SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Trikafta 100mg/50mg/75mg & 150mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Elexacaftor/Tezacaftor/Ivacaftor tablet:
Each film-coated tablet contains 100 mg elexacaftor, 50 mg tezacaftor and 75 mg ivacaftor

Ivacaftor tablet:
Each film-coated tablet contains 150 mg ivacaftor.

Excipients with known effect:
Each Ivacaftor tablet contains 167.2 mg of lactose.

For the full list of excipients, *see Description (12)*.

3 PHARMACEUTICAL FORM
Film-coated tablets

Elexacaftor/Tezacaftor/Ivacaftor tablet:
Orange film-coated tablet, debossed with "T100" on one face and plain on the other face.

Ivacaftor tablet:
Light blue film-coated tablet, printed in black ink with "V 150" on one face.

4 THERAPEUTIC INDICATION
Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data [*see Clinical Pharmacology (13.1)*].

5 DOSAGE AND ADMINISTRATION
5.1 General Dosing Information
Swallow the tablets whole.
Trikafta 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, peanut butter, cheeses, nuts, whole milk, or meats *[see Clinical Pharmacology (13.3)]*.

5.2 Recommended Dosage in Adults and Pediatric Patients Aged 12 Years and Older
The recommended dosage is two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg) taken in the morning and one ivacaftor tablet (containing ivacaftor 150 mg) taken in the evening, administered orally, approximately 12 hours apart.

Information for Missed Doses:
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.

5.3 Recommended Dosage for Patients with Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) *[see Use in Specific Populations (10.6) and Clinical Pharmacology (13.3)]*. See Table 1. Liver function tests should be closely monitored *[see Warnings and Precautions (7.1) and Adverse Reactions (8)]*.

Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B). Use of Trikafta in patients with moderate hepatic impairment should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used, Trikafta should be used with caution at a reduced dose (see Table 1) *[see Use in Specific Populations (10.6) and Clinical Pharmacology (13.3)]*. Liver function tests should be closely monitored *[see Warnings and Precautions (7.1) and Adverse Reactions (8)]*.

Trikafta has not been studied 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. Trikafta should not be used in patients with severe hepatic impairment *[see Warnings and Precautions (7.1), Adverse Reactions (8), Use in Specific Populations (10.6) and Clinical Pharmacology (13.3)]*.

Table 1: Recommended Dosage for use of Trikafta in patients with hepatic impairment		
Mild (Child-Pugh Class A)	**Moderate (Child-Pugh Class B)**	**Severe (Child-Pugh Class C)**
No dose adjustment	Use of Trikafta should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used, Trikafta should be used with caution at a reduced dose, as follows: • Day 1: take two elexacaftor/tezacaftor/ivacaftor tablets in the morning • Day 2: take one elexacaftor/tezacaftor/ivacaftor tablet in the morning • Continue alternating Day 1 and Day 2 dosing thereafter. • No evening dose of ivacaftor tablet should be taken.	Should not be used

5.4 Dosage Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

Table 2 describes the recommended dosage modification for Trikafta when co-administered with strong (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate (e.g., fluconazole, erythromycin) CYP3A inhibitors. Avoid food or drink containing grapefruit during Trikafta treatment *[see Warnings and Precautions (7.3), Drug Interactions (9.2) and Clinical Pharmacology (13.3)]*.

Table 2: Dosage Adjustment for Concomitant Use of Trikafta with Moderate and Strong CYP3A Inhibitors				
Moderate CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet
Evening Dose^	No dose			
* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days. ^ The evening dose of ivacaftor should not be taken.				
Strong CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4[#]**
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	No dose	No dose	Two elexacaftor/tezacaftor/ivacaftor tablets
Evening Dose^	No dose			
[#] Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart. ^ The evening dose of ivacaftor tablet should not be taken.				

6 CONTRAINDICATIONS

Hypersensitivity to the active substances (elexacaftor, ivacaftor or tezacaftor) or to any of the excipients listed in section 12.

7 WARNINGS AND PRECAUTIONS

7.1 Elevated Transaminases and Hepatic Injury

Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving Trikafta. Avoid use of Trikafta in patients with pre-existing advanced liver disease (e.g., as evidenced by cirrhosis, portal hypertension, ascites, hepatic encephalopathy) unless the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment *[see Dosage and Administration (5.3), Adverse Reactions (8), Use in Specific Populations (10.6) and Clinical Pharmacology (13.3)]*.

Isolated elevations of transaminases or bilirubin have been observed in patients with CF treated with Trikafta. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including in patients without a history of pre-existing liver disease.

