SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 25 mg granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 25 mg of ivacaftor.

Excipient with known effect

Each sachet contains 36.6 mg of lactose 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 infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have an *R117H CFTR* mutation or 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 an indicated mutation in at least one allele of the *CFTR* gene (see section 4.1). The phase of the poly-T variant identified with the *R117H* mutation should be determined in accordance with local clinical recommendation.

Posology

Infants aged at least 4 months, toddlers, children, adolescents and adults should be dosed according to Table 1.

Table 1: Dosing recommendations for patients aged 4 months and older

Age	Weight	Dose	Total daily dose
4 months to less than 6 months	≥ 5 kg	25 mg granules taken orally every 12 hours with fat-containing food	50 mg
6 months and older	≥ 5 kg to < 7 kg	25 mg granules taken orally every 12 hours with fat-containing food	50 mg
	≥ 7 kg to < 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 6 hours or less have passed since the missed morning or evening dose, the patient should be advised 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 advised to wait until the next scheduled dose.

Concomitant use of CYP3A inhibitors

When co-administered with strong inhibitors of CYP3A in patients aged 6 months and older, the ivacaftor dose should be reduced to one sachet (ivacaftor 25 mg for patients 5 kg to < 7 kg; ivacaftor 50 mg for patients 7 kg to < 14 kg; ivacaftor 75 mg for patients 14 kg to < 25 kg) twice a week (see sections 4.4 and 4.5).

When co-administered with moderate inhibitors of CYP3A in patients aged 6 months and older, the ivacaftor dose is as above recommended but administered once daily (see sections 4.4 and 4.5).

Due to the variability in maturation of the cytochrome (CYP) enzymes involved in ivacaftor metabolism, treatment with ivacaftor is not recommended when co-administered with moderate or strong inhibitors of CYP3A in patients aged 4 months to less than 6 months, unless the benefits outweigh the risks. In such cases, the recommended dose is one packet of 25 mg granules twice weekly or less frequently (see sections 4.4 and 4.5). Dosing intervals should be modified according to clinical response and tolerability (see sections 4.4 and 5.2)

Special populations

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended 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 aged 6 months and older with mild hepatic impairment (Child-Pugh Class A). For patients aged 6 months and older with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of one sachet (ivacaftor 25 mg for patients 5 kg to < 7 kg; ivacaftor 50 mg for patients 7 kg to < 14 kg; ivacaftor 75 mg for patients 14 kg to < 25 kg) once daily

is recommended. There is no experience of the use of ivacaftor in patients aged 6 months and older with severe hepatic impairment (Child-Pugh Class C); therefore, its use is not recommended unless the benefits outweigh the risks. In such cases, the starting dose should be as above recommended, administered every other day. Dosing intervals should be modified according to clinical response and tolerability (see sections 4.4 and 5.2).

Due to variability in maturation of cytochrome (CYP) enzymes involved in ivacaftor metabolism, treatment with ivacaftor is not recommended in patients aged 4 months to less than 6 months with hepatic impairment, unless the benefits outweigh the risks. In such cases, the recommended dose is one sachet (ivacaftor 25 mg) once daily or less frequently. 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 ivacaftor in children aged less than 4 months have not been established. No data are available.

Limited data are available in patients less than 6 years of age with an *R117H* mutation in the *CFTR* gene. Available data in patients aged 6 years and older are described in sections 4.8, 5.1 and 5.2.

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 or drink containing grapefruit should be avoided during treatment (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, S1251N, S1255P, S549N* or *S549R* gating (class III) or *G970R* mutation in at least one allele of the *CFTR* gene were included in studies 1, 2, 5 and 7 (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 in study 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 ivacaftor as monotherapy 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. Transaminase elevations have been observed in some patients treated with ivacaftor as monotherapy. 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. In the event of significant elevations of transaminases (e.g., patients with ALT or AST > 5 x the upper limit of normal (ULN), or ALT or AST > 3 x ULN with bilirubin > 2 x ULN), dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered (see section 4.8).

Hepatic impairment

Use of ivacaftor is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks (see sections 4.2 and 5.2). No safety data are available in infants aged 4 to less than 12 months of age with moderate or severe hepatic impairment treated with ivacaftor.

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 is significantly decreased by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy; therefore, co-administration of ivacaftor with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

Exposure to ivacaftor is increased when co-administered with strong or moderate CYP3A inhibitors. The dose of ivacaftor must be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see sections 4.2 and 4.5). No safety data are available in infants aged 4 to less than 12 months of age who are treated with ivacaftor and moderate or strong CYP3A inhibitors (see sections 4.2 and 4.5).

