ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 of lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light blue, capsule-shaped film-coated 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 tablet shape).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R* (see sections 4.4 and 5.1).

Kalydeco tablets are also indicated for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* 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 before starting treatment to confirm the presence of one of the above-listed gating (class III) mutations or an *R117H* mutation in at least one allele of the *CFTR* gene. The phase of the poly-T variant identified with the *R117H* mutation should be determined in accordance with local clinical recommendations.

Posology

Adults, adolescents and children aged 6 years and older and weighing 25 kg or more
The recommended dose of Kalydeco tablets is 150 mg taken orally every 12 hours (300 mg total daily dose) with fat-containing food.

Missed dose
If a dose is missed within 6 hours of the time it is usually taken, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. If more than 6 hours have passed since the time the dose is usually taken, the patient should be told to wait until the next scheduled dose.

Concomitant use of CYP3A inhibitors
When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), the Kalydeco dose should be reduced to 150 mg twice a week (see sections 4.4 and 4.5).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the Kalydeco dose should be reduced to 150 mg once daily (see sections 4.4 and 4.5).

Special populations

Elderly
Although very limited data are available for elderly patients with an *R117H-CFTR* mutation treated with ivacaftor in study 6, no dose adjustment is considered necessary unless moderate hepatic impairment exists. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using Kalydeco in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of 150 mg once daily is recommended. There is no experience of the use of Kalydeco in patients with severe hepatic impairment and therefore its use is not recommended unless the benefits outweigh the risks. In such cases, 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).

Paediatric population
The safety and efficacy of Kalydeco in children aged less than 2 years with a gating (class III) mutation have not been established. No data are available.

An appropriate dose for children under 6 years of age and weighing less than 25 kg cannot be achieved with Kalydeco tablets.

The efficacy of Kalydeco in patients less than 18 years of age with an *R117H* mutation in the *CFTR* gene has not been established. Currently available data are described in sections 4.4, 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

For oral use.

Kalydeco should be taken with fat-containing food.

Food containing grapefruit or Seville oranges should be avoided during treatment with Kalydeco (see section 4.5).

Patients should be instructed to swallow the tablets whole (i.e., patients should not chew, break or dissolve the tablets).

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*, *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N*, *S549R* gating (class III) or an *R117H* mutation in at least one allele of the *CFTR* gene were included in studies 1, 2, 5 and 6 (see section 5.1).

In study 5, four patients with the *G970R* mutation were included. In three of four patients the change in the sweat chloride test was <5 mmol/L and this group did not demonstrate a clinically relevant improvement in FEV_1 after 8 weeks of treatment. Clinical efficacy in patients with the *G970R* mutation of the *CFTR* gene could not be established (see section 5.1).

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). Therefore, use of Kalydeco in these patients is not recommended.

Efficacy was not demonstrated in patients aged 6 to 11 years with CF who have an *R117H* mutation while only two adolescent patients were enrolled in study 6 (see section 5.1).

Less evidence of a positive effect of ivacaftor has been shown for patients with an *R117H-7T* mutation associated with less severe disease (see section 5.1). Whenever possible the phase of the poly-T variant identified with the *R117H* mutation should be determined as this may be informative in considering treatment of patients with an *R117H* mutation (see section 4.2).

Effect on liver function tests
Moderate transaminase (alanine transaminase [ALT] or aspartate transaminase [AST]) elevations are common in subjects with CF. In placebo-controlled studies (studies 1 and 2), the incidence of transaminase elevations (>3 x upper limit of normal [ULN]) were 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 has been reported more frequently in patients receiving ivacaftor compared to placebo. Therefore, liver function tests are recommended for all patients prior to initiating ivacaftor, every 3 months during the first year of treatment and annually thereafter. For all patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered.

Patients who develop increased transaminase levels should be monitored closely until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the ULN. Following resolution of transaminase elevations, the benefits and risks of resuming Kalydeco dosing should be considered.

Hepatic impairment
Use of ivacaftor is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of overexposure. In such cases, the starting dose should be 150 mg every other day (see sections 4.2 and 5.2).

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

Patients after organ transplantation
Ivacaftor 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 ciclosporin or tacrolimus.

Interactions with medicinal products
CYP3A inducers
Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy. Therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors
The dose of Kalydeco must be adjusted when concomitantly used with strong or moderate CYP3A inhibitors (see sections 4.2 and 4.5).

Cataracts
Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating ivacaftor treatment.

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

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 P-gp and a potential inhibitor of CYP2C9.

Medicinal products affecting the pharmacokinetics of ivacaftor:

CYP3A inducers
Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, decreased ivacaftor exposure (AUC) by 89% and decreased M1 to a lesser extent than ivacaftor. Co-administration with strong CYP3A inducers, such as rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*), is not recommended (see section 4.4).

Concomitant use of weak to moderate inducers of CYP3A (e.g., dexamethasone, high-dose prednisone) may decrease the exposure of ivacaftor. No dose adjustment for ivacaftor is recommended. Patients should be monitored for reduced ivacaftor efficacy when ivacaftor is co-administered with moderate CYP3A inducers.

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 increased hydroxymethyl-ivacaftor (M1) to a lesser extent than ivacaftor. 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 (see sections 4.2 and 4.4).

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold and increased M1 to a lesser extent than ivacaftor. 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 (see sections 4.2 and 4.4).

Co-administration of ivacaftor 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 (see section 4.2).

Ciprofloxacin
Co-administration of ciprofloxacin with ivacaftor did not affect the exposure of ivacaftor. No dose adjustment is required when Kalydeco is co-administered with ciprofloxacin.

Medicinal products affected by ivacaftor:

CYP3A, P-gp or CYP2C9 substrates
Based on *in vitro* results, ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with (oral) midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor. Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with midazolam, alprazolam, diazepam or triazolam, Kalydeco should be used with caution and patients should be monitored for benzodiazepine-related undesirable effects. Caution and appropriate monitoring are recommended when co-administering Kalydeco with digoxin, ciclosporin 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 CYP2D6 substrate desipramine. No significant effect on desipramine exposure was found. Therefore, no dose adjustment of CYP2D6 substrates such as desipramine is necessary.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ivacaftor in pregnant women. Animals studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Kalydeco during pregnancy.

Breast-feeding
It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of ivacaftor into the milk of lactating female rats. As such, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kalydeco therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (resulting in exposures approximately 8 and 5 times, respectively, the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its major 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 (resulting in exposures

approximately 6 and 3 times, respectively, the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its major metabolites).

4.7 Effects on ability to drive and use machines

Kalydeco has minor influence on the ability to drive or use machines. Ivacaftor may cause dizziness (see section 4.8) and, therefore, patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions experienced by patients aged 6 years and older who received ivacaftor in the pooled 48-week placebo-controlled Phase 3 studies that occurred with an incidence of at least 3% and up to 9% higher than in the placebo arm were headache (23.9%), oropharyngeal pain (22.0%), upper respiratory tract infection (22.0%), nasal congestion (20.2%), abdominal pain (15.6%), nasopharyngitis (14.7%), diarrhoea (12.8%), dizziness (9.2%), rash (12.8%) and bacteria in sputum (12.8%). Transaminase elevations occurred in 12.8% of ivacaftor-treated patients versus 11.5% of placebo-treated patients.

In patients aged 2 to less than 6 years the most common adverse reactions were nasal congestion (26.5%), upper respiratory tract infection (23.5%), transaminase elevations (14.7%), rash (11.8%), and bacteria in sputum (11.8%).

Serious adverse reactions in patients who received ivacaftor included abdominal pain and transaminase elevations (see section 4.4).

Tabulated list of adverse reactions

Table 1 reflects the adverse reactions observed with ivacaftor in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16 weeks to 144 weeks. The frequency of adverse reactions is defined as follows: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions in ivacaftor-treated patients aged 2 years and older

System organ class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Rhinitis	common
Nervous system disorders	Headache	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common
	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea	very common

Table 1. Adverse reactions in ivacaftor-treated patients aged 2 years and older		
System organ class	**Adverse reactions**	**Frequency**
Hepatobiliary disorders	Transaminase elevations	very common
Skin and subcutaneous tissue disorders	Rash	very common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common

Description of selected adverse reactions

Hepatobiliary disorders

Transaminase elevations

During the 48-week placebo-controlled studies 1 and 2 in patients aged 6 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 3.7%, 3.7% and 8.3% in ivacaftor-treated patients and 1.0%, 1.9% and 8.7% in placebo-treated patients, respectively. Two patients, one on placebo and one on ivacaftor permanently discontinued treatment for elevated transaminases, each >8 x ULN. No ivacaftor-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >1.5 x ULN. In ivacaftor-treated patients, most transaminase elevations up to 5 x ULN resolved without treatment interruption. Ivacaftor dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4).

