

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

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (dimensions 7.9 mm x 15.5 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see section 5.1).

4.2 Posology and method of administration

Kaftrio should only be prescribed by healthcare professionals with experience in the treatment of CF. If the patient’s genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of at least one *F508del* mutation using a genotyping assay (see section 5.1).

Posology

The recommended dose is two tablets (each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg) taken in the morning, and one ivacaftor 150 mg tablet taken in the evening, approximately 12 hours apart (see Method of administration).

Missed dose

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

If more than 6 hours have passed since:

- the missed morning dose, the patient should take the missed dose as soon as possible and should not take the evening dose. The next scheduled morning dose should be taken at the usual time.
- the missed evening dose, the patient should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

Concomitant use of CYP3A inhibitors

When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin, verapamil) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose should be reduced as in Table 1 (see sections 4.4 and 4.5).

Table 1: Dosing schedule for concomitant use with moderate and strong CYP3A inhibitors				
Moderate CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4*
Morning Dose	Two IVA/TEZ/ELX tablets	One IVA tablet	Two IVA/TEZ/ELX tablets	One IVA tablet
Evening Dose[^]	No dose			
* Continue dosing with two IVA/TEZ/ELX tablets and one IVA tablet on alternate days.				
[^] The evening dose of IVA tablet should not be taken.				
Strong CYP3A Inhibitors				
	Day 1	Day 2	Day 3	Day 4[#]
Morning Dose	Two IVA/TEZ/ELX tablets	No dose	No dose	Two IVA/TEZ/ELX tablets
Evening Dose[^]	No dose			
[#] Continue dosing with two IVA/TEZ/ELX tablets twice a week, approximately 3 to 4 days apart.				
[^] The evening dose of IVA tablet should not be taken.				

Special populations

Elderly population

No dose adjustment is recommended for the elderly patient population (see sections 4.4 and 5.2).

Hepatic impairment

Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients with moderate hepatic impairment, the use of Kaftrio 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 2).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with Kaftrio.

No dose adjustment is recommended for patients with mild (Child-Pugh Class A) hepatic impairment (see Table 2) (see sections 4.4 and 5.2).

Table 2: Recommendation for use in patients with hepatic impairment			
	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)*	Severe (Child-Pugh Class C)
Morning	No dose adjustment (Two IVA/TEZ/ELX tablets)	Use not recommended* If used: alternate each day between two IVA/TEZ/ELX tablets and one IVA/TEZ/ELX tablet	Should not be used
Evening	No dose adjustment (One IVA tablet)	No IVA tablet	Should not be used
* For patients with moderate hepatic impairment, use of IVA/TEZ/ELX should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.			

Renal impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment. There is no experience in patients with severe renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Kaftrio in combination with ivacaftor in children aged less than 12 years have not yet been established.

No data are available (see section 5.1).

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; chewing or crushing the tablet is not recommended.

Kaftrio tablets should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats (see section 5.2).

Food or drink containing grapefruit should be avoided during treatment with Kaftrio (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect on liver function tests

Elevated transaminases are common in patients with CF and have been observed in some patients treated with Ivacaftor/Tezacaftor/Elexacaftor (IVA/TEZ/ELX) in combination with ivacaftor (IVA). Assessments of transaminases (ALT and AST) are recommended for all patients prior to initiating treatment, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered (see section 4.8).

Hepatic impairment

Treatment of patients with moderate hepatic impairment is not recommended. For patients with moderate hepatic impairment, the use of IVA/TEZ/ELX 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 2).

Patients with severe hepatic impairment should not be treated with IVA/TEZ/ELX (see sections 4.2 and 5.2).

Renal impairment

There is no experience in patients with severe renal impairment/end-stage renal disease therefore caution is recommended in this population (see section 5.2).

Patients after organ transplantation

IVA/TEZ/ELX in combination with IVA 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 commonly used immunosuppressants.

Rash events

The incidence of rash events 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 IVA/TEZ/ELX in combination with IVA and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming IVA/TEZ/ELX in combination with IVA without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see section 4.8).

Elderly population

Clinical studies of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults. Dose recommendations are based on the pharmacokinetic profile and knowledge from studies with tezacaftor/ivacaftor in combination with ivacaftor, and ivacaftor monotherapy.

Interactions with medicinal products

CYP3A inducers

Exposure to IVA is significantly decreased and exposures to ELX and TEZ are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduced efficacy of IVA/TEZ/ELX, and IVA; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

Exposure to ELX, TEZ and IVA are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of IVA/TEZ/ELX, and IVA should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors (see section 4.5 and Table 1 in section 4.2).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with IVA-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation) a possible risk attributable to treatment with IVA cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with IVA/TEZ/ELX in combination with IVA (see section 5.3).

