 data were obtained from CFQ-R for children 6 to 11 years of age.

[d] Hazard ratio for time to first pulmonary exacerbation

[e] In subjects under 20 years of age (CDC growth charts)

Study 3: Study in Patients with CF with the *F508del* Mutation in the *CFTR* Gene

Study 3 (Part A) was a 16-week, 4:1 randomised, double-blind, placebo-controlled, parallel-group Phase 2 study of ivacaftor (150 mg every 12 hours) 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 (see PRECAUTIONS).

The mean absolute change from baseline through Week 16 in percent predicted FEV_1 (primary efficacy endpoint) was 1.5 percentage points in the ivacaftor group and -0.2 percentage points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 1.7 percentage points (95% CI: -0.6, 4.1); this difference was not statistically significant (*P* = 0.15).

Study 4: Open-Label Extension Study
Study 4 is an ongoing, open-label extension study to evaluate the efficacy and safety of long-term treatment of orally administered ivacaftor (150 mg every 12 hours) in patients continuing from studies 1 and 2. It enrolled 144 adolescents/adults who completed Study 1 (age ≥12 years) and 48 children who completed Study 2 (age 6-11 years). The percent predicted FEV_1 range at the beginning of study 4 was 29.1% to 126.7%. The use of inhaled hypertonic saline was permitted. A pre-specified interim analysis was performed after all patients from study 1 received 48 weeks and all patients from study 2 received 24 weeks of treatment with ivacaftor in study 4.

In patients treated with placebo in study 1, 48-week treatment with ivacaftor in study 4 (63 patients) resulted in an improvement in the mean absolute change in percent predicted FEV_1 through Week 48 of 9.4 percentage points, similar to that observed in patients treated with ivacaftor in the placebo-controlled study 1. In patients treated with ivacaftor in study 1, 48-week treatment with ivacaftor in study 4 (73 patients) resulted in a mean absolute change in percent predicted FEV_1 from the baseline value in study 1 to Week 96 of 9.5 percentage points, similar to that observed at Week 48 (9.4 percentage points) in study 1.

In patients treated with placebo in study 2, 24-week treatment with ivacaftor in study 4 (22 patients) resulted in an improvement in the mean absolute change in percent predicted FEV_1 through Week 24 of 8.1 percentage points, similar to that observed in patients treated with ivacaftor in the placebo-controlled study 2. In patients treated with ivacaftor in study 2, 24-week treatment with ivacaftor in study 4 (26 patients) resulted in a mean absolute change in percent predicted FEV_1 from the baseline value in study 2 to Week 72 of 10.1 percentage points, similar to that observed at Week 48 (10.2 percentage points) in study 2.

INDICATIONS

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of this medication, patients should not be treated with this medicine.

PRECAUTIONS

Only patients with CF who had a *G551D* mutation in at least one allele of the *CFTR* gene were included in studies 1 and 2 (see CLINICAL TRIALS). Limited data are available in patients with percent predicted FEV_1 of less than 40% (4 patients treated for 96 weeks and 8 patients treated for 48 weeks). Maximum length of treament has been 96 weeks in patients treated with ivacaftor; longer term safety data are currently unavailable.

Patients with CF who do not have a *G551D* Mutation in the *CFTR* Gene
Efficacy results from a Phase 2 study in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene showed no statistically significant difference in FEV_1 over 16 weeks of ivacaftor treatment compared to placebo (see CLINICAL TRIALS). Ivacaftor has not been studied in other populations of patients with CF. Therefore, use of KALYDECO in these patients is not recommended.

Effects on Fertility
Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding approximately 5 and 6 times, respectively, the systemic exposure anticipated in patients at the maximum recommended human dose (MRHD) based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy. The pregnancy rate was decreased, oestrus cycling was disrupted and pre-implantation loss was increased. These effects occurred in the presence of significant maternal toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (yielding approximately 3 times the exposure at the MRHD based on summed AUCs of ivacaftor and its metabolites).