Assessments of liver function tests (ALT, AST, and bilirubin) are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. In the event of significant elevations in liver function tests, e.g., 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 liver function test elevations, consider the benefits and risks of resuming treatment. For patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered *[see Dosage and Administration (5.3), Adverse Reactions (8), Use in Specific Populations (10.6) and Clinical Pharmacology (13.3)]*.

7.2 Concomitant Use with CYP3A Inducers

Exposure to ivacaftor is significantly decreased and exposure to elexacaftor and tezacaftor are expected to decrease by the concomitant use of strong CYP3A inducers, which may reduce the therapeutic effectiveness of Trikafta. Therefore, co-administration with strong CYP3A inducers is not recommended *[see Drug Interactions (9.1) and Clinical Pharmacology (13.3)]*.

7.3 Concomitant Use with CYP3A Inhibitors

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. Therefore, the dose of Trikafta should be reduced when used concomitantly with moderate or strong CYP3A inhibitors *[see Dosage and Administration (5.4), Drug Interactions (9.2) and Clinical Pharmacology (13.3)]*.

7.4 Cataracts

Cases of non-congenital lens opacities have been reported in pediatric 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 pediatric patients initiating treatment with Trikafta *[see Use in Specific Populations (10.3)]*.

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Elevated Transaminases and Hepatic Injury *[see Warnings and Precautions (7.1)]*
- Cataracts *[see Warnings and Precautions (7.4)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety profile of Trikafta is based on data from 510 CF patients aged 12 years and older in two double-blind, controlled trials of 24 weeks and 4 weeks treatment duration (Trials 1 and 2). Eligible patients were also able to participate in an open-label extension safety study (up to 96 weeks of Trikafta). In the two controlled trials, a total of 257 patients aged 12 years and older received at least one dose of Trikafta.

In Trial 1, the proportion of patients who discontinued study drug prematurely due to adverse events was 1% for Trikafta-treated patients and 0% for placebo-treated patients.
In Trial 1, serious adverse reactions that occurred more frequently in Trikafta-treated patients compared to placebo were rash (1% vs <1%) and influenza (1% vs 0%). There were no deaths in Trials 1 and 2.

Table 3 shows adverse reactions occurring in ≥5% of Trikafta-treated patients and higher than placebo by ≥1% in the 24-week placebo-controlled, parallel-group trial (Trial 1).

Table 3: Adverse Drug Reactions in ≥5% of Trikafta-Treated Patients and Higher than Placebo by ≥1% in Trial 1

Adverse Drug Reactions (Preferred Term)	Trikafta N=202 n (%)	Placebo N=201 n (%)
Headache	35 (17)	30 (15)
Upper respiratory tract infection[a]	32 (16)	25 (12)
Abdominal pain[b]	29 (14)	18 (9)
Diarrhea	26 (13)	14 (7)
Rash[c]	21 (10)	10 (5)
Alanine aminotransferase increased	20 (10)	7 (3)
Nasal congestion	19 (9)	15 (7)
Blood creatine phosphokinase increased	19 (9)	9 (4)
Aspartate aminotransferase increased	19 (9)	4 (2)
Rhinorrhea	17 (8)	6 (3)
Rhinitis	15 (7)	11 (5)
Influenza	14 (7)	3 (1)
Sinusitis	11 (5)	8 (4)
Blood bilirubin increased	10 (5)	2 (1)

a Includes upper respiratory tract infection and viral upper respiratory tract infection
b Includes abdominal pain, abdominal pain upper, abdominal pain lower
c Includes: rash, rash generalized, rash erythematous, rash macular, rash pruritic

Additional adverse reactions that occurred in Trikafta-treated patients at a frequency of 2 to <5% and higher than placebo by ≥1% include the following: Flatulence, abdominal distension, conjunctivitis, pharyngitis, respiratory tract infection, tonsillitis, urinary tract infection, c-reactive protein increased, hypoglycemia, dizziness, dysmenorrhea, acne, eczema and pruritus.

The safety profile for the CF patients enrolled in Trial 2 was similar to that observed in Trial 1.

Rash Events
In Trial 1, the overall incidence of rash events was 10% in Trikafta-treated and 5% in placebo-treated patients (see Table 3). The incidence of rash events was higher in female Trikafta-treated patients (16%) than in male Trikafta-treated patients (5%).

Hormonal contraceptives may play a role in the occurrence of rash. For patients taking hormonal contraceptives who develop rash, consider interrupting Trikafta and hormonal contraceptives. Following the resolution of rash, consider resuming Trikafta without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

Laboratory and Vital Sign Abnormalities
Liver Function Test Elevations
In Trial 1, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN was 1%, 2%, and 8% in Trikafta-treated patients and 1%, 1%, and 5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations (AST and/or ALT) was 11% in Trikafta-treated patients and 4% in placebo-treated patients.