Paediatric population

The safety data were evaluated in 34 patients between 2 to less than 6 years of age, 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age.

The safety profile is generally consistent among children and adolescents and is also consistent with adult patients.

During the 24-week open-label Phase 3 clinical study in 34 patients aged 2 to less than 6 years (study 7), the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of dosing with ivacaftor granules. Ivacaftor was permanently discontinued in one patient. In children aged 6 to less than 12 years, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients who received placebo. A single ivacaftor-treated patient (2.5%) in this age range had an elevation of ALT and AST >8 x ULN. Peak LFT (ALT or AST) elevations were generally higher in paediatric patients than in older patients. In almost all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4). Cases suggestive of positive rechallenge were observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific antidote is available for overdose with ivacaftor. 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: R07AX02

Mechanism of action
Ivacaftor is a potentiator of the CFTR protein, i.e., *in vitro* ivacaftor increases CFTR channel gating to enhance chloride transport in specified gating mutations (as listed in section 4.1) with reduced channel-open probability compared to normal CFTR. Ivacaftor also potentiated the channel-open probability of R117H-CFTR, which has both low channel-open probability (gating) and reduced channel current amplitude (conductance). *In vitro* responses seen in single channel patch clamp experiments using membrane patches from rodent cells expressing mutant CFTR forms do not necessarily correspond to *in vivo* pharmacodynamic response (e.g., sweat chloride) or clinical benefit. The exact mechanism leading ivacaftor to potentiate the gating activity of normal and some mutant CFTR forms in this system has not been completely elucidated.

Pharmacodynamic effects
In 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) reductions in sweat chloride concentration.

In study 5, part 1 in patients who had a non-*G551D* gating mutation in the *CFTR* gene, treatment with ivacaftor led to a rapid (15 days) and substantial mean change from baseline in sweat chloride of -49 mmol/L (95% CI -57, -41) through 8 weeks of treatment. However, in patients with the *G970R-CFTR* mutation, the mean (SD) absolute change in sweat chloride at Week 8 was -6.25 (6.55) mmol/L. Similar results to part 1 were seen in part 2 of the study. At the 4-week follow-up visit (4 weeks after dosing with ivacaftor ended), mean sweat chloride values for each group were trending to pre-treatment levels.

In study 6 in patients aged 6 years or older with CF who had an *R117H* mutation in the *CFTR* gene, the treatment difference in mean change in sweat chloride from baseline through 24 weeks of treatment was -24 mmol/L (95% CI -28, -20).

Clinical efficacy and safety
Study 1 and 2: studies in patients with CF with G551D gating mutations
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 $FEV_1 \geq 40\%$ predicted.

Patients in both studies were randomised 1:1 to receive either 150 mg of ivacaftor 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 sodium chloride was not permitted.

Study 1 evaluated 161 patients who were 12 years of age or older; 122 (75.8%) 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%) 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%) patients in the placebo group and 4 (15.4%) 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 for 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

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]				
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 analysed 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 5: study in patients with CF with non-G551D gating mutations
Study 5 was a Phase 3, two-part, randomised, double-blind, placebo-controlled, crossover study (part 1) followed by a 16-week open-label extension period (part 2) to evaluate the efficacy and safety of ivacaftor in patients with CF aged 6 years and older who have a non-*G551D* gating mutation in the *CFTR* gene (*G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P* or *G1349D*).

In part 1, patients were randomised 1:1 to receive either 150 mg of ivacaftor or placebo every 12 hours with fat-containing food for 8 weeks in addition to their prescribed CF therapies and crossed over to the other treatment for the second 8 weeks after a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted. In part 2, all patients received ivacaftor as indicated in part 1 for 16 additional weeks. The duration of continuous ivacaftor treatment was 24 weeks for patients randomised to part 1 placebo/ivacaftor treatment sequence and 16 weeks for patients randomised to part 1 ivacaftor/placebo treatment sequence.

Thirty-nine patients (mean age 23 years) with baseline $FEV_1 \geq 40\%$ predicted (mean FEV_1 78% predicted [range: 43% to 119%]) were enrolled. Sixty-two percent (24/39) of them carried the *F508del-CFTR* mutation in the second allele. A total of 36 patients continued into part 2 (18 per treatment sequence).

In part 1 of study 5, the mean FEV_1 percent predicted at baseline in placebo-treated patients was 79.3% while in ivacaftor-treated patients this value was 76.4%. The mean overall post-baseline value was 76.0% and 83.7%, respectively. The mean absolute change from baseline through Week 8 in percent predicted FEV_1 (primary efficacy endpoint) was 7.5% in the ivacaftor period and -3.2% in the placebo period. The observed treatment difference (95% CI) between ivacaftor and placebo was 10.7% (7.3, 14.1) ($P<0.0001$).

The effect of ivacaftor in the overall population of study 5 (including the secondary endpoints absolute change in BMI at 8 weeks of treatment and absolute change in the respiratory domain score of the CFQ-R through 8 weeks of treatment) and by individual mutation (absolute change in sweat chloride and in percent predicted FEV_1 at Week 8) is shown in Table 3. Based on clinical (percent predicted FEV_1) and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established.

Table 3. Effect of ivacaftor for efficacy variables in the overall population and for specific *CFTR* mutations		
Absolute change in percent predicted FEV_1	**BMI (kg/m^2)**	**CFQ-R respiratory domain score (points)**
Through Week 8	**At Week 8**	**Through Week 8**
All patients (N=39) Results shown as mean (95% CI) change from baseline ivacaftor vs placebo-treated patients:		
10.7 (7.3, 14.1)	0.66 (0.34, 0.99)	9.6 (4.5, 14.7)

Patients grouped under mutation types (n) Results shown as mean (minimum, maximum) change from baseline for ivacaftor-treated patients at Week 8*:		
Mutation (n)	**Absolute change in sweat chloride (mmol/L)**	**Absolute change in percent predicted FEV_1 (percentage points)**
	At Week 8	**At Week 8**
G1244E (5)	-55 (-75, -34)	8 (-1, 18)
G1349D (2)	-80 (-82, -79)	20 (3, 36)
G178R (5)	-53 (-65, -35)	8 (-1, 18)
G551S (2)	-68†	3†
G970R (4)	-6 (-16, -2)	3 (-1, 5)
S1251N (8)	-54 (-84, -7)	9 (-20, 21)
S1255P (2)	-78 (-82, -74)	3 (-1, 8)
S549N (6)	-74 (-93, -53)	11 (-2, 20)
S549R (4)	-61†† (-71, -54)	5 (-3, 13)
* Statistical testing was not performed due to small numbers for individual mutations. † Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point. †† n=3 for the analysis of absolute change in sweat chloride.		

In part 2 of study 5, the mean (SD) absolute change in percent predicted FEV_1 following 16 weeks (patients randomised to the ivacaftor/placebo treatment sequence in part 1) of continuous ivacaftor treatment was 10.4% (13.2%). At the follow-up visit, 4 weeks after ivacaftor dosing had ended, the mean (SD) absolute change in percent predicted FEV_1 from part 2 Week 16 was -5.9% (9.4%). For patients randomised to the placebo/ivacaftor treatment sequence in part 1 there was a further mean (SD) change of 3.3% (9.3%) in percent predicted FEV_1 after the additional 16 weeks of treatment with ivacaftor. At the follow up visit, 4 weeks after ivacaftor dosing had ended, the mean (SD) absolute change in percent predicted FEV_1 from part 2 Week 16 was -7.4% (5.5%).

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 $FEV_1 \geq 40\%$ 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
In study 4 patients who completed treatment in studies 1 and 2 with placebo were switched to ivacaftor while patients on ivacaftor continued to receive it for a minimum of 96 weeks, i.e., the length of treatment with ivacaftor was at least 96 weeks for patients in the placebo/ivacaftor group and at least 144 weeks for patients in the ivacaftor/ivacaftor group.

