ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation (see section 5.1).

4.2 Posology and method of administration

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 two *F508del* mutations or the presence of one *F508del* mutation and a minimal function 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 ivacaftor/tezacaftor/elexacaftor tablets	One ivacaftor tablet	Two ivacaftor/tezacaftor/elexacaftor tablets	One ivacaftor tablet
Evening Dose^	No dose			

***** Continue dosing with two ivacaftor/tezacaftor/elexacaftor tablets and one ivacaftor tablet on alternate days.
^ The evening dose of ivacaftor tablet should not be taken.

Strong CYP3A Inhibitors

	Day 1	**Day 2**	**Day 3**	**Day 4[#]**
Morning Dose	Two ivacaftor/tezacaftor/elexacaftor tablets	No dose	No dose	Two ivacaftor/tezacaftor/elexacaftor tablets
Evening Dose^	No dose			

[#] Continue dosing with two ivacaftor/tezacaftor/elexacaftor tablets twice a week, approximately 3 to 4 days apart.
^ The evening dose of ivacaftor 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 ivacaftor/tezacaftor/elexacaftor tablets)	Use not recommended* If used: alternate each day between two ivacaftor/tezacaftor/elexacaftor tablets and one ivacaftor/tezacaftor/elexacaftor tablet	Should not be used
Evening	No dose adjustment (One ivacaftor tablet)	No ivacaftor tablet	Should not be used

***** For patients with moderate hepatic impairment, use of Kaftrio 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. 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 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 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 ivacaftor and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming IVA/TEZ/ELX in combination with ivacaftor 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 ivacaftor did not include any patients over 59 years of age. 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 ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduced efficacy of IVA/TEZ/ELX and ivacaftor; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors
Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. The dose of IVA/TEZ/ELX and ivacaftor 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 ivacaftor-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 ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with IVA/TEZ/ELX in combination with ivacaftor (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 elexacaftor, tezacaftor and/or ivacaftor

CYP3A inducers
Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor 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 ivacaftor with rifampicin, a strong CYP3A

inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor 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 elexacaftor AUC by 2.8-fold and tezacaftor AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of IVA/TEZ/ELX and ivacaftor 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 elexacaftor and tezacaftor AUC by approximately 1.9- to 2.3-fold. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dose of IVA/TEZ/ELX and ivacaftor 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 elexacaftor, tezacaftor and ivacaftor. Food or drink containing grapefruit should be avoided during treatment with IVA/TEZ/ELX and ivacaftor (see section 4.2).

Potential for interaction with transporters
In vitro studies showed that elexacaftor 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 elexacaftor 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 tezacaftor is a substrate for the uptake transporter OATP1B1, and efflux transporters P-gp and BCRP. Tezacaftor is not a substrate for OATP1B3. Exposure to tezacaftor 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 (tezacaftor 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 ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-gp. 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.

Medicinal products affected by elexacaftor, tezacaftor and/or ivacaftor

CYP2C9 substrates
Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalised ratio (INR) during co-administration of warfarin with IVA/TEZ/ELX and ivacaftor 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 ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of IVA/TEZ/ELX and 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, and tacrolimus, caution and appropriate monitoring should be used.

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Tezacaftor/ivacaftor increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration with IVA/TEZ/ELX in combination with ivacaftor 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 elexacaftor and M23-ELX.

Elexacaftor and ivacaftor are inhibitors of BCRP. Co-administration of IVA/TEZ/ELX and ivacaftor 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 ivacaftor 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 ivacaftor 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 elexacaftor, tezacaftor or 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 IVA/TEZ/ELX during pregnancy.

Breast-feeding

It is unknown whether elexacaftor, tezacaftor, ivacaftor, or their metabolites are excreted in human milk. Available pharmacokinetic/toxicological data in animals have shown excretion of elexacaftor, tezacaftor and ivacaftor 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 elexacaftor, tezacaftor and ivacaftor on fertility in humans. Tezacaftor had no effects on fertility and reproductive performance indices in male and female rats at clinically relevant exposures. Elexacaftor and ivacaftor 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 ivacaftor 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 ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor as well as ivacaftor monotherapy (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 ivacaftor 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 ivacaftor 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 ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor monotherapy. Adverse reactions are listed by MedDRA system organ class and frequency: 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).