In Trial 1, the incidence of maximum total bilirubin elevation >2 x ULN was 4% in Trikafta-treated patients and <1% in placebo-treated patients. Maximum indirect and direct bilirubin elevations >1.5 x ULN occurred in 11% and 3% of Trikafta-treated patients, respectively. No Trikafta-treated patients developed maximum direct bilirubin elevation >2 x ULN.

Increased Creatine Phosphokinase
In Trial 1, the incidence of maximum creatine phosphokinase elevation >5 x ULN was 10% in Trikafta-treated and 5% in placebo-treated patients. Among the Trikafta-treated patients with creatine phosphokinase elevation >5 x ULN, 14% (3/21) required treatment interruption and none discontinued treatment.

Increased Blood Pressure
In Trial 1, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for Trikafta-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 and 10 mmHg increase from baseline on at least two occasions was 4% in Trikafta-treated patients and 1% in placebo-treated patients. The proportion of patients who had diastolic blood pressure >90 mmHg and 5 mmHg increase from baseline on at least two occasions was 1% in Trikafta-treated patients and 2% in placebo-treated patients.

With the exception of sex differences in rash, the safety profile of Trikafta was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$) and geographic regions.

8.2 Post-marketing Experience
The following adverse reactions have been identified during post approval use of Trikafta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension. Liver injury characterized by concomitant transaminase (ALT and AST) and total bilirubin elevations *[see Warnings and Precautions (7.1)]*.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

9 DRUG INTERACTIONS

Potential for other drugs to affect elexacaftor/tezacaftor/ivacaftor

9.1 Inducers of CYP3A
Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced Trikafta efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers. Therefore, co-administration of Trikafta with strong CYP3A inducers is not recommended *[see Warnings and Precautions (7.2) and Clinical Pharmacology (13.3)]*.

Examples of strong CYP3A inducers include:
- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's wort (*Hypericum perforatum*)

9.2 Inhibitors of CYP3A
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 dosage of Trikafta should be reduced when co-administered with strong CYP3A inhibitors *[see Dosage and Administration (5.4), Warnings and Precautions (7.3) and Clinical Pharmacology (13.3)]*.

Examples of strong CYP3A inhibitors include:
- ketoconazole, itraconazole, posaconazole and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9 to 2.3-fold and 2.1-fold, respectively. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dosage of Trikafta should be reduced when co administered with moderate CYP3A inhibitors *[see Dosage and Administration (5.4), Warnings and Precautions (7.3) and Clinical Pharmacology (13.3)]*.

Examples of moderate CYP3A inhibitors include:
- fluconazole
- erythromycin

Co-administration of Trikafta with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor; therefore, food or drink containing grapefruit should be avoided during treatment with Trikafta *[see Dosage and Administration (5.4)]*.

9.3 Ciprofloxacin
Ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to affect the exposure of elexacaftor. Therefore, no dose adjustment is necessary during concomitant administration of Trikafta with ciprofloxacin *[see Clinical Pharmacology (13.3)]*.

Potential for elexacaftor/tezacaftor/ivacaftor to affect other drugs

9.4 CYP2C9 Substrates

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co administration of Trikafta with warfarin is recommended. Other medicinal products for which exposure may be increased by Trikafta include glimepiride and glipizide; these medicinal products should be used with caution *[see Clinical Pharmacology (13.3)]*.

9.5 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 Trikafta 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 cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used *[see Clinical Pharmacology (13.3)]*.

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Co-administration of Trikafta 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 *[see Clinical Pharmacology (13.3)]*. Bilirubin is an OATP1B1 and OATP1B3 substrate.

9.6 Hormonal Contraceptives

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

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There are limited and incomplete human data from clinical trials on the use of Trikafta or its individual components, elexacaftor, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk. Although there are no animal reproduction studies with the concomitant administration of elexacaftor, tezacaftor and ivacaftor, separate reproductive and developmental studies were conducted with each active component of Trikafta in pregnant rats and rabbits.

