

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of ivacaftor.

Excipient with known effect

Each film-coated tablet contains 167.2 mg of lactose 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:

- As monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an *R117H* *CFTR* mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R* (see sections 4.4 and 5.1).
- In a combination regimen with tezacaftor 100 mg/ivacaftor 150 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T*.
- In a combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation in the *CFTR* gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation (see section 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 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 recommendations.

Posology

Adults, adolescents and children aged 6 years and older should be dosed according to Table 1.

Table 1: Dosing recommendations

	Morning	Evening
Ivacaftor as monotherapy		
6 years and older, ≥25 kg	One ivacaftor 150 mg tablet	One ivacaftor 150 mg tablet
Ivacaftor in combination with tezacaftor/ivacaftor		
12 years and older	One tezacaftor 100 mg/ivacaftor 150 mg tablet	One ivacaftor 150 mg tablet
Ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor		
12 years and older	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One ivacaftor 150 mg tablet

The morning and evening dose should be taken approximately 12 hours apart with fat-containing food (see Method of administration).

Missed dose

If 6 hours or less have passed since the missed morning or evening dose, the patient should take it as soon as possible and continue on the original schedule. 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.

Patients receiving ivacaftor in a combination regimen should not take more than one dose of either medicine at the same time.

Concomitant use of CYP3A inhibitors

When co-administered with moderate or strong inhibitors of CYP3A, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, the dose should be reduced (see Table 2 for the recommended dose). Dosing intervals should be modified according to clinical response and tolerability (see sections 4.4 and 4.5).

Table 2: Dosing recommendations for concomitant use with moderate or strong CYP3A inhibitors

	Moderate CYP3A inhibitors	Strong CYP3A inhibitors
Ivacaftor as monotherapy		
6 years and older, ≥25 kg	One morning tablet of ivacaftor 150 mg once daily. No evening dose.	One morning tablet of ivacaftor 150 mg twice a week, approximately 3 to 4 days apart. No evening dose.
Ivacaftor in a combination regimen with tezacaftor/ivacaftor		
12 years and older	Alternate each morning: - one tablet of tezacaftor 100 mg/ivacaftor 150 mg on the first day - one tablet of ivacaftor 150 mg on the next day Continue alternating tablets each day. No evening dose.	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, approximately 3 to 4 days apart. No evening dose.
Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor		

	Moderate CYP3A inhibitors	Strong CYP3A inhibitors
12 years and older	Alternate each morning: <ul style="list-style-type: none"> - two tablets of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg on the first day - one tablet of ivacaftor 150 mg on the next day Continue alternating tablets each day. No evening dose.	Two morning dose tablets of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg twice a week, approximately 3 to 4 days apart. No evening dose.

Special populations

Elderly

Very limited data are available for elderly patients treated with ivacaftor (administered as monotherapy or in a combination regimen). No dose adjustment specific to this patient population is required (see section 5.2).

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 ivacaftor as monotherapy or in a combination regimen in patients with mild hepatic impairment (Child-Pugh Class A).

For patients with moderate hepatic impairment (Child-Pugh Class B) the dose of ivacaftor as monotherapy should be reduced to 150 mg once daily.

For patients with severe hepatic impairment (Child-Pugh Class C), the dose of ivacaftor as monotherapy should be reduced to 150 mg every other day or less frequently.

For use as an evening dose in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor see Table 3 for dosing regimen recommendations.

Table 3: Recommendations for patients with moderate or severe hepatic impairment

	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
Ivacaftor as monotherapy		
6 years and older, ≥ 25 kg	One morning tablet of ivacaftor 150 mg once daily. No evening dose.	Use is not recommended unless the benefits are expected to outweigh the risks. In such cases, take one morning tablet of ivacaftor 150 mg every other day or less frequently. Dosing interval should be modified according to clinical response and tolerability. No evening dose.

