ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of ivacaftor.

Excipient with known effect: each film-coated tablet contains 167.2 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light blue capsule-shaped tablets, printed with “V 150” in black ink on one side and plain on the other (16.5 mm x 8.4 mm in modified caplet shape).

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 (see sections 4.4 and 5.1).

4.2 Posology and method of 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.

Posology

Adults, adolescents and children aged 6 years and older
The recommended dose is 150 mg taken orally every 12 hours (300 mg total daily dose).

Kalydeco should be taken with fat-containing food. Meals and snacks recommended in CF guidelines or 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 section 4.5).

Special populations

Elderly
The efficacy and safety of Kalydeco in patients age 65 years or older have not been evaluated.

Renal impairment
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 sections 4.4 and 5.2.)

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of 150 mg once daily is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). 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 sections 4.4 and 5.2).

Concomitant use of CYP3A inhibitors
When co-administered with potent 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 sections 4.4 and 4.5).

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 sections 4.4 and 4.5).

Paediatric population
The safety and efficacy of Kalydeco in children aged less than 6 years have not been established. No data are available.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 section 5.1). Limited data are available in patients with percent predicted FEV_1 (forced expiratory volume exhaled in the first second) of less than 40% (4 patients treated for 96 weeks and 8 patients treated for 48 weeks). Maximum length of treatment 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 section 5.1). Ivacaftor has not been studied in other populations of patients with CF. Therefore, use of Kalydeco in these patients is not recommended.

Effect on 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 section 4.8). 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 and consideration should be given to the continuation of treatment after assessment of the individual benefits and risks.

Renal impairment
Caution is recommended while using Kalydeco in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

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 sections 4.2 and 5.2).

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 section 4.5 for interactions with cyclosporine or tacrolimus.

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 section 4.5). 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 potent 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 sections 4.2 and 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Medicinal products affecting the pharmacokinetics of 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.

Medicinal products affected by ivacaftor:

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
No adequate and well-controlled studies of Kalydeco in pregnant women have been conducted. Developmental toxicity studies have been performed in rats and rabbits at daily doses up to 5 times the human daily dose and have revealed no evidence of harm to the foetus due to ivacaftor (see section 5.3). Because animal reproduction studies are not always predictive of human response, Kalydeco should be used during pregnancy only if clearly needed.

Breast-feeding
It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Ivacaftor was shown to be excreted into the milk of lactating female 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.

Fertility
Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 5 and 6 times, respectively, the maximum recommended human dose (MRHD) based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy (see section 5.3). No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 3 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

4.7 Effects on ability to drive and use machines

Dizziness has been reported in patients receiving Kalydeco, which could influence the ability to drive or operate machines (see section 4.8). Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile
The safety profile of Kalydeco is based on pooled data from placebo-controlled Phase 3 clinical studies 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 studies 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). Two patients in the ivacaftor group reported a serious adverse reaction: abdominal pain.

Tabulated list of adverse reactions
Adverse reactions identified in patients who had a *G551D* mutation in at least one allele, age 6 years and older (pooled Phase 3 studies) are presented in Table 1 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 1. 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 studies, 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 studies, 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 studies, 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 studies, 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 studies, 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 48-week, placebo-controlled clinical studies, 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 section 4.4).

Paediatric population

Table 2 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 2. 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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products ATC code: not yet assigned

Mechanism of action

Ivacaftor is a selective potentiator of the 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The efficacy of Kalydeco has been evaluated in two Phase 3 randomised, double-blinded, 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 ≥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. 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.

The treatment difference between ivacaftor and placebo for the mean absolute change (95% CI) in percent predicted FEV_1 from baseline through Week 24 in patients 12 to 17 years of age in study 1 was 11.9 percentage points (5.9; 17.9). The treatment difference between ivacaftor and placebo for the mean absolute change (95% CI) in percent predicted FEV_1 from baseline through Week 24 in patients with baseline predicted FEV_1 greater than 90% in study 2 was 6.9 percentage points (-3.8; 17.6). The results on clinically relevant secondary endpoints are shown in Table 3.

Table 3. 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.

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. 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 (10.5 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 (10.0 percentage points) in study 2.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Kalydeco in one or more subsets of the paediatric population in cystic fibrosis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

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 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.

Biotransformation
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.

Elimination
Following oral administration, the majority of ivacaftor (87.8%) 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. 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.

Dose/time proportionality
The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg.

Pharmacokinetic/pharmacodynamic relationships

Based on pooled data from Phase 2a and Phase 3 studies in patients with a *G551D* mutation, population PK/PD analysis showed a relationship between FEV_1 and ivacaftor exposure in an E_{max} model with an EC_{50} of 45 ng/mL and a corresponding EC_{90} of 405 ng/mL. Therefore, median C_{min} at EC_{90} was chosen as the target PK parameter for efficacy.