In animal embryo fetal development (EFD) studies oral administration of elexacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 2 times the exposure at the maximum recommended human dose (MRHD) in rats and 4 times the MRHD in rabbits [based on summed AUCs of elexacaftor and its metabolite (for rat) and AUC of elexacaftor (for rabbit)]. Oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the MRHD in rats and 0.2 times the MRHD in rabbits (based on summed AUCs of tezacaftor and M1-TEZ). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 5 and 14 times the exposure at the MRHD, respectively [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. No adverse developmental effects were observed after oral administration of elexacaftor, tezacaftor or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 1 time, approximately 1 time and 3 times the exposures at the MRHD, respectively [based on summed AUCs of parent and metabolite(s)] (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Elexacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17, elexacaftor was not teratogenic and did not affect fetal survival at exposures up to 9 times the MRHD (based on summed AUC for elexacaftor and its metabolite at maternal doses up to 40 mg/kg/day). Lower mean fetal body weights were observed at doses ≥25 mg/kg/day that produced maternal exposures ≥4 times the MRHD. In an EFD study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, elexacaftor was not teratogenic at exposures up to 4 times the MRHD (based on AUC of elexacaftor at maternal doses up to 125 mg/kg/day). In a pre- and postnatal development (PPND) study in pregnant rats dosed from gestation Day 6 through lactation Day 18, elexacaftor did not cause developmental defects in pups at maternal doses up to 10 mg/kg/day (approximately 1 time the MRHD based on summed AUCs of elexacaftor and its metabolite). Placental transfer of elexacaftor was observed in pregnant rats.

Tezacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 3 and 0.2 times, respectively the MRHD (based on summed AUCs of tezacaftor and M1-TEZ). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 1 time the MRHD (based on summed AUCs of tezacaftor and M1-TEZ at a maternal dose of 50 mg/kg/day). In a PPND study in pregnant rats dosed from gestation Day 6 through lactation Day 18, tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 1 time the exposure at the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal oral dose of 50 mg/kg/day). Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 7-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-19, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 5 and 14 times, respectively, the MRHD [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. In a PPND study in pregnant rats dosed from gestation Day 7 through lactation Day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 3 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 5 times the MRHD (based on summed AUCs of ivacaftor and its metabolites). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

10.2 Lactation

Risk Summary

There is no information regarding the presence of elexacaftor, tezacaftor, or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Elexacaftor, tezacaftor, and ivacaftor are excreted into the milk of lactating rats *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Trikafta and any potential adverse effects on the breastfed child from Trikafta or from the underlying maternal condition.

Data

Elexacaftor

Lacteal excretion of elexacaftor in rats was demonstrated following a single oral dose (10 mg/kg) of ^{14}C-elexacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-elexacaftor in milk was approximately 0.4 times the value observed in plasma (based on $AUC_{0\text{-}72h}$).

Tezacaftor

Lacteal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C-tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-tezacaftor in milk was approximately 3 times higher than in plasma (based on $AUC_{0\text{-}72h}$).

Ivacaftor

Lacteal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ^{14}C-ivacaftor in milk was approximately 1.5 times higher than in plasma (based on $AUC_{0\text{-}24h}$).

10.3 Pediatric Use

The safety and effectiveness of Trikafta for the treatment of CF in pediatric patients 12 years and older who have at least one *F508del* mutation in the *CFTR* gene has been established. Use of Trikafta for this indication was supported by evidence from two adequate and well-controlled studies in CF patients 12 years and older (Trial 1 and Trial 2) *[see Clinical Studies (15)].* In these trials, a total of 72 adolescents (aged 12 to 17 years) received Trikafta, including:

- In Trial 1, 56 adolescents who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor *[see Adverse Reactions (8) and Clinical Studies (15)].*
- In Trial 2, 16 adolescents who were homozygous for the *F508del* mutation *[see Adverse Reactions (8) and Clinical Studies (15)].*

Trikafta is not indicated for pediatric patients under 12 years old.
The safety and effectiveness of Trikafta in patients with CF younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.21 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals *[see Warnings and Precautions (7.4)].*

10.4 Geriatric Use

Clinical studies of Trikafta did not include any patients aged 65 years and older.

10.5 Renal Impairment

Trikafta has not been studied in patients with severe renal impairment or end-stage renal disease. No dosage adjustment is recommended in patients with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment. Use with caution in patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment or end-stage renal disease *[see Clinical Pharmacology (13.3)].*

10.6 Hepatic Impairment

No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B). In a clinical study of 11 subjects with moderate hepatic impairment, one subject developed total and direct bilirubin elevations >2 x ULN, and a second subject developed direct bilirubin elevation >4.5 x ULN. Use of Trikafta in patients with moderate hepatic impairment should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used in patients with moderate hepatic impairment, Trikafta should be used with caution at a reduced dose (see Table 1). Liver function tests should be closely monitored in patients with mild and moderate hepatic impairment. Trikafta has not been studied 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. Trikafta should not be used in patients with severe hepatic impairment *[see Dosage and Administration (5.3), Warnings and Precautions (7.1), Adverse Reactions (8) and Clinical Pharmacology (13.3)].*

10.7 Patients with Severe Lung Dysfunction

Trial 1 included a total of 18 patients receiving Trikafta with $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population.