Ivacaftor in a combination regimen with tezacaftor/ivacaftor		
12 years and older	<p>One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily.</p> <p>No evening dose.</p>	<p>Use is not recommended unless the benefits are expected to outweigh the risks.</p> <p>In such cases, take one morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently.</p> <p>Dosing interval should be modified according to clinical response and tolerability.</p> <p>No evening dose.</p>
Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor		
12 years and older	<p>Use not recommended.</p> <p>Use should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.</p> <p>If used: alternate each day between two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets and one ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablet.</p> <p>No evening dose.</p>	<p>Should not be used.</p> <p>No morning ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg dose.</p> <p>No evening dose.</p>

Paediatric population

The safety and efficacy of ivacaftor monotherapy in children aged less than 4 months 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 ivacaftor tablets.

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.

The safety and efficacy of ivacaftor in a combination regimen with tezacaftor/ivacaftor and ivacaftor/tezacaftor/elexacaftor in children aged less than 12 years have not been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing because there are no clinical data currently available to support other methods of administration.

Ivacaftor tablets should be taken with fat-containing food.

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*, *S549R* gating (class III), *G970R* or *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 FEV₁ 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 FEV₁ 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.

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).

Ivacaftor in a combination regimen with tezacaftor/ivacaftor should not be prescribed in patients with CF who are heterozygous for the *F508del* mutation and have a second *CFTR* mutation not listed in section 4.1.

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 and in combination regimens with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor. 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, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor, is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks. Patients with severe hepatic impairment should not be treated with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor. (See Table 3 and sections 4.2 and 5.2).

For patients with moderate hepatic impairment, use of ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor is not recommended. Treatment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 3 and sections 4.2 and 5.2).

Renal impairment

Caution is recommended while using ivacaftor, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Patients after organ transplantation

Ivacaftor, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, 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.

Rash events

The incidence of rash events with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor was higher in females than in males, particularly in females taking hormonal contraceptives. A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, interrupting treatment with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see section 4.8).

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy; therefore, co-administration of ivacaftor (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

Exposure to ivacaftor, tezacaftor and elexacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of ivacaftor (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) must be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see Table 2 and 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 and ivacaftor-containing regimens. 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, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor (see section 5.3).

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, tezacaftor and/or elexacaftor

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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) is co-administered with ciprofloxacin.

Medicinal products affected by ivacaftor, tezacaftor and/or elexacaftor

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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor). 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor).

Hormonal contraceptives

Ivacaftor (as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) 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 to 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 who received ivacaftor 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 4 reflects the adverse reactions observed with ivacaftor monotherapy in clinical trials (placebo-controlled and uncontrolled studies) in which the length of exposure to ivacaftor ranged from 16 weeks to 144 weeks. Additional adverse reactions observed with ivacaftor in a combination regimen with tezacaftor/ivacaftor and/or in a combination regimen with ivacaftor/tezacaftor/elexacaftor are also provided in Table 4. The frequency of adverse reactions is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 4: Adverse reactions in patients treated with ivacaftor monotherapy and/or in a combination regimen

System organ class	Adverse reactions	Frequency
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Influenza †	common
	Rhinitis	common
Metabolism and nutrition disorders	Hypoglycaemia †	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
	Abnormal breathing †	common
	Rhinorrhoea †	common
	Sinus congestion	common
	Pharyngeal erythema	common
	Wheezing †	uncommon
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea	very common
	Abdominal pain upper †	common
	Flatulence †	common
	Nausea *	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased †	common
	Aspartate aminotransferase increased †	common
Skin and subcutaneous tissue disorders	Rash	very common
	Acne †	common
	Pruritus †	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon

System organ class	Adverse reactions	Frequency
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase increased †	common
	Blood pressure increased †	uncommon

* Adverse reaction and frequency reported from clinical studies with ivacaftor in combination with tezacaftor/ivacaftor

† Adverse reaction and frequency reported from clinical studies with ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor

Description of selected adverse reactions

Transaminase elevations

During the 48-week placebo-controlled studies 1 and 2 of ivacaftor as monotherapy 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.

Rash events

Rash events, generally mild to moderate in severity, have been observed with the use of ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor and occurred more frequently in female-treated patients (16.3%) and in those taking hormonal contraceptives (20.5%). See section 4.4.

Increased creatine phosphokinase

Generally transient and asymptomatic increases in creatine phosphokinase were observed in patients treated with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor, which did not lead to treatment discontinuation.