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting the pharmacokinetics of ELX, TEZ and/or IVA

CYP3A inducers

ELX, TEZ and IVA are substrates of CYP3A (IVA is a sensitive substrate of CYP3A). Concomitant use of strong CYP3A inducers may result in reduced exposures and thus reduced IVA/TEZ/ELX efficacy. Co-administration of IVA with rifampicin, a strong CYP3A inducer, significantly decreased

IVA area under the curve (AUC) by 89%. ELX and TEZ exposures are also expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration with strong CYP3A inducers is not recommended.

Examples of strong CYP3A inducers include:

- rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased ELX AUC by 2.8-fold and TEZ AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, IVA AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of IVA/TEZ/ELX, and IVA should be reduced when co-administered with strong CYP3A inhibitors (see Table 1 in section 4.2 and section 4.4).

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors fluconazole, erythromycin, and verapamil, may increase ELX and TEZ AUC by approximately 1.9- to 2.3-fold. Co-administration of fluconazole increased IVA AUC by 2.9-fold. The dose of IVA/TEZ/ELX, and IVA should be reduced when co-administered with moderate CYP3A inhibitors (see Table 1 in section 4.2 and section 4.4).

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

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

Potential for interaction with transporters

In vitro studies showed that ELX is a substrate for the efflux transporters P-gp and Breast Cancer Resistance Protein (BCRP) but is not a substrate for OATP1B1 or OATP1B3. Exposure to ELX is not expected to be affected significantly by concomitant use of P-gp and BCRP inhibitors due to its high intrinsic permeability and low likelihood of being excreted intact.

In vitro studies showed that TEZ is a substrate for the uptake transporter OATP1B1, and efflux transporters P-gp and BCRP. TEZ is not a substrate for OATP1B3. Exposure to TEZ is not expected to be affected significantly by concomitant inhibitors of OATP1B1, P-gp, or BCRP due to its high intrinsic permeability and low likelihood of being excreted intact. However, exposure to M2-TEZ (TEZ metabolite) may be increased by inhibitors of P-gp. Therefore, caution should be used when P-gp inhibitors (e.g. ciclosporin) are used with IVA/TEZ/ELX.

In vitro studies showed that IVA is not a substrate for OATP1B1, OATP1B3, or P-gp. IVA 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 IVA and M1-IVA, while any potential changes in M6-IVA exposures are not expected to be clinically relevant.

Medicinal products affected by ELX, TEZ and/or IVA

CYP2C9 substrates

IVA may inhibit CYP2C9; therefore, monitoring of the international normalised ratio (INR) during co-administration of warfarin with IVA/TEZ/ELX, and IVA is recommended. Other medicinal

products for which exposure may be increased include glimepiride and glipizide; these medicinal products should be used with caution.

Potential for interaction with transporters

Co-administration of IVA or TEZ/IVA with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by IVA. Administration of IVA/TEZ/ELX, and IVA 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, and tacrolimus, caution and appropriate monitoring should be used.

ELX and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. TEZ/IVA increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration with IVA/TEZ/ELX in combination with IVA may increase exposures of medicinal products that are substrates of these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. In study 445-102, mild increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by ELX and M23-ELX.

ELX and IVA are inhibitors of BCRP. Co-administration of IVA/TEZ/ELX, and IVA may increase exposures of medicinal products that are substrates of BCRP, such as rosuvastatin. When used concomitantly with substrates of BCRP, appropriate monitoring should be used.

Hormonal contraceptives

IVA/TEZ/ELX in combination with IVA has been studied with ethinyl estradiol/levonorgestrel and was found to have no clinically relevant effect on the exposures of the oral contraceptive. IVA/TEZ/ELX, and IVA is not expected to have an impact on the efficacy of oral contraceptives.

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 ELX, TEZ or IVA 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 IVA/TEZ/ELX during pregnancy.

Breast-feeding

It is unknown whether ELX, TEZ, IVA, or their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of ELX, TEZ and IVA into the milk of lactating female rats (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from IVA/TEZ/ELX 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 ELX, TEZ and IVA on fertility in humans. TEZ had no effects on fertility and reproductive performance indices in male and female rats at clinically relevant exposures. ELX and IVA had an effect on fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

IVA/TEZ/ELX in combination with IVA has a minor influence on the ability to drive or use machines. Dizziness has been reported in patients receiving IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA as well as IVA (see section 4.8). 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 12 years and older who received IVA/TEZ/ELX in combination with IVA were headache (17.3%), diarrhoea (12.9%) and upper respiratory tract infection (11.9%).

Serious adverse reactions of rash were reported in 3 (1.5%) patients treated with IVA/TEZ/ELX in combination with IVA compared to 1 (0.5%) in placebo.