Use in Pregnancy
Category B3

Category B3drugs have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There are no adequate and well-controlled studies of KALYDECO in pregnant women. Developmental toxicity studies in animals revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day (yielding 6 times the summed AUC for ivacaftor and its major metabolites anticipated in patients) or in rabbits at up to 100 mg/kg/day (relative exposure based on summed AUCs, 1.5). Fetal weight was decreased and the incidence of minor fetal skeletal abnormalities was increased in rats treated at 200 mg/kg/day; these effects were observed in conjunction with maternal toxicity. Ivacaftor and/or its metabolites were shown to cross the placenta in rats and rabbits. Because animal reproduction studies are not always predictive of human response, KALYDECO should be used during pregnancy only if clearly needed.

Use in Lactation
It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Ivacaftor and/or its metabolites were shown to be excreted into the milk of lactating rats. The safe use of KALYDECO during breast-feeding has not been established. KALYDECO should only be used during breast-feeding if the potential benefit outweighs the potential risk.

Paediatric Use
The safety and efficacy of KALYDECO in children aged less than 6 years have not been established. Cataracts were seen in juvenile rats treated with ivacaftor from postnatal day 7-35 at oral doses ≥10 mg/kg/day, yielding exposure to ivacaftor and its major metabolites (summed AUCs) more than 7 times lower than that in patients at the MRHD. This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Use in the Elderly
Clinical studies of ivacaftor did not include patients age 65 years and older. Thus, the efficacy and safety of ivacaftor in elderly patients have not been evaluated.

Renal Impairment

Caution is recommended while using ivacaftor in patients with severe renal impairment (creatinine clearance less than or equal to 30 ml/min) or end-stage renal disease (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

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 interval should be 150 mg of KALYDECO every other day (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

Patients after Organ Transplantation
KALYDECO has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See INTERACTIONS WITH OTHER MEDICINES for interactions with cyclosporine or tacrolimus.

Lactose
KALYDECO contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Genotoxicity
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.

Carcinogenicity
Two-year oral 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 0.6 to 1.2 times higher with respect to the summed AUC 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 17- to 31-fold higher than the plasma levels measured in humans following ivacaftor therapy, and 3.1- to 4.5-fold higher with respect to the summed AUC for ivacaftor and its major metabolites.

Effect on Laboratory tests
Liver Function Tests
Moderate transaminase [alanine transaminase (ALT) or aspartate transaminase (AST)] elevations are common in subjects with CF. Overall, the incidence and clinical features of transaminase elevations in clinical trials was similar between subjects in the ivacaftor and placebo treatment groups (see ADVERSE EFFECTS). In the subset of patients with a medical history of elevated transaminases, increased ALT or AST have been reported more frequently in patients receiving ivacaftor compared to placebo. Therefore, liver function tests are recommended prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop unexplained increased transaminase levels during treatment 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, consideration should be given to the continuation of treatment after assessment of the individual benefits and risks.

Interactions with Medicinal Products
Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Medicinal products that inhibit or induce CYP3A activity, may impact the pharmacokinetics of ivacaftor (see INTERACTIONS WITH OTHER MEDICINES). Ivacaftor is a weak CYP3A inhibitor and may modify the pharmacokinetics of medicinal products metabolised through the CYP3A system. *In vitro* studies indicated that ivacaftor has the potential to inhibit P-glycoprotein (P-gp) and CYP2C9. The dose of KALYDECO must be adjusted when concomitantly used with strong and moderate CYP3A inhibitors. Exposure to ivacaftor is reduced by the concomitant use of CYP3A inducers, therefore potentially resulting in loss of efficacy of KALYDECO (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES).