11 OVERDOSAGE

No specific antidote is available for overdosage with Trikafta. Treatment of overdosage consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

12 DESCRIPTION

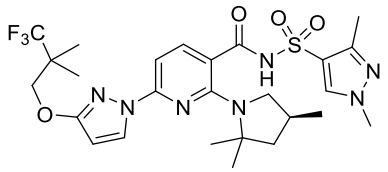
Trikafta is a co-package of elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Both tablets are for oral administration.

The elexacaftor, tezacaftor and ivacaftor tablets are available as an orange, film-coated fixed-dose combination tablet containing 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor, and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate (HPMCAS), Hypromellose (HPMC), magnesium stearate and sodium lauryl sulfate (SLS). The tablet film coat contains opadry orange 20A130036.

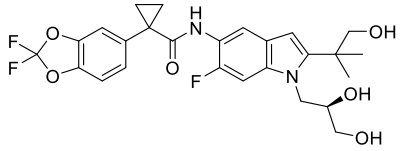
The ivacaftor tablet is available as a light blue, film-coated tablet containing 150 mg of ivacaftor and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose acetate succinate (HPMCAS), croscarmellose sodium, magnesium stearate, sodium lauryl sulfate (SLS), and colloidal silicon dioxide. The tablet film coat contains polyvinyl alcohol, titanium dioxide, PEG 3350, talc, FD&C Blue #2/indigo carmine aluminum lake, and carnauba wax. The printing ink contains shellac, iron oxide black, n-Butyl alcohol, propylene glycol, and ammonium hydroxide.

The active ingredients of Trikafta are described below.

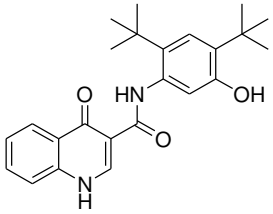
Elexacaftor
Elexacaftor is a white solid that is practically insoluble in water (<1 mg/mL). Its chemical name is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide. Its molecular formula is $C_{26}H_{34}N_7O_4SF_3$ and its molecular weight is 597.66. Elexacaftor has the following structural formula:



Tezacaftor
Tezacaftor is a white to off-white solid that is practically insoluble in water (<5 microgram/mL). Its chemical name is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is $C_{26}H_{27}N_2F_3O_6$ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Ivacaftor
Ivacaftor is a white to off-white crystalline solid that is practically insoluble in water (<0.05 microgram/mL). Pharmacologically it is a CFTR potentiator. Its chemical name is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including 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 CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR
The chloride transport response of mutant CFTR protein to elexacaftor/tezacaftor/ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Elexacaftor/tezacaftor/ivacaftor increased chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

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

Table 4 lists responsive *CFTR* mutations based on *in vitro* data in FRT cells indicating that elexacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline.

Table 4: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA					
3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del**	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (15)]*.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

13.2 Pharmacodynamics

Sweat Chloride Evaluation

In Trial 1 (patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive ivacaftor and tezacaftor/ivacaftor), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period *[see Clinical Studies (15.1)]*. In Trial 2 (patients homozygous for the *F508del* mutation), a reduction in sweat chloride was observed from baseline at Week 4 *[see Clinical Studies (15.2)]*.

Cardiac Electrophysiology

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.

13.3 Pharmacokinetics

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. The pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor in patients with CF aged 12 years and older are shown in Table 5.

Table 5: Pharmacokinetic Parameters of Trikafta Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
General Information			
AUC_{ss} (SD), mcg·h/mL[a]	162 (47.5)[b]	89.3 (23.2)[b]	11.7 (4.01)[c]
C_{max} (SD), mcg/mL[a]	9.2 (2.1)	7.7 (1.7)	1.2 (0.3)
Time to Steady State, days	Within 7 days	Within 8 days	Within 3-5 days
Accumulation Ratio	2.2	2.07	2.4
Absorption			
Absolute Bioavailability	80%	Not determined	Not determined
Median T_{max} (range), hours	6 (4 to 12)	3 (2 to 4)	4 (3 to 6)
Effect of Food	AUC increases 1.9- to 2.5-fold (moderate-fat meal)	No clinically significant effect	Exposure increases 2.5- to 4-fold
Distribution			
Mean (SD) Apparent Volume of	53.7 (17.7)	82.0 (22.3)	293 (89.8)

