PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TRIKAFTA®

Elexacaftor 100 mg / Tezacaftor 50 mg / Ivacaftor 75 mg Tablets
and
Ivacaftor 150 mg Tablets, Oral

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

ATC R07AX32

Distributed by:
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Date of Preparation:
June 17, 2021

Submission Control Number: 246955

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRIKAFTA (elexacaftor/tezacaftor/ivacaftor and ivacaftor) tablets are indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [see *10.1 CLINICAL PHARMACOLOGY* and *14 CLINICAL TRIALS*].

1.1 Pediatrics

Pediatrics (<12 years of age): No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 12 years of age.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical trials of TRIKAFTA did not include sufficient number of patients 65 years of age and over to determine whether they respond differently from younger patients.

2 CONTRAINDICATIONS

TRIKAFTA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING*.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

TRIKAFTA should only be administered to patients who have at least one *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of at least one *F508del* mutation [see *10 CLINICAL PHARMACOLOGY* and *14 CLINICAL TRIALS*].

TRIKAFTA dosing may be impacted in the following patient groups:

- Hepatic Impairment: moderate or severe hepatic impairment
- Hepatic Injury
- Elevated Transaminases (ALT/AST) levels
- Rash Events
- Renal Impairment: severe renal impairment or end-stage renal disease
- Interactions with Medicinal Products:
  - Concomitant use of moderate and strong CYP3A inhibitors
  - Concomitant use of strong CYP3A inducers

4.2 Recommended Dose and Dosage Adjustment

Adults, adolescents, and children aged 12 years and older
The recommended dose is two tablets (each containing elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening

approximately 12 hours apart, with fat-containing food.

Health Canada has not authorized an indication for use in pediatric patients less than 12 years of age [see *7.1 Special Populations* and *10.3 Pharmacokinetics*].

Hepatic Impairment
Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose (see Table 1).

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 TRIKAFTA. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see Table 1) [see *7 WARNINGS AND PRECAUTIONS*, *8 ADVERSE REACTIONS* and *10.3 Pharmacokinetics*].

Table 1: **Recommendation for Use in Patients with Hepatic Impairment**

Hepatic Impairment	Morning	Evening
Mild (Child-Pugh Class A)	No dose adjustment (2 elexacaftor/tezacaftor/ivacaftor tablets)	No dose adjustment (1 ivacaftor tablet)
Moderate (Child-Pugh Class B)*	Use not recommended*	
Severe (Child-Pugh Class C)	Should not be used	

* Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose, as follows: 2 elexacaftor/tezacaftor/ivacaftor tablets alternating with 1 elexacaftor/tezacaftor/ivacaftor tablet taken in the morning, on alternate days. The evening dose of the ivacaftor tablet should not be taken.

Concomitant use of CYP3A inhibitors
The dose of TRIKAFTA should be adjusted when co-administered with moderate and strong CYP3A inhibitors [see *7 WARNING AND PRECAUTIONS* and *9.4 Drug-Drug Interactions*].

Concomitant use of Moderate CYP3 inhibitors
When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the dose should be reduced as in Table 2.

Table 2: Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate CYP3A Inhibitors

Days	Morning Dose	Evening Dose^
Day 1	2 elexacaftor/tezacaftor/ivacaftor tablets	No Dose
Day 2	1 ivacaftor tablet	
Day 3	2 elexacaftor/tezacaftor/ivacaftor tablets	
Day 4*	1 ivacaftor tablet	

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

Concomitant use of Strong CYP3 Inhibitors
When co-administered with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin), the dose should be reduced. See Table 3 for dosing adjustments.

Table 3: Dosing Schedule for Concomitant Use of Trikafta with Strong CYP3A Inhibitors		
Days	**Morning Dose**	**Evening Dose^**
Day 1	2 elexacaftor/tezacaftor/ivacaftor tablets	No Dose
Day 2	No dose	
Day 3	No dose	
Day 4#	2 elexacaftor/ tezacaftor/ ivacaftor tablets	
# Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart. ^ The evening dose of ivacaftor should not be taken.		

Concomitant use of strong CYP3A inducers
Co-administration with strong CYP3A inducers [e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)] is not recommended [see *7 WARNING AND PRECAUTIONS* and *9.4 Drug-Drug Interactions*].

Hepatic Injury
TRIKAFTA should be used with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment *[*see *7 WARNINGS AND PRECAUTIONS* and *8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data]*.

