SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ivacaftor STADA 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of ivacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light blue, capsule-shaped film-coated tablets, “150” embossed in one side and plain on the other, with dimensions 16.5 x 8.4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> is 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 non-Class I mutation in the *CFTR* gene (see sections 4.2 and 5.1).

4.2 Posology and method of administration

<Product name> 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.

<Product name> in combination with ivacaftor/tezacaftor/elexacaftor

There are a limited number of patients who harbour mutations not listed in Table 6 that may be responsive to ivacaftor/tezacaftor/elexacaftor (IVA/TEZ/ELX). In these cases, ivacaftor (IVA) in combination with IVA/TEZ/ELX can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes patients with two Class I (null) mutations

(mutations that are known not to produce CFTR protein) as they are not expected to respond to modulator therapy (see sections 4.1, 4.4 and 5.1).

Posology

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

Table 1: Dosing recommendations

Age/weight	Morning dose	Evening dose
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

***<**[Product name> is only available as 150 mg tablets. Thus, it is not possible to administer <Product name> to paediatric patients that require less than a full 150 mg dose. Other ivacaftor products, offering such an option, should be used in these cases.

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 <Product name> 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

During concomitant administration with moderate or strong inhibitors of CYP3A, the ivacaftor dose should be adjusted as detailed in Table 2. 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

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

12 years and older	Alternate each day: - two morning tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg on the first day - one morning tablet of ivacaftor 150 mg on the next day No evening ivacaftor dose.	Two morning tablets of ivacaftor 75 mg/tezacaftor 50 mg/ elexacaftor 100 mg twice a week, approximately 3 to 4 days apart. No evening ivacaftor dose.

*****<[Product name> is only available as 150 mg tablets. Thus, it is not possible to administer <Product name> to paediatric patients that require less than a full 150 mg dose. Other ivacaftor products, offering such an option, should be used in these cases.

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 in patients with mild hepatic impairment (Child-Pugh Class A).

In patients with moderate hepatic impairment (Child-Pugh Class B) or severe hepatic impairment (Child-Pugh Class C), the ivacaftor dose should be adjusted as detailed in Table 3 (see sections 4.4, 4.8, and 5.2).

Table 3: Dosing recommendations for patients with moderate or severe hepatic impairment

Age/Weight	**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 ivacaftor dose.	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used: one morning tablet of ivacaftor 150 mg every other day or less frequently according to clinical response and tolerability. No evening ivacaftor dose.
Ivacaftor in a combination regimen with tezacaftor/ivacaftor		

Age/Weight	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
6 years to < 12 years, < 30 kg	One morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily. No evening ivacaftor dose.	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, one morning tablet of tezacaftor 50 mg/ivacaftor 75 mg once daily or less frequently according to clinical response and tolerability. No evening ivacaftor dose.
6 years to < 12 years, ≥ 30 kg	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily. No evening ivacaftor dose.	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, one morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently according to clinical response and tolerability. No evening ivacaftor dose.
12 years and older	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily. No evening ivacaftor dose.	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, one morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently according to clinical response and tolerability. No evening ivacaftor dose.
Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor		
6 years to < 12 years, < 30 kg	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, the dose should be adjusted as follows: • Day 1: two ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg tablets in the morning • Day 2: one ivacaftor 37.5mg/tezacaftor 25 mg/elexacaftor 50 mg tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. No evening ivacaftor dose.	Should not be used.

Age/Weight	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
6 years to < 12 years, ≥ 30 kg	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, the dose should be adjusted as follows: • Day 1: two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets in the morning • Day 2: one ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. No evening ivacaftor dose.	Should not be used.
12 years and older	**Use is not recommended,** unless the benefits are expected to outweigh the risks. If used, the dose should be adjusted as follows: • Day 1: two ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets in the morning • Day 2: one ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. No evening ivacaftor dose.	Should not be used.

Paediatric population

The safety and efficacy of ivacaftor as monotherapy have not been established in children less than 1 month of age or in children less than 6 months of age born prematurely (less than 37 weeks of gestational age), 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.

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 770-102, 770-103, 770-111 and 770-110 (see section 5.1).

In study 770-111, 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 770-110 (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. This medicinal product should be used 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 aged 6 years and older with severe hepatic impairment unless the benefits are expected to outweigh the risks. These patients should not be treated with ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor (see Table 3 in section 4.2, and sections 4.8 and 5.2).

