**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 × 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/ivacaftor tablets for the treatment of adults, adolescents, and children aged 6 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/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who have at least one *F508del* mutation in the *CFTR* gene (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.

<u>Posology</u>

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** | | |
| 6 years to < 12 years, < 30 kg | One tezacaftor 50 mg/ivacaftor 75 mg tablet | One ivacaftor 75 mg tablet |
| 6 years to < 12 years, ≥ 30 kg | One tezacaftor 100 mg/ivacaftor 150 mg tablet | One ivacaftor 150 mg tablet |
| 12 years and older | One tezacaftor 100 mg/ivacaftor 150 mg tablet | One ivacaftor 150 mg tablet |
| **Ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor** | | |
| 6 years to < 12 years, < 30 kg | Two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets | One ivacaftor 75 mg tablet |
| 6 years to < 12 years, ≥ 30 kg | Two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets | One ivacaftor 150 mg tablet |
| 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 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.

Patients receiving Kalydeco in a combination regimen should be advised not to take more than one dose of either medicinal product 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 based on dosing recommended for the age and weight (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.<br><br>No evening dose. | One morning tablet of ivacaftor 150 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |
| **Ivacaftor in a combination regimen with tezacaftor/ivacaftor** | | |
| 6 years to < 12 years, < 30 kg | Alternate each morning:<br>- one tablet of tezacaftor 50 mg/ivacaftor 75 mg on the first day<br>- one tablet of ivacaftor 75 mg on the next day<br>Continue alternating tablets each day.<br><br>No evening dose. | One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |
| 6 years to < 12 years, ≥ 30 kg | Alternate each morning:<br>- one tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily on the first day<br>- one tablet of ivacaftor 150 mg on the next day<br>Continue alternating each day.<br><br>No evening dose. | One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |
| 12 years and older | Alternate each morning:<br>- one tablet of tezacaftor 100 mg/ivacaftor 150 mg on the first day<br>- one tablet of ivacaftor 150 mg on the next day<br>Continue alternating tablets each day.<br><br>No evening dose. | One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |

| | Moderate CYP3A inhibitors | Strong CYP3A inhibitors |
|---|---|---|
| **Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor** | | |
| 6 years to < 12 years,< 30 kg | Alternate each morning:<br>- two tablets of ivacaftor 37.5 mg/tezacaftor 25 mg/ elexacaftor 50 mg on the first day<br>- one tablet of ivacaftor 75 mg on the next day<br>Continue alternating tablets each day.<br><br>No evening dose. | Two morning tablets of ivacaftor 37.5 mg/tezacaftor 25 mg/ elexacaftor 50 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |
| 6 years to < 12 years, ≥ 30 kg | Alternate each morning:<br>- two tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg on the first day<br>- one tablet of ivacaftor 150 mg on the next day<br>Continue alternating tablets each day.<br><br>No evening dose. | Two morning tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |
| 12 years and older | Alternate each morning:<br>- two tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg on the first day<br>- one tablet of ivacaftor 150 mg on the next day<br>Continue alternating tablets each day.<br><br>No evening dose. | Two morning tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg twice a week, approximately 3 to 4 days apart.<br><br>No evening dose. |

<u>Special populations</u>

*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: Dosing 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.<br><br>No evening dose. | Use is not recommended unless the benefits are expected to outweigh the risks.<br><br>If used: one morning tablet of ivacaftor 150 mg every other day or less frequently.<br><br>Dosing interval should be modified according to clinical response and tolerability.<br><br>No evening dose. |
| **Ivacaftor in a combination regimen with tezacaftor/ivacaftor** | | |
| 6 years to < 12 years, < 30 kg | One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily.<br><br>No evening dose. | Use is not recommended unless the benefits are expected to outweigh the risks.<br><br>If used: one morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily or less frequently.<br><br>Dosing interval should be modified according to clinical response and tolerability.<br><br>No evening dose. |

| | Moderate<br>(Child-Pugh Class B) | Severe<br>(Child-Pugh Class C) |
|---|---|---|
| 6 years to < 12 years, ≥ 30 kg | One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily.<br><br>No evening dose. | Use is not recommended unless the benefits are expected to outweigh the risks.<br><br>If used: one morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently.<br><br>Dosing interval should be modified according to clinical response and tolerability.<br><br>No evening dose. |
| 12 years and older | One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily.<br><br>No evening dose. | Use is not recommended unless the benefits are expected to outweigh the risks.<br><br>If used: one morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently.<br><br>Dosing interval should be modified according to clinical response and tolerability.<br><br>No evening dose. |
| **Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor** | | |
| 6 years to < 12 years, < 30 kg | Use not recommended.<br>Use should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.<br><br>If used: alternate each day between two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets and one ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablet.<br><br>No evening dose. | Should not be used. |

| | Moderate<br>(Child-Pugh Class B) | Severe<br>(Child-Pugh Class C) |
|---|---|---|
| 6 years to < 12 years, ≥ 30 kg | Use not recommended.<br>Use should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.<br><br>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.<br><br>No evening dose. | Should not be used. |
| 12 years and older | Use not recommended.<br>Use should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. *<br><br>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.<br><br>No evening dose. | Should not be used. * |