Elevated transaminases
Elevated transaminases have been observed in CF patients treated with TRIKAFTA. In some instances, these elevations have been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating TRIKAFTA, every three months during the first year of treatment, and annually thereafter. For patients with a history of liver disease or 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, consider the benefits and risks of resuming treatment [see *7 WARNINGS AND* PRECAUTIONS and *8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data*].

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 TRIKAFTA and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming TRIKAFTA without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered [see *8.2 Clinical Trial Adverse Reactions*].

Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) or end-stage renal disease [see *7 WARNINGS AND PRECAUTIONS* and *10.3 Pharmacokinetics*].

4.4 Administration

For oral use. Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break, or dissolve the tablets).

TRIKAFTA should be taken with fat-containing food such as food recommended in CF guidelines or in standard nutritional guidelines. Examples of meals or snacks that contain adequate amounts of fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats [see *9.4 Drug-Food* Interactions and *10.3 Pharmacokinetics*].

Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA [see *9.4 Drug-Food Interactions*].

4.5 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 with fat-containing food and continue the original schedule.
- If >6 hours have passed since the **missed morning dose**, the patient should take the missed morning dose as soon as possible and should **not** take the evening dose. The next scheduled morning dose should be taken at the usual time.
- If >6 hours have passed since the **missed evening dose**, the patient should **not** take the missed evening 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 OVERDOSAGE

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

The highest repeated dose for elexacaftor was 400 mg once daily administered to 32 healthy subjects for 7 days in an ECG assessment study, following 7 days of elexacaftor dosed 200 mg once daily. The most common adverse event reported during dosing of elexacaftor 400 mg once daily and which was more common than during the dosing of elexacaftor 200 mg once daily was headache.

The highest repeated dose for tezacaftor was 300 mg once daily administered to 47 healthy subjects for 7 days in an ECG assessment study, following 7 days of tezacaftor dosed 100 mg once daily. The most common adverse events reported during dosing of tezacaftor 300 mg once daily and which were more common than during dosing of tezacaftor 100 mg once daily were headache and nausea.

The highest repeated dose for ivacaftor was 450 mg every 12 hours for 4.5 days (9 doses) in an ECG assessment study with 72 healthy subjects. Adverse events reported at a higher incidence

compared to placebo included dizziness and diarrhea.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Tablet elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg (fixed-dose combination) and ivacaftor 150 mg	Elexacaftor/tezacaftor/ivacaftor *Tablet core* Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate *Tablet film coat* Hydroxypropyl cellulose, hypromellose, Iron oxide red, iron oxide yellow, talc, titanium dioxide Ivacaftor *Tablet core* Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate *Tablet film coat* Carnauba wax, indigo carmine aluminum lake, PEG 3350, polyvinyl alcohol, talc, titanium dioxide *Printing ink* Ammonium hydroxide, iron oxide black, propylene glycol, shellac

6.1 Physical Characteristics

Morning dose
Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (7.85 mm x 15.47 mm). Contains 100 mg of elexacaftor, 50 mg of tezacaftor, and 75 mg of ivacaftor as a fixed-dose combination tablet.

Evening dose
Light blue, capsule-shaped tablet printed with “V 150” in black ink on one side and plain on the other (16.5 mm x 8.4 mm). Contains 150 mg of ivacaftor.

Nature and contents of container
Blister consisting of PCTFE (polychlorotrifluoroethylene)/ film laminated to PVC (polyvinyl chloride) and sealed with a blister foil lidding.

Pack Size
84 tablets (4 weekly wallets, each with 21 tablets):
Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg film-coated tablets co-packaged with ivacaftor 150 mg film-coated tablets.

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery
Dizziness has been reported in patients receiving TRIKAFTA, which could influence the ability to drive or operate machines [see *8.2 Clinical Trial Adverse Reactions*]. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. Patients experiencing dizziness should be advised not to drive or operate machines until symptoms abate.

Hepatic/Biliary/Pancreatic
Hepatic Injury
Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving TRIKAFTA. TRIKAFTA should be used with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment [see *4.2 Recommended Dose and Dosage Adjustment*, *8.5 Post-market adverse reactions*, and *10.3 Pharmacokinetics*].

Hepatic Impairment
Treatment of patients with moderate hepatic impairment is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, TRIKAFTA should be used with caution at a reduced dose (see Table 1). Patients with severe hepatic impairment should not be treated with TRIKAFTA [see *4.2 Recommended Dose and Dosage Adjustments*, *8 ADVERSE REACTIONS* and *10.3 Pharmacokinetics*].

Concomitant Use with 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 reduction of TRIKAFTA efficacy; therefore, co-administration with strong CYP3A inducers is not recommended [see *4.2 Recommended Dose and Dosage Adjustment* and *9.4 Drug-Drug Interactions*].