Paediatric population

Cases of non-congenital lens opacities/cataracts 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 treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating ivacaftor treatment.

Lactose content

Kalydeco contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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. *In vitro* studies showed that ivacaftor is not a substrate for P-gp.

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 hydroxymethyl ivacaftor (M1) to a lesser extent than ivacaftor. Co-administration of ivacaftor 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).

No dose adjustment is recommended when ivacaftor is used with moderate or weak 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 M1 to a lesser extent than ivacaftor. A reduction of the ivacaftor dose 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 ivacaftor dose is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole, erythromycin, and verapamil (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 or drink containing grapefruit should be avoided during treatment with ivacaftor (see section 4.2).

Potential for ivacaftor to interact with transporters

In vitro studies showed that ivacaftor is not a substrate for OATP1B1 or OATP1B3. Ivacaftor and its metabolites are substrates of BCRP *in vitro*. Due to its high intrinsic permeability and low likelihood of being excreted intact, co-administration of BCRP inhibitors is not expected to alter exposure of ivacaftor and M1-IVA, while any potential changes in M6-IVA exposures are not expected to be clinically relevant.

Ciprofloxacin

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

Medicinal products affected by ivacaftor

Administration of ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of CYP2C9, and/or P-gp, and/or CYP3A which may increase or prolong their therapeutic effect and adverse reactions.

CYP2C9 substrates

Ivacaftor may inhibit CYP2C9. Therefore, monitoring of the international normalised ratio (INR) is recommended during co-administration of warfarin with ivacaftor. Other medicinal products for which exposure may be increased include glimepiride and glipizide; these medicinal products should be used with caution.

Digoxin and other P-gp substrates

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 P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index, such as ciclosporin, everolimus, sirolimus or tacrolimus, caution and appropriate monitoring should be used.

CYP3A substrates

Co-administration with (oral) midazolam, a sensitive CYP3A substrate, increased midazolam exposure 1.5-fold, consistent with weak inhibition of CYP3A by ivacaftor. No dose adjustment of CYP3A substrates, such as midazolam, alprazolam, diazepam or triazolam, is required when these are co-administered with ivacaftor.

Hormonal contraceptives

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. Therefore, no dose adjustment of oral contraceptives 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 ivacaftor 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 ivacaftor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of ivacaftor on fertility in humans. Ivacaftor had an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Ivacaftor 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 are 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions

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

System organ class	Adverse reactions	Frequency
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
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

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).

During the placebo controlled phase 3 studies (up to 24 weeks) of tezacaftor/ivacaftor, the incidence of maximum transaminase (ALT or AST) > 8, > 5, or > 3 x ULN were 0.2%, 1.0%, and 3.4% in tezacaftor/ivacaftor treated patients, and 0.4%, 1.0%, and 3.4% in placebo-treated patients. One patient (0.2%) on therapy and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. No patients treated with tezacaftor/ivacaftor experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

During the 24-week, placebo-controlled, phase 3 study of ivacaftor/tezacaftor/elexacaftor, these figures were 1.5%, 2.5%, and 7.9% in ivacaftor/tezacaftor/elexacaftor-treated patients and 1.0%, 1.5%, and 5.5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations was 10.9% in ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor treated patients and 4.0% in placebo-treated patients.

Paediatric population

The safety data of ivacaftor were evaluated in 6 patients between 4 months to less than 6 months of age, 11 patients between 6 months to less than 12 months of age, 19 patients between 12 months to less than 24 months of age, 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 paediatric patients aged 4 months and older and is also consistent with adult patients.

The incidence of transaminase elevations (ALT or AST) observed in studies 2, 5 and 6 (patients aged 6 to less than 12 years), study 7 (patients aged 2 to less than 6 years), and study 8 (patients aged 6 to less than 24 months) are described in Table 3. In the placebo controlled studies, the incidence of transaminase elevations were similar between treatment with ivacaftor (15.0%) and placebo (14.6%). Peak LFT elevations were generally higher in paediatric patients than in older patients. Across all populations, peak LFT elevations returned to baseline levels following interruption, and 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. In study 7 ivacaftor was permanently discontinued in one patient. In study 8 no patients had elevations in total bilirubin or discontinued ivacaftor treatment due to transaminase elevations in either age cohort (see section 4.4 for management of elevated transaminases).