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
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 ivacaftor.		

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 ivacaftor.

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 ivacaftor was evaluated in 72 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 ivacaftor was generally similar across all subgroups of patients, including analysis by age, baseline percent predicted forced expiratory volume in one second ($ppFEV_1$), 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 system listed in Appendix V.

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

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 F508del-CFTR to

increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elexacaftor, tezacaftor and ivacaftor 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 MF-CFTR variant it is not clear whether and to what extent the combination of elexacaftor, tezacaftor and ivacaftor also increases the amount of mutated MF-CFTR variant 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 is not responsive to ivacaftor and tezacaftor/ivacaftor *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 between IVA/TEZ/ELX in combination with ivacaftor and placebo for mean absolute change in sweat chloride from baseline through week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3; $P<0.0001$).

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

Cardiovascular effects

Effect on QT interval
At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, 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 ivacaftor in patients with CF was demonstrated in two Phase 3 studies. Study 445-102 was a study of patients who had one F508del mutation and a second minimal function (MF) mutation. An MF mutation is defined as one that either leads to no CFTR protein being produced (e.g. Class I) or a CFTR protein that does not function to transport chloride and is unlikely to respond to other CFTR modulators (TEZ, IVA, or TEZ/IVA). Study 445-103 was a study of patients homozygous for the *F508del* mutation. Not all CF genotypes have been clinically evaluated with IVA/TEZ/ELX in combination with ivacaftor; to date there are clinical data only for F/MF and F/F genotypes.

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 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)), as well as missense mutations which results in CFTR protein that does not transport chloride and is not responsive to ivacaftor and tezacaftor/ ivacaftor *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*. Not all genotypes were assessed in the study. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomised and dosed to receive IVA/TEZ/ELX in combination with ivacaftor or placebo. Patients

had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ 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 are homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received tezacaftor/ivacaftor and ivacaftor regimen (tezacaftor/ivacaftor) during a 4-week open-label run-in period and were then randomised and dosed to receive IVA/TEZ/ELX in combination with ivacaftor or tezacaftor/ivacaftor during a 4-week double-blind treatment period. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline, following the tezacaftor/ivacaftor run-in period was 60.9% (range: 35.0%, 89.0%).

Patients in studies 445-102 and 445-103 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies. 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 ≥3 x ULN, or total bilirubin ≥2 x ULN), were excluded. Patients in studies 445-102 and 445-103 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 $ppFEV_1$ from baseline through week 24. Treatment with IVA/TEZ/ELX in combination with ivacaftor compared to placebo resulted in statistically significant improvement in $ppFEV_1$ of 14.3 percentage points (95% CI: 12.7, 15.8; $P<0.0001$) (Table 4). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15 and sustained through the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region.
A total of 18 patients receiving IVA/TEZ/ELX in combination with ivacaftor had $ppFEV_1$ <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 between IVA/TEZ/ELX in combination with ivacaftor and placebo-treated patients for absolute change in $ppFEV_1$ 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 ivacaftor 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) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key Secondary			
Absolute change in $ppFEV_1$ from baseline at week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Baseline sweat chloride (mmol/L)	Mean (SD)	102.9 (9.8)	102.3 (11.9)

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 ivacaftor N=200**
Absolute change in sweat chloride from baseline through week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in sweat chloride from baseline at week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Baseline CF Questionnaire - Revised (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) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 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) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 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 $ppFEV_1$ from baseline at week 4 of the double-blind treatment period. Treatment with IVA/TEZ/ELX in combination with ivacaftor compared to the tezacaftor/ivacaftor and ivacaftor regimen (tezacaftor/ivacaftor) resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; *P*<0.0001) (Table 5). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ 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 $ppFEV_1$ 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**	**Tezacaftor/ Ivacaftor# N=52**	**IVA/TEZ/ELX in combination with ivacaftor N=55**
Primary			
Baseline $ppFEV_1$ (percentage points)	Mean (SD)	60.2 (14.4)	61.6 (15.4)
Average absolute change in $ppFEV_1$ from baseline at week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key secondary			
Baseline Sweat Chloride (mmol/L)	Mean (SD)	90.0 (12.3)	91.4 (11.0)
Average absolute change in sweat chloride from baseline at week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Baseline CF Questionnaire - Revised (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) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 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 tezacaftor/ivacaftor and ivacaftor run-in period. # Regimen of tezacaftor/ivacaftor and ivacaftor			