Concomitant Use with CYP3A inhibitors
Exposure to elexacaftor, tezacaftor, and ivacaftor are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose of TRIKAFTA should be reduced when used concomitantly with strong or moderate CYP3A inhibitors [see *Tables 2 and 3 in 4.2 Recommended Dose and Dosage Adjustment*].

Monitoring and Laboratory Tests
Effect on liver function tests
Elevated transaminases have been observed in CF patients treated with TRIKAFTA. In some instances, these elevations have been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating TRIKAFTA, every three months during the first year of treatment, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x 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, consider the benefits and risks of resuming treatment [see *4.2 Recommended Dose and Dosage Adjustment*, *8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and*

Other Quantitative Data and *8.5 Post-market adverse reactions*].

Ophthalmologic
Cataracts
Cases of non-congenital lens opacities without impact on vision 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 *16 NON-CLINICAL TOXICOLOGY*].

Renal
Caution is recommended while using TRIKAFTA in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease [see *4.2 Recommended Dose and Dosage Adjustment* and *10.3 Pharmacokinetics*].

Reproductive Health: Female and Male Potential
Fertility
There are no data available on the effect of elexacaftor, tezacaftor, and ivacaftor on fertility in humans. Tezacaftor had no effect on fertility and reproductive performance indices in male and female rats at doses up to 100 mg/kg/day. Elexacaftor and ivacaftor had an effect on fertility in rats [see *16 NON-CLINICAL TOXICOLOGY*].

7.1 Special Populations

7.1.1 Pregnant Women

No adequate and well-controlled studies of TRIKAFTA in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, TRIKAFTA should be used during pregnancy only if the potential benefits outweigh the potential risks.

7.1.2 Breast-feeding

It is unknown if the components of TRIKAFTA (elexacaftor, tezacaftor, ivacaftor), or their metabolites are excreted in human milk. TRIKAFTA should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant. Precaution should be exercised because many drugs can be excreted in human milk. Elexacaftor, tezacaftor, and ivacaftor are excreted into the milk of lactating female rats. Exposure of ^{14}C-elexacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.4, 3, and 1.5 times, respectively, the value observed in plasma (based on $AUC_{0\text{-}72h}$ for elexacaftor and tezacaftor and $AUC_{0\text{-}24h}$ for ivacaftor).

7.1.3 Pediatrics

No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication of pediatric use in patients 12 years of age.

7.1.4 Geriatrics

Clinical trials of TRIKAFTA did not include sufficient number of patients 65 years of age and over to determine whether they respond differently from younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of TRIKAFTA is based on data from 768 patients in three double-blind, controlled, phase 3 studies of 24 weeks, 4 weeks and 8 weeks treatment duration (Trial 1, Trial 2, and Trial 3), respectively. In the three controlled phase 3 studies, a total of 389 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.

Serious adverse drug reactions that occurred more frequently in TRIKAFTA-treated patients compared to placebo were rash (1.5% vs 0.5%) and influenza (1.5% vs 0).

The most common (≥10%) adverse drug reactions in TRIKAFTA-treated patients were headache, diarrhea and upper respiratory tract infection.

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 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

Table 5 shows adverse drug reactions occurring in ≥5% of TRIKAFTA-treated patients and at a frequency higher than placebo by ≥1% in Trial 1.

Table 5: Incidence of Adverse Drug Reactions in ≥5% of TRIKAFTA-Treated Patients and Higher than Placebo by ≥1%			
System Organ Class (SOC)	**Adverse Drug Reactions (Preferred Term)**	**TRIKAFTA N=202 n (%)**	**Placebo N=201 n (%)**
Infections and Infestations	Upper Respiratory Tract Infection[a]	32 (16)	25 (12)
	Influenza	14 (7)	3 (1)
Nervous System Disorder	Headache	35 (17)	30 (15)
Respiratory Thoracic and Mediastinal Disorders	Nasal congestion	19 (9)	15 (7)
	Rhinorrhoea	17 (8)	6 (3)
	Sinusitis	11 (5)	8 (4)
	Rhinitis	15 (7)	11 (5)
Gastrointestinal Disorders	Diarrhoea	26 (13)	14 (7)
	Abdominal pain[b]	29 (14)	18 (9)
Skin and Subcutaneous Tissue disorders	Rash[c]	21 (10)	10 (5)
Investigations	Alanine aminotransferase increased	20 (10)	7(3)
	Aspartate aminotransferase increased	19 (9)	4 (2)
	Blood creatine phosphokinase increased	19 (9)	9 (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			