For patients aged 6 years and older 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 in section 4.2, and sections 4.8 and 5.2).

Depression

Depression (including suicidal ideation and suicide attempt) has been reported in patients while receiving ivacaftor, mainly in a combination regimen with tezacaftor/ivacaftor or ivacaftor/tezacaftor/elexacaftor, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders. In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Renal impairment

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

Mutations unlikely to respond to modulator therapy

Patients with a genotype consisting of two CFTR mutations that are known not to produce CFTR protein (i.e., two Class I mutations) are not expected to respond to CFTR modulator therapy.

Clinical studies comparing ivacaftor/tezacaftor/elexacaftor to tezacaftor/ivacaftor or ivacaftor

No clinical study has been conducted to directly compare ivacaftor/tezacaftor/elexacaftor to tezacaftor/ivacaftor or ivacaftor in patients not harbouring F508del variants.

Patients after organ transplantation

Ivacaftor has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See section 4.5 for interactions with ciclosporin or tacrolimus.

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

CYP3A inhibitors

Exposure to ivacaftor, tezacaftor and elexacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of ivacaftor must be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see Table 2 in section 4.2 and section 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 (see section 5.3).

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-glycoprotein (P-gp) and a potential inhibitor of CYP2C9. In vitro studies showed that ivacaftor is not a substrate for P-gp.

Medicinal products affecting the pharmacokinetics of ivacaftor

CYP3A inducers

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

No dose adjustment is recommended when ivacaftor is used with moderate or weak CYP3A inducers.

CYP3A inhibitors

Ivacaftor is a sensitive CYP3A substrate. Co-administration with ketoconazole, a strong CYP3A inhibitor, increased ivacaftor exposure (measured as area under the curve [AUC]) by 8.5-fold and increased M1 to a lesser extent than ivacaftor. A reduction of the ivacaftor dose is recommended for co-administration with strong CYP3A inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin (see Table 2 in section 4.2 and section 4.4).

Co-administration with fluconazole, a moderate inhibitor of CYP3A, increased ivacaftor exposure by 3-fold and increased M1 to a lesser extent than ivacaftor. A reduction of the ivacaftor dose is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole, erythromycin, and verapamil (see Table 2 in section 4.2 and section 4.4).

Co-administration of ivacaftor with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure to ivacaftor. Food or drink containing grapefruit should be avoided during treatment with ivacaftor (see section 4.2).

Potential for ivacaftor to interact with transporters

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

Ciprofloxacin

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

Medicinal products affected by ivacaftor

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

CYP2C9 substrates

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

Digoxin and other P-gp substrates

Co-administration with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index, such as ciclosporin, everolimus, sirolimus or tacrolimus, caution and appropriate monitoring should be used.

CYP3A substrates

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

Hormonal contraceptives

Ivacaftor has been studied with an oestrogen/progesterone oral contraceptive and was found to have no significant effect on the exposures of the oral contraceptive. Therefore, no dose adjustment of oral contraceptives is necessary.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of ivacaftor in pregnant women. Animal 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
Limited data show that ivacaftor is excreted into human milk. 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 included abdominal pain (0.9%) and transaminase elevations (1.8%) in patients who received ivacaftor, while serious adverse reactions of rash were reported in 1.5% patients aged 12 years and older treated with a combination regimen with ivacaftor/tezacaftor/elexacaftor (see section 4.4).

Tabulated list of adverse reactions

Table 4 reflects the adverse reactions observed with ivacaftor monotherapy in clinical trials (placebocontrolled 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
Psychiatric disorders	Depression	not known
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
	Oropharyngeal pain	very common

System organ class	Adverse reactions	Frequency
Respiratory, thoracic and mediastinal disorders	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†	very common
	Aspartate aminotransferase increased†	common
	Liver injury^	not known
	Total bilirubin increase^	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
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase	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 increase) 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.

Description of selected adverse reactions

Transaminase elevations

During the 48-week placebo-controlled studies 770-102 and 770-103 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

In study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in ivacaftor/tezacaftor/elexacaftor-treated patients and 6.5% in placebo-treated patients. The rash events were generally mild to moderate in severity. The incidence of rash events by patient sex was 5.8% in males and 16.3% in females in ivacaftor/tezacaftor/elexacaftor-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients. In patients treated with ivacaftor/tezacaftor/elexacaftor, the incidence of rash events was 20.5% in females taking hormonal contraceptive and 13.6% in females not taking hormonal contraceptive (see section 4.4).