One hundred and forty-four (144) patients from study 1 were rolled over in study 4, 67 in the placebo/ivacaftor group and 77 in the ivacaftor/ivacaftor group. Forty-eight (48) patients from study 2 were rolled over in study 4, 22 in the placebo/ivacaftor group and 26 in the ivacaftor/ivacaftor group.

Table 4 shows the results of the mean (SD) absolute change in percent predicted FEV_1 for both groups of patients. For patients in the placebo/ivacaftor group baseline percent predicted FEV_1 is that of study 4 while for patients in the ivacaftor/ivacaftor group the baseline value is that of studies 1 and 2.

Table 4. Effect of ivacaftor on percent predicted FEV_1 in study 4

Original study and treatment group	Duration of ivacaftor treatment (Weeks)	Absolute change from baseline in percent predicted FEV_1 (percentage points)	
		N	Mean (SD)
Study 1			
Ivacaftor	48*	77	9.4 (8.3)
	144	72	9.4 (10.8)
Placebo	0*	67	-1.2 (7.8)†
	96	55	9.5 (11.2)
Study 2			
Ivacaftor	48*	26	10.2 (15.7)
	144	25	10.3 (12.4)
Placebo	0*	22	-0.6 (10.1)†
	96	21	10.5 (11.5)

* Treatment occurred during blinded, controlled, 48-week Phase 3 study.

† Change from prior study baseline after 48 weeks of placebo treatment.

When the mean (SD) absolute change in percent predicted FEV_1 is compared from study 4 baseline for patients in the ivacaftor/ivacaftor group (n=72) who rolled over from study 1, the mean (SD) absolute change in percent predicted FEV_1 was 0.0% (9.05), while for patients in the ivacaftor/ivacaftor group (n=25) who rolled over from study 2 this figure was 0.6% (9.1). This shows that patients in the ivacaftor/ivacaftor group maintained the improvement seen at Week 48 of the initial study (Day 0 through Week 48) in percent predicted FEV_1 through Week 144. There were no additional improvements in study 4 (Week 48 through Week 144).

For patients in the placebo/ivacaftor group from study 1, the annualised rate of pulmonary exacerbations was higher in the initial study when patients were on placebo (1.34 events/year) than during the subsequent study 4 when patients rolled over to ivacaftor (0.48 events/year across Day 1 to Week 48, and 0.67 events/year across Weeks 48 to 96). For patients in the ivacaftor/ivacaftor group from study 1, the annualised rate of pulmonary exacerbations was 0.57 events/year across Day 1 to Week 48 when patients were on ivacaftor. When they rolled over into study 4, the rate of annualised pulmonary exacerbations was 0.91 events/year across Day 1 to Week 48 and 0.77 events/year across Weeks 48 to 96.

For patients who rolled over from study 2 the number of events was, overall, low.

Study 6: study in patients with CF with an R117H mutation in the CFTR gene
Study 6 evaluated 69 patients who were 6 years of age or older; 53 (76.8%) of patients had the *F508del* mutation in the second allele. The confirmed *R117H* poly-T variant was *5T* in 38 patients and *7T* in 16 patients. At baseline, mean predicted FEV_1 was 73% (range: 32.5% to 105.5%) and mean age was 31 years (range: 6 to 68 years). The mean absolute change from baseline through Week 24 in percent predicted FEV_1 (primary efficacy endpoint) was 2.57 percentage points in the ivacaftor group and 0.46 percentage points in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 2.1 percentage points (95% CI -1.1, 5.4).

A pre-planned subgroup analysis was conducted in patients 18 years and older (26 patients on placebo and 24 on ivacaftor). Treatment with ivacaftor resulted in a mean absolute change in percent predicted FEV_1 through Week 24 of 4.5 percentage points in the ivacaftor group versus -0.46 percentage points

in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 5.0 percentage points (95% CI 1.1, 8.8).

In a subgroup analysis in patients 6 to 11 years of age (8 patients on placebo and 9 patients on ivacaftor), the placebo group showed an improvement in mean percent predicted FEV_1 from 94.0% at baseline to 98.4% post-baseline; the ivacaftor group showed a slight decline in mean FEV_1 from 97.5% at baseline to 96.2% overall post-baseline. The mean absolute change from baseline through Week 24 in percent predicted FEV_1 was -2.8 percentage points in the ivacaftor group and 3.5 percentage points in the placebo group. The treatment difference for ivacaftor versus placebo was -6.3 percentage points (95% CI -12.0, -0.7). No statistical analysis was conducted for subjects 12 to 17 years of age because only 2 patients were enrolled in this study.

In a subgroup analysis in patients with a confirmed *R117H-5T* genetic variant, the difference in the mean absolute change from baseline through Week 24 in percent predicted FEV_1 between ivacaftor and placebo was 5.3% (95% CI 1.3, 9.3). In patients with a confirmed *R117H-7T* genetic variant, the treatment difference between ivacaftor and placebo was 0.2% (95% CI -8.1, 8.5).

Secondary efficacy variables included absolute change from baseline in sweat chloride through 24 weeks of treatment, absolute change from baseline in BMI at 24 weeks of treatment, absolute change in the CFQ-R respiratory domain score through 24 weeks of treatment and time to first pulmonary exacerbation. No treatment differences for ivacaftor versus placebo were observed except for the respiratory domain of the CFQ-R (the treatment difference through 24 weeks of ivacaftor versus placebo was 8.4 [2.2, 14.6] points) and for the mean change from baseline in sweat chloride (see Pharmacodynamic effects).

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 2.5- 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.

Ivacaftor granules (2 x 75 mg sachets) had similar bioavailability as the 150 mg tablet when given with fat-containing food to healthy adult subjects. The geometric least squares mean ratio (90% CI) for the granules relative to tablets was 0.951 (0.839, 1.08) for $AUC_{0-\infty}$ and 0.918 (0.750, 1.12) for C_{max}. The effect of food on ivacaftor absorption is similar for both formulations, i.e., tablets and granules.

Distribution
Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

After oral administration of 150 mg every 12 hours for 7 days 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%) was eliminated in the faeces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The mean (±SD) CL/F for a single 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.

Linearity/non-linearity
The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg.

Hepatic impairment
Following a single dose of 150 mg of ivacaftor, adult 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, adults with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in adults without hepatic impairment. Therefore in patients with moderate hepatic impairment, a reduced dose of 150 mg once daily is recommended. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than 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 ivacaftor in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such cases, 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
Predicted ivacaftor exposure based on observed ivacaftor concentrations in Phase 2 and 3 studies as determined using population PK analysis is presented by age group in Table 5. Exposures in 6- to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

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

5.3 Preclinical safety data

Effects in 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 a 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's 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 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 reductions in the 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 resulting in exposures approximately 5 times (based on the summed AUCs for ivacaftor and its major metabolites) and 11 times (based on the AUC for ivacaftor), respectively, the exposure in humans at the MRHD. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight and 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% reductions of survival and lactation indices, respectively, as well as reductions in pup body weights.

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with dose levels of 10 mg/kg/day and higher (resulting in exposures 0.22 times the human exposure at the MRHD based on systemic exposure of ivacaftor and its major metabolites). This finding has not been observed in foetuses derived from rat dams treated on gestation Day 7 to 17, in rat pups exposed to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 4- to 5-month-old dogs. The potential relevance of these findings in humans is unknown.

Two-year studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in male and female

mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4- and 7-fold higher, respectively, than the exposure measured in humans following ivacaftor therapy, and at least 1.2- and 2.4-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in male and female rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 16- and 29-fold higher, respectively, than the exposure measured in humans following ivacaftor therapy, and 6- and 9-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites.

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 (PEG 3350)
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

4 years.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

The film-coated tablets are packed in a thermoform (PolyChloroTriFluoroEthylene [PCTFE]/foil) blister or a High-Density PolyEthylene (HDPE) bottle with a polypropylene child-resistant closure, foil-lined induction seal and molecular sieve desiccant.

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 and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2012
Date of latest renewal:

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.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 50 mg granules in sachet
Kalydeco 75 mg granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kalydeco 50 mg granules in sachet
Each sachet contains 50 mg of ivacaftor.

Excipient with known effect
Each sachet contains 73.2 mg of lactose (as monohydrate)

Kalydeco 75 mg granules in sachet
Each sachet contains 75 mg of ivacaftor.