The safety profile of TRIKAFTA from the following studies were consistent with the safety profile observed in Trial 1:

- a 4-week, randomized, double-blind, active-controlled study in 107 patients
- an 8-week, randomized, double-blind, active-controlled study in 258 patients

Rash Events

In Trial 1, the incidence of rash events (e.g., rash, rash pruritic) was 10.4% in TRIKAFTA- and 5.0% in placebo-treated patients. The rash events were generally mild to moderate in severity. The incidence of rash events by patient sex was 4.8% in males and 16.3% in females in TRIKAFTA-treated patients and 3.8% in males and 6.3% in females in placebo-treated patients.

In patients treated with TRIKAFTA, the incidence of rash events was 20.5% in females taking hormonal contraceptive and 13.6% in females not taking hormonal contraceptive. A role for hormonal contraceptives in the occurrence of rash cannot be excluded. 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 [see *4 DOSAGE AND ADMINISTRATION*].

8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

The safety profile is generally consistent among adolescent and adult patients. Pediatric patients under the age of 12 years have not been studied.

8.3 Less Common Clinical Trial Adverse Reactions

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:

- *Gastrointestinal disorders:* abdominal distension, flatulence
- *Infections and infestations:* conjunctivitis, pharyngitis, respiratory tract infection, tonsillitis, urinary tract infection
- *Investigations:* c-reactive protein increased
- *Metabolism and nutrition disorders:* hypoglycemia
- *Nervous system disorders:* dizziness
- *Reproductive system and breast disorders:* dysmenorrhea
- *Skin and subcutaneous tissue disorders:* acne, eczema, pruritus

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Transaminase Elevations

In Trial 1, the incidence of adverse reactions of transaminase elevations was 10.9% in TRIKAFTA-treated patients and 4.0% in placebo-treated patients. No TRIKAFTA-treated patients discontinued treatment for elevated transaminases.

Table 6: Threshold Analysis of Liver Function Tests During Overall Treatment-emergent Period: Placebo-controlled Safety Set

Threshold Analysis Criteria	Placebo N = 201 n/N1 (%)	TRIKAFTA N = 202 n/N1 (%)
ALT or AST		
>3 × ULN	11/201 (5.5)	16/202 (7.9)
>5 × ULN	3/201 (1.5)	5/202 (2.5)
>8 × ULN	2/201 (1.0)	3/202 (1.5)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal

Increased Creatine Phosphokinase

In Trial 1, the incidence of maximum creatine phosphokinase >5 x the ULN was 10.4% in TRIKAFTA- and 5.0% in placebo-treated patients. Among the TRIKAFTA-treated patients with creatine phosphokinase elevations >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 or diastolic blood pressure >90 mmHg on at least two occasions was 5.0% and 3.0% in TRIKAFTA-treated patients respectively, compared with 3.5% and 3.5% in placebo-treated patients, respectively.

8.5 Post-market adverse reactions

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 *4.2 Recommended Dose and Dosage Adjustment* and *7 WARNINGS AND PRECAUTIONS*].

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Exposures to elexacaftor, tezacaftor and ivacaftor may be reduced by concomitant use of CYP3A inducers and increased by concomitant use of CYP3A inhibitors.

Clinical studies showed that ivacaftor is not an inhibitor of CYP2C8 or CYP2D6. *In vitro*, ivacaftor was not an inducer of CYP isozymes. Ivacaftor is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3. *In vitro* studies showed that ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-glycoprotein (P-gp).

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.

Based on *in vitro* results, tezacaftor has a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Tezacaftor has a low potential to induce CYP3A, but it is not an inducer of CYP1A2 and CYP2B6. Tezacaftor has a low potential to inhibit transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

Elexacaftor is a potential inhibitor of OATP1B1 and OATP1B3, based on *in vitro* data.

9.4 Drug-Drug Interactions

The drugs listed in Tables 7 and 8 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Effects of Other Drugs on TRIKAFTA

Table 7: Established or Potential Drug-Drug Interactions - Effect of Other Drugs on Elexacaftor/Tezacaftor/Ivacaftor or Ivacaftor