Tabulated list of adverse reactions

Table 3 reflects adverse reactions observed with IVA/TEZ/ELX in combination with IVA, TEZ/IVA in combination with IVA, and IVA. Adverse reactions are listed by MedDRA system organ class and frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 3: Adverse reactions		
MedDRA System Organ Class	Adverse Reactions	Frequency
Infections and infestations	Upper respiratory tract infection*, Nasopharyngitis	very common
	Rhinitis*, Influenza*	common
Metabolism and nutrition disorders	Hypoglycaemia*	common
Nervous system disorders	Headache*, Dizziness*	very common
Ear and labyrinth disorders	Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain, Nasal congestion*	very common
	Rhinorrhoea*, Sinus congestion, Pharyngeal erythema, Abnormal breathing*	common
	Wheezing*	uncommon
Gastrointestinal disorders	Diarrhoea*, Abdominal pain*	very common
	Nausea, Abdominal pain upper*, Flatulence*	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*, Aspartate aminotransferase increased*	common

Table 3: Adverse reactions		
MedDRA System Organ Class	Adverse Reactions	Frequency
Skin and subcutaneous tissue disorders	Rash*	very common
	Acne*, Pruritus*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain	uncommon
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase increased*	common
	Blood pressure increased*	uncommon

*Adverse reactions observed during clinical studies with IVA/TEZ/ELX in combination with IVA.

Safety data from the following studies were consistent with the safety data observed in study 445-102.

- A 4-week, randomised, double-blind, active-controlled study in 107 patients (study 445-103).
- A 96-week, open-label safety and efficacy study (study 445-105) for patients rolled over from studies 445-102 and 445-103, with interim analysis performed on 510 patients including 271 patients with ≥ 48 weeks of cumulative treatment with IVA/TEZ/ELX in combination with IVA.
- A 8-week, randomised, double-blind, active-controlled study in 258 patients (study 445-104)

Description of selected adverse reactions

Transaminase elevations

In study 445-102, the incidence of maximum transaminase (ALT or AST) >8 , >5 , or >3 x the ULN was 1.5%, 2.5%, and 7.9% in IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients and 4.0% in placebo-treated patients. No patients treated with IVA/TEZ/ELX discontinued treatment for elevated transaminases (see section 4.4).

Rash events

In study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in IVA/TEZ/ELX- 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 IVA/TEZ/ELX-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients. In patients treated with IVA/TEZ/ELX, 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 IVA/TEZ/ELX- and 5.0% in placebo-treated patients. The observed creatine phosphokinase elevations were generally transient and asymptomatic, and many were preceded by exercise. No IVA/TEZ/ELX-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 IVA/TEZ/ELX-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 IVA/TEZ/ELX-treated patients compared with 3.5% and 3.5%, respectively in placebo-treated patients.

Paediatric population

The safety data of IVA/TEZ/ELX in combination with IVA in studies 102, 103 and 104 was evaluated in 87 patients between 12 to less than 18 years of age. The safety profile is generally consistent among adolescents and adult patients.

Other special populations

With the exception of sex differences in rash, the safety profile of IVA/TEZ/ELX in combination with IVA was generally similar across all subgroups of patients, including analysis by age, baseline percent predicted forced expiratory volume in one second (ppFEV₁), and geographic regions.

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 systems:

Ireland

HPRA Pharmacovigilance

Website: www.hpra.ie

United Kingdom (Northern Ireland)

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 IVA/TEZ/ELX. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code: R07AX32

Mechanism of action

ELX and TEZ 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 F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of ELX, TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. With regard to non-F508del CFTR variants on the second allele, it is not clear whether and to what extent the combination of elexacaftor, tezacaftor and ivacaftor also increases the amount of these mutated CFTR variants on the cell surface and potentiates its channel open probability (or gating).

Pharmacodynamic effects

Effects on sweat chloride

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 other CFTR modulators [IVA and TEZ/IVA] *in vitro*), a reduction in sweat chloride was observed from baseline at week 4 and sustained through the 24-week treatment period. The treatment difference of IVA/TEZ/ELX in combination with IVA 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; $P < 0.0001$).

In study 445-103 (patients homozygous for the *F508del* mutation), the treatment difference of IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA for mean absolute change in sweat chloride from baseline at week 4 was -45.1 mmol/L (95% CI: -50.1, -40.1; $P < 0.0001$).

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 mean absolute change in sweat chloride from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group was -22.3 mmol/L (95% CI: -24.5, -20.2; $P < 0.0001$). The treatment difference of IVA/TEZ/ELX in combination with IVA compared to the control group (IVA group or TEZ/IVA in combination with IVA group) was -23.1 mmol/L (95% CI: -26.1, -20.1; $P < 0.0001$).

Cardiovascular effects

Effect on QT interval

At doses up to 2 times the maximum recommended dose of ELX and 3 times the maximum recommended dose of TEZ and IVA, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Heart rate

In study 445-102, mean decreases in heart rate of 3.7 to 5.8 beats per minute (bpm) from baseline (76 bpm) were observed in IVA/TEZ/ELX-treated patients.