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 ivacaftor 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. 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 ivacaftor in study 445-103, and continued on the same treatment in study 445-105, showed sustained improvements in $ppFEV_1$, 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 ivacaftor 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 elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of elexacaftor and tezacaftor and twice-daily dosing of ivacaftor, plasma concentrations of elexacaftor, tezacaftor and ivacaftor reach steady state within approximately 7 days for elexacaftor, within 8 days for tezacaftor, and within 3-5 days for ivacaftor. Upon dosing IVA/TEZ/ELX to steady state, the accumulation ratio is

approximately 3.6 for elexacaftor, 2.8 for tezacaftor and 4.7 for ivacaftor. Key pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor at steady state in patients with CF aged 12 years and older are shown in Table 6.

Table 6: Mean (SD) pharmacokinetic parameters of elexacaftor, tezacaftor and ivacaftor at steady state in patients with CF aged 12 years and older

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

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

Absorption

The absolute bioavailability of elexacaftor when administered orally in the fed state is approximately 80%. Elexacaftor 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 tezacaftor and ivacaftor is approximately 3 hours (2 to 4 hours) and 4 (3 to 6 hours), respectively.
Elexacaftor exposure (AUC) increases approximately 1.9- to 2.5-fold when administered with a moderate-fat meal relative to fasted conditions. Ivacaftor 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 tezacaftor.

Distribution

Elexacaftor is >99% bound to plasma proteins and tezacaftor is approximately 99% bound to plasma proteins, in both cases primarily to albumin. Ivacaftor 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 ivacaftor, the mean (±SD) apparent volume of distribution of elexacaftor, tezacaftor and ivacaftor was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.

Biotransformation

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

Tezacaftor is metabolized extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of tezacaftor in humans. M1-TEZ has similar potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. Another minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor.

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

The effect of the CYP3A4*22 heterozygous genotype on tezacaftor, ivacaftor and elexacaftor exposure is consistent with the effect of co-administration of a weak CYP3A4 inhibitor, which is not

clinically relevant. No dose-adjustment of tezacaftor, ivacaftor or elexacaftor is considered necessary. The effect in CYP3A4*22 homozygous genotype patients is expected to be stronger. However, no data are available for such patients.

Elimination

Following multiple dosing in the fed state, the mean (±SD) apparent clearance values of elexacaftor, tezacaftor and ivacaftor 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 elexacaftor, tezacaftor and ivacaftor following administration of the ivacaftor/tezacaftor/elexacaftor 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 tezacaftor following administration of the ivacaftor/tezacaftor/elexacaftor fixed-dose combination tablets is 11.9 (3.79) hours.

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

Following oral administration of ^{14}C-tezacaftor 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-ivacaftor alone, the majority of ivacaftor (87.8%) was eliminated in the faeces after metabolic conversion.

For elexacaftor, tezacaftor and ivacaftor there was negligible urinary excretion of unchanged medicine.

Hepatic impairment

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of elexacaftor, tezacaftor and ivacaftor 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 elexacaftor, 73% higher AUC and a 70% higher C_{max} for M23-ELX, 20% higher AUC but similar C_{max} for tezacaftor, 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 ivacaftor compared with healthy subjects matched for demographics. The effect of moderately impaired hepatic function on total exposure (based on summed values of elexacaftor 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 tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and a 10% higher C_{max} for tezacaftor, and a 1.5-fold higher AUC but similar C_{max} for ivacaftor compared with healthy subjects matched for demographics.

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

Renal impairment

Elexacaftor alone or in combination with tezacaftor and ivacaftor 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 elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor 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 elexacaftor 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 tezacaftor alone or in combination with ivacaftor 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 tezacaftor significantly.