Drug	Source of Evidence	Effect	Clinical comment
Strong CYP3A Inducers			
Rifampin	CT[1] T	↓ AUC of ivacaftor by 89% ↓ AUC of tezacaftor and elexacaftor	Co-administration of strong CYP3A inducers is not recommended. Concomitant use can substantially decrease exposure of ivacaftor and may decrease the exposure of tezacaftor and elexacaftor, which may reduce therapeutic effectiveness.
Strong CYP3A Inhibitors			
Itraconazole	CT[2] CT[2,3]	↑ 15.6-fold in ivacaftor AUC ↑ 2.8-fold in elexacaftor AUC ↑ 4.0 - 4.5-fold in tezacaftor AUC	Reduction in dose of ELX/TEZ/IVA is recommended with co-administration of strong CYP3A inhibitors [see Table 3]
Ketoconazole	CT[1] T	↑ 8.5-fold in ivacaftor AUC ↑ AUC of tezacaftor and elexacaftor	
Moderate CYP3A Inhibitors			
Fluconazole	CT[1] M	↑ 2.9-fold in ivacaftor AUC ↑ AUC of tezacaftor and elexacaftor	Reduction in dose of ELX/TEZ/IVA is recommended with co-administration of moderate CYP3A inhibitors [see Table 2]

↑ = increase, ↓ = decrease
Legend: CT = Clinical Trial; T = Theoretical; M = Modeling; AUC = Area Under the Curve
[1] data derived from a trial conducted with ivacaftor alone
[2] data derived from a trial conducted with ivacaftor + tezacaftor
[3] data derived from a trial conducted with deuterated ivacaftor + tezacaftor + elexacaftor

CYP3A inducers
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, substantially decreased ivacaftor 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 [e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)] is not recommended [see *4.2 Recommended Dose and Dosage Adjustment* and *7 WARNING AND PRECAUTIONS*].

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 TRIKAFTA should be reduced when co-administered with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin) [see Table 3 *4.2 Recommended Dose and Dosage Adjustment* and *7 WARNING* AND *PRECAUTIONS*]. Simulations indicated that co-administration with moderate CYP3A inhibitors 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 TRIKAFTA should be reduced when co-administered with moderate CYP3A inhibitors (e.g., fluconazole and erythromycin) (see *Table 2 in 4.2 Recommended Dose and Dosage Adjustment* and *7 WARNING AND PRECAUTIONS*].

The effects of elexacaftor/tezacaftor/ivacaftor (or ivacaftor alone) on the exposure of co-administered drugs are shown in Table 8.

Effect of TRIKAFTA on Other Drugs

Table 8: Established or Potential Drug-Drug Interactions - Effect of Elexacaftor/Tezacaftor/Ivacaftor or Ivacaftor on Other Drugs

Drug	Source of Evidence	Effect	Clinical comment
CYP3A Substrates			
Midazolam	CT[2]	↔ midazolam	No dose adjustment for midazolam or CYP3A substrates is recommended
CYP2D6 Substrates			
Desipramine	CT[1]	↔ Desipramine	No dose adjustment for desipramine or CYP2D6 substrates is recommended
CYP2C8 Substrates			
Rosiglitazone	CT[1]	↔ Rosiglitazone	No dose adjustment for rosiglitazone or CYP2C8 substrates is recommended
P-glycoprotein Substrates			
Digoxin	CT[2]	↑ 1.3-fold in digoxin AUC	Caution is warranted and therapeutic concentration monitoring of sensitive p-gp substrate is recommended
OATP1B1 Substrates			
Pitavastatin	CT[2]	↑ 1.2-fold in pitavastatin AUC	Caution and appropriate monitoring is recommended
Hormonal Contraceptives			
Oral Contraceptive Ethinyl estradiol/ Levonorgestrel	CT[3]	↑ 1.33-fold in ethinyl estradiol AUC ↑ 1.23-fold in levonorgestrel AUC	No dose adjustment of the hormonal contraceptives is recommended

↑ = increase, ↓ = decrease, ↔ = no change
Legend: CT = Clinical Trial; AUC = Area Under the Curve
[1] data derived from a trial conducted with ivacaftor alone
[2] data derived from a trial conducted with ivacaftor + tezacaftor
[3] data derived from a trial conducted with ivacaftor + tezacaftor + elexacaftor

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.

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 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.

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 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. Bilirubin is an OATP1B1 and OATP1B3 substrate. In Trial 1, 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.

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.

9.5 Drug-Food Interactions

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. Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA [see *4.4 Administration*].

Food increases the rate and extent of absorption of elexacaftor and ivacaftor but not tezacaftor when TRIKAFTA is administered with food [*see 10.3 Pharmacokinetics*].

9.6 Drug-Herb Interactions

Co-administration with St. John's wort (*Hypericum perforatum*) is not recommended. As with other strong CYP3A inducers, concomitant use may decrease the exposure of elexacaftor, tezacaftor and substantially decrease exposure of ivacaftor, which may reduce the therapeutic effectiveness of TRIKAFTA [see *4.2 Recommended Dose and Dosage Adjustment* and *7 WARNING AND PRECAUTIONS*].