Table 5: Pharmacokinetic Parameters of Trikafta Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
Distribution, L[d]			
Protein Binding[e]	> 99%	approximately 99%	approximately 99%
Elimination			
Mean (SD) Effective Half-Life, hours[f]	27.4 (9.31)	25.1 (4.93)	15.0 (3.92)
Mean (SD) Apparent Clearance, L/hours	1.18 (0.29)	0.79 (0.10)	10.2 (3.13)
Metabolism			
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active Metabolites	M23-ELX	M1-TEZ	M1-IVA
Metabolite Potency Relative to Parent	Similar	Similar	approximately 1/6th of parent
Excretion[g]			
Primary Pathway	• Feces: 87.3% (primarily as metabolites) • Urine: 0.23%	• Feces: 72% (unchanged or as M2-TEZ) • Urine: 14% (0.79% unchanged)	• Feces: 87.8% • Urine: 6.6%

[a] Based on elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours at steady state in patients with CF aged 12 years and older.
[b] $AUC_{0\text{-}24h}$.
[c] $AUC_{0\text{-}12h}$.
[d] Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.
[e] Elexacaftor and tezacaftor bind primarily to albumin. Ivacaftor primarily bind to albumin, alpha 1-acid glycoprotein and human gamma-globulin.
[f] Mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.
[g] Following radiolabeled doses.
AUC_{ss}: area under the concentration versus time curve at steady state; SD: Standard Deviation; C_{max}: maximum observed concentration; T_{max}: time of maximum concentration; AUC: area under the concentration versus time curve.

Specific Populations

Pediatric patients 12 to less than 18 years of age

The following conclusions about exposures between adults and the pediatric population are based on population pharmacokinetic (PK) analyses.
Following oral administration of Trikafta to patients 12 to less than 18 years of age (elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h), the mean (±SD) AUC_{ss} was 147 (36.8) mcg·h/mL, 88.8 (21.8) mcg·h/mL and 10.6 (3.35) mcg·h/mL, respectively for elexacaftor, tezacaftor and ivacaftor, similar to the AUC_{ss} in adult patients.

Patients with Renal Impairment

Renal excretion of elexacaftor, tezacaftor and ivacaftor is minimal. Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe (eGFR <30 mL/min/1.73 m^2) renal impairment or end stage renal disease. Based on population PK analyses, the clearance of elexacaftor and tezacaftor was similar in subjects with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment relative to patients with normal renal function *[see Use in Specific Populations (10.5)]*.

Patients with 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). In a clinical study, 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 25% higher AUC and 12% higher C_{max} for elexacaftor, 73% higher AUC and 70% higher C_{max} for M23-ELX, 36% higher AUC and 24% higher C_{max} for combined elexacaftor and M23-ELX, 20% higher AUC but similar C_{max} for tezacaftor and 1.5-fold higher AUC and 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics *[see Dosage and Administration (5.3) ,Warnings and Precautions (7.1), Adverse Reactions (8) and Use in Specific Populations (10.6)]*.

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 in 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 $AUC_{0\text{-}\infty}$ compared with healthy subjects matched for demographics.

Male and Female Patients

Based on population PK analysis, the exposures of elexacaftor, tezacaftor and ivacaftor are similar in males and females.

Drug Interaction Studies

Drug interaction studies were performed with elexacaftor, tezacaftor and/or ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies *[see Drug Interactions (9)]*.

Potential for Elexacaftor, Tezacaftor and/or Ivacaftor to Affect Other Drugs
Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, whereas ivacaftor has the potential to inhibit CYP2C8, CYP2C9 and CYP3A. However, clinical studies showed that the combination regimen of tezacaftor/ivacaftor is not an inhibitor of CYP3A and ivacaftor is not an inhibitor of CYP2C8 or CYP2D6.

Based on *in vitro* results, elexacaftor, tezacaftor and ivacaftor are not likely to induce CYP3A, CYP1A2 and CYP2B6.

Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit the transporter P-gp, while ivacaftor has the potential to inhibit P-gp. Co-administration of tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold in a clinical study. Based on *in vitro* results, elexacaftor and M23-ELX may inhibit OATP1B1 and OATP1B3 uptake. Tezacaftor has a low potential to inhibit BCRP, OCT2, OAT1, or OAT3. Ivacaftor is not an inhibitor of the transporters OCT1, OCT2, OAT1, or OAT3.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 6 *[see Drug Interactions (9)]*.

Table 6: Impact of Elexacaftor, Tezacaftor and/or Ivacaftor on Other Drugs

Dose and Schedule		Effect on Other Drug PK	Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0	
			AUC	C_{max}
Midazolam 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol* ↑ Levonorgestrel*	1.33 (1.20, 1.49) 1.23 (1.10, 1.37)	1.26 (1.14, 1.39) 1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939; 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect not clinically significant *[*see *Drug Interactions (7.6)]*.