Gender

The pharmacokinetic parameters of elexacaftor (244 males compared to 174 females), tezacaftor and ivacaftor are similar in males and females.

Race

Race had no clinically meaningful effect on elexacaftor 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 tezacaftor 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 ivacaftor 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 ivacaftor did not include any patients over 59 years of age to determine whether response in these patients is different from younger adults.

Paediatric population

Elexacaftor, tezacaftor and ivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 7. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 12 to less than 18 years of age are similar to that of adult patients.

Table 7. Mean (SD) elexacaftor, tezacaftor and ivacaftor exposures by age group

Age group	Dose	Elexacaftor $AUC_{0\text{-}24h,ss}$ (mcg·h/mL)	Tezacaftor $AUC_{0\text{-}24h,ss}$ (mcg·h/mL)	Ivacaftor $AUC_{0\text{-}12h,ss}$ (mcg·h/mL)
Adolescent patients (12 to <18 years) (N=72)	ivacaftor 150 mg q12h/ tezacaftor 100 mg qd/ elexacaftor 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 elexacaftor 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 elexacaftor and its metabolite) in male rats and 25 mg/kg/day (4 times the MRHD based on summed AUCs of elexacaftor 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 elexacaftor (14 times the MRHD based on summed AUCs of elexacaftor and its metabolite) that did not resolve during the recovery period, however without further sequelae. The human relevance of these findings is unknown.

Elexacaftor 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 elexacaftor and its metabolites [for rat] and AUC of elexacaftor [for rabbit]) with developmental findings being limited to lower mean foetal body weight at ≥25 mg/kg/day.

Placental transfer of elexacaftor 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 tezacaftor 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 ivacaftor and its metabolites) in male rats and 100 mg/kg/day (3 times the MRHD based on summed AUCs of ivacaftor and its metabolites) in female rats.

In the pre- and post-natal study 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 in adult humans at the MRHD. Placental transfer of ivacaftor 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 ivacaftor exposure levels of 0.21 times the MRHD based on systemic exposure of ivacaftor and its metabolites. This finding has not been observed in foetuses derived from rat dams treated with ivacaftor on gestation days 7 to day 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.

Ivacaftor/tezacaftor/elexacaftor

Combination repeat-dose toxicity studies in rats and dogs involving the co-administration of elexacaftor, tezacaftor and ivacaftor 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

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 August 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

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

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

Open

Insert tab below to close

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kaftrio

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Take the tablets with fat-containing food.

You may start taking Kaftrio on any day of the week.

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

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1468/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Kaftrio 75 mg/50 mg/100 mg tablets
ivacaftor/tezacaftor/elexacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kaftrio 75 mg/50 mg/100 mg film-coated tablets
ivacaftor/tezacaftor/elexacaftor

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

What is in this leaflet

1. What Kaftrio is and what it is used for

Kaftrio contains three active substances: ivacaftor, tezacaftor and elexacaftor. The medicine helps lung cells to work better in some patients with cystic fibrosis (CF). CF is an inherited condition in which the lungs and the digestive system can become clogged with thick, sticky mucus.

Kaftrio taken with ivacaftor is for **patients aged 12 years and over who have CF, with certain genetic mutations.** These can be either two F508del mutations or an F508del mutation and a second mutation called a minimal function mutation. A minimal function mutation is defined as one that results either in no CFTR protein being produced or a CFTR protein that does not function, and which is unlikely to respond to other CFTR modulator treatments (ivacaftor and tezacaftor/ivacaftor). Kaftrio is intended as a long-term treatment.

Kaftrio works on a protein called CFTR (*cystic fibrosis transmembrane conductance regulator*). The protein is damaged in some people with CF, if they have a mutation in the *CFTR* gene.

Kaftrio is normally taken with another medicine, ivacaftor. Ivacaftor causes the protein to work better, while tezacaftor and elexacaftor increase the amount of protein at the cell surface.

Kaftrio (taken with ivacaftor) helps your breathing by improving your lung function. You may also notice that you do not get ill as often, or that it is easier to gain weight.