Clinical efficacy and safety

The efficacy of IVA/TEZ/ELX in combination with IVA in patients with CF was demonstrated in three Phase 3 studies. Patients enrolled in these studies were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a mutation with minimal function (MF), a gating defect, or residual CFTR activity on the second allele. Not all *F508del* heterozygotes have been clinically evaluated with IVA/TEZ/ELX in combination with IVA.

Study 445-102 was a 24-week, randomised, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and an MF mutation on the second allele. CF patients eligible for this study were required to either have Class I mutations that predicted no CFTR protein being produced (including nonsense mutations, canonical splice mutations, and insertion/deletion frameshift mutations both small (≤ 3 nucleotide) and non-small (> 3 nucleotide)), or missense mutations which results in CFTR protein that does not transport chloride and is not responsive to IVA and TEZ/IVA *in vitro*. The most frequent alleles with minimal function assessed in the study were *G542X*, *W1282X*, *R553X*, and *R1162X*; *621+1G→T*, *1717-1G→A*, and *1898+1G→A*; *3659delC*, and *394delTT*; *CFTRdele2,3*; and *N1303K*, *I507del*, *G85E*, *R347P*, and *R560T*. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomised and dosed to receive placebo or IVA/TEZ/ELX in combination with IVA. Patients had a ppFEV₁ at screening between 40-90%. The mean ppFEV₁ at baseline was 61.4% (range: 32.3%, 97.1%).

Study 445-103 was a 4-week, randomised, double-blind, active-controlled study in patients who were homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received TEZ/IVA in combination with IVA during a 4-week open-label run-in period and were then randomised and dosed to receive either IVA/TEZ/ELX in combination with IVA or

TEZ/IVA in combination with IVA during a 4-week double-blind treatment period. Patients had a ppFEV₁ at screening between 40-90%. The mean ppFEV₁ at baseline, following the run-in period was 60.9% (range: 35.0%, 89.0%).

Study 445-104 was an 8-week, randomised, double-blind, active-controlled study in patients who were heterozygous for the *F508del* mutation and a mutation on the second allele with a gating defect (Gating) or residual CFTR activity (RF). A total of 258 patients aged 12 years and older (mean age 37.7 years) received either IVA (F/Gating) or TEZ/IVA in combination with IVA (F/RF) during a 4-week open-label run-in period, and were then randomised and dosed to receive either IVA/TEZ/ELX in combination with IVA or remained on the CFTR modulator therapy received during the run-in period. Patients with the F/R117H genotype received IVA during the run-in period. The mean ppFEV₁ at baseline, following the run-in period, was 67.6% (range: 29.7%, 113.5%).

Patients in studies 445-102, 445-103 and 445-104 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies, except for study drugs. Patients had a confirmed diagnosis of CF.

Patients who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT $\geq 3 \times$ ULN, or total bilirubin $\geq 2 \times$ ULN), were excluded. Patients in studies 445-102, 445-103 and 445-104 were eligible to roll over into a 96-week open-label extension study.

Study 445-102

In study 445-102 the primary endpoint was mean absolute change in ppFEV₁ from baseline through week 24. Treatment with IVA/TEZ/ELX in combination with IVA compared to placebo resulted in statistically significant improvement in ppFEV₁ of 14.3 percentage points (95% CI: 12.7, 15.8; $P < 0.0001$) (Table 4). Mean improvement in ppFEV₁ was observed at the first assessment on Day 15 and sustained through the 24-week treatment period. Improvements in ppFEV₁ were observed regardless of age, baseline ppFEV₁, sex, and geographic region.

A total of 18 patients receiving IVA/TEZ/ELX in combination with IVA had ppFEV₁ <40 percentage points at baseline. The safety and efficacy in this subgroup were consistent to those observed in the overall population. The mean treatment difference of IVA/TEZ/ELX in combination with IVA- compared to placebo-treated patients for absolute change in ppFEV₁ through week 24 in this subgroup was 18.4 percentage points (95% CI: 11.5, 25.3).

See Table 4 for a summary of primary and key secondary outcomes.