Potential for Other Drugs to Affect Elexacaftor, Tezacaftor and/or Ivacaftor
In vitro studies showed that elexacaftor, tezacaftor and ivacaftor are all metabolized by CYP3A. Exposure to elexacaftor, tezacaftor and ivacaftor may be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors.

In vitro studies showed that elexacaftor and tezacaftor are substrates for the efflux transporter P-gp, but ivacaftor is not. Elexacaftor and ivacaftor are not substrates for OATP1B1 or OATP1B3; tezacaftor is a substrate for OATP1B1, but not OATP1B3. Tezacaftor is a substrate for BCRP.

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 7 *[see Dosage and Administration (5.4) and Drug Interactions (9)]*.

Table 7: Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor

Dose and Schedule		Effect on ELX, TEZ and/or IVA PK	Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0	
			AUC	C_{max}
Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd	TEZ 25 mg qd + IVA 50 mg qd	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
		↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Itraconazole 200 mg qd	ELX 20 mg + TEZ 50 mg single dose	↑ Elexacaftor	2.83 (2.59, 3.10)	1.05 (0.977, 1.13)
		↑ Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
Ketoconazole 400 mg qd	IVA 150 mg single dose	↑ Ivacaftor	8.45 (7.14, 10.0)	2.65 (2.21, 3.18)
Ciprofloxacin 750 mg q12h	TEZ 50 mg q12h + IVA 150 mg q12h	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
		↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Rifampin 600 mg qd	IVA 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd	IVA 150 mg q12h	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)

Table 7: Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor			
Dose and Schedule	**Effect on ELX, TEZ and/or IVA PK**	**Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0**	
		AUC	**C_{max}**
↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics * Effect is not clinically significant *[see Drug Interactions (9.3)]*.			

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below.

Elexacaftor

A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested.

A 2-year study was conducted in rats to assess the carcinogenic potential of elexacaftor. No evidence of tumorigenicity was observed in rats at elexacaftor oral doses up to 10 mg/kg/day (approximately 2 and 5 times the MRHD based on summed AUCs of elexacaftor and its metabolite in male and female rats, respectively).

Elexacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* mammalian cell micronucleus assay in TK6 cells, and *in vivo* mouse micronucleus test.

Elexacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elexacaftor and its metabolite). Elexacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MRHD (based on summed AUCs of elexacaftor and its metabolite). Lower male and female fertility, male copulation and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elexacaftor and its metabolite).

Tezacaftor

A 2-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1-TEZ).

Ivacaftor

Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.

15 CLINICAL STUDIES

Efficacy:

The efficacy of Trikafta in patients with CF aged 12 years and older was evaluated in two double-blind, controlled trials (Trials 1 and 2).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. An interim analysis was planned when at least 140 patients completed Week 4 and at least 100 patients completed Week 12.

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. Patients received tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week open-label run-in period and were then randomized and dosed to receive Trikafta or tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week double-blind treatment period.

Patients in Trials 1 and 2 had a confirmed diagnosis of CF and at least one *F508del* mutation. Patients discontinued any previous CFTR modulator therapies, but continued on their other standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa and hypertonic saline). Patients had a $ppFEV_1$ at

screening between 40-90%. Patients with a history of colonization 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 from the trials. Patients in Trials 1 and 2 were eligible to roll over into a 96-week open-label extension study.

15.1 Trial 1

Trial 1 evaluated 403 patients (200 Trikafta, 203 placebo) with CF aged 12 years and older (mean age 26.2 years). The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%). The primary endpoint assessed at the time of interim analysis was mean absolute change in $ppFEV_1$ from baseline at Week 4. The final analysis tested all key secondary endpoints in the 403 patients who completed the 24-week study participation, including absolute change in $ppFEV_1$ from baseline through Week 24; absolute change in sweat chloride from baseline at Week 4 and through Week 24; number of pulmonary exacerbations through Week 24; absolute change in BMI from baseline at Week 24, and absolute change in CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production and difficulty breathing) from baseline at Week 4 and through Week 24.

Of the 403 patients included in the interim analysis, the treatment difference between Trikafta and placebo for the mean absolute change from baseline in $ppFEV_1$ at Week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; $P<0.0001$).

The treatment difference between Trikafta and placebo for mean absolute change in $ppFEV_1$ from baseline through Week 24 was 14.3 percentage points (95% CI: 12.7, 15.8; $P<0.0001$). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15 and sustained through the 24-week treatment period (see Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex and geographic region. See Table 8 for a summary of primary and key secondary outcomes in Trial 1.