Increased creatine phosphokinase

In study 445-102, the incidence of maximum creatine phosphokinase > 5 x the ULN was 10.4% in ivacaftor/tezacaftor/elexacaftor-treated patients and 5.0% in placebo-treated patients. The observed creatine phosphokinase elevations were generally transient and asymptomatic and many were preceded by exercise. No ivacaftor/tezacaftor/elexacaftor-treated patients discontinued treatment for increased creatine phosphokinase.

Increased blood pressure

In study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for ivacaftor/tezacaftor/elexacaftor-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).

The proportion of patients who had systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg on at least two occasions was 5.0% and 3.0%, respectively in ivacaftor/tezacaftor/elexacaftor-treated patients compared with 3.5% and 3.5%, respectively in placebo-treated patients.

Paediatric population

Ivacaftor as monotherapy

Safety of ivacaftor as monotherapy for 24 weeks was evaluated in 43 patients between 1 month to less than 24 months of age (with 7 of them less than 4 months old), 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 770-103, 770-111 and 770-

110 (patients aged 6 to less than 12 years), study 770-108 (patients aged 2 to less than 6 years), and study 770-124 (patients aged 1 to less than 24 months) are described in Table 5. In the placebo-controlled studies, the incidence of transaminase elevations was 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 770-108 ivacaftor was permanently discontinued in one patient. In study 770-124, in the cohort of patients aged 1 month to less than 4 months, a 1-month old (14.3%) patient had transaminase values of ALT > 8 × ULN and AST > 3 to ≤ 5 × ULN, which led to discontinuation of ivacaftor treatment (see section 4.4 for management of elevated transaminases).

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

Age group	**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)
1 to < 12 months	24	8.3% (2)	4.2% (1)	4.2% (1)

Ivacaftor in a combination regimen with tezacaftor/ivacaftor

The safety of tezacaftor/ivacaftor in combination with ivacaftor was evaluated in 124 patients between 6 to less than 12 years of age. The tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg dose has not been investigated in clinical studies in children aged 6 to less than 12 years weighing 30 to < 40 kg.The safety profile is generally consistent among children and adolescents, and is also consistent with adult patients.

During the 24-week, open-label phase 3 study in patients aged 6 to less than 12 years (study 661-113 part B, n = 70), the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 × ULN were 1.4%, 4.3%, and 10.0%, respectively. No tezacaftor/ivacaftor treated patients experienced a transaminase elevation > 3 × ULN associated with elevated total bilirubin > 2 × ULN or discontinued tezacaftor/ivacaftor treatment due to transaminase elevations. One patient interrupted treatment due to elevated transaminases, and subsequently resumed tezacaftor/ivacaftor treatment successfully (see section 4.4 for management of elevated transaminases).

Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor

The safety data of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor in studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124 was evaluated in 272 patients between 2 to less than 18 years of age. The safety profile is generally consistent among paediatric and adult patients.

During study 445-106 in patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 × ULN were 0.0%, 1.5%, and 10.6%, respectively. No ivacaftor/tezacaftor/elexacaftor-treated patients had transaminase elevation > 3 × ULN associated with elevated total bilirubin > 2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

During study 445-111 in patients aged 2 to less than 6 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 × ULN were 1.3%, 2.7%, and 8.0%, respectively. No ivacaftor/tezacaftor/elexacaftor-treated patients had transaminase elevation > 3 × ULN associated with elevated total bilirubin > 2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

Rash

During study 445-111 in patients aged 2 to less than 6 years, 15 (20.0%) subjects had at least 1 rash event, 4 (9.8%) females and 11 (32.4%) males.

Lenticular opacity

One patient had an adverse event of lenticular opacity.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code: R07AX02

Mechanism of action

Ivacaftor as monotherapy

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 770-111 (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.

Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor

Elexacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. When ivacaftor is administered in combination with ivacaftor/tezacaftor/elexacaftor, the combined effect is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR

The chloride transport response of mutant CFTR protein to ivacaftor/tezacaftor/elexacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Ivacaftor/tezacaftor/elexacaftor increased chloride transport in FRT cells expressing

select *CFTR* mutations.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical response. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

In CF, the presence of one *CFTR* mutation responsive to ivacaftor/tezacaftor/elexacaftor based on *in vitro* data in FRT cells, will likely result in a clinical response.