* See sections 4.4 and 4.8

<u>Paediatric population</u>

The safety and efficacy of ivacaftor have not been established in children less than 1 month of age as monotherapy, neither in combination with tezacaftor/ivacaftor in children less than 6 years of age or in combination with ivacaftor/tezacaftor/elexacaftor in children less than 2 years of age. 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.

<u>Method of administration</u>

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 $FEV_1$ 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.

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.

Elevated transaminases and hepatic injury

In a patient with cirrhosis and portal hypertension, liver failure leading to transplantation has been reported while receiving ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor. Use with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment (see sections 4.2, 4.8, and 5.2).

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. In patients taking ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor, these elevations have sometimes been associated with concomitant elevations in total bilirubin. Therefore, assessments of transaminases (ALT and AST) and total bilirubin 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 liver disease or 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 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with bilirubin > 2 × 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 sections 4.2, 4.8, and 5.2).

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, 4.8, 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, 4.8, 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 medicinal product.

Sodium content

This medicinal product 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 (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 Table 2 and 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 Table 2 and 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

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 in 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 and 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 (≥ 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 4: Adverse reactions**

| 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 |
| | Liver injury^ | not known |
| | Total bilirubin elevations^ | not known |
| 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.

^ Liver injury (ALT and AST and total bilirubin elevations) reported from post-marketing data with ivacaftor in combination with ivacaftor/tezacaftor/elexacaftor. This also included liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension. Frequency cannot be estimated from the available data.

<u>Description of selected adverse reactions</u>

*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 × 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 × ULN. No ivacaftor-treated patients experienced a transaminase elevation > 3 × ULN associated with elevated total bilirubin > 1.5 × ULN. In ivacaftor-treated patients, most transaminase elevations up to 5 × ULN resolved without treatment interruption. Ivacaftor dosing was interrupted in most patients with transaminase elevations > 5 × 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 × 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 × ULN associated with elevated total bilirubin > 2 × 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. Post-marketing cases of treatment discontinuation due to elevated transaminases have been reported (see section 4.4).

*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.

<u>Paediatric population</u>

The safety data of ivacaftor as monotherapy were evaluated in 7 patients between 1 month to less than 4 months of age, 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 1 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%). 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, in the cohort of patients aged 1 month to less than 4 months, 1 patient had maximum ALT or AST > 3 × ULN (ALT > 8 × ULN and AST of > 3 to ≤ 5 × ULN); the subject discontinued ivacaftor treatment (see section 4.4 for management of elevated transaminases).

**Table 5: Transaminase elevations in patients 1 month to < 12 years treated with ivacaftor as monotherapy**

| | **n** | **% of Patients > 3 × ULN** | **% of Patients >5 × ULN** | **% of Patients > 8 × 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) |
| 1 to < 4 months | 7 | 14.3% (1) | 14.3% (1) | 14.3% (1) |

Age-appropriate formulation and strengths are available for paediatric patients 1 month and older. Refer to the Summary of Product Characteristics for Kalydeco granules.

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 and safety).

*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.

In patients aged 6 to less than 12 years who were homozygous or heterozygous for the *F508del* mutation and a second mutation associated with residual *CFTR* activity, mean within-group absolute change in sweat chloride from baseline at week 8 was -12.3 mmol/L (95% CI: -15.3, -9.3) in the tezacaftor/ivacaftor group.

*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 predicts either no production of a CFTR protein or a CFTR protein that does not transport chloride and is not responsive to ivacaftor and tezacaftor/ivacaftor (minimal function mutation) *in vitro*, the treatment difference of ivacaftor/tezacaftor/elexacaftor compared to 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 of ivacaftor/tezacaftor/elexacaftor compared to 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).

In patients heterozygous for the *F508del* mutation and a mutation on the second allele with a gating defect or residual CFTR activity, the treatment difference of ivacaftor/tezacaftor/elexacaftor compared to the control group (ivacaftor monotherapy group plus tezacaftor/ivacaftor group) for mean absolute change in sweat chloride from baseline through week 8 was -23.1 mmol/L (95% CI: -26.1, -20.1).