Driving and Operating Machinery
Dizziness has been reported in patients receiving KALYDECO, which could influence the ability to drive or operate machines (see ADVERSE EFFECTS). Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

INTERACTIONS WITH OTHER MEDICINES

Ivacaftor is a substrate of CYP3A4 and CYP3A5. It is a weak inhibitor of CYP3A and a potential inhibitor of P-gp and CYP2C9.

Effects of Other Medicines on Ivacaftor

CYP3A Inhibitors
Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, increased ivacaftor exposure [measured as area under the curve (AUC)] by 8.5-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.7-fold. A reduction of the KALYDECO dose to 150 mg twice-a-week is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold and M1 exposure by 1.9-fold. A reduction of the KALYDECO dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

Co-administration of KALYDECO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure to ivacaftor. Food containing grapefruit or Seville oranges should be avoided during treatment with KALYDECO.

CYP3A Inducers
Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, decreased ivacaftor exposure (AUC) by 89% and M1 exposure by 75%. Co-administration with strong CYP3A inducers, such as rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's Wort (*Hypericum perforatum*) is not recommended. Concomitant use of weak to moderate inducers of CYP3A (e.g., dexamethasone, high-dose prednisone) may decrease the exposure of ivacaftor and thus may reduce KALYDECO efficacy.

Effects of Ivacaftor on Other Medicines

CYP3A, P-gp, or CYP2C9 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. Administration of KALYDECO may increase systemic exposure of medicinal products which are substrates of CYP3A and /or P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Use with caution and monitor for benzodiazepine-related side effects when using concomitant midazolam, alprazolam, diazepam or triazolam. Use with caution and appropriate monitoring when using concomitant digoxin, cyclosporine, or tacrolimus. Ivacaftor may inhibit CYP2C9. Therefore, monitoring of the INR during co-administration with warfarin is recommended.

Other Recommendations
Ivacaftor has been studied with an oestrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the oral contraceptive. Ivacaftor is not expected to modify the efficacy of oral contraceptives. Therefore, no dose adjustment of oral contraceptives is necessary.

Ivacaftor has been studied with the CYP2C8 substrate rosiglitazone. No significant effect on rosiglitazone exposure was found. Therefore, no dose adjustment of CYP2C8 substrates such as rosiglitazone is necessary.

Ivacaftor has been studied with the CYP2D6 substrate desipramine. No significant effect on desipramine exposure was found. Therefore, no dose adjustment of CYP2D6 substrates such as desipramine is necessary.

Interaction studies have only been performed in adults.

ADVERSE EFFECTS

Experience from Clinical Trials
The safety profile of KALYDECO is based on pooled data from placebo-controlled Phase 3 clinical trials conducted in 109 patients who received ivacaftor and 104 patients who received placebo up to 48 weeks.

The most common adverse reactions experienced by patients who received ivacaftor in the pooled placebo-controlled Phase 3 trials were abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo). One patient in the ivacaftor group reported a serious adverse reaction: abdominal pain.

In two double-blind, placebo-controlled 48-week Phase 3 clinical trials there were 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 3 shows adverse events with an incidence of at least 10% in any treatment group from the two double-blind, placebo controlled trials.

Table 3 - Adverse Events with an incidence of at least 10% in any treatment group of patients age 6 years and older with the *G551D* mutation in the *CFTR* gene

Preferred Term	**KALYDECO N= 109 (%)**	**Placebo N= 104 (%)**
Cystic fibrosis lung	42 (38.5)	58 (55.8)
Cough	40 (36.7)	52 (50.0)
Headache	26 (23.9)	17 (16.3)
Oropharyngeal pain	24 (22.0)	19 (18.3)
Upper respiratory tract infection	25 (22.9)	14 (13.5)
Nasal congestion	22 (20.2)	16 (15.4)
Abdominal pain	17 (15.6)	13 (12.5)
Pyrexia	16 (14.7)	16 (15.4)
Nasopharyngitis	16 (14.7)	12 (11.5)
Productive cough	14 (12.8)	16 (15.4)
Diarrhoea	14 (12.8)	10 (9.6)
Rash	14 (12.8)	7 (6.7)
Nausea	13 (11.9)	11 (10.6)
Vomiting	11 (10.1)	17 (16.3)
Rales	11 (10.1)	12 (11.5)
Haemoptysis	9 (8.3)	17 (16.3)
Pulmonary function test decreased	5 (4.6)	15 (14.4)
Abdominal pain upper	10 (9.2)	11 (10.6)