2. What you need to know before you take Kaftrio

Do not take Kaftrio:
- **If you are allergic** to ivacaftor, tezacaftor, elexacaftor, or any other ingredients of this medicine (listed in section 6).

Talk to your doctor and do not take the tablets, if this applies to you.

Warnings and precautions
- **Talk to your doctor if you have liver problems,** or have had them previously. Your doctor may need to adjust your dose.
- Your doctor will do some **blood tests to check your liver** before and during treatment with Kaftrio, especially if your blood tests showed high liver enzymes in the past. Liver enzymes in the blood can increase in patients receiving Kaftrio.

Tell your doctor right away if you have any symptoms of liver problems. These are listed in section 4.
- **Talk to your doctor if you have kidney problems,** or you have previously had them.

- **Talk to your doctor** before starting treatment with Kaftrio if you have received **an organ transplant**.

- **Talk to your doctor** if you are using hormonal contraception – for example, women using the contraceptive pill. This may mean you are more likely to get a rash while taking Kaftrio.

- **Your doctor may do eye examinations** before and during treatment with Kaftrio. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving this treatment.

Children under 12
Do not give this medicine to children under the age of 12 years because it is not known if Kaftrio is safe and effective in this age group.

Other medicines and Kaftrio
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Some medicines can affect how Kaftrio works or may make side effects more likely. In particular, tell your doctor if you take any of the medicines listed below. Your doctor may change the dose of one of the medicines if you take any of these.
- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifampicin, rifabutin, and telithromycin.
- **Epilepsy medicines** (used for the treatment of epileptic seizures or fits). These include carbamazepine, phenobarbital, and phenytoin.
- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).
- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus, and tacrolimus.
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.
- **Medicines for diabetes.** These include glimepiride, glipizide, glyburide, nateglinide, and repaglinide.
- **Medicines for lowering blood cholesterol.** These include pitavastatin, and rosuvastatin.
- **Medicines for lowering blood pressure.** These include verapamil.

Kaftrio with food and drink
Avoid food or drinks containing grapefruit during treatment as these may increase the side effects of Kaftrio by increasing the amount of Kaftrio in your body.

Pregnancy and breast-feeding
- **Ask your doctor for advice** before taking this medicine if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.
  - **Pregnancy:** It may be better to avoid using this medicine during pregnancy. Your doctor will help you decide what is best for you and your child.
  - **Breast-feeding:** It is not known if ivacaftor, tezacaftor or elexacaftor pass into breast milk. Your doctor will consider the benefit of breast-feeding for your baby and the benefit of treatment for you to help you decide whether to stop breast-feeding or to stop treatment.

Driving and using machines
Kaftrio can make you dizzy. If you feel dizzy, do not drive, cycle, or use machines unless you are not affected.

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

3. How to take Kaftrio

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Recommended dose for patients aged 12 years and over
Kaftrio is usually taken with ivacaftor.
- **In the morning, take two Kaftrio tablets.** They are stamped with "T100".
- **In the evening, take one ivacaftor 150 mg tablet.**

Take the morning and evening tablets about 12 hours apart.

The tablets are for oral use.

Take both Kaftrio and ivacaftor tablets with food that contains fat. Meals or snacks that contain fat include those prepared with butter or oils or those containing eggs. Other fat-containing foods are:
- Cheese, whole milk, whole milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

Avoid food and drink containing grapefruit while you are taking Kaftrio. See *Kaftrio with food and drink* in section 2 for more details.

Swallow the tablets whole. Do not chew, crush or break the tablets before swallowing.

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

If you have liver problems, either moderate or severe, your doctor may reduce the dose of your tablets or decide to stop treatment with Kaftrio. See also *Warnings and precautions* in section 2.

If you take more Kaftrio than you should
Contact your doctor or pharmacist for advice. If possible, take your medicine and this leaflet with you. You may get side effects, including those mentioned in section 4 below.

If you forget to take Kaftrio
If you forget a dose, work out how long it is since the dose you missed.
- **If less than 6 hours** have passed since you missed a dose, either morning or evening, take the forgotten tablet(s) as soon as possible. Then go back to your usual schedule.