Table 3: Transaminase elevations in patients 4 months to < 12 years treated with ivacaftor as monotherapy

	n	% of Patients > 3 x ULN	% of Patients >5 x ULN	% of Patients > 8 x ULN
6 to <12 years	40	15.0% (6)	2.5% (1)	2.5% (1)
2 to <6 years	34	14.7% (5)	14.7% (5)	14.7% (5)
12 to <24 months	18	27.8% (5)	11.1% (2)	11.1% (2)
6 to <12 months	11	9.1% (1)	0.0% (0)	0.0% (0)
4 to <6 months	6	0.0% (0)	0.0% (0)	0.0% (0)

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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). The *G970R* mutation causes a splicing defect resulting in

little-to-no CFTR protein at the cell surface which may explain the results observed in subjects with this mutation in study 5 (see Pharmacodynamic effects and Clinical efficacy data).

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). In subgroup analyses by age, the treatment difference was -21.87 mmol/L (95% CI: -26.46, -17.28) in patients aged 18 years or older, and -27.63 mmol/L (95% CI: -37.16, -18.10) in patients aged 6-11 years. Two patients 12 to 17 years of age were enrolled in this study.

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.

In study 8 in patients with CF aged less than 24 months, the mean absolute change from baseline in sweat chloride was -65.1 mmol/L (95% CI -74.1, -56.0) at week 24. Results were consistent in the 12 months to less than 24 months, 6 months to less than 12 months, and 4 months to less than 6 months age cohorts.

Clinical efficacy and safety

Studies 1 and 2: studies in patients with CF with G551D gating mutations

The efficacy of ivacaftor 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 $FEV_1 \geqslant 40\%$ 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 4.

Table 4: 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

Endpoint	Study 1		Study 2	
	Treatment difference[a] (95% CI)	***P* value**	**Treatment difference[a] (95% CI)**	***P* value**
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 *G970R* or non-*G551D* gating mutation in the *CFTR* gene (*G178R, S549N, S549R, G551S, 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 $FEV_1 \geqslant 40\%$ 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 5. 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 5: 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.
# Causes a splicing defect resulting in little-to-no CFTR protein at the cell surface

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 6 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 6: 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%) 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 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).

For secondary efficacy variables, no treatment differences were observed for ivacaftor versus placebo in absolute change from baseline in BMI at week 24 or time to first pulmonary exacerbation. Treatment differences were observed in absolute change in CFQ-R respiratory domain score through week 24 (treatment difference of ivacaftor versus placebo was 8.4 [95% CI 2.2, 14.6] points) and for the mean change from baseline in sweat chloride (see Pharmacodynamic effects).

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).

Study 8: study in paediatric patients with CF aged less than 24 months

The pharmacokinetic profile, safety, and efficacy of ivacaftor in patients with CF aged 6 months to less than 24 months were assessed in a completed cohort of patients in an on-going 24-week, open-label, phase 3 clinical study in patients aged less than 24 months (study 8).

Part B of study 8 enrolled 19 patients aged 12 months to less than 24 months (mean age 15.2 months at baseline), with 18 patients completing the 24-week treatment period, 11 patients aged 6 months to less than 12 months (mean age 9.0 months at baseline) with all 11 patients completing the 24-week treatment period, and 6 patients aged 4 months to less than 6 months (mean age 4.5 months at baseline) with all 6 patients completing the 24-week treatment period. Patients received ivacaftor 25 mg, 50 mg or 75 mg according to their age and weight at each study visit (see section 4.2). Ivacaftor was administered orally every 12 hours with fat−containing food. Patients continued on their prescribed standard-of-care CF therapies.

In part B of study 8 the primary endpoint of safety was evaluated through 24 weeks (see section 4.8). Secondary endpoints were evaluation of pharmacokinetics and the absolute change from baseline in sweat chloride through 24 weeks of treatment (see Pharmacodynamic effects). Tertiary endpoints included efficacy measures such as faecal elastase-1 and growth parameters.

For patients aged 4 months to less than 24 months, with both baseline and week 24 values available, mean (SD) weight-for-age, length-for-age, and weight-for-length z-scores are provided in Table 7.

Table 7: Effect of ivacaftor on growth parameters in patients aged 4 months to less than 24 months with baseline and week 24 values

Parameter	Number of patients	Baseline		Absolute change at week 24	
		Mean (SD)	Median (min, max)	Mean (SD)	Median (min, max)
Weight–for-age z-score	35	0.17 (0.85)	0.20 [-1.92, 1.79]	0.33 (0.53)	0.26 [-0.54, 1.63]
Length-for-age z-score	34	0.06 (1.03)	0.12 [-1.99, 2.79]	0.32 (0.92)	0.47 [-1.81, 3.38]
Weight-for-length z-score	34	0.24 (1.01)	0.26 [-1.72, 2.16]	0.24 (0.98)	0.29 [-2.04, 2.22]

In patients aged 4 months to less than 24 months, with both baseline and week 24 values available, 18 patients were pancreatic insufficient at baseline (defined as faecal elastase-1 < 200 µg/g) with mean (SD) faecal elastase-1 values at baseline and week 24 of 25.5 µg/g (27.6) and 253.6 µg/g (128.3), respectively (mean [SD] absolute change 228.41 µg/g [128.3]). Results were consistent in the 12 months to less than 24 months, 6 months to less than 12 months, and 4 months to less than 6 months age cohorts.