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, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than two-fold. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.
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 sections 4.2 and 4.4).

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 sections 4.2 and 4.4).

Paediatric population
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/mL.h for children 6 to 11 years old, 8122 and 8536 (3064) ng/mL.h for adolescents 12 to 17 years old, and 8770 and 9508 (3763) ng/mL.h for adults.

Elderly population
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 established.

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.

5.3 Preclinical safety data

Effects on non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Ivacaftor produced concentration-dependent inhibitory effect on hERG (human ether-a-go-go related gene) tail currents, with an IC_{15} of 5.5 μM, which is comparable to the C_{max} (5.0 μM) for ivacaftor at the therapeutic dosage. However, no ivacaftor-induced QT prolongation was observed in a dog telemetry study at single doses of up to 60 mg/kg, or in ECG measurements from repeat-dose studies of up to 1 year duration at the 60 mg/kg/day dose level in dogs (C_{max} after 365 days = 36.2 to 47.6 μM). Ivacaftor produced a dose-related, but transient increase in the blood pressure parameters in dogs at single oral doses of up to 60 mg/kg.

Ivacaftor did not cause reproductive system toxicity in male and female rats at 200 and 100 mg/kg/day, respectively. In females, dosages above this were associated with reduction in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the oestrous cycle. In males, slight decreases of the seminal vesicle weights were observed. Ivacaftor was not teratogenic when orally dosed to pregnant rats and rabbits during the organogenesis stage of foetal development at doses approximately 12 times the exposure in humans at the therapeutic dose. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight, an increase in the incidence of cervical ribs, hypoplastic ribs, wavy ribs and sternal irregularities, including fusions. The significance of these findings for humans is unknown.

Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day. Dosages above this produced 92% and 98% reduction of survival and lactation indices, respectively, as well as reductions in pup body weights.

Two-year studies in mice and rats to assess 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. 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.

Ivacaftor was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline

Lactose monohydrate
Hypromellose acetate succinate
Croscarmellose sodium
Sodium laurilsulfate
Colloidal silicon dioxide
Magnesium stearate

Tablet film coat
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine aluminum lake (E132)
Carnauba wax

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

Kalydeco tablets are packaged in a thermoform (polychlorotrifluoroethylene (PCTFE)/foil) blister or a high-density polyethylene (HDPE) bottle with a polypropylene, foil-lined induction seal closure and molecular sieve dessicant.

The following pack sizes are available:
- Blister pack containing 56 film-coated tablets
- Bottle containing 56 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (U.K.) Limited
Cardinal Point
Park Road
Rickmansworth

Herts WD3 1RE
United Kingdom
Tel: +44 (0) 1923 437672
Fax: +44 (0)1923 432870

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Almac Pharma Services Ltd.
Seagoe Industrial Estate
Craigavon
Co. Armagh BT63 5UA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OBLIGATION TO CONDUCT POST-AUTHORISATION MEASURES**

The MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
The applicant should conduct a 5-year long-term observational study with	December 2017

ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations), according to a protocol agreed with the CHMP. The applicant should submit yearly interim analyses and the final CSR by December 2017	
The applicant should submit the final clinical study report of the ongoing study VX08-770-105 which evaluates the long-term safety and efficacy in patients with cystic fibrosis by December 2015. The applicant should also submit yearly interim reports within PSURs.	December 2015
The active substance quality is assured when manufactured under the normal operating ranges (NORs) of the design space, as defined in Module 3.2.S of the marketing authorisation dossier. In order to verify the validity of the design space at commercial scale a verification protocol should be submitted by December 2012	December 2012

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets
ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 150 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (U.K.) Limited

Cardinal Point
Park Road
Rickmansworth
Herts WD3 1RE
United Kingdom
Tel: +44 (0) 1923 437672
Fax: +44 (0)1923 432870

12. MARKETING AUTHORISATION NUMBER(S)

EU

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 150 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg tablets
ivacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (U.K.) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets
ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 150 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 150 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets
ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kalydeco 150 mg film-coated tablets
ivacaftor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Kalydeco is and what it is used for

Kalydeco contains the active substance ivacaftor.

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

2. What you need to know before you take Kalydeco

Do not take Kalydeco
- if you are allergic to ivacaftor or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor if you have been told you have liver or kidney disease, as your doctor may need to adjust the dose of Kalydeco.