Table 6 lists ivacaftor/tezacaftor/elexacaftor-responsive *CFTR* mutations. The occurrence of *CFTR* mutations listed in this table should not be used in lieu of a diagnosis of cystic fibrosis, nor as a sole determinant for prescribing purposes.

Table 6: *CFTR* mutations identified to be responsive to ivacaftor/tezacaftor/elexacaftor based on clinical and/or *in vitro* data

293A→G	E217G	H620Q	N900K	S50P
314del9	E264V	H939R	N1088D	S108F
546insCTA	E282D	H939R;H949L‡	N1195T	S158N
548insTAC	E292K	H954P	N1303I	S182R
711+3A→G*	E384K	H1054D	N1303K*	S308P
1140-1151dup	E403D	H1079P	P5L†	S341P
1336K	E474K	H1085P	P67L*	S364P
1461insGAT	E527G	H1085R	P111L	S434P
1507_1515del9	E588V	H1375N	P140S	S492F
2055del9	E822K	H1375P	P205S	S519G
2183A→G	E831X	I86M	P439S	S531P
2789+5G→A*	E1104K	I105N	P499A	S549I
2851A/G	E1104V	I125T	P574H	S549N
3007del6	E1126K	I148L	P750L	S549R*
3132T→G	E1221V	I148N	P798S	S557F
3141del9	E1228K	I175V	P988R	S589I
3143del9	E1409K	I331N	P1013H	S589N
3272-26A→G*†	E1433K	I336L	P1013L	S624R
3331del6	F87L	I444S	P1021L	S686Y
3410T→C	F191V	I497S	P1021T	S737F
3523A→G	F200I	I502T	P1372T	S821G
3601A→C	F311del	I506L	Q30P	S898R
3761T→G	F311L	I506V	Q98P	S912L
3791C/T	F312del	I506V;D1168G‡	Q98R	S912L;G1244V‡
3849+10kbC→T*†	F433L	I521S	Q151K	S912T
3850G→A	F508C;S1251 N‡	I530N	Q179K	S945L*†
3978G→C	F508del*	I556V	Q237E	S955P
A46D	F508del;R1438W‡	I586V	Q237H	S977F
A62P	F575Y	I601F	Q237P	S977F;R1438W‡
A107G	F587I	I618N	Q359K;T360K‡	S1045Y
A120T	F587L	I618T	Q359R	S1118F
A141D	F693L(TTG)	I980K	Q372H	S1159F
A155P	F932S	I1023R	Q493L	S1159P
A234D	F1016S	I1139V	Q493R	S1188L
A234V	F1052V	I1203V	Q552P	S1251N
A238V	F1074L	I1234L	Q1012P	S1251N

A309D	F1078S	I1234V	Q1209P	S1255P
A349V	F1099L	I1269N	Q1291H	T338I
A357T	F1107L	I1366N	Q1291R	T351I
A455E*†	G27E	I1366T	Q1313K	T351S
A455V	G27R	K162E	Q1352H	T351S;R851L‡
A457T	G126D	K464E	R31L	T388M
A462P	G178E	K464N	R74Q	T465I
A534E	G178R	K522E	R74Q;R297Q‡	T501A
A554E	G194R	K522Q	R74Q;V201M;D1270N‡	T582S
A566D	G194V	K951E	R74W	T908N
A872E	G213E	K1060T	R74W;D1270N‡	T990I
A1006E	G213E;R668C‡	L15P	R74W;R1070W;D1270N‡	T1036N*
A1025D	G213V	L15P;L1253F‡	R74W;S945L‡	T1057R
A1067P	G226R	L32P	R74W;V201M‡	T1086A
A1067T	G239R	L88S	R74W;V201M;D1270N‡	T1086I
A1067V	G253R	L102R;F1016S‡	R74W;V201M;L997F‡	T1299I
A1081V	G314E	L137P	R75L	T1299K
A1087P	G314R	L159S	R75Q;L1065P‡	V11I
A1319E	G424S	L165S	R75Q;N1088D‡	V93D
A1374D	G437D	L167R	R75Q;S549N‡	V201M
A1466S	G461R	L206W*†	R117C†	V232A
C225R	G461V	L210P	R117C;G576A;R668C‡	V232D
C491R	G463V	L293P	R117G	V317A
C590Y	G480C	L327P	R117H*	V322M
C866Y	G480D	L333F	R117L	V392G
c.1367_1369dupTTG	G480S	L333H	R117L;L997F‡	V456A
D58H	G500D	L346P	R117P	V456F
D58V	G545R	L441P	R248K	V520I
D110E	G551A	L453S	R258G	V562I;A1006E‡
D110H	G551D*	L467F	R297Q	V562L
D110N	G551R	L558F	R334L	V591A
D192G	G551S	L619S	R334Q	V603F
D192N	G576A;R668C‡	L633P	R334W	V920L
D373N	G576A;S1359Y‡	L636P	R347H*	V920M
D426N	G622D	L927P	R347L	V1008D
D443Y	G622V	L967F;L1096R‡	R347P	V1010D
D443Y;G576A;R668C‡	G628A	L973F	R352Q	V1153E
D529G	G628R	L1011S	R352W	V1240G
D565G	G85E*†	L1065R	R516S	V1293G
D567N	G930E	L1077P*†	R553Q	V1293I
D579G	G970D	L1227S	R555G	V1415F
D614G	G970S	L1324P	R600S	W202C
D651H	G970V	L1335P	R709Q	W361R
D651N	G1047D	L1388P	R751L	W496R
D806G	G1047R	L1480P	R792G	W1098C
D924N	G1061R	M150K	R792Q	W1282G
D979A	G1069R	M150R	R810G	W1282R
D979V	G1123R	M152L		