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. When given with fat-containing food the exposure of ivacaftor increased approximately 2.5- to 4-fold. 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 ivacaftor 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, the mean (± SD) apparent volume of distribution was 353 L (122) .

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.

The effect of the CYP3A4*22 heterozygous genotype on ivacaftor exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose adjustment of ivacaftor is considered necessary. The effect in CYP3A4*22 homozygous genotype patients is expected to be stronger. However, no data are available for such patients.

Elimination

Following oral administration in healthy volunteers, 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.

Special populations

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. Based on these results, a modified regimen of Kalydeco as monotherapy is recommended for patients with moderate hepatic impairment (see section 4.2)

The impact of severe hepatic impairment (Child Pugh Class C, score 10 to15) on the pharmacokinetics of ivacaftor have not been studied. The magnitude of increase in exposure in these patients is unknown but is expected to be higher than that observed in patients with moderate hepatic impairment. The use of Kalydeco in patients with severe hepatic impairment is therefore not recommended unless the benefits outweigh the risks (see section 4.2 and section 4.4).

No dose adjustment is considered necessary for patients with mild hepatic impairment.

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).

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).

Race

Race had no clinically meaningful effect on the PK of ivacaftor in white (n = 379) and non-white (n = 29) patients based on a population PK analysis.

Gender

The pharmacokinetic parameters of ivacaftor are similar in males and females.

Elderly

Clinical studies of ivacaftor as monotherapy did not include sufficient numbers of patients aged 65 years and older to determine whether pharmacokinetic parameters are similar or not to those in younger adults.

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 8.

Table 8: Mean (SD) ivacaftor exposure by age group

Age group	Dose	$C_{min, ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng*h/mL)
4 months to less than 6 months (≥5 kg)	25 mg q12h	371 (183)	6480 (2520)
6 months to less than 12 months (5 kg to < 7 kg) *	25 mg q12h	336	5410
6 months to less than 12 months (7 kg to < 14 kg)	50 mg q12h	508 (252)	9140 (4200)
12 months to less than 24 months (7 kg to < 14 kg)	50 mg q12h	440 (212)	9050 (3050)
12 months to less than 24 months (≥ 14 kg to < 25 kg)	75 mg q12h	451 (125)	9600 (1800)
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)

* Values based on data from a single patient; standard deviation not reported.

† Exposures in 6- to 11-year-olds are predictions based on simulations from the population PK model using data obtained for this age group.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Pregnancy and fertility

Ivacaftor was associated with slight decreases of the seminal vesicle weights, a decrease of overall fertility index and number of pregnancies in females mated with treated males and significant reductions in number of corpora lutea and implantation sites with subsequent reductions in the average litter size and average number of viable embryos per litter in treated females. The No-Observed-Adverse-Effect-Level (NOAEL) for fertility findings provides an exposure level of approximately 4 times the systemic exposure of ivacaftor and its metabolites when administered as ivacaftor monotherapy in adult humans at the maximum recommended human dose (MRHD). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

Peri- and post-natal development

Ivacaftor decreased survival and lactation indices and caused a reduction in pup body weights. The NOAEL for viability and growth in the offspring provides an exposure level approximately 3 times the systemic exposure of ivacaftor and its metabolites when administered as ivacaftor monotherapy in adult humans at the MRHD.

Juvenile animal studies

Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through 35 at ivacaftor exposure levels of 0.22 times the MRHD based on systemic exposure of ivacaftor and its metabolites when administered as ivacaftor monotherapy. This finding has not been observed in foetuses derived from rat dams treated with ivacaftor on gestation days 7 to 17, in rat pups exposed to ivacaftor through milk ingestion up to postnatal day 20, in 7-week old rats, nor in 3.5 to 5-month old dogs treated with ivacaftor. The potential relevance of these findings in humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Croscarmellose sodium
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Mannitol
Sucralose
Sodium laurilsulfate (E487)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street
London, W2 6BD
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 22352/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

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