In patients aged 6 to less than 12 years, homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation, the mean absolute change in sweat chloride from baseline (n=62) through week 24 (n=60*) was -60.9 mmol/L

(95% CI: -63.7, -58.2). ≠ The mean absolute change in sweat chloride from baseline through week 12 (n=59‡) was -58.6 mmol/L (95% CI: -61.1, -56.1).
* The through week 24 endpoint is analyzed using mixed model with repeated measures (MMRM) including data from week 4, week 12 and week 24.
‡ The through week 12 endpoint is analyzed using MMRM including data from week 4 and week 12.
≠ Not all participants included in the analyses had data available for all follow-up visits, especially from week 16 onwards. The ability to collect data at week 24 was hampered by the COVID-19 pandemic. Week 12 data were less impacted by the pandemic.

<u>Clinical efficacy and safety</u>

*Ivacaftor as monotherapy*

*<u>Studies 1 and 2: studies in patients with CF with G551D gating mutations</u>*

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 $FEV_1 \geq 40\%$ predicted.

Patients in both studies were randomised 1:1 to receive either 150 mg of ivacaftor or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies (e.g., tobramycin, dornase alfa). The use of inhaled hypertonic sodium chloride was not permitted.

Study 1 evaluated 161 patients who were 12 years of age or older; 122 (75.8%) patients had the *F508del* mutation in the second allele. At the start of the study, patients in the placebo group used some medicinal products at a higher frequency than the ivacaftor group. These medicinal products 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 6.

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

| | Study 1 | | Study 2 | |
|---|---|---|---|---|
| **Endpoint** | **Treatment difference[a] (95% CI)** | ***P* value** | **Treatment difference[a] (95% CI)** | ***P* value** |
| **Mean absolute change from baseline in CFQ-R[b] respiratory domain score (points)[c]** | | | | |
| Through week 24 | 8.1 (4.7, 11.4) | < 0.0001 | 6.1 (-1.4, 13.5) | 0.1092 |
| Through week 48 | 8.6 (5.3, 11.9) | < 0.0001 | 5.1 (-1.6, 11.8) | 0.1354 |
| **Relative risk of pulmonary exacerbation** | | | | |
| Through week 24 | 0.40[d] | 0.0016 | NA | NA |
| Through week 48 | 0.46[d] | 0.0012 | NA | NA |
| **Mean absolute change from baseline in body weight (kg)** | | | | |
| At week 24 | 2.8 (1.8, 3.7) | < 0.0001 | 1.9 (0.9, 2.9) | 0.0004 |
| At week 48 | 2.7 (1.3, 4.1) | 0.0001 | 2.8 (1.3, 4.2) | 0.0002 |
| **Mean absolute change from baseline in BMI ($kg/m^2$)** | | | | |
| At week 24 | 0.94 (0.62, 1.26) | < 0.0001 | 0.81 (0.34, 1.28) | 0.0008 |
| At week 48 | 0.93 (0.48, 1.38) | < 0.0001 | 1.09 (0.51, 1.67) | 0.0003 |
| **Mean change from baseline in z-scores** | | | | |
| Weight-for-age z-score at week 48[e] | 0.33 (0.04, 0.62) | 0.0260 | 0.39 (0.24, 0.53) | < 0.0001 |
| BMI-for-age z-score at week 48[e] | 0.33 (0.002, 0.65) | 0.0490 | 0.45 (0.26, 0.65) | < 0.0001 |

CI: confidence interval; NA: not analysed due to low incidence of events
[a] Treatment difference = effect of ivacaftor – effect of placebo
[b] CFQ-R: Cystic Fibrosis Questionnaire-Revised is a disease-specific, health-related quality-of-life measure for CF.
[c] Study 1 data were pooled from CFQ-R for adults/adolescents and CFQ-R for children 12 to 13 years of age; Study 2 data were obtained from CFQ-R for children 6 to 11 years of age.
[d] Hazard ratio for time to first pulmonary exacerbation
[e] In subjects under 20 years of age (CDC growth charts)

*Study 5: study in patients with CF with non-G551D gating mutations*

Study 5 was a phase 3, two-part, randomised, double-blind, placebo-controlled, crossover study (part 1) followed by a 16-week open-label extension period (part 2) to evaluate the efficacy and safety of ivacaftor in patients with CF aged 6 years and older who have a *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 $FEV_1 \geq 40\%$ predicted (mean $FEV_1$ 78% predicted [range: 43% to 119%]) were enrolled. Sixty-two percent (24/39) of them carried the *F508del-CFTR* mutation in the second allele. A total of 36 patients continued into part 2 (18 per treatment sequence).