D985H	G1173S	M152V	R851L	Y89C
D985Y	G1237V	M265R	R933G	Y109H
D993A	G1244E	M348K	R1048G	Y109N
D993G	G1244R	M394L	R1066C	Y122C
D993Y	G1247R	M469V	R1066G	Y161C
D1152A	G1249E	M498I	R1066H*†	Y161D
D1152H*†	G1249R	M952I	R1070P	Y161S
D1270N*	G1265V	M952T	R1070Q	Y301C
D1270Y	G1298V	M961L	R1070W	Y563N
D1312G	G1349D	M1101K*†	R1162Q	Y913S
	G149R;G576A;R668C			
D1377H	‡	M1137R	R1239S	Y919C
D1445N	H139L	M1137V	R1283G	Y1014C
E56K	H139R	M1210K	R1283M	Y1032C
E60K	H146R	N186K	R1283S	Y1032N
E92K	H199Q	N187K	R1438W	Y1073C
E116K	H199Y	N396Y	S13F	Y1092H
E116Q	H609L	N418S	S13P	Y1381H
E193K	H620P		S18I	
			S18N	

There are people with CF harbouring two, rare non-*F508del CFTR* mutations not listed in Table 6. Provided that they do not harbour two class I (null) mutations (mutations that are known not to produce CFTR protein) (see section 4.1), they may respond to treatment. In these cases, ivacaftor/tezacaftor/elexacaftor can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.
The individual diagnosis of CF should be based on diagnostic guidelines and clinical judgement as considerable variability exists in phenotype for patients harbouring the same genotype.
∗ Mutations supported by clinical data.
† Mutations supported by Real-World data in ≥ 5 patients.
‡ Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
Non-annotated mutations are included based on the FRT assay in which a positive response is indicative of a clinical response.

Pharmacodynamic effects

Ivacaftor as monotherapy

In studies 770-102 and 770-103 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 770-111, 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 770-110 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 to 11 years. Two patients 12 to 17 years of age were enrolled in this study.

Ivacaftor in a combination regimen with tezacaftor/ivacaftor

In study 661-106 (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 study 661-108 (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 in combination with ivacaftor and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo.

In study 661-115 (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), the within treatment mean 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 study 445-102 (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 study 445-103 (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 study 445-104 (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 or tezacaftor/ivacaftor in combination with 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 study 445-106 (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).

* 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.

In study 445-116 (patients aged 6 to less than 12 years who are heterozygous for the *F508del* mutation and a minimal function mutation), the mean treatment difference for the ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor group versus placebo for the absolute change in sweat chloride from baseline through week 24 was -51.2 mmol/L (95% CI: -55.3, -47.1).

In study 445-124 (patients aged 6 years and older with a qualifying non-*F508del*, ivacaftor/tezacaftor/elexacaftor-responsive *CFTR* mutation), the mean absolute change in sweat chloride from baseline through week 24 compared to placebo was -28.3 mmol/L (95% CI: -32.1, -24.5 mmol/L; $P < 0.0001$).