10 CLINICAL PHARMACOLOGY

10.1 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. Clinical outcomes indicate that a single *F508del* mutation is sufficient to result in a significant clinical response.

10.2 Pharmacodynamics

Effects on sweat chloride
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 to ivacaftor and tezacaftor/ivacaftor), the treatment difference between TRIKAFTA compared to placebo for mean absolute change in sweat chloride from baseline through Week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3; P<0.0001).

In Trial 2 (patients homozygous for the *F508del* mutation), the treatment difference between TRIKAFTA compared tezacaftor/ivacaftor and 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).

In Trial 3 (patients heterozygous for the *F508del* mutation and a mutation on the second allele with a gating defect or residual CFTR activity), following a 4-week ivacaftor or tezacaftor/ivacaftor run-in period, the mean absolute change in sweat chloride from baseline through week 8 for the TRIKAFTA group was -22.3 mmol/L (95% CI: -24.5, -20.2; P<0.0001). The treatment difference of TRIKAFTA compared to the control group (ivacaftor group or tezacaftor/ivacaftor group) was -23.1 mmol/L (95% CI: -26.1, -20.1; P<0.0001).

Cardiovascular Effects
Cardiac Electrophysiology
Elexacaftor: In a randomized, double-blind, placebo- and positive-controlled, parallel group (nested crossover cohorts for positive control and placebo) ECG assessment study in healthy subjects (N=32/treatment), elexacaftor was administered at the therapeutic dose of 200 mg once daily for 7 days followed by a supratherapeutic dose of 400 mg once daily for an additional 7 days. There was no evidence of any meaningful effect of elexacaftor on the QTcF interval, the QRS duration or the PR interval after 7 days of treatment with the 200 mg or 400 mg once daily doses. No meaningful effect of elexacaftor on heart rate was observed after 7 days of treatment with the 200 mg once daily dose. On the seventh day of treatment with the supratherapeutic 400 mg once daily dose, heart rate was increased, with the difference from placebo in mean change from baseline heart rate ranging from 4 to 7 bpm.

Tezacaftor: In a randomized, double-blind, placebo- and positive-controlled, parallel group (nested crossover cohorts for positive control and placebo) ECG assessment study in healthy subjects (N=48/treatment), tezacaftor was administered at the therapeutic dose of 100 mg once daily from days 1 to 7 and at a supratherapeutic dose of 300 mg once daily from days 8 to 14. On days 7 and 14, there was no evidence of any meaningful effect on the QTcF interval, the QRS duration, the PR interval or heart rate.

Ivacaftor: In a double-blind, randomized, placebo- and positive-controlled, 4-period crossover ECG assessment study in healthy subjects (N=72), the ivacaftor 150 mg twice daily (therapeutic

dose) and 450 mg twice daily (3X multiple of therapeutic dose) treatments administered for 5 days were not associated with any meaningful effect on the QTcF interval, the QRS duration, the PR interval, or heart rate.

10.3 Pharmacokinetics

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 seven days for elexacaftor, within eight days for tezacaftor, and within 3-5 days for ivacaftor. Upon dosing elexacaftor/tezacaftor/ivacaftor 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 are shown in Table 9.

Table 9: Mean (SD) Pharmacokinetic Parameters of Elexacaftor, Tezacaftor and Ivacaftor at Steady State in Persons Aged 12 Years and Older

Dose	Drug	C_{max} (mcg/mL)	Terminal t½ (h)	AUC_{0-24h} or AUC_{0-12h} (mcg·h/mL)*	Apparent Clearance (L/hr)	Apparent Volume of Distribution (L)
Elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Elexacaftor	9.15 (2.09)	24.7 (4.87)	162 (47.5)	1.18 (0.29)	53.7 (17.7)
	Tezacaftor	7.67 (1.68)	60.3 (15.7)	89.3 (23.2)	0.79 (0.10)	82.0 (22.3)
	Ivacaftor	1.24 (0.34)	13.1 (2.98)	11.7 (4.01)	10.2 (3.13)	293 (89.8)

*AUC_{0-24h} for elexacaftor and tezacaftor and AUC_{0-12h} for ivacaftor
SD= standard deviation, AUC = Area Under the Curve; C_{max} = peak maximum concentration

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.