Excipient with known effect
Each sachet contains 109.8 mg of lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules in sachet.

White to off-white granules approximately 2 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R* (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 before starting treatment to confirm the presence of one of the above-listed gating (class III) mutations in at least one allele of the *CFTR* gene.

Posology

Children aged 2 years and older, adolescents and adults should be dosed according to Table 1.

Table 1. Dosing recommendations for patients aged 2 years and older		
Weight	**Dose**	**Total daily dose**
<14 kg	50 mg granules taken orally every 12 hours with fat-containing food	100 mg
≥14 kg to <25 kg	75 mg granules taken orally every 12 hours with fat-containing food	150 mg
≥25 kg	See Kalydeco tablets SmPC for further details.	

Missed dose
If a dose is missed within 6 hours of the time it is usually taken, the patient should be told to take it as soon as possible and then take the next dose at the regularly scheduled time. If more than 6 hours have passed since the time the dose is usually taken, the patient should be told to wait until the next scheduled dose.

Concomitant use of CYP3A inhibitors
When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), the Kalydeco dose should be reduced to 50 mg twice a week in patients aged 2 years and older with body weight less than 14 kg and 75 mg twice a week for those with body weight 14 kg to less than 25 kg (see sections 4.4 and 4.5).

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the Kalydeco dose is as above recommended, but administered once daily (see sections 4.4 and 4.5).

Special populations

Renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using Kalydeco in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of 50 mg once daily is recommended in patients aged 2 years and older with body weight less than 14 kg and 75 mg once daily for those with body weight 14 kg to less than 25 kg. There is no experience of the use of Kalydeco in patients with severe hepatic impairment and therefore its use is not recommended unless the benefits outweigh the risks. In such cases, the starting dose should be as above recommended, but administered every other day. Dosing intervals should be modified according to clinical response and tolerability (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Kalydeco in children aged less than 2 years have not been established. No data are available.

Method of administration

For oral use.

Each sachet is for single use only.

Each sachet of granules should be mixed with 5 mL of age-appropriate soft food or liquid and completely and immediately consumed. Food or liquid should be at room temperature or below. If not immediately consumed, the mixture has been shown to be stable for one hour and therefore should be

ingested during this period. A fat-containing meal or snack should be consumed just before or just after dosing.

Food containing grapefruit or Seville oranges should be avoided during treatment with Kalydeco (see section 4.5).

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, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N* or *S549R* gating (class III) mutation in at least one allele of the *CFTR* gene were included in studies 1, 2, 5 and 7 (see section 5.1).

In study 5, four patients with the *G970R* mutation were included. In three of four patients the change in the sweat chloride test was <5 mmol/L and this group did not demonstrate a clinically relevant improvement in FEV_1 after 8 weeks of treatment. Clinical efficacy in patients with the *G970R* mutation of the *CFTR* gene could not be established (see section 5.1).

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). 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. In placebo-controlled studies (studies 1 and 2), the incidence of transaminase elevations (>3 x upper limit of normal [ULN]) were 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 has been reported more frequently in patients receiving ivacaftor compared to placebo. Therefore, liver function tests are recommended for all patients prior to initiating ivacaftor, every 3 months during the first year of treatment and annually thereafter. For all patients with a history of transaminase elevations, more frequent monitoring of liver function tests should be considered.

Patients who develop increased transaminase levels should be monitored closely until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the ULN. Following resolution of transaminase elevations, the benefits and risks of resuming Kalydeco dosing should be considered.

Hepatic impairment
Use of ivacaftor is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of overexposure. In such cases, the starting dose should be 50 mg every other day for patients aged 2 years and older with body weight less than 14 kg and 75 mg every other day for those with body weight 14 kg to less than 25 kg (see sections 4.2 and 5.2).

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

Patients after organ transplantation
Ivacaftor 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 ciclosporin or tacrolimus.

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy. Therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

The dose of Kalydeco must be adjusted when concomitantly used with strong or moderate CYP3A inhibitors (see sections 4.2 and 4.5).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating ivacaftor treatment.

Lactose

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

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 P-gp and a potential inhibitor of CYP2C9.

Medicinal products affecting the pharmacokinetics of ivacaftor:

CYP3A inducers

Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, decreased ivacaftor exposure (AUC) by 89% and decreased M1 to a lesser extent than ivacaftor. Co-administration with strong CYP3A inducers, such as rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*), is not recommended (see section 4.4).

Concomitant use of weak to moderate inducers of CYP3A (e.g., dexamethasone, high-dose prednisone) may decrease the exposure of ivacaftor. No dose adjustment for ivacaftor is recommended. Patients should be monitored for reduced ivacaftor efficacy when ivacaftor is co-administered with moderate CYP3A inducers.

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 increased hydroxymethyl-ivacaftor (M1) to a lesser extent than ivacaftor. A reduction of the Kalydeco dose to 50 mg twice a week in patients aged 2-years and older with body weight less than 14 kg and 75 mg twice a week for those with body weight 14 kg to less than 25 kg is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin (see sections 4.2 and 4.4).

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold and increased M1 to a lesser extent than ivacaftor. A reduction of the Kalydeco dose as above recommended, but administered once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin (see sections 4.2 and 4.4).

Co-administration of ivacaftor 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 (see section 4.2).

Ciprofloxacin
Co-administration of ciprofloxacin with ivacaftor did not affect the exposure of ivacaftor. No dose adjustment is required when Kalydeco is co-administered with ciprofloxacin.

Medicinal products affected by ivacaftor:

CYP3A, P-gp or CYP2C9 substrates
Based on *in vitro* results, ivacaftor and its M1 metabolite have the potential to inhibit CYP3A and P-gp. Co-administration with (oral) midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor. Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of CYP3A and/or P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with midazolam, alprazolam, diazepam or triazolam, Kalydeco should be used with caution and patients should be monitored for benzodiazepine-related undesirable effects. Caution and appropriate monitoring are recommended when co-administering Kalydeco with digoxin, ciclosporin 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 CYP2D6 substrate desipramine. No significant effect on desipramine exposure was found. Therefore, no dose adjustment of CYP2D6 substrates such as desipramine is necessary.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ivacaftor in pregnant women. Animals studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable avoid the use of Kalydeco during pregnancy.

Breast-feeding
It is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of ivacaftor into the milk of lactating female rats. As such, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kalydeco therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (resulting in exposures approximately 8 and 5 times, respectively, the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its major 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 (resulting in exposures approximately 6 and 3 times, respectively, the exposure in humans at the MRHD based on summed AUCs of ivacaftor and its major metabolites).

4.7 Effects on ability to drive and use machines

Kalydeco has minor influence on the ability to drive or use machines. Ivacaftor may cause dizziness (see section 4.8) and, therefore, patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions experienced by patients aged 6 years and older who received ivacaftor in the pooled 48-week placebo-controlled Phase 3 studies that occurred with an incidence of at least 3% and up to 9% higher than in the placebo arm were headache (23.9%), oropharyngeal pain (22.0%), upper respiratory tract infection (22.0%), nasal congestion (20.2%), abdominal pain (15.6%), nasopharyngitis (14.7%), diarrhoea (12.8%), dizziness (9.2%), rash (12.8%) and bacteria in sputum (12.8%). Transaminase elevations occurred in 12.8% of ivacaftor-treated patients versus 11.5% of placebo-treated patients.

In patients aged 2 to less than 6 years the most common adverse reactions were nasal congestion (26.5%), upper respiratory tract infection (23.5%), transaminase elevations (14.7%), rash (11.8%), and bacteria in sputum (11.8%).

Serious adverse reactions in patients who received ivacaftor included abdominal pain and transaminase elevations (see section 4.4).

Tabulated list of adverse reactions

Table 2 reflects the adverse reactions observed with ivacaftor in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16 weeks to 144 weeks. The frequency of adverse reactions is defined as follows: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions in ivacaftor-treated patients aged 2 years and older

System organ class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Rhinitis	common
Nervous system disorders	Headache	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common
	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea	very common
Hepatobiliary disorders	Transaminase elevations	very common

Table 2. Adverse reactions in ivacaftor-treated patients aged 2 years and older		
System organ class	**Adverse reactions**	**Frequency**
Skin and subcutaneous tissue disorders	Rash	very common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common

Description of selected adverse reactions

Hepatobiliary disorders

Transaminase elevations

During the 48-week placebo-controlled studies 1 and 2 in patients aged 6 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5 or >3 x ULN was 3.7%, 3.7% and 8.3% in ivacaftor-treated patients and 1.0%, 1.9% and 8.7% in placebo-treated patients, respectively. Two patients, one on placebo and one on ivacaftor, permanently discontinued treatment for elevated transaminases, each >8 x ULN. No ivacaftor-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >1.5 x ULN. In ivacaftor-treated patients, most transaminase elevations up to 5 x ULN resolved without treatment interruption. Ivacaftor dosing was interrupted in most patients with transaminase elevations >5 x ULN. In all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4).