Adverse reactions identified in patients who had a *G551D* mutation in at least one allele, age 6 years and older (pooled Phase 3 trials) are presented in Table 4 and are listed by system organ class, preferred term, and frequency. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000) to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (frequency cannot be estimated using the available data).

Table 4. Adverse reactions in KALYDECO-treated patients age 6 years and older with the *G551D* mutation in the *CFTR* gene

System Organ Class	Frequency Category	Adverse Reactions (Preferred term) KALYDECO N=109
Infections and infestations	very common	Nasopharyngitis
	very common	Upper respiratory tract infection
	common	Rhinitis
Nervous system disorders	very common	Headache
	common	Dizziness
Ear and labyrinth disorders	common	Ear discomfort
	common	Ear pain
	common	Tinnitus
	common	Tympanic membrane hyperaemia
	uncommon	Ear congestion
	uncommon	Vestibular disorder
Respiratory, thoracic and mediastinal disorders	very common	Nasal congestion
	very common	Oropharyngeal pain
	common	Pharyngeal erythema
	common	Sinus congestion
Gastrointestinal disorders	very common	Abdominal pain
	very common	Diarrhoea
Skin and subcutaneous tissue disorders	very common	Rash
Reproductive system and breast disorders	uncommon	Breast inflammation
	uncommon	Breast mass
	uncommon	Gynaecomastia
	uncommon	Nipple disorder
	uncommon	Nipple pain
Investigations	common	Bacteria in sputum

Description of selected adverse reactions

Rash
During 48-week placebo-controlled clinical trials, the incidence of rash was 12.8% in KALYDECO-treated patients. These events were described as mild to moderate in severity, none were serious, and no patients discontinued treatment because of rash.

Ear and labyrinth disorders
During 48-week placebo-controlled clinical trials, the incidence of ear and labyrinth disorders was 9.2% in KALYDECO-treated patients. Most events were described as mild to moderate in severity, 1 event of ear pain was described as severe; none were serious; no patients discontinued treatment because of ear and labyrinth disorders.

Nervous system disorders

Headache

During 48-week placebo-controlled clinical trials, the incidence of headache was 23.9% in KALYDECO-treated patients. These events were described as mild to moderate in severity, none were serious, and no patients discontinued treatment because of headache.

Dizziness

During 48-week placebo-controlled clinical trials, the incidence of dizziness was 9.2% in the KALYDECO-treated patients. These events were described as mild to moderate in severity, none were serious, and no patients discontinued treatment because of dizziness.

Upper respiratory tract reactions

During 48-week placebo-controlled clinical trials, the incidence of *upper respiratory tract reactions* (upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) was 63.3% in KALYDECO-treated patients. Most events were described as mild to moderate in severity, 1 event of upper respiratory tract infection and 1 event of nasal congestion were considered to be severe, none were serious, and no patients discontinued treatment because of upper respiratory tract reactions.

Laboratory abnormalities

Transaminase elevations

During the placebo-controlled Phase 2b/3 clinical trials, up to 48 weeks, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 1.8%, 2.7% and 6.3% in KALYDECO-treated patients and 1.5%, 2.3% and 8.4% in placebo-treated patients, respectively. Three patients, 2 (1.5%) on placebo and 1 (0.5%) on KALYDECO permanently discontinued treatment for elevated transaminases, all >8x ULN. No KALYDECO-treated patients experienced a transaminase elevation >3x ULN associated with elevated total bilirubin >1.5x ULN. In KALYDECO-treated patients, most transaminase elevations up to 5x ULN resolved without treatment interruption. KALYDECO dosing was interrupted in most patients with transaminase elevations >5x ULN. In all instances where dosing was interrupted for elevated transaminases, KALYDECO dosing was able to be resumed (see PRECAUTIONS).