Table 8: Primary and Key Secondary Efficacy Analyses (Trial 1)

Analysis	Statistic	Treatment Difference* for Trikafta (N=200) vs Placebo (N=203)
Primary (Interim Full Analysis Set)**		
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value	13.8 (12.1, 15.4) *P*<0.0001
Key Secondary (Full Analysis Set)#		
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value	14.3 (12.7, 15.8) *P*<0.0001
Number of pulmonary exacerbations from baseline through Week 24‡$	Rate ratio (95% CI) *P* value	0.37 (0.25, 0.55) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value	-41.8 (-44.4, -39.3) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value	20.2 (17.5, 23.0) *P*<0.0001
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value	1.04 (0.85, 1.23) *P*<0.0001
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value	-41.2 (-44.0, -38.5) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value	20.1 (16.9, 23.2) *P*<0.0001

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index.

* Treatment difference provided as the outcome measure for changes in $ppFEV_1$, sweat chloride, CFQ-R and BMI; Rate ratio provided as the outcome measure for the number of pulmonary exacerbations.

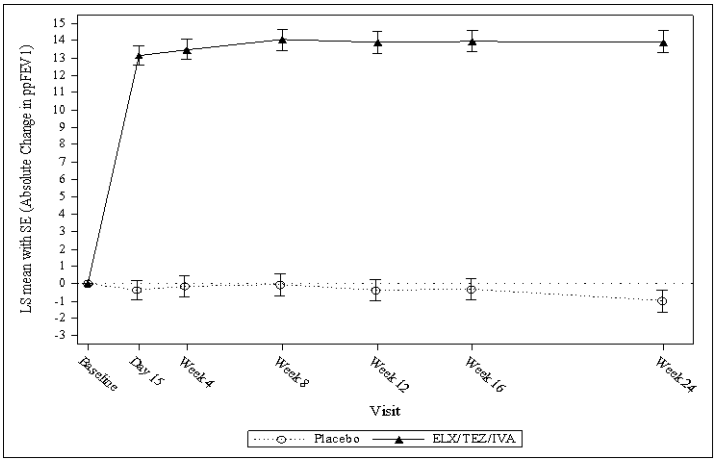
** Primary endpoint was based on interim analysis in 403 patients.

Key secondary endpoints were tested at the final analysis in 403 patients.

‡ 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.

$ Number of pulmonary exacerbation events (event rate per year calculated based on 48 weeks per year) in the Trikafta group were 41 (0.37) and 113 (0.98) in the placebo group.

Figure 1: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Trial 1



15.2 Trial 2

Trial 2 evaluated 107 patients with CF aged 12 years and older (mean age 28.4 years). The mean $ppFEV_1$ at baseline, following the 4-week open-label run-in period with tezacaftor/ivacaftor was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. The key secondary efficacy endpoints were absolute change in sweat chloride and CFQ-R Respiratory Domain Score from baseline at Week 4. Treatment with Trikafta compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; $P<0.0001$). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15. Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ and geographic region. See Table 9 for a summary of primary and key secondary outcomes.

Table 9: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 2)

Analysis*	Statistic	Treatment Difference for Trikafta (N=55) vs Tezacaftor/Ivacaftor# (N=52)
Primary		
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value	10.0 (7.4, 12.6) *P*<0.0001
Key Secondary		
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value	-45.1 (-50.1, -40.1) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value	17.4 (11.8, 23.0) *P*<0.0001

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
* Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor run-in period.
# Regimen of tezacaftor 100 mg qd/ivacaftor 150 mg q12h.

16 HOW SUPPLIED/STORAGE AND HANDLING

Trikafta is supplied as a co-packaged blister pack sealed into a printed wallet, containing elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Four such wallets are placed in a printed outer carton. The elexacaftor, tezacaftor and ivacaftor tablets are supplied as orange, film-coated tablets; each containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor. Each tablet is debossed with "T100" on one face and plain on the other. Ivacaftor tablets are supplied as light blue, film coated, tablets; each containing 150 mg of ivacaftor. Each tablet is printed in black ink with "V 150" in black ink on one face.

The package contains 84 film-coated tablets. The tablets are packaged in 4 blisters. Each blister contains 21 tablets (14 elexacaftor/tezacaftor/ivacaftor and 7 ivacaftor tablets).

Store below 25ºC.

The expiry date of the product is indicated on the packaging materials.

17 MANUFACTURER

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street, London W2 6BD
United Kingdom

18 LICENSE HOLDER

Vertex Pharmaceuticals (U.K.) Limited
7 Rival St., Tel Aviv-Yafo, Israel

19 REGISTRATION NUMBER
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