Abnormal blood tests of the liver have been seen in some people receiving Kalydeco. Tell your doctor right away if you have any of these symptoms, which may be a sign of liver problems:
- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of your skin or the white part of your eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Your doctor will do some blood tests to check your liver while you are taking Kalydeco, particularly during the first year.

Children

It is not known if Kalydeco is safe and effective in children under 6 years of age. Therefore, Kalydeco is not for use in children under the age of 6 years.

Other medicines and Kalydeco
Kalydeco might interact with other medicines. Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, such as herbal supplements.

Tell your doctor if you take any of the following medicines:
Antifungal medicines (used for the treatment of fungal infections):
ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole

Antibiotic medicines (used for the treatment of bacterial infections):
telithromycin, clarithromycin, erythromycin, rifampicin, rifabutin

Anticonvulsant medicines (used for the treatment of epileptic seizures):
phenobarbital, carbamazepine, phenytoin

Herbal medicines:
St. John's Wort (*Hypericum perforatum*)

Benzodiazepines (used for the treatment of anxiety, insomnia, agitation, etc.):
midazolam, alprazolam, diazepam, triazolam

Immunosuppressants (used after an organ transplantation):
cyclosporine, tacrolimus

Cardiac glycosides (used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation):
digoxin

Anticoagulants (used to prevent blood clots from forming or growing larger in blood and blood vessels):
warfarin

Kalydeco with food and drink
Avoid food containing grapefruit or Seville oranges during treatment with Kalydeco as they may increase the amount of Kalydeco in your system.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will help you decide what is best for you and your child.

It is unknown whether Kalydeco is excreted in human milk. If you plan to breast-feed, ask your doctor for advice before taking Kalydeco.

Driving and using machines
Dizziness has been reported in patients receiving Kalydeco, which could influence the ability to drive or operate machines. If you experience dizziness, you should not drive or operate machines until these symptoms disappear.

Kalydeco contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Kalydeco

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose for patients age 6 years and over is one 150 mg tablet every 12 hours (in total 2 tablets (300 mg) per day). If you have liver problems, your doctor may need to reduce the dose to 1 tablet (150 mg) per day as your liver is not clearing Kalydeco as fast as in people who do not have moderate or severe problems with liver function.

Take 1 tablet (150 mg) of Kalydeco every 12 hours by mouth with fat-containing food. 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. Taking Kalydeco with fat-containing food is important to get the right levels of medicine in your body.

Patients or caregivers may use scissors (✂) to separate the blister card.

If you take more Kalydeco than you should
You may experience side effects, including those mentioned in section 4 below. If so, contact your doctor or pharmacist to ask for advice. If possible, have your medicine and this leaflet with you.

If you forget to take Kalydeco
Take the missed dose if less than 6 hours have passed since the time you missed the dose. Otherwise, wait until your next scheduled dose as you normally would. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Kalydeco
Tell your doctor. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects due to ivacaftor were uncommon (fewer than 1 in 100 people) and included stomach (abdominal) pain.

Very common side effects (may affect more than 1 in 10 people)
- Upper respiratory tract infection (the common cold), including sore throat and nasal congestion
- Headache
- Abdominal pain (stomach ache)
- Diarrhoea
- Rash

Common side effects (may affect up to 1 in 10 people)
- Sinus congestion
- Runny nose
- Dizziness
- Changes in the type of bacteria in mucus
- Ear pain
- Ringng in the ears
- Redness inside the ear

Uncommon side effects (may affect up to 1 in 100 people)
- Ear congestion

- Breast inflammation
- Breast mass
- Enlargement of the breast
- Nipple changes or pain

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Kalydeco

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Kalydeco contains
- The active substance is ivacaftor. Each film-coated tablet contains 150 mg of ivacaftor.

- The other ingredients are:
    - Tablet core: Cellulose, microcrystalline; lactose monohydrate; hypromellose acetate succinate; croscarmellose sodium; sodium laurilsulfate; colloidal silicon dioxide; and magnesium stearate.
    - Coating: Polyvinyl alcohol, titanium dioxide, macrogol, talc, indigo carmine aluminium lake, and carnauba wax.
    - Printing ink: Shellac, iron oxide black, propylene glycol, and ammonium hydroxide.

What Kalydeco looks like and contents of the pack
Kalydeco 150 mg film-coated tablets are light blue, capsule-shaped, 16.5 mm x 8.4 mm, and printed with “V 150” in black ink on one side and plain on the other.

Kalydeco is available in the following pack sizes:
- Blister pack containing 56 film-coated tablets
- Bottle containing 56 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Vertex Pharmaceuticals (U.K.) Limited
Cardinal Point
Park Road
Rickmansworth
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.