Increased blood pressure

An increase from baseline in mean systolic and diastolic blood pressure of 3.5 mmHg and 1.9 mmHg, respectively was observed in patients treated with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor.

Paediatric population

The safety data of ivacaftor as monotherapy 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 of ivacaftor (as monotherapy or in a combination regimen) is generally consistent among paediatric patients 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 5. In the placebo controlled studies, the incidence of transaminase elevations were similar between treatment with ivacaftor (15.0%) and placebo (14.6%). 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 cohort (see section 4.4 for management of elevated transaminases).

Table 5: 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 HPRA Pharmacovigilance, website: www.hpra.ie.

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

Ivacaftor as monotherapy

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.

Ivacaftor in a combination regimen with tezacaftor/ivacaftor

In patients homozygous for the *F508del* mutation, the treatment difference between ivacaftor in combination with tezacaftor/ivacaftor and placebo in mean absolute change from baseline in sweat chloride through week 24, was -10.1 mmol/L (95% CI: -11.4, -8.8).

In patients heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity, the treatment difference in mean absolute change from baseline in sweat chloride through week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between tezacaftor/ivacaftor and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo.

Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor

In patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor, the treatment difference between ivacaftor/tezacaftor/elexacaftor and placebo for mean absolute change in sweat chloride from baseline through week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3).

In patients homozygous for the *F508del* mutation, the treatment difference between ivacaftor/tezacaftor/elexacaftor and tezacaftor/ivacaftor for mean absolute change in sweat chloride from baseline at week 4 was -45.1 mmol/L (95% CI: -50.1, -40.1).

Clinical efficacy and safety

Ivacaftor as monotherapy

Study 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 FEV₁ ≥ 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 FEV₁ 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 FEV₁ 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 FEV₁ less than 70% predicted at baseline.

The primary efficacy endpoint in both studies was the mean absolute change from baseline in percent predicted FEV₁ through 24 weeks of treatment.

The treatment difference between ivacaftor and placebo for the mean absolute change (95% CI) in percent predicted FEV₁ 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 FEV₁ 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 FEV₁ (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 FEV₁ 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 FEV₁ 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 FEV₁ from baseline through week 24 in patients with baseline predicted FEV₁ 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 6.

Table 6: Effect of ivacaftor on other efficacy endpoints in studies 1 and 2

Endpoint	Study 1		Study 2	
	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

Endpoint	Study 1		Study 2	
	Treatment difference ^a (95% CI)	P value	Treatment difference ^a (95% CI)	P value
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/m²)				
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 *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 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 FEV₁ ≥ 40% predicted (mean FEV₁ 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 FEV₁ 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 FEV₁ (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 FEV₁ at week 8) is shown in Table 7. Based on clinical (percent predicted FEV₁) and pharmacodynamic (sweat chloride) responses to ivacaftor, efficacy in patients with the *G970R* mutation could not be established.

Table 7: 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
<i>G1244E</i> (5)	-55 (-75, -34)	8 (-1, 18)
<i>G1349D</i> (2)	-80 (-82, -79)	20 (3, 36)
<i>G178R</i> (5)	-53 (-65, -35)	8 (-1, 18)
<i>G551S</i> (2)	-68 [†]	3 [†]
<i>G970R</i> [#] (4)	-6 (-16, -2)	3 (-1, 5)
<i>S1251N</i> (8)	-54 (-84, -7)	9 (-20, 21)
<i>S1255P</i> (2)	-78 (-82, -74)	3 (-1, 8)
<i>S549N</i> (6)	-74 (-93, -53)	11 (-2, 20)
<i>S549R</i> (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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ ≥ 40% predicted.

The mean absolute change from baseline through week 16 in percent predicted FEV₁ (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 8 shows the results of the mean (SD) absolute change in percent predicted FEV₁ for both groups of patients. For patients in the placebo/ivacaftor group baseline percent predicted FEV₁ is that of study 4 while for patients in the ivacaftor/ivacaftor group the baseline value is that of studies 1 and 2.

Table 8: Effect of ivacaftor on percent predicted FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ (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 FEV₁ 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 FEV₁ 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).