Clinical efficacy and safety

Ivacaftor as monotherapy

Studies 770-102 and 770-103: 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 one 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 770-102 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 770-103 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 770-102 and 12.5 percentage points (6.6, 18.3) in study 770-103. 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 770-102 and 15.8% (8.4, 23.2) in study 770-103. 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 770-102 and 0.30 L in the ivacaftor group and 0.07 L in the placebo group in study 770-103. 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 770-102 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 770-103 was 6.9 percentage points (-3.8, 17.6).

The results for clinically relevant secondary endpoints are shown in Table 7.

Table 7: Effect of ivacaftor on other efficacy endpoints in studies 770-102 and 770-103

	Study 770-102		**Study 770-103**	
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

Endpoint	Study 770-102		Study 770-103	
	Treatment difference[a] (95% CI)	*P* value	Treatment difference[a] (95% CI)	*P* value
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 770-102 data were pooled from CFQ-R for adults/adolescents and CFQ-R for children 12 to 13 years of age; Study 770-103 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 770-111: study in patients with CF with non-G551D gating mutations

Study 770-111 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 770-111, 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 770-111 (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 8. 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 8: Effect of ivacaftor for efficacy variables in the overall population and for specific CFTR mutations

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

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

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

Statistical testing was not performed due to small numbers for individual mutations.
† Reflects results from the one patient with the *G551S* mutation with data at the 8-week time point.
†† n = 3 for the analysis of absolute change in sweat chloride.
# Causes a splicing defect resulting in little-to-no CFTR protein at the cell surface.

In part 2 of study 770-111, 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 770-104: study in patients with CF with the F508del mutation in the CFTR gene

Study 770-104 (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 aged 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 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 770-105: open-label extension study

In study 770-105 patients who completed treatment in studies 770-102 and 770-103 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 770-102 were rolled over in study 770-105, 67 in the placebo/ivacaftor group and 77 in the ivacaftor/ivacaftor group. Forty-eight (48) patients from study 770-103 were rolled over in study 770-105, 22 in the placebo/ivacaftor group and 26 in the ivacaftor/ivacaftor

group.

Table 9 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 770-105 while for patients in the ivacaftor/ivacaftor group the baseline value is that of studies 770-102 and 770-103.

Table 9: Effect of ivacaftor on percent predicted FEV1 in study 770-105

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 770-102			
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 770-103			
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 770-105 baseline for patients in the ivacaftor/ivacaftor group (n = 72) who rolled over from study 770-102, 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 770-103 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 770-105 (week 48 through week 144).

For patients in the placebo/ivacaftor group from study 770-102, 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 770-105 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 770-102, 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 770-105, 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 770-103 the number of events was, overall, low.

Study 770-110: study in patients with CF with an R117H mutation in the CFTR gene

Study 770-110 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 aged 18 years and older (26 patients on placebo and 24 patients 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 (study 661-106); 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 (study 661-108). 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 (study 661-110). 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 tablets in patients aged 12 years and older was demonstrated in three, phase 3, randomised, double-blind, placebo-controlled studies (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 (study 445-102), 4 (study 445-103), and 8 weeks (study 445-104) of duration respectively. Patients from all studies were eligible to enter open-label, rollover, long-term extension studies (study 445-105 or study 445-110).

The efficacy and safety of ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets in patients aged 6 years and older with non-*F508del*, ivacaftor/tezacaftor/elexacaftor-responsive *CFTR* mutations was demonstrated in a phase 3, randomised, double-blind, placebo-controlled study (n = 307) and an observational retrospective study (CFD-016; n = 422) of Real-World clinical outcomes.

Refer to the Summary of Product Characteristics of ivacaftor/tezacaftor/elexacaftor for additional data.

Paediatric population

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 (study 661-115) 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 (study 661-116 part A). Refer to the Summary of Product Characteristics of tezacaftor/ivacaftor for additional data.

Ivacaftor in a combination regimen with ivacaftor/tezacaftor/elexacaftor

The pharmacokinetics and safety in patients aged 6 to less than 12 years (n = 66) and in those from 2 to less than 6 years (n = 75) who have at least one *F508del* mutation were assessed in two 24-week open-label studies (study 445-106 and 445-116). 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 the reference medicinal product containing ivacaftor 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 Cmax were 10.60 (5.26) μg·h/mL and 0.768 (0.233) μg/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 coadministered 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) tmax is approximately 4.0 (3.0; 6.0) hours in the fed state.