Following administration of elexacaftor 100 mg tablets under moderate fat, moderate calorie fed conditions, AUC_T and C_{max} increased by approximately 149% and 262% when compared to administration under fasting conditions. Based on previous studies conducted for SYMDEKO® and KALYDECO®, AUC_T and C_{max} for ivacaftor increased by approximately 173% to 228% and 200% to 332%, respectively but were equivalent for tezacaftor under high fat, high calorie fed conditions when compared to administration under fasting conditions.

The effect of food containing varying calories and fat was also determined for a fixed dose combination tablet containing 100 mg elexacaftor, 50 mg tezacaftor and 75 mg deuterated ivacaftor. Except for the deuteration of ivacaftor, the formulation of the fixed dose combination tablet containing deuterated ivacaftor was not significantly different than the TRIKAFTA fixed dose combination core tablet, and the food effect on the pharmacokinetics of ivacaftor and deuterated-ivacaftor are within similar ranges. Following administration of two 100 mg elexacaftor/50 mg tezacaftor/75 mg deuterated ivacaftor fixed dose combination tablets under light fat, light calorie fed conditions there was an increase in elexacaftor and deuterated-

ivacaftor AUC_T and C_{max} by approximately 55% and 126%, and 120% and 299%, respectively when compared to administration under fasting conditions. When the same dose of the 100 mg elexacaftor/50 mg tezacaftor/75 mg deuterated-ivacaftor fixed dose combination tablets were administered under moderate fat, moderate calorie fed conditions, there was a greater effect of food on the rate and extent of absorption when compared to administration under fasting conditions such that elexacaftor and deuterated-ivacaftor AUC_T and C_{max} increase by approximately 108% and 293%, and 226% and 519%, respectively. The rate and extent of absorption for tezacaftor were equivalent when administered under fasting and fed conditions (both meal types) [see *4 DOSAGE AND ADMINISTRATION*].

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 TRIKAFTA, 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.

Metabolism: 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.

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 elexacaftor/tezacaftor/ivacaftor 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-lives of elexacaftor, tezacaftor and ivacaftor following administration of the elexacaftor/tezacaftor/ivacaftor fixed-dose combination tablets are approximately 27.4 (9.31) hours, 25.1 (4.93) hours and 15.0 (3.92) hours, respectively.

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

Following oral administration of ^{14}C-tezacaftor alone, the majority of the dose (72%) was excreted in the feces (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 feces after metabolic conversion.

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

Special Populations and Conditions
Pediatrics (<12 years of age): Elexacaftor, tezacaftor and ivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 10. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 12 to less than 18 years are similar to that of adult patients.

Table 10: 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)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	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)

qd = once daily, q12h= every 12 hours, SD = standard deviation, AUC = Area Under the Curve

Pediatrics (<12 years of age): No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 12 years of age [see *7.1 Special Populations*].

Geriatrics (≥65 years of age): Clinical trials of TRIKAFTA did not include sufficient number of patients 65 years of age and over to determine whether they respond differently from younger patients [see *7.1 Special Populations*].

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

Pregnancy and Breast-feeding: The extent of exposure to TRIKAFTA in pregnant women during clinical trials is very limited. No adequate and well-controlled studies of TRIKAFTA in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, TRIKAFTA should be used during pregnancy only if the potential benefits outweigh the potential risks [see *7.1 Special Populations*].

Elexacaftor, tezacaftor and ivacaftor are excreted into the milk of lactating female rats. Because it is not known if elexacaftor, tezacaftor, ivacaftor, or their metabolites are excreted in human milk, TRIKAFTA should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant [see *7.1 Special Populations*].

Hepatic Insufficiency: 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 to 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, 20% higher AUC but similar C_{max} for tezacaftor, and a 1.5-fold higher AUC and a 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics [see *Table 2* in *4.2 Recommended Dose and Dosage Adjustment*, *7 WARNINGS AND PRECAUTIONS* and *8.5 Post-market adverse reactions*].

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 Insufficiency: Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in patients with severe renal impairment (eGFR <30mL/min/1.73 m^2) 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 drug), and 6.6% of total radioactivity, respectively].

Based on population pharmacokinetic (PK) analysis, exposure of elexacaftor was similar in patients with mild renal impairment (N=75, eGFR 60 to <90 mL/min/1.73 m^2) relative to those with normal renal function (N=341, eGFR 90 mL/min/1.73 m^2 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 <90 mL/min/1.73 m^2) and moderate renal impairment (N=8; eGFR 30 to <60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly [see *7 WARNINGS AND PRECAUTIONS*].

11 STORAGE, STABILITY AND DISPOSAL

Store at or below 30ºC. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines:
No special requirements for disposal.