Table 4: Primary and key secondary efficacy analyses, full analysis set (study 445-102)			
Analysis	Statistic	Placebo N=203	IVA/TEZ/ELX in combination with IVA N=200
Primary			
Baseline ppFEV ₁ (percentage points)	Mean (SD)	61.3 (15.5)	61.6 (15.0)
Absolute change in ppFEV ₁ from baseline through week 24 (percentage points)	Treatment difference (95% CI)	NA	14.3 (12.7, 15.8)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-0.4 (0.5)	13.9 (0.6)
Key Secondary			
Absolute change in ppFEV ₁ from baseline at week 4 (percentage points)	Treatment difference (95% CI)	NA	13.7 (12.0, 15.3)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-0.2 (0.6)	13.5 (0.6)
Number of pulmonary exacerbations from baseline through week 24 [‡]	Number of events (event rate per year ^{††})	113 (0.98)	41 (0.37)
	Rate ratio (95% CI)	NA	0.37 (0.25, 0.55)
	<i>P</i> value	NA	<i>P</i> <0.0001
Baseline sweat chloride (mmol/L)	Mean (SD)	102.9 (9.8)	102.3 (11.9)
Absolute change in sweat chloride from baseline through week 24 (mmol/L)	Treatment difference (95% CI)	NA	-41.8 (-44.4, -39.3)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-0.4 (0.9)	-42.2 (0.9)
Absolute change in sweat chloride from baseline at week 4 (mmol/L)	Treatment difference (95% CI)	NA	-41.2 (-44.0, -38.5)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	0.1 (1.0)	-41.2 (1.0)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	70.0 (17.8)	68.3 (16.9)
Absolute change in CFQ-R respiratory domain score from baseline through week 24 (points)	Treatment difference (95% CI)	NA	20.2 (17.5, 23.0)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-2.7 (1.0)	17.5 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference (95% CI)	NA	20.1 (16.9, 23.2)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-1.9 (1.1)	18.1 (1.1)
Baseline BMI (kg/m ²)	Mean (SD)	21.31 (3.14)	21.49 (3.07)
Absolute change in BMI from baseline at week 24 (kg/m ²)	Treatment difference (95% CI)	NA	1.04 (0.85, 1.23)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	0.09 (0.07)	1.13 (0.07)
ppFEV ₁ : percent predicted forced expiratory volume in 1 second; CI: confidence interval; SD: Standard Deviation; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index.			
‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.			
†† Estimated event rate per year was calculated based on 48 weeks per year.			

Study 445-103

In study 445-103 the primary endpoint was mean absolute change in ppFEV₁ from baseline at week 4 of the double-blind treatment period. Treatment with IVA/TEZ/ELX in combination with IVA compared to TEZ/IVA in combination with IVA resulted in a statistically significant improvement in ppFEV₁ of 10.0 percentage points (95% CI: 7.4, 12.6; *P*<0.0001) (Table 5). Improvements in ppFEV₁ were observed regardless of age, sex, baseline ppFEV₁ geographic region.

See Table 5 for a summary of primary and key secondary outcomes in the overall trial population.

In a post hoc analysis of patients with (N=66) and without (N=41) recent CFTR modulator use, an improvement in ppFEV₁ of 7.8 percentage points (95% CI: 4.8, 10.8) and 13.2 percentage points (95% CI: 8.5, 17.9), respectively was observed.

Table 5: Primary and key secondary efficacy analyses, full analysis set (study 445-103)			
Analysis*	Statistic	TEZ/IVA in combination with IVA N=52	IVA/TEZ/ELX in combination with IVA N=55
Primary			
Baseline ppFEV ₁ (percentage points)	Mean (SD)	60.2 (14.4)	61.6 (15.4)
Absolute change in ppFEV ₁ from baseline at week 4 (percentage points)	Treatment difference (95% CI)	NA	10.0 (7.4, 12.6)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	0.4 (0.9)	10.4 (0.9)
Key secondary			
Baseline sweat chloride (mmol/L)	Mean (SD)	90.0 (12.3)	91.4 (11.0)
Absolute change in sweat chloride from baseline at week 4 (mmol/L)	Treatment difference (95% CI)	NA	-45.1 (-50.1, -40.1)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	1.7 (1.8)	-43.4 (1.7)
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	72.6 (17.9)	70.6 (16.2)
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference (95% CI)	NA	17.4 (11.8, 23.0)
	<i>P</i> value	NA	<i>P</i> <0.0001
	Within-group change (SE)	-1.4 (2.0)	16.0 (2.0)
ppFEV ₁ : percent predicted forced expiratory volume in 1 second; CI: confidence interval; SD: Standard Deviation; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week run-in period of TEZ/IVA in combination with IVA.			

Study 445-104

In study 445-104 the primary endpoint was within-group mean absolute change in ppFEV₁ from baseline through week 8 for the IVA/TEZ/ELX in combination with IVA group. Treatment with IVA/TEZ/ELX in combination with IVA resulted in statistically significant improvement in ppFEV₁ from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; *P*<0.0001) (See Table 6). Overall improvements in ppFEV₁ were observed regardless of age, sex, baseline ppFEV₁ geographic region, and genotype groups (F/Gating or F/RF).

See Table 6 for a summary of primary and secondary outcomes in the overall trial population.

In a subgroup analysis of patients with an F/Gating genotype, the treatment difference of IVA/TEZ/ELX in combination with IVA (N=50) compared with IVA (N=45) for mean absolute change in ppFEV₁ was 5.8 percentage points (95% CI: 3.5, 8.0). In a subgroup analysis of patients with an F/RF genotype, the treatment difference of IVA/TEZ/ELX in combination with IVA (N=82) compared with TEZ/IVA in combination with IVA (N=81) for mean absolute change in ppFEV₁ was 2.0 percentage points (95% CI: 0.5, 3.4). The results of the F/Gating and the F/RF genotype subgroups for improvement in sweat chloride and CFQ-R respiratory domain score were consistent with the overall results.