Distribution

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells. After oral administration of ivacaftor 150 mg every 12 hours for 7 days in healthy volunteers in a fed state, the mean (± SD) apparent volume of distribution was 353 L (122).

Biotransformation

Ivacaftor is extensively metabolised in humans. In vitro and in vivo data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the potency of ivacaftor and is not considered pharmacologically active.

The effect of the CYP3A4*22 heterozygous genotype on ivacaftor, 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 Cmax (mean [± SD] of 0.735 [0.331] μg/mL) but an approximately two-fold increase in ivacaftor AUC0-∞ (mean [± SD] of 16.80 [6.14] μg·h/mL) compared with healthy subjects matched for demographics. Simulations for predicting the steady-state exposure of ivacaftor showed that by reducing the dose from 150 mg q12h to 150 mg once daily, adults with moderate hepatic impairment would have comparable steady-state Cmin 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 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. 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 to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.2 and 4.4).

Race

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

Gender

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

Elderly

Clinical studies of ivacaftor 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.

Paediatric population

Predicted ivacaftor exposure based on observed ivacaftor concentrations in phase 2 and 3 studies as determined using compartmental analysis is presented by age group in Table 10.

Table 10: Mean (SD) ivacaftor exposure by age group

Age group	Dose	$C_{min, ss}$ (µg/mL)	$AUC_{0-12h, ss}$ (µg·h/mL
1 month to less than 2 months (≥ 3 kg)*	13.4 mg q24h	0.300 (0.221)†	5.84 (2.98)†
2 months to less than 4 months (≥ 3 kg)*	13.4 mg q12h	0.406 (0.266)†	6.45 (3.43)†
4 months to less than 6 months (≥ 5 kg)*	25 mg q12h	0.371 (0.183)	6.48 (2.52)
6 months to less than 12 months (≥5 kg to < 7 kg)‡	25 mg q12h	0.336	5.41
6 months to less than 12 months (7 kg to < 14 kg)	50 mg q12h	0.508 (0.252)	9.14 (4.20)
12 months to less than 24 months (7 kg to < 14 kg)	50 mg q12h	0.440 (0.212)	9.05 (3.05)
12 months to less than 24 months (≥ 14 kg to < 25 kg)	75 mg q12h	0.451 (0.125)	9.60 (1.80)
2- to 5-year-olds (< 14 kg)	50 mg q12h	0.577 (0.317)	10.50 (4.26)
2- to 5-year-olds (≥ 14 kg to < 25 kg)	75 mg q12h	0.629 (0.296)	11.30 (3.82)
6- to 11-year-olds§ (≥ 14 kg to < 25 kg)	75 mg q12h	0.641 (0.329)	10.76 (4.47)
6- to 11-year-olds§ (≥ 25 kg)	150 mg q12h	0.958 (0.546)	15.30 (7.34)
12- to 17-year-olds	150 mg q12h	0.564 (0.242)	9.24 (3.42)
Adults (≥ 18 years old)	150 mg q12h	0.701 (0.317)	10.70 (4.10)

* Patients 1 month to less than 6 months of age were ≥37 weeks gestational age.

† Exposures for 1 month to less than 4 months of age are predictions based on simulations from the physiologically based 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.

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

Core
Hypromellose acetate succinate
Sodium laurilsulfate (E487)
Silicified microcrystalline cellulose
(*comprises of microcrystalline cellulose and silica, colloidal anhydrous*)
Mannitol (E421)
Croscarmellose sodium
Magnesium stearate

Coating
Polyvinyl alcohol part. hydrolyzed (E1203)
Calcium carbonate (E170)
Macrogol 3350 (E1521)
Talc (E553b)
Indigo carmine aluminum lake (E132)
Carnauba wax powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packs: 3 years.
Bottle: 30 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- OPA/Aluminum/PVC//Aluminum blisters or transparent PVC/PCTFE(Aclar)//Aluminum blisters
- Polyethylene (HDPE) bottles

The following pack sizes are available:

Blister packs containing 7, 14, 28, 56 & 98 film-coated tablets.
Unit-dose blisters containing 14x1, 28x1, 56x1 & 98x1 film-coated tablets.
Bottles containing 56 & 60 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

21 January 2026