Paediatric population

Table 5 lists the adverse reactions by system organ class, preferred term, and frequency in KALYDECO–treated paediatric patients age 6 through to 17 in the two 48-week Phase 3 studies in patients with CF with a *G551D* mutation. The safety data is limited to 23 patients between 6 to 11 years of age, and 22 patients between 12 to 17 years of age. Adverse reactions are ranked under the MedDRA frequency classification: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), and unknown (frequency cannot be estimated using the available data).

Table 5. Adverse reactions in KALYDECO-treated patients age 6 through 17 years with the *G551D* mutation in the *CFTR* gene

System Organ Class	Frequency Category		Adverse Reactions KALYDECO (Preferred Term)
	6 to 11 Years N=23	12 to 17 Years N=22	
Infections and infestations	very common	very common	Nasopharyngitis
	very common	very common	Upper respiratory tract infection
	common	very common	Rhinitis
Nervous system disorders	very common	very common	Headache
	not observed	very common	Dizziness
Ear and labyrinth disorders	common	common	Ear pain
	common	not observed	Tympanic membrane hyperaemia
Respiratory, thoracic, and mediastinal disorders	very common	very common	Nasal congestion
	very common	very common	Oropharyngeal pain
	common	not observed	Pharyngeal erythema
Gastrointestinal disorders	very common	very common	Abdominal pain
	very common	not observed	Diarrhoea
Skin and subcutaneous tissue disorders	common	very common	Rash
Investigations	common	very common	Bacteria in sputum

Post-Marketing Experience
There are no relevant updates from the post-marketing experience.

DOSAGE AND ADMINISTRATION

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 to confirm the presence of the *G551D* mutation in at least one allele of the *CFTR* gene before starting treatment.

The recommended dose for adults and paediatric patients is 150 mg taken orally every 12 hours (300 mg total daily dose).

KALDYECO should be taken with a fat-containing meal or snack. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. 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 during treatment with KALYDECO (see INTERACTIONS WITH OTHER MEDICINES).

Use in the elderly*:*
The efficacy and safety of KALYDECO in patients age 65 years or older have not been evaluated.

Use in Renal Insufficiency
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using ivacaftor in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see PRECAUTIONS and PHARMACOLOGY).

Use in Hepatic Insufficiency
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of 150 mg once daily is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There is no experience of use of KALYDECO in patients with severe hepatic impairment. The use of KALYDECO in these patients is therefore not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 150 mg every other day. Dosing intervals should be modified according to clinical response and tolerability (see PRECAUTIONS and PHARMACOLOGY).

Use in Combination with Other Medicinal Compounds
When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), KALYDECO should be administered at a dose of 150 mg twice a week (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), KALYDECO should be administered at a single daily dose of 150 mg (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

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

OVERDOSAGE
For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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

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

PRESENTATION AND STORAGE CONDITIONS

KALYDECO (ivacaftor) film-coated tablets are supplied as light blue, capsule-shaped tablets (16.5 mm x 8.4 mm in modified caplet shape) containing 150 mg of ivacaftor. Each tablet is printed with “V 150” in black ink on one side only.

KALYDECO tablets are packaged in a blister pack or a child-resistant bottle with desiccant.

The following pack sizes are available:

- Blister pack containing 56 film-coated tablets
- Bottle containing 56 film-coated tablets

Store below 30ºC.

NAME AND ADDRESS OF THE SPONSOR
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Australia

POISON SCHEDULE OF THE MEDICINE
S4 -Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS
09 July 2013

DATE OF MOST RECENT AMENDMENT
1ST Oct 2013