Table 6: Primary and secondary efficacy analyses, full analysis set (study 445-104)			
Analysis*	Statistic	Control group# N=126	IVA/TEZ/ELX in combination with IVA N=132
Primary			
Baseline ppFEV ₁ (percentage points)	Mean (SD)	68.1 (16.4)	67.1 (15.7)
Absolute change in ppFEV ₁ from baseline through week 8 (percentage points)	Within-group change (95% CI) <i>P</i> value	0.2 (-0.7, 1.1) NA	3.7 (2.8, 4.6) <i>P</i> <0.0001
Key and other secondary			
Absolute change in ppFEV ₁ from baseline through week 8 compared to the control group (percentage points)	Treatment difference (95% CI) <i>P</i> value	NA NA	3.5 (2.2, 4.7) <i>P</i> <0.0001
Baseline sweat chloride (mmol/L)	Mean (SD)	56.4 (25.5)	59.5 (27.0)
Absolute change in sweat chloride from baseline through week 8 (mmol/L)	Within-group change (95% CI) <i>P</i> value	0.7 (-1.4, 2.8) NA	-22.3 (-24.5, -20.2) <i>P</i> <0.0001
Absolute change in sweat chloride from baseline through week 8 compared to the control group (mmol/L)	Treatment difference (95% CI) <i>P</i> value	NA NA	-23.1 (-26.1, -20.1) <i>P</i> <0.0001
Baseline CFQ-R respiratory domain score (points)	Mean (SD)	77.3 (15.8)	76.5 (16.6)
Absolute change in CFQ-R respiratory domain score from baseline through week 8 (points)	Within-group change (95% CI)	1.6 (-0.8, 4.1)	10.3 (8.0, 12.7)
Absolute change in CFQ-R respiratory domain score from baseline through week 8 (points) compared to the control group	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)
ppFEV ₁ : percent predicted forced expiratory volume in 1 second; CI: confidence interval; SD: Standard Deviation; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and secondary endpoints is defined as the end of the 4-week run-in period of IVA or TEZ/IVA in combination with IVA. # IVA group or TEZ/IVA in combination with IVA group.			

Study 445-105

An ongoing, 96-week open-label extension study to evaluate the safety and efficacy of long-term treatment with IVA/TEZ/ELX in combination with IVA is being conducted in patients who rolled over from studies 445-102 and 445-103. In this open-label extension study all patients received IVA/TEZ/ELX in combination with IVA. For patients who rolled over from studies 445-102 (N=400) and 445-103 (N=107), an interim efficacy analysis was conducted when they completed the week 24 visit of study 445-105.

Patients homozygous for the *F508del* mutation who received IVA/TEZ/ELX in combination with IVA in study 445-103, and continued on the same treatment in study 445-105, showed sustained improvements in ppFEV₁, CFQ-R respiratory domain score, and sweat chloride, through 28 weeks of cumulative treatment (i.e., through week 24 in study 445-105). The outcomes of annualised pulmonary exacerbation event rate through 28 weeks of cumulative treatment (i.e. through week 24 in study 445-105), and BMI and BMI-z score at 28 weeks of cumulative treatment (at week 24 in study 445-105), were consistent with those seen in patients with the genotypes studied in study 445-102.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with IVA/TEZ/ELX in combination with IVA in one or more subset of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of ELX, TEZ and IVA are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of ELX and TEZ and twice-daily dosing of IVA, plasma concentrations of ELX, TEZ and IVA reach steady state within approximately 7 days for ELX, within 8 days for TEZ, and within 3-5 days for IVA. Upon dosing IVA/TEZ/ELX to steady state, the accumulation ratio is approximately 3.6 for ELX, 2.8 for TEZ and 4.7 for IVA. Key pharmacokinetic parameters for ELX, TEZ and IVA at steady state in patients with CF aged 12 years and older are shown in Table 7.

	Active Substance	C_{max} (mcg/mL)	AUC_{0-24h} or AUC_{0-12h} (mcg·h/mL)*
IVA 150 mg every 12 hours/TEZ 100 mg and ELX 200 mg once daily	ELX	9.15 (2.09)	162 (47.5)
	TEZ	7.67 (1.68)	89.3 (23.2)
	IVA	1.24 (0.34)	11.7 (4.01)

*AUC_{0-24h} for ELX and TEZ and AUC_{0-12h} for IVA
SD: Standard Deviation; C_{max}: maximum observed concentration; AUC: area under the concentration versus time curve.

Absorption

The absolute bioavailability of ELX when administered orally in the fed state is approximately 80%. ELX is absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 6 hours (4 to 12 hours) while the median (range) t_{max} of TEZ and IVA is approximately 3 hours (2 to 4 hours) and 4 (3 to 6 hours), respectively.