Ivacaftor in a combination regimen with tezacaftor/ivacaftor or with ivacaftor/tezacaftor/elexacaftor

The efficacy and safety of ivacaftor in a combination regimen with tezacaftor/ivacaftor in patients with CF aged 12 years and older was assessed in two clinical studies; a 24 week, randomised, double-blind, placebo-controlled study with 504 patients who were homozygous for the *F508del* mutation; and a randomised, double-blind, placebo-controlled and ivacaftor controlled, 2 period, 3 treatment, 8-week crossover study with 244 patients who were heterozygous for the *F508del* mutation and a second mutation associated with residual *CFTR* activity. The long-term safety and efficacy of the combination regimen was also assessed in both patient populations in a 96-week open-label, rollover, long-term extension study. Refer to the Summary of Product Characteristics of tezacaftor/ivacaftor for additional data.

The efficacy and safety of ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older was demonstrated in two, phase 3 studies, randomised, double blind, placebo-controlled (heterozygous *F508del* patients, n=403) and active-controlled (homozygous *F508del* patients, n=107) of 24 and 4 weeks of duration, respectively. Heterozygous *F508del* patients had a minimal function mutation on the second allele defined as one that either leads to no *CFTR* protein being produced (e.g. Class I) or a *CFTR* protein that does not function to transport chloride and is unlikely to respond to other *CFTR* modulators (tezacaftor, ivacaftor or the combination of both). Homozygous *F508del* patients received tezacaftor/ivacaftor and ivacaftor regimen during a 4-week open-label run-in period and were then randomised and dosed to receive ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor during a 4-week double-blind treatment period. Patients from both studies were eligible to enter an open-label, rollover, 96-week study. Refer to the Summary of Product Characteristics of ivacaftor/tezacaftor/elexacaftor for additional data.

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 (\pm 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. When co-administered with tezacaftor and elexacaftor, the increase in AUC was similar (approximately 3-fold and 2.5-to 4-fold respectively). Therefore, ivacaftor, administered as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, 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 (\pm 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 tezacaftor, ivacaftor and elexacaftor exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose-adjustment of tezacaftor, ivacaftor or elexacaftor 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 (\pm 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 [\pm SD] of 735 [331] ng/mL) but an approximately two-fold increase in ivacaftor $AUC_{0-\infty}$ (mean [\pm 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.

In subjects with moderately impaired hepatic function (Child Pugh Class B, score 7 to 9), ivacaftor AUC increased approximately by 50% following multiple doses for 10 days of either tezacaftor and ivacaftor or of ivacaftor, tezacaftor and elexacaftor.

The impact of severe hepatic impairment (Child Pugh Class C, score 10 to 15) on the pharmacokinetics of ivacaftor as monotherapy or in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor has 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.

For guidance on appropriate use and dose modification see Table 3 in section 4.2.

Renal impairment

Pharmacokinetic studies have not been performed with ivacaftor in patients with renal impairment, either as monotherapy or in a combination regimen with tezacaftor/ivacaftor or with ivacaftor/tezacaftor/elexacaftor. In a human pharmacokinetic study with ivacaftor monotherapy, 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. Caution is recommended when administering ivacaftor, either as monotherapy or in a combination with tezacaftor/ivacaftor or with ivacaftor/tezacaftor/elexacaftor, 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, either as monotherapy or in combination with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, are similar in males and females.

Elderly

Clinical studies of ivacaftor 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.

The pharmacokinetic parameters of ivacaftor in combination with tezacaftor in the elderly patients (65-72 years) are comparable to those in younger adults. No patients aged 65 years and older were included in the clinical studies of ivacaftor/tezacaftor/elexacaftor and therefore it cannot be determined 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 9.

Table 9: Mean (SD) ivacaftor exposure by age group

Age group	Dose	C _{min, ss} (ng/mL)	AUC _{τ, ss} (ng*h/mL)
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.

The pharmacokinetic parameters of ivacaftor in combination with tezacaftor and with tezacaftor/elexacaftor in adolescent patients (12 to 17-year-olds) are similar to that of adult patients (see Table 10).