- **If more than 6 hours** have passed:
  - **If you missed a morning dose** of Kaftrio, take it as soon as you remember. Do not take the evening dose of ivacaftor. Take the next morning dose at the usual time.
  - **If you missed an evening** dose of ivacaftor, do not take the missed dose. Wait for the next day and take the morning dose of Kaftrio tablets as usual.

Do not take a double dose to make up for any missed tablets.

If you stop taking Kaftrio
Your doctor will tell you how long you need to keep taking Kaftrio. It is important to take this medicine regularly. Do not make changes unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Possible signs of liver problems
Increased liver enzymes in the blood are common in patients with CF. These may be signs of liver problems:
- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Tell your doctor straight away if you have any of these symptoms.

Very common side effects (may affect more than 1 in 10 people)
- Rash (more common in women that in men)

Tell your doctor straight away if you notice a rash.

Other side effects seen with Kaftrio:
Very common (may affect more than 1 in 10 people)
- Headache
- Dizziness
- Upper respiratory tract infection (common cold)
- Oropharyngeal pain (sore throat)
- Nasal congestion
- Stomach or abdominal pain
- Diarrhoea
- Increased liver enzymes (signs of stress on the liver)
- Changes in the type of bacteria in mucus

Common (may affect up to 1 in 10 people)
- Flu
- Abnormal breathing (Shortness of breath or difficulty breathing)
- Low blood sugar (hypoglycaemia)
- Runny nose
- Sinus problems (sinus congestion)
- Redness or soreness in the throat
- Ear problems: ear pain or discomfort, ringing in the ears, inflamed eardrum
- Spinning sensation (inner ear disorder)
- Wind (flatulence)

- Spots (acne)
- Itchy skin
- Breast mass
- Feeling nauseous
- Increased creatine phosphokinase (sign of muscle breakdown) seen in blood tests

Uncommon (may affect up to 1 in 100 people)
- Breast and nipple problems: inflammation, pain
- Enlargement of the breast in men
- Increases in blood pressure
- Wheezing
- Blocked ears (ear congestion)

Additional side effects in adolescents
Side effects in adolescents are similar to those observed in adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kaftrio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Kaftrio contains
- The active substances are ivacaftor, tezacaftor and elexacaftor. Each film-coated tablet contains 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg elexacaftor.
- The other ingredients are:
  - Tablet core: Hypromellose (E464), hypromellose acetate succinate, sodium laurilsulfate (E487), croscarmellose sodium (E468), microcrystalline cellulose (E460(i)), and magnesium stearate (E470b).
  - Tablet film coating: Hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), and iron oxide red (E172).

See the end of section 2 for important information about the contents of Kaftrio.

What Kaftrio looks like and contents of the pack
Kaftrio 75 mg/50 mg/100 mg film-coated tablets are orange, capsule-shaped tablets stamped with "T100" on one side and plain on the other.

Kaftrio is available in pack size of 56 tablets (4 blister cards, each with 14 tablets).

Marketing Authorisation Holder
Vertex Pharmaceuticals (Ireland) Limited
28-32 Pembroke Street Upper
Dublin 2, D02 EK84
Ireland
Tel: +353 (0)1 761 7299

Manufacturer
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Deutschland, Eesti, France, Hrvatska, Ireland, Ísland, Κύπρος, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska, Portugal, România, Slovenija, Slovenská republika, Suomi/Finland, Sverige, United Kingdom
Vertex Pharmaceuticals (Ireland) Limited
Tél/Tel/Тел/Tlf/Sími/Τηλ/Puh:
+353 (0) 1 761 7299

España
Vertex Pharmaceuticals Spain, S.L.
Tel: + 34 91 7892800

Ελλάδα
Vertex Φαρμακευτική Μονοπρόσωπη Ανώνυμη Εταιρία
Λ. Κηφισίας 62
GR-151 25 Αθήνα
Τηλ: +30 (211) 2120535

Italia
Vertex Pharmaceuticals (Italy) S.r.l.
Tel: +39 0697794000

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.