ELX exposure (AUC) increases approximately 1.9- to 2.5-fold when administered with a moderate-fat meal relative to fasted conditions. IVA exposure increases approximately 2.5- to 4-fold when administered with fat-containing meals relative to fasted conditions, while food has no effect on the exposure of TEZ.

Distribution

ELX is >99% bound to plasma proteins and TEZ is approximately 99% bound to plasma proteins, in both cases primarily to albumin. IVA is approximately 99% bound to plasma proteins, primarily to albumin, and also to alpha 1-acid glycoprotein and human gamma-globulin. After oral administration of IVA/TEZ/ELX in combination with IVA, the mean (±SD) apparent volume of distribution of ELX, TEZ and IVA was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. ELX, TEZ and IVA do not partition preferentially into human red blood cells.

Biotransformation

ELX is metabolized extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 200 mg ¹⁴C-ELX to healthy male subjects, M23-ELX was the only major circulating metabolite. M23-ELX has similar potency to ELX and is considered pharmacologically active.

TEZ is metabolized extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 100 mg ¹⁴C-TEZ to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of TEZ in humans. M1-TEZ has similar potency to that of TEZ and is

considered pharmacologically active. M2-TEZ is much less pharmacologically active than TEZ or M1-TEZ, and M5-TEZ is not considered pharmacologically active. Another minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of TEZ.

IVA is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that IVA is metabolized primarily by CYP3A4/5. M1-IVA and M6-IVA are the two major metabolites of IVA in humans. M1-IVA has approximately one-sixth the potency of IVA and is considered pharmacologically active. M6-IVA is not considered pharmacologically active.

The effect of the CYP3A4*22 heterozygous genotype on TEZ, IVA and ELX exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not clinically relevant. No dose-adjustment of TEZ, IVA or ELX 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 multiple dosing in the fed state, the mean (\pm SD) apparent clearance values of ELX, TEZ and IVA at steady state were 1.18 (0.29) L/h, 0.79 (0.10) L/h and 10.2 (3.13) L/h, respectively. The mean (SD) terminal half-lives of ELX, TEZ and IVA following administration of the IVA/TEZ/ELX fixed-dose combination tablets are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively. The mean (SD) effective half-life of TEZ following administration of the IVA/TEZ/ELX fixed-dose combination tablets is 11.9 (3.79) hours.

Following oral administration of 14 C-ELX alone, the majority of ELX (87.3%) was eliminated in the faeces, primarily as metabolites.

Following oral administration of 14 C-TEZ alone, the majority of the dose (72%) was excreted in the faeces (unchanged or as the M2-TEZ) and about 14% was recovered in urine (mostly as M2-TEZ), resulting in a mean overall recovery of 86% up to 26 days after the dose.

Following oral administration of 14 C-IVA alone, the majority of IVA (87.8%) was eliminated in the faeces after metabolic conversion.

For ELX, TEZ and IVA there was negligible urinary excretion of unchanged medicine.

Hepatic impairment

ELX alone or in combination with TEZ and IVA has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of ELX, TEZ and IVA for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 25% higher AUC and a 12% higher C_{max} for ELX, 73% higher AUC and a 70% higher C_{max} for M23-ELX, 20% higher AUC but similar C_{max} for TEZ, 22% lower AUC and a 20% lower C_{max} for M1-TEZ, and a 1.5-fold higher AUC and a 10% higher C_{max} for IVA compared with healthy subjects matched for demographics. The effect of moderately impaired hepatic function on total exposure (based on summed values of ELX and its M23-ELX metabolite) was 36% higher AUC and a 24% higher C_{max} compared with healthy subjects matched for demographics.

Tezacaftor and ivacaftor

Following multiple doses of TEZ and IVA for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and a 10% higher C_{max} for TEZ, and a 1.5-fold higher AUC but similar C_{max} for IVA compared with healthy subjects matched for demographics.

Ivacaftor

In a study with IVA alone, subjects with moderately impaired hepatic function had similar IVA C_{max} , but an approximately 2.0-fold higher IVA AUC_{0-∞} compared with healthy subjects matched for demographics.

Renal impairment

ELX alone or in combination with TEZ and IVA has not been studied in patients with severe renal impairment (eGFR less than 30 mL/min) or in patients with end-stage renal disease.

In human pharmacokinetic studies of ELX, TEZ, and IVA, there was minimal elimination of ELX, TEZ, and IVA in urine (only 0.23%, 13.7% [0.79% as unchanged medicine], and 6.6% of total radioactivity, respectively).

Based on population pharmacokinetic (PK) analysis, exposure of ELX was similar in those with mild renal impairment (N=75, eGFR 60 to less than 90 mL/min) relative to those with normal renal function (N=341, eGFR 90 mL/min or greater).

In population PK analysis conducted in 817 patients administered TEZ alone or in combination with IVA in Phase 2 or Phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min) did not affect the clearance of TEZ significantly.