Paediatric population

The safety data were evaluated in 34 patients between 2 to less than 6 years of age, 61 patients between 6 to less than 12 years of age and 94 patients between 12 to less than 18 years of age.

The safety profile is generally consistent among children and adolescents and is also consistent with adult patients.

During the 24-week open-label Phase 3 clinical study in 34 patients aged 2 to less than 6 years (study 7), the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 14.7% (5/34). All 5 patients had maximum ALT or AST levels >8 x ULN, which returned to baseline levels following interruption of dosing with ivacaftor granules. Ivacaftor was permanently discontinued in one patient. In children aged 6 to less than 12 years, the incidence of patients experiencing transaminase elevations (ALT or AST) >3 x ULN was 15.0% (6/40) in ivacaftor-treated patients and 14.6% (6/41) in patients who received placebo. A single ivacaftor-treated patient (2.5%) in this age range had an elevation of ALT and AST >8 x ULN. Peak LFT (ALT or AST) elevations were generally higher in paediatric patients than in older patients. In almost all instances where dosing was interrupted for elevated transaminases and subsequently resumed, ivacaftor dosing was able to be resumed successfully (see section 4.4). Cases suggestive of positive rechallenge were observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific antidote is available for overdose with ivacaftor. 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: R07AX02

Mechanism of action
Ivacaftor is a potentiator of the CFTR protein, i.e., *in vitro* ivacaftor increases CFTR channel gating to enhance chloride transport. *In vitro* responses seen in single channel patch clamp experiments using membrane patches from rodent cells expressing mutant CFTR forms do not necessarily correspond to *in vivo* pharmacodynamic response (e.g., sweat chloride) or clinical benefit. The exact mechanism leading ivacaftor to potentiate the gating activity of normal and some mutant CFTR forms in this system has not been completely elucidated.

Pharmacodynamic effects
In 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) reductions in sweat chloride concentration.

In study 5, part 1 in patients who had a non-*G551D* gating mutation in the *CFTR* gene, treatment with ivacaftor led to a rapid (15 days) and substantial mean change from baseline in sweat chloride of -49 mmol/L (95% CI -57, -41) through 8 weeks of treatment. However, in patients with the *G970R-CFTR* mutation, the mean (SD) absolute change in sweat chloride at Week 8 was -6.25 (6.55) mmol/L. Similar results to part 1 were seen in part 2 of the study. At the 4-week follow-up visit (4 weeks after dosing with ivacaftor ended), mean sweat chloride values for each group were trending to pre-treatment levels.

In study 7 in patients aged 2 to less than 6 years with a gating mutation on at least 1 allele of the *CFTR* gene administered either 50 mg or 75 mg of ivacaftor twice daily, the mean absolute change from baseline in sweat chloride was -47 mmol/L (95% CI -58, -36) at Week 24.

Clinical efficacy and safety
Study 1 and 2: studies in patients with CF with G551D gating mutations
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 ≥40% predicted.

Patients in both studies were randomised 1:1 to receive either 150 mg of ivacaftor 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 sodium chloride was not permitted.

Study 1 evaluated 161 patients who were 12 years of age or older; 122 (75.8%) 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%) 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%) patients in the placebo group and 4 (15.4%) 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 for 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 analysed 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 5: study in patients with CF with non-G551D gating mutations
Study 5 was a Phase 3, two-part, randomised, double-blind, placebo-controlled, crossover study (part 1) followed by a 16-week open-label extension period (part 2) to evaluate the efficacy and safety of ivacaftor in patients with CF aged 6 years and older who have a non-*G551D* gating mutation in the *CFTR* gene (*G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P* or *G1349D*).

In part 1, patients were randomised 1:1 to receive either 150 mg of ivacaftor or placebo every 12 hours with fat-containing food for 8 weeks in addition to their prescribed CF therapies and crossed over to the other treatment for the second 8 weeks after a 4- to 8-week washout period. The use of inhaled hypertonic saline was not permitted. In part 2, all patients received ivacaftor as indicated in part 1 for 16 additional weeks. The duration of continuous ivacaftor treatment was 24 weeks for patients randomised to the part 1 placebo/ivacaftor treatment sequence and 16 weeks for patients randomised to part 1 ivacaftor/placebo treatment sequence.

Thirty-nine patients (mean age 23 years) with baseline FEV_1 ≥40% predicted (mean FEV_1 78% predicted [range: 43% to 119%]) were enrolled. Sixty-two percent (24/39) of them carried the *F508del-CFTR* mutation in the second allele. A total of 36 patients continued into part 2 (18 per treatment sequence).

In part 1 of study 5, the mean FEV_1 percent predicted at baseline in placebo-treated patients was 79.3% while in ivacaftor-treated patients this value was 76.4%. The mean overall post-baseline value was 76.0% and 83.7%, respectively. The mean absolute change from baseline through Week 8 in percent predicted FEV_1 (primary efficacy endpoint) was 7.5% in the ivacaftor period and -3.2% in the placebo period. The observed treatment difference (95% CI) between ivacaftor and placebo was 10.7% (7.3, 14.1) (P<0.0001).

The effect of ivacaftor in the overall population of study 5 (including the secondary endpoints absolute change in BMI at 8 weeks of treatment and absolute change in the respiratory domain score of the CFQ-R through 8 weeks of treatment) and by individual mutation (absolute change in sweat chloride and in percent predicted FEV_1 at Week 8) is shown in Table 4. Based on clinical (percent predicted FEV_1) and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established.

Table 4. Effect of ivacaftor for efficacy variables in the overall population and for specific *CFTR* mutations

Absolute change in percent predicted FEV_1	**BMI (kg/m^2)**	**CFQ-R respiratory domain score (points)**
Through Week 8	**At Week 8**	**Through Week 8**
All patients (N=39) Results shown as mean (95% CI) change from baseline ivacaftor vs placebo-treated patients:		
10.7 (7.3, 14.1)	0.66 (0.34, 0.99)	9.6 (4.5, 14.7)

Patients grouped under mutation types (n)
Results shown as mean (minimum, maximum) change from baseline for ivacaftor-treated patients at Week 8*:

Mutation (n)	**Absolute change in sweat chloride (mmol/L)**	**Absolute change in percent predicted FEV_1 (percentage points)**
	At Week 8	**At Week 8**
G1244E (5)	-55 (-75, -34)	8 (-1, 18)
G1349D (2)	-80 (-82, -79)	20 (3, 36)
G178R (5)	-53 (-65, -35)	8 (-1, 18)
G551S (2)	-68†	3†
G970R (4)	-6 (-16, -2)	3 (-1, 5)
S1251N (8)	-54 (-84, -7)	9 (-20, 21)
S1255P (2)	-78 (-82, -74)	3 (-1, 8)
S549N (6)	-74 (-93, -53)	11 (-2, 20)
S549R (4)	-61†† (-71, -54)	5 (-3, 13)

* Statistical testing was not performed due to small numbers for individual mutations.
† Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point.
†† n=3 for the analysis of absolute change in sweat chloride.

In part 2 of study 5, the mean (SD) absolute change in percent predicted FEV_1 following 16 weeks (patients randomised to the ivacaftor/placebo treatment sequence in part 1) of continuous ivacaftor treatment was 10.4% (13.2%). At the follow-up visit 4 weeks after ivacaftor dosing had ended, the mean (SD) absolute change in percent predicted FEV_1 from part 2 Week 16 was -5.9% (9.4%). For patients randomised to the placebo/ivacaftor treatment sequence in part 1 there was a further mean (SD) change of 3.3% (9.3%) in percent predicted FEV_1 after the additional 16 weeks of treatment with ivacaftor. At the follow up visit 4 weeks after ivacaftor dosing had ended, the mean (SD) absolute change in percent predicted FEV_1 from part 2 Week 16 was -7.4% (5.5%).