Table 10: Mean (SD) of ivacaftor exposure when used in combination with tezacaftor and in combination with tezacaftor/elexacaftor, by age group

Age group	Dose	Ivacaftor Mean (SD) AUC _{0-12h,ss} (ng*h/mL)
Adolescent patients (12 to <18 years) n = 97	tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	11400 (5500)
Adult patients (≥ 18 years) n = 389		11400 (4140)
Adolescent patients (12 to <18 years) n = 69	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	10600 (3350)
Adult patients (≥18 years) n = 186		12100 (4170)

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 of 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

Tablet core

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

Tablet film coat

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol (PEG 3350)
Talc
Indigo carmine aluminium lake (E132)
Carnauba wax

Printing ink

Shellac
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonia solution, concentrated

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 card pack containing 28 film-coated tablets
- 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

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

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/001
EU/1/12/782/002
EU/1/12/782/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 July 2012

Date of latest renewal: 28 April 2017

10. DATE OF REVISION OF THE TEXT

11/2020

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 (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Ltd.
Seagoe Industrial Estate
Craigavon
Co. Armagh BT63 5UA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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
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 – 56-TABLET PACK

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 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Take 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

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 (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

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
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – 56-TABLET PACK

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg tablets
ivacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER CARD – 28-TABLET PACK

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

28 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Always take this medicine exactly as your doctor has told you to.

Take with fat-containing food.

Do not break, chew or dissolve the tablets.

Insert tab below to close

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

9. SPECIAL STORAGE CONDITIONS

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 (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/005

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
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD – 28-TABLET PACK

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg film-coated tablets
ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Kalydeco tablet contains 150 mg of ivacaftor.

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Always take this medicine exactly as your doctor has told you to.

Take with fat-containing food.

Do not break, chew or dissolve the tablets.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

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

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 (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/782/005

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

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – 28-TABLET PACK

1. NAME OF THE MEDICINAL PRODUCT

Kalydeco 150 mg tablets
ivacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

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 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Instructions for use

Take 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

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 (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

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
SN
NN

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 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

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 (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland

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

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kalydeco 150 mg film-coated tablets ivacaftor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kalydeco is and what it is used for
2. What you need to know before you take Kalydeco
3. How to take Kalydeco
4. Possible side effects
5. How to store Kalydeco
6. Contents of the pack and other information

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:

- As monotherapy for patients aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an *R117H* *CFTR* mutation or one of the following gating mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.
- In combination with tezacaftor/ivacaftor tablets for patients aged 12 years and older with CF who have two *F508del* mutations in the *CFTR* gene (homozygous for the *F508del* mutation) or who have an *F508del* mutation and certain other second mutations (heterozygous for the *F508del* mutation). If you have been prescribed Kalydeco to be taken with tezacaftor/ivacaftor, read the tezacaftor/ivacaftor package leaflet. It contains important information about how to take these two medicines.
- In combination with ivacaftor/tezacaftor/elexacaftor tablets for patients aged 12 years and over with CF who are homozygous for the *F508del* mutation in the *CFTR* gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation. A minimal function mutation is defined as one that results either in no CFTR protein being produced or a CFTR protein that does not function, and which is unlikely to respond to ivacaftor alone and tezacaftor/ivacaftor. If you have been prescribed Kalydeco to be taken with ivacaftor/tezacaftor/elexacaftor, read the ivacaftor/tezacaftor/elexacaftor package leaflet. It contains important information about how to take these two medicines.

2. What you need to know before you take Kalydeco

Do not take Kalydeco

- if you are allergic to ivacaftor or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

- Talk to your doctor if you have liver problems or have previously had them. Your doctor may need to adjust your dose.
- Increased liver enzymes in the blood have been seen in some people receiving Kalydeco (alone or in combination with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor). 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 before and during treatment, particularly during the first year and especially if your blood tests showed high liver enzymes in the past.

- Talk to your doctor if you have kidney problems or have previously had them.
- Kalydeco (alone or in combination with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) is not recommended if you have undergone an organ transplant.
- Talk to your doctor if you are using hormonal contraception – for example, women using the contraceptive pill. This may mean you are more likely to get a rash while taking Kalydeco in combination with ivacaftor/tezacaftor/elexacaftor.
- Abnormality of the eye lens (cataract) without any effect on vision has been noted in some children and adolescents treated with Kalydeco (alone or in combination with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor). Your doctor may perform some eye examinations prior to and during treatment.
- Kalydeco (alone or in combination with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor) should only be used if you have one of the mutations in the *CFTR* gene indicated in section 1 (What Kalydeco is and what it is used for).