Gender

The pharmacokinetic parameters of ELX (244 males compared to 174 females), TEZ and IVA are similar in males and females.

Race

Race had no clinically meaningful effect on ELX exposure based on population PK analysis in whites (N=373) and non-whites (N=45). The non-white races consisted of 30 Black or African American, 1 with multiple racial background and 14 with other ethnic background (no Asian).

Very limited PK data indicate comparable exposure of TEZ in whites (N=652) and non-whites (N=8). The non-white races consisted of 5 Black or African American and 3 Native Hawaiian or other Pacific Islander.

Race had no clinically meaningful effect on the PK of IVA in whites (N=379) and non-whites (N=29) based on a population PK analysis. The non-white races consisted of 27 African American and 2 Asian.

Elderly

Clinical trials of IVA/TEZ/ELX in combination with IVA did not include sufficient number of patients aged 65 years and older to determine whether response in these patients is different from younger adults.

Paediatric population

ELX, TEZ and IVA exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 8. Exposures of ELX, TEZ and IVA in patients aged 12 to less than 18 years of age are similar to that of adult patients.

Table 8. Mean (SD) ELX, TEZ and IVA exposures by age group				
Age group	Dose	ELX AUC_{0-24h,SS} (mcg·h/mL)	TEZ AUC_{0-24h,SS} (mcg·h/mL)	IVA AUC_{0-12h,SS} (mcg·h/mL)
Adolescent patients (12 to <18 years) (N=72)	IVA150 mg q12h/TEZ 100 mg qd/ELX 200 mg qd	147 (36.8)	88.8 (21.8)	10.6 (3.35)
Adult patients (≥18 years) (N=179)		168 (49.9)	89.5 (23.7)	12.1 (4.17)
SD: Standard Deviation; AUC _{ss} : area under the concentration versus time curve at steady state.				

5.3 Preclinical safety data

Elexacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity. Assessment of the carcinogenic potential of ELX is currently being conducted.

Fertility and pregnancy

The No Observed Adverse Effect Level (NOAEL) for fertility findings was 55 mg/kg/day (2 times the maximum recommended human dose (MRHD) based on summed AUCs of ELX and its metabolite) in male rats and 25 mg/kg/day (4 times the MRHD based on summed AUCs of ELX and its metabolite) in female rats. In rat, at doses exceeding the maximum tolerated dose (MTD), degeneration and atrophy of seminiferous tubules are correlated to oligo-/aspermia and cellular debris in epididymides. In dog testes, minimal or mild, bilateral degeneration/atrophy of the seminiferous tubules was present in males administered 14 mg/kg/day ELX (14 times the MRHD based on summed AUCs of ELX and its metabolite) that did not resolve during the recovery period, however without further sequelae. The human relevance of these findings is unknown.

ELX was not teratogenic in rats at 40 mg/kg/day and at 125 mg/kg/day in rabbits (approximately 9 and 4 times, respectively, the MRHD based on summed AUCs of ELX and its metabolites [for rat] and AUC of ELX [for rabbit]) with developmental findings being limited to lower mean foetal body weight at ≥25 mg/kg/day.

Placental transfer of ELX was observed in pregnant rats.

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. Placental transfer of TEZ was observed in pregnant rats.

Ivacaftor

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

Fertility and pregnancy

The NOAEL for fertility findings was 100 mg/kg/day (5 times the MRHD based on summed AUCs of IVA and its metabolites) in male rats and 100 mg/kg/day (3 times the MRHD based on summed AUCs of IVA and its metabolites) in female rats.

In the pre- and post-natal study IVA 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 IVA and its metabolites in adult humans at the MRHD. Placental transfer of IVA was observed in pregnant rats and rabbits.

Juvenile animals

Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through day 35 at IVA exposure levels of 0.21 times the MRHD based on systemic exposure of IVA and its metabolites. This finding has not been observed in foetuses derived from rat dams treated with IVA on gestation days 7 to day 17, in rat pups exposed to IVA through milk ingestion up to postnatal day 20, in 7-week-old rats, nor in 3.5- to 5-month-old dogs treated with IVA. The potential relevance of these findings in humans is unknown.

Ivacaftor/tezacaftor/elixacaftor

Combination repeat-dose toxicity studies in rats and dogs involving the co-administration of ELX, TEZ and IVA to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions. The potential for synergistic toxicity on male reproduction has not been assessed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose (E464)
Hypromellose acetate succinate
Sodium laurilsulfate (E487)
Croscarmellose sodium (E468)
Microcrystalline cellulose (E460(i))
Magnesium stearate (E470b)

Tablet film coat

Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper backed aluminium foil lidding.

Pack size of 56 tablets (4 blister cards, each with 14 tablets).

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 (Ireland) Limited
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Dublin 2, D02 EK84
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 August 2020

10. DATE OF REVISION OF THE TEXT

04/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.