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

The effect of ivacaftor in the overall population of study 5 (including the secondary endpoints absolute change in BMI at 8 weeks of treatment and absolute change in the respiratory domain score of the CFQ-R through 8 weeks of treatment) and by individual mutation (absolute change in sweat chloride and in percent predicted $FEV_1$ at week 8) is shown in Table 7. 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 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)<br>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)**<br>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 8 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 8: 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).

*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 three, phase 3, randomised, double blind, placebo-controlled (patients were heterozygous for the *F508del* mutation and a mutation with minimal function on the second allele, n = 403) and active-controlled (patients were homozygous for the *F508del* mutation, n = 107, or heterozygous for the *F508del* mutation and a gating or residual CFTR activity mutation on the second allele, n = 258) studies of 24, 4, and 8 weeks of duration respectively. Patients from all studies were eligible to enter an open-label, rollover, long-term extension studies. Refer to the Summary of Product Characteristics of ivacaftor/tezacaftor/elexacaftor for additional data.

<u>Paediatric population</u>

*Ivacaftor in a combination regimen with tezacaftor/ivacaftor*

The efficacy and safety in patients aged 6 to less than 12 years (mean age 8.6 years) were assessed in an 8-week, double-blind, phase 3 trial with 67 patients who were randomised 4:1 to either ivacaftor in a combination regimen with tezacaftor/ivacaftor or a blinding group. Forty-two patients were homozygous for the *F508del* mutation (F/F) and 12 were heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR activity (F/RF). Patients were eligible to enter an open-label, rollover, 96-week study. Refer to the Summary of Product Characteristics of tezacaftor/ivacaftor for additional data.

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

The pharmacokinetics, efficacy, and safety in patients aged 6 to less than 12 years (mean age at baseline 9.3 years) who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation were assessed in a 24-week open-label study with 66 patients. Refer to the Summary of Product Characteristics of ivacaftor/tezacaftor/elexacaftor for additional data.

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. 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 × 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 ivacaftor150 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, tezacaftor, 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 ivacaftor, tezacaftor, 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 (± 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.

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 to15) 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 as monotherapy, or in a combination regimen with ivacaftor/tezacaftor/elexacaftor 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.

<u>Paediatric population</u>

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) | $AUC_{\tau, ss}$ (ng*h/mL) |
|---|---|---|---|
| 1 month to less than 3 months (≥ 3 kg)[□] | 13.4 mg q12h | 678 (331)[†] | 10300 (4210)[†] |
| 3 months to less than 4 months (≥ 3 kg)[□] | 25 mg q12h | 846 (776)[†] | 12900 (8720)[†] |
| 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) |

□ Subjects were required to be at least 43 weeks post-menstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth).

† Exposures for 1 month to less than 4 months of age are predictions based on simulations from the population PK model incorporating data from the given age group.

‡ 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.

Ivacaftor exposure in combination with tezacaftor and with tezacaftor/elexacaftor is presented in Table 10.

**Table 10: Mean (SD) ivacaftor exposure when used in combination, by age group**

| Age group | Dose | Ivacaftor Mean (SD) $AUC_{0-12h}$,ss (ng*h/mL) |
|---|---|---|
| Children (6 years to less than 12 years; < 30 kg) n = 71 | tezacaftor 50 mg qd/ ivacaftor 75 mg q12h | 7100 (1950) |
| Children (6 years to less than 12 years; ≥ 30 kg)* n = 51 | tezacaftor 100 mg qd/ ivacaftor 150 mg q12h | 11800 (3890) |
| Adolescent patients (12 years to less than 18 years) n = 97 | tezacaftor 100 mg qd/ ivacaftor 150 mg q12h | 11400 (5500) |
| Adult patients (18 years and older) n = 389 | | 11400 (4140) |
| Children (6 years to less than 12 years; < 30 kg) n = 36 | elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h | 9780 (4500) |
| Children (6 years to less than 12 years; ≥ 30 kg) n = 30 | elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h | 17500 (4970) |
| Adolescent patients (12 years to less than 18 years) n = 69 | | 10600 (3350) |
| Adult patients (18 years and older) n = 186 | | 12100 (4170) |

* Exposures in ≥ 30 kg to < 40 kg weight range are predictions derived from the population PK model.

## 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.

<u>Peri- and post-natal development</u>

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.

<u>Juvenile animals studies</u>

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

<u>Tablet core</u>

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

<u>Tablet film coat</u>

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

<u>Printing ink</u>

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

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

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 22352/0008

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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# 10 DATE OF REVISION OF THE TEXT

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