Children and adolescents

Do not give this medicine to children under 4 months of age as it is not known if ivacaftor is safe and effective in these children.

Do not give this medicine in combination with tezacaftor/ivacaftor or with ivacaftor/tezacaftor/elexacaftor to children under 12 years of age as it is not known if they are safe and effective for them.

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 side effects more likely. In particular, tell your doctor if you are taking any of the medicines listed below. Your doctor may decide to adjust your dose or that you need extra check-ups.

- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifabutin, rifampicin, and telithromycin .
- **Epilepsy medicines** (used for the treatment of epileptic seizures). These include carbamazepine, phenobarbital, and phenytoin.
- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).
- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus, and tacrolimus, .
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.
- **Medicines for diabetes.** These include glimepiride and glipizide.
- **Medicines for lowering blood pressure.** These include verapamil.

Kalydeco with food and drink

Avoid food or drink containing grapefruit during treatment with Kalydeco as they may increase the side effects of Kalydeco by increasing the amount of ivacaftor 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. If you feel dizzy, do not drive, cycle or use machines.

Important information about the contents of Kalydeco

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.

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

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.

Your doctor will determine which medicine and dose is right for you.

Kalydeco dosing recommendations are provided in Table 1.

Table 1: Dosing recommendations

	Morning	Evening
Kalydeco as monotherapy		
6 years and older, ≥ 25 kg	One Kalydeco 150 mg tablet	One Kalydeco 150 mg tablet
Kalydeco in combination with tezacaftor/ivacaftor		
12 years and older	One tezacaftor 100 mg/ivacaftor 150 mg tablet	One Kalydeco 150 mg tablet
Kalydeco in combination with ivacaftor/tezacaftor/elexacaftor		
12 years and older	Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets	One Kalydeco 150 mg tablet

Take the tablets morning and evening doses approximately 12 hours apart with food that contains fat.

You must keep using all other medicines you use, unless your doctor tells you to stop using any.

If you have liver problems, either moderate or severe, your doctor may need to reduce the dose of your tablets, because your liver will not clear the medicine as fast as in people who have normal liver function.

Use in children

Other forms of this medicine (granules in sachet) are more suitable for children under 6 years of age; ask your doctor or pharmacist.

This medicine is for oral use.

Swallow the tablet whole. Do not break, chew or dissolve the tablets. Take Kalydeco tablets with food that contains fat.

Meals or snacks that contain fat include 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

Stomach (abdominal) ache and increased liver enzymes in the blood.

Possible signs of liver problems

Increased liver enzymes in the blood are common in patients with CF. These may be signs of liver problems:

- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Tell 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
- Stomach or abdominal pain
- Changes in the type of bacteria in mucus
- Increased liver enzymes (signs of stress on the liver)
- Rash

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 problems (sinus congestion)
- Redness in the throat
- Breast mass
- Feeling sick (nausea)
- Flu
- Low blood sugar (hypoglycaemia)
- Abnormal breathing (shortness of breath or difficulty breathing)
- Wind (flatulence)
- Spots (acne)
- Itchy skin
- Increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests

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

- Ear congestion
- Breast inflammation
- Enlargement of the breast in males
- Nipple changes or pain
- Wheezing
- Increased blood pressure

Additional side effects in children and adolescents

Side effects seen in children and adolescents are similar to those observed in adults. 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 HPRA Pharmacovigilance, website: www.hpra.ie.

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.

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Kalydeco contains

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

The other ingredients are:

- Tablet core: cellulose microcrystalline, lactose monohydrate, hypromellose acetate succinate, croscarmellose sodium, sodium laurilsulfate (E487), silica, colloidal anhydrous, 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 (E1520) and ammonia solution, concentrated.

See the end of section 2 - Important information about the contents of Kalydeco.

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 card pack containing 28 film-coated tablets
- Blister pack containing 56 film-coated tablets
- Bottle containing 56 film-coated tablets

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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.