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
In study 4, patients who completed treatment in studies 1 and 2 with placebo were switched to ivacaftor while patients on ivacaftor continued to receive it for a minimum of 96 weeks, i.e., the length of treatment with ivacaftor was at least 96 weeks for patients in the placebo/ivacaftor group and at least 144 weeks for patients in the ivacaftor/ivacaftor group.

One hundred and forty-four (144) patients from study 1 were rolled over in study 4, 67 in the placebo/ivacaftor group and 77 in the ivacaftor/ivacaftor group. Forty-eight (48) patients from study 2 were rolled over in study 4, 22 in the placebo/ivacaftor group and 26 in the ivacaftor/ivacaftor group.

Table 5 shows the results of the mean (SD) absolute change in percent predicted FEV_1 for both groups of patients. For patients in the placebo/ivacaftor group baseline percent predicted FEV_1 is that of study 4 while for patients in the ivacaftor/ivacaftor group the baseline value is that of studies 1 and 2.

Table 5. Effect of ivacaftor on percent predicted FEV_1 in study 4

Original study and treatment group	**Duration of ivacaftor treatment (Weeks)**	**Absolute change from baseline in percent predicted FEV_1 (percentage points)**	
		N	**Mean (SD)**
Study 1			
Ivacaftor	48*	77	9.4 (8.3)
	144	72	9.4 (10.8)
Placebo	0*	67	-1.2 (7.8)†
	96	55	9.5 (11.2)
Study 2			
Ivacaftor	48*	26	10.2 (15.7)
	144	25	10.3 (12.4)
Placebo	0*	22	-0.6 (10.1)†
	96	21	10.5 (11.5)

* Treatment occurred during blinded, controlled, 48-week Phase 3 study.
† Change from prior study baseline after 48 weeks of placebo treatment.

When the mean (SD) absolute change in percent predicted FEV_1 is compared from study 4 baseline for patients in the ivacaftor/ivacaftor group (n=72) who rolled over from study 1, the mean (SD) absolute change in percent predicted FEV_1 was 0.0% (9.05), while for patients in the ivacaftor/ivacaftor group (n=25) who rolled over from study 2 this figure was 0.6% (9.1). This shows that patients in the ivacaftor/ivacaftor group maintained the improvement seen at Week 48 of the initial study (Day 0 through Week 48) in percent predicted FEV_1 through Week 144. There were no additional improvements in study 4 (Week 48 through Week 144).

For patients in the placebo/ivacaftor group from study 1, the annualised rate of pulmonary exacerbations was higher in the initial study when patients were on placebo (1.34 events/year) than during the subsequent study 4 when patients rolled over to ivacaftor (0.48 events/year across Day 1 to Week 48, and 0.67 events/year across Weeks 48 to 96). For patients in the ivacaftor/ivacaftor group from study 1, the annualised rate of pulmonary exacerbations was 0.57 events/year across Day 1 to Week 48 when patients were on ivacaftor. When they rolled over into study 4, the rate of annualised pulmonary exacerbations was 0.91 events/year across Day 1 to Week 48 and 0.77 events/year across Weeks 48 to 96.

For patients who rolled over from study 2 the number of events was, overall, low.

Study 7: study in paediatric patients with CF aged 2 to less than 6 years with G551D or another gating mutation
The pharmacokinetic profile, safety and efficacy of ivacaftor in 34 patients aged 2 to less than 6 years with CF who had a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R* mutation in the *CFTR* gene were assessed in a 24-week uncontrolled study with ivacaftor (patients weighing less than 14 kg received ivacaftor 50 mg and patients weighing 14 kg or more received ivacaftor 75 mg). Ivacaftor was administered orally every 12 hours with fat-containing food in addition to their prescribed CF therapies.

Patients in study 7 were aged 2 to less than 6 years (mean age 3 years). Twenty-six patients out of the 34 enrolled (76.5%) had a *CFTR* genotype *G551D/F508del* with only 2 patients with a non-*G551D* mutation (*S549N*). The mean (SD) sweat chloride at baseline (n=25) was 97.88 mmol/L (14.00). The mean (SD) Faecal Elastase-1 value at baseline (n=27) was 28 µg/g (95).

The primary endpoint of safety was evaluated through Week 24 (see section 4.8). Secondary and exploratory efficacy endpoints evaluated were absolute change from baseline in sweat chloride through 24 weeks of treatment, absolute change from baseline in weight, body mass index (BMI) and stature (supported by weight, BMI and stature z-scores) at 24 weeks of treatment, and measures of pancreatic function such as Faecal Elastase-1. Data on percent predicted FEV_1 (exploratory endpoint) were available for 3 patients in the ivacaftor 50 mg group and 17 patients in the 75 mg dosing group.

The mean (SD) overall (both ivacaftor dosing groups combined) absolute change from baseline in BMI at Week 24 was 0.32 kg/m^2 (0.54) and the mean (SD) overall change in BMI-for-age z-score was 0.37 (0.42). The mean (SD) overall change in stature-for-age z-score was -0.01 (0.33). The mean (SD) overall change from baseline in Faecal Elastase-1 (n=27) was 99.8 µg/g (138.4). Six patients with initial levels below 200 µg/g achieved, at Week 24, a level of ≥200 µg/g. The mean (SD) overall change in percent predicted FEV_1 from baseline at Week 24 (exploratory endpoint) was 1.8 (17.81).

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 2.5- 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.

Ivacaftor granules (2 x 75 mg sachets) had similar bioavailability as the 150 mg tablet when given with fat-containing food to healthy adult subjects. The geometric least squares mean ratio (90% CI) for the granules relative to tablets was 0.951 (0.839, 1.08) for $AUC_{0-\infty}$ and 0.918 (0.750, 1.12) for C_{max}. The effect of food on ivacaftor absorption is similar for both formulations, i.e., tablets and granules.

Distribution
Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

After oral administration of 150 mg every 12 hours for 7 days 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%) was eliminated in the faeces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent. The apparent terminal half-life was approximately 12 hours following a single dose in the fed state. The apparent clearance (CL/F) of ivacaftor was similar for healthy subjects and patients with CF. The mean (±SD) CL/F for a single 150 mg dose was 17.3 (8.4) L/hr in healthy subjects.

Linearity/non-linearity
The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg.

Hepatic impairment
Following a single dose of 150 mg of ivacaftor, adult 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, adults with moderate hepatic impairment would have comparable steady-state C_{min} values as those obtained with a dose of 150 mg q12h in adults without hepatic impairment. Therefore in patients with moderate hepatic impairment, a reduced dose of 50 mg once daily is recommended in patients aged 2 years and older with body weight less than 14 kg and 75 mg once daily for those with body weight 14 kg to less than 25 kg. The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on the pharmacokinetics of ivacaftor has not been studied, but the increase in ivacaftor $AUC_{0-\infty}$ is expected to be less than 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 ivacaftor in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks. In such cases, the starting dose should be as above recommended, but administered 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

Predicted ivacaftor exposure based on observed ivacaftor concentrations in Phase 2 and 3 studies as determined using population PK analysis is presented by age group in Table 6. Exposures in 6- to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

Table 6. Mean (SD) ivacaftor exposure by age group

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

5.3 Preclinical safety data

Effects in 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 a 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's 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 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 reductions in the 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 resulting in exposures approximately 5 times (based on the summed AUCs for ivacaftor and its major metabolites) and 11 times (based on the AUC for ivacaftor), respectively, the exposure in humans at the MRHD. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight and 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% reductions of survival and lactation indices, respectively, as well as reductions in pup body weights.

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with dose levels of 10 mg/kg/day and higher (resulting in exposures 0.22 times the human exposure at the MRHD based on systemic exposure of ivacaftor and its major metabolites). This finding has not been observed in foetuses derived from rat dams treated on gestation Day 7 to 17, in rat pups exposed to a

certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 4- to 5-month-old dogs. The potential relevance of these findings in humans is unknown.

Two-year studies in mice and rats to assess the carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in male and female mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 4- and 7-fold higher, respectively, than the exposure measured in humans following ivacaftor therapy, and at least 1.2- and 2.4-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in male and female rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 16- and 29-fold higher, respectively, than the exposure measured in humans following ivacaftor therapy and 6- and 9-fold higher, respectively, with regard to the summed AUCs for ivacaftor and its major metabolites.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once mixed, the mixture has been shown to be stable for one hour.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

The granules are packed in a Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet.

Pack size of 56 sachets (contains 4 individual wallets with 14 sachets per wallet)

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/003-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2012
Date of latest renewal:

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

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

Description	**Due date**
The applicant should conduct a 5-year long-term observational study with 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.	December 2017
Long-term effectiveness study to compare disease progression among children with CF who have a specified CFTR gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment.	Interim analysis 1: December 2017 Interim analysis 2: December 2019 Interim analysis 3: December 2021 Final report: December 2023

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(S)

Each 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(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one tablet (150 mg) of Kalydeco every 12 hours. Kalydeco should be taken with fat-containing food. Do not break, chew or dissolve the tablets.

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

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 150 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

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 (Europe) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

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(S)

Each 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(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one tablet (150 mg) of Kalydeco every 12 hours. Kalydeco should be taken with fat-containing food. Do not break, chew or dissolve the tablets.

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

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
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United Kingdom
Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 150 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

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 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(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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Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 50 mg granules in sachet
Ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 50 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

56 sachets

4 individual wallets with 14 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one sachet (50 mg) of Kalydeco granules every 12 hours. Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature and consume it completely. Use within one hour after mixing, just before or after a fat-containing meal or snack.

Lift here to open

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
Use within one hour after mixing.

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 (Europe) Limited
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Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 50 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}

NN: {number}

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 50 mg granules in sachet
Ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 50 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one sachet (50 mg) of Kalydeco granules every 12 hours.

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature and consume it completely.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Use all 7 days' doses before starting a new wallet.

Morning

Evening

SUN MON TUE WED THU FRI SAT

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

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 (Europe) Limited
2 Kingdom Street
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/003

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kalydeco 50 mg granules
Ivacaftor
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Vertex Pharmaceuticals (Europe) Limited

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 75 mg granules in sachet
Ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 75 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

56 sachets

4 individual wallets with 14 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one sachet (75 mg) of Kalydeco granules every 12 hours. Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature and consume it completely. Use within one hour after mixing, just before or after a fat-containing meal or snack.

Lift here to open

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
Use within one hour after mixing.

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 (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kalydeco 75 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 75 mg granules in sachet
Ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE

Each sachet of granules contains 75 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules in sachet

14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

INSTRUCTIONS FOR USE

Take one sachet (75 mg) of Kalydeco granules every 12 hours.

Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature and consume it completely.

Use within one hour after mixing, just before or after a fat-containing meal or snack.

Use all 7 days' doses before starting a new wallet.

Morning

Evening

SUN MON TUE WED THU FRI SAT

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

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/1/12/782/004

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kalydeco 75 mg granules
Ivacaftor
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Vertex Pharmaceuticals (Europe) Limited

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kalydeco 150 mg film-coated tablets
Ivacaftor

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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. See section 4.

What is in this leaflet

1. What Kalydeco is and what it is used for

Kalydeco contains the active ingredient ivacaftor. Ivacaftor acts at the level of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that forms a channel at the cell surface that allows the movement of particles such as chloride in and out of the cell. Due to mutations in the *CFTR* gene (see below), chloride movement is reduced in those with cystic fibrosis (CF). Ivacaftor helps certain abnormal CFTR proteins open more often to improve chloride movement in and out of the cell.

Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*.

Kalydeco tablets are also indicated for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* 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 before taking Kalydeco.
- Ivacaftor should only be used in patients who have at least one of the mutations in their *CFTR* gene listed in section 1 (What Kalydeco is and what it is used for).
- Increased liver enzymes in the blood have been seen in some people receiving ivacaftor. 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 the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Your doctor will do some blood tests to check your liver prior to and while you are taking ivacaftor, particularly during the first year and especially if you have had high liver enzymes in the past.

- Talk to your doctor if you have been told you have liver or kidney disease. Your doctor may need to adjust the dose of Kalydeco if you have any moderate or severe problems with your liver function (please refer to section 3 on How to take Kalydeco).

- Kalydeco is not recommended for patients who have undergone an organ transplant.

- Abnormality of the eye lens (cataract) without any effect on vision has been noted in some children and adolescents receiving ivacaftor.
  Your doctor may perform some eye examinations prior to and during treatment with ivacaftor.

Children
Do not give this medicine to children under 2 years of age with gating mutations as it is not known if ivacaftor is safe and effective in these children, or to subjects under 18 years of age with an *R117H* mutation as ivacaftor may not work in them.

Kalydeco tablets are not adequate for children under 6 years of age.

Other medicines and Kalydeco
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Some medicines can affect how Kalydeco works, or make it more likely that you will have side effects. Kalydeco can also affect how some other medicines work.

Tell your doctor if you take any of the following medicines:
- Ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole, antifungal medicines used for the treatment of fungal infections
- Telithromycin, clarithromycin, erythromycin, rifampicin, rifabutin, antibiotic medicines used for the treatment of bacterial infections
- Phenobarbital, carbamazepine, phenytoin, anticonvulsant medicines used for the treatment of epileptic seizures
- Herbal medicines, i.e., St. John's wort (*Hypericum perforatum*)
- Midazolam, alprazolam, diazepam or triazolam, benzodiazepines used for the treatment of anxiety, insomnia, agitation, etc.
- Ciclosporin, tacrolimus, immunosuppressants used after an organ transplantation
- Digoxin, cardiac glycosides used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation
- Warfarin, anticoagulants used to prevent blood clots from forming or growing larger in blood and blood vessels

Tell your doctor if you are taking any of these. Your doctor may decide to adjust your dose or that you need extra checkups.

Kalydeco with food and drink
Avoid food containing grapefruit or Seville oranges during treatment with Kalydeco as they may increase ivacaftor exposure in your body.

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. It may be better to avoid using Kalydeco during pregnancy, if possible, and your doctor will help you decide what is best for you and your child.

It is unknown whether ivacaftor is excreted in human milk. If you plan to breast-feed, ask your doctor for advice before taking Kalydeco. Your doctor will decide whether to recommend that you stop breast-feeding or for you to stop ivacaftor therapy. Your doctor will take into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines
Kalydeco can make you dizzy. Do not drive or use machines unless you are sure you are not affected.

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 to. Check with your doctor if you are not sure.

The recommended dose is one 150 mg tablet every 12 hours (in total 2 tablets: 300 mg per day) with fat-containing food. You must keep using all other medicines you use, unless your doctor tells you to stop using any.

If you have moderate or severe problems with liver function, your doctor may need to reduce the dose of Kalydeco, as your liver is not clearing ivacaftor as fast as in people who have normal liver function.
- Moderate liver problems: the dose may be reduced to one 150 mg tablet once daily.
- Severe liver problems: the use is not recommended but your doctor may decide if it is appropriate for you to use this medical product in which case the dose must be reduced to one 150 mg tablet every other day.

Kalydeco is for oral use.

Swallow the tablet whole. Do not break, chew or dissolve the tablets.

Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs. Other fat-containing foods are:
- Cheese, whole milk, whole-milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

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 dose.

If you stop taking Kalydeco
Take Kalydeco for as long as your doctor recommends. Do not stop unless your doctor advises you to. 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 include stomach (abdominal) ache and increased liver enzymes in the blood. Contact your doctor straight away if you get any of these.

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
- Dizziness
- Diarrhoea
- Rash
- Changes in the type of bacteria in mucus

Common side effects (may affect up to 1 in 10 people)
- Runny nose
- Ear pain, ear discomfort
- Ringing in the ears
- Redness inside the ear
- Inner ear disorder (feeling dizzy or spinning)
- Sinus congestion
- Redness in the throat
- Breast mass

Uncommon side effects (may affect up to 1 in 100 people)
- Ear congestion
- Breast inflammation
- Enlargement of the breast
- Nipple changes or pain

Additional side effects in children
Side effects seen in children are similar to those observed in adults and adolescents. However, increased liver enzymes in the blood are more frequently seen in young children.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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 (see section 2 – Kalydeco contains lactose), hypromellose acetate succinate, croscarmellose sodium, sodium laurilsulfate, colloidal silicon dioxide, and magnesium stearate.
  - Coating: polyvinyl alcohol, titanium dioxide (E171), macrogol (PEG 3350), talc, indigo carmine aluminium lake (E132) and carnauba wax.
  - Printing ink: shellac, iron oxide black (E172), 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

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

Manufacturer:
Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

This leaflet was last revised in

Other sources of information

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

Package leaflet: Information for the patient

Kalydeco 50 mg granules in sachet
Kalydeco 75 mg granules in sachet
Ivacaftor

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kalydeco is and what it is used for

Kalydeco contains the active ingredient ivacaftor. Ivacaftor acts at the level of the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that forms a channel at the cell surface that allows the movement of particles such as chloride in and out of the cell. Due to mutations in the *CFTR* gene (see below), chloride movement is reduced in those with cystic fibrosis (CF). Ivacaftor helps certain abnormal CFTR proteins open more often to improve chloride movement in and out of the cell.

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

2. What you need to know before your child takes Kalydeco

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

Warnings and precautions
Talk to your child's doctor before your child takes Kalydeco.
- Ivacaftor should only be used in patients who have at least one of the mutations in their *CFTR* gene listed in section 1 (What Kalydeco is and what it is used for).

- Increased liver enzymes in the blood have been seen in some people receiving ivacaftor. Tell your child's doctor right away if your child has any of these symptoms, which may be a sign of liver problems:
  - Pain or discomfort in the upper right stomach (abdominal) area

- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Your child's doctor will do some blood tests to check your child's liver prior to and while your child is taking ivacaftor, particularly during the first year and especially if he/she has had high liver enzymes in the past.

- Talk to your child's doctor if you have been told your child has liver or kidney disease. Your child's doctor may need to adjust the dose of Kalydeco if your child has moderate or severe problems with their liver function (please refer to section 3 on How to take Kalydeco).

- Kalydeco is not recommended for patients who have undergone an organ transplant.

- Abnormality of the eye lens (cataract) without any effect on vision has been noted in some children and adolescents receiving ivacaftor.
  Your child's doctor may perform some eye examinations prior to and during treatment with ivacaftor.

Children
Do not give this medicine to children under 2 years of age with gating mutations as it is not known if ivacaftor is safe and effective in these children.

Other medicines and Kalydeco
Tell your child's doctor or pharmacist if your child is using, has recently used or might use any other medicines.

Some medicines can affect how Kalydeco works, or make it more likely that your child will have side effects. Kalydeco can also affect how some other medicines work.

Tell your child's doctor if your child takes any of the following medicines:
- Ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole, antifungal medicines used for the treatment of fungal infections
- Telithromycin, clarithromycin, erythromycin, rifampicin, rifabutin, antibiotic medicines used for the treatment of bacterial infections
- Phenobarbital, carbamazepine, phenytoin, anticonvulsant medicines used for the treatment of epileptic seizures
- Herbal medicines, i.e., St. John's wort (*Hypericum perforatum*)
- Midazolam, alprazolam, diazepam or triazolam, benzodiazepines used for the treatment of anxiety, insomnia, agitation, etc.
- Ciclosporin, tacrolimus, immunosuppressants used after an organ transplantation
- Digoxin, cardiac glycosides used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation
- Warfarin, anticoagulants used to prevent blood clots from forming or growing larger in blood and blood vessels

Tell your child's doctor if he/she is taking any of these. Your child's doctor may decide to adjust your child's dose or that your child needs extra checkups.

Kalydeco with food and drink
Avoid giving your child food containing grapefruit or Seville oranges during treatment with Kalydeco as they may increase ivacaftor exposure in your child's body.

Driving and using machines
Kalydeco can make your child dizzy. It is advised that your child does not ride his/her bike or do anything else that needs his/her full attention unless you are sure that your child is not affected.

Kalydeco contains lactose
If you have been told by your child's doctor that your child has an intolerance to some sugars, contact your child's doctor before your child takes this medicine.

3. How to take Kalydeco

Always give your child this medicine exactly as your child's doctor has told you to. Check with your child's doctor if you are not sure.

Your child's doctor will determine the correct dose for your child. Your child must keep using all other medicines, unless your child's doctor tells him/her to stop using any.

Ivacaftor dosing recommendations are provided in Table 1.

Table 1. Dosing recommendations for patients aged 2 years and older

Weight	Dose	Total daily dose
Less than 14 kg	One sachet of 50 mg granules taken orally every 12 hours with fat-containing food	100 mg
14 kg to less than 25 kg	One sachet of 75 mg granules taken orally every 12 hours with fat-containing food	150 mg
25 kg or more	Please refer to Kalydeco tablets Package Leaflet	

If your child has moderate or severe problems with liver function, your child's doctor may need to reduce the dose of Kalydeco, as your child's liver is not clearing ivacaftor as fast as in children who have normal liver function.
- Moderate liver problems: the dose may be reduced to one sachet once daily (50 mg for children weighing less than 14 kg and 75 mg for children weighing 14 kg to less than 25 kg).
- Severe liver problems: the use is not recommended but your child's doctor will decide if it is appropriate for your child to use this medical product in which case the dose must be reduced to one sachet every other day (50 mg for children weighing less than 14 kg and 75 mg for children weighing 14 kg to less than 25 kg).

Kalydeco is for oral use.

Each sachet is for single use only.

Giving Kalydeco to your child
- Hold sachet of granules with cut line on top.
- Shake sachet gently to settle contents.
- Tear or cut sachet open along cut line.
- Mix the entire content of a sachet with 5 mL of age-appropriate soft food or liquid. Food or liquid should be at room temperature or below. Some examples of age-appropriate soft foods or liquids include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice.
- Once mixed, give the product to your child immediately. If this is not possible, give it within the following hour after mixing. Ensure that the mixture is completely and immediately consumed.
- A fat-containing meal or snack should be given to your child just before or just after dosing (some examples are provided below).

Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs. Other fat-containing foods are:
- Cheese, whole milk, whole-milk dairy products, yogurt, chocolate

- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

If your child takes more Kalydeco than he/she should
Your child may experience side effects, including those mentioned in section 4 below. If so, contact your child's doctor or pharmacist to ask for advice. If possible, have your child's medicine and this leaflet with you.

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

If you stop giving your child Kalydeco
Give Kalydeco to your child for as long as your child's doctor recommends. Do not stop unless your child's doctor advises you to. If you have any further questions on the use of this medicine, ask your child's doctor or pharmacist.

4. Possible side effects

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

Serious side effects include stomach (abdominal) ache and increased liver enzymes in the blood. Contact your child's doctor straight away if he/she gets any of these.

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
- Dizziness
- Diarrhoea
- Rash
- Changes in the type of bacteria in mucus

Common side effects (may affect up to 1 in 10 people)
- Runny nose
- Ear pain, ear discomfort
- Ringing in the ears
- Redness inside the ear
- Inner ear disorder (feeling dizzy or spinning)
- Sinus congestion
- Redness in the throat
- Breast mass

Uncommon side effects (may affect up to 1 in 100 people)
- Ear congestion
- Breast inflammation
- Enlargement of the breast
- Nipple changes or pain

Additional side effects in children
Side effects seen in children are similar to those observed in adults and adolescents. However, increased liver enzymes in the blood are more frequently seen in young children.

Reporting of side effects
If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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.

Once mixed, the mixture has been shown to be stable for one hour.

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
- Kalydeco 50 mg granules in sachet: The active substance is ivacaftor. Each sachet contains 50 mg of ivacaftor.
- Kalydeco 75 mg granules in sachet: The active substance is ivacaftor. Each sachet contains 75 mg of ivacaftor.
- The other ingredients are: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate (see section 2 – Kalydeco contains lactose), magnesium stearate, mannitol, sucralose and sodium laurilsulfate.

What Kalydeco looks like and contents of the pack
Kalydeco 50 mg granules in sachet are white to off-white granules
Kalydeco 75 mg granules in sachet are white to off-white granules

The granules are supplied in sachets.
- Pack size of 56 sachets (contains 4 individual wallets with 14 sachets per wallet)

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

Manufacturer:
Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

This leaflet was last revised in

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

ANNEX IV

GROUNDS FOR ONE ADDITIONAL RENEWAL

Grounds for one additional renewal

Based upon the data that have become available since the granting of the initial Marketing authorisation, the CHMP considers that the benefit-risk balance of Kalydeco remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

There is a PASS category 1 ongoing. The fourth annual analysis will be completed by December 2016, with the final report submitted by December 2017. Long term safety is considered a key element to evaluate the benefit-risk balance of the product and therefore a second renewal is required.