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems” if available.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

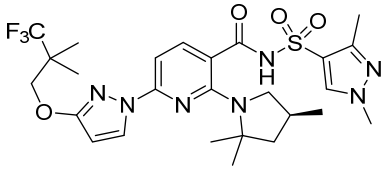
Proper name: elexacaftor/tezacaftor/ivacaftor

Chemical name: elexacaftor: 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
tezacaftor: 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
ivacaftor: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

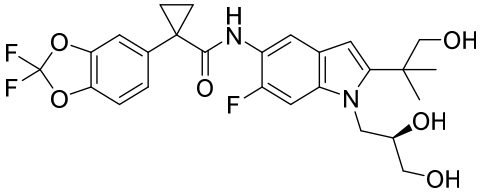
Molecular formula and molecular mass: elexacaftor: $C_{26}H_{34}N_7O_4SF_3$; 597.66
tezacaftor: $C_{26}H_{27}N_2F_3O$; 520.50
ivacaftor: $C_{24}H_{28}N_2O_3$; 392.49

Structural formula:

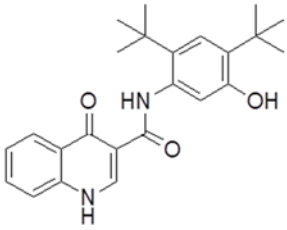
elexacaftor



tezacaftor



ivacaftor



Physicochemical properties: elexacaftor is a white crystalline solid that is practically insoluble in water (<1 mg/mL).
tezacaftor is a white to off white powder that is practically insoluble in water (<5 µg/mL).
ivacaftor is a white to off white powder that is practically insoluble in water (<0.05 µg/mL).

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of TRIKAFTA (elexacaftor/tezacaftor/ivacaftor; ivacaftor) in patients with CF was demonstrated in three Phase 3 trials. Trial 1 was a randomized, double blind, placebo-controlled trial and Trials 2 and 3 were randomized, double blind, active controlled trials. These studies enrolled CF patients with at least one *F508del* mutation. Not all *F508del* heterozygotes have been clinically evaluated with TRIKAFTA.

Table 11: Summary of Patient Demographics for Clinical Trials in CF Patients with CFTR Mutations

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Trial 1 (heterozygous for the *F508del* mutation and a minimal function mutation [F/MF])	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h or placebo; Oral 24 weeks	403	26.2 years (12 to 64)	Male: 52 % Female: 48%
Trial 2 (homozygous for the *F508del* mutation [F/F])	Randomized, active-controlled, parallel-group, multicenter	Run-in with 4 weeks: TEZ 100 mg qd / IVA 150 mg q12h. Randomized to: Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h or Tezacaftor / Ivacaftor group (Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h) Oral 4 weeks	107	28.4 years (12 to 61)	Male: 45% Female: 55%
Trial 3 (heterozygous for the *F508del* mutation and a gating or residual function mutation [F/G or F/RF])	Randomized, active-controlled, parallel-group, multicenter	Run-in for 4 weeks: Tezacaftor / Ivacaftor (Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h) or Ivacaftor (Ivacaftor 150 mg q12h) group based on the genotype. Randomized to: Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h or remained on the CFTR modulator therapy received during the run-in period Oral 8 weeks	258	37.7 years (12 to 73)	Male: 50% Female: 50%

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled trial in patients who had an *F508del* mutation on one allele and an MF mutation on the second allele. CF patients eligible for

this study were required to either have Class I mutations that predicted no CFTR protein being produced (including nonsense mutations, canonical splice mutations, and insertion/deletion frameshift mutations both small (≤3 nucleotide) and non-small (>3 nucleotide)), or missense mutations which results in CFTR protein that does not transport chloride and is not responsive to 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*. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomized and dosed to receive TRIKAFTA or placebo. Patients had a $ppFEV_1$ at screening between 40 to 90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).

Trial 2 was a 4-week, randomized, 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 randomized and dosed to receive TRIKAFTA or tezacaftor/ivacaftor during a 4-week double-blind treatment period. Patients had a $ppFEV_1$ at screening between 40 to 90%. The mean $ppFEV_1$ at baseline, following the tezacaftor/ivacaftor run-in period was 60.9% (range: 35.0%, 89.0%).

Trial 3 was an 8-week, randomized, double-blind, active-controlled study in patients who were heterozygous for the *F508del* mutation and a mutation on the second allele with a gating defect (Gating) or residual CFTR activity (RF). The most frequent alleles with gating defect assessed in the study were *G551D, R117H* and the most frequent alleles with residual CFTR activity were *3849+10kbC>T, 2789+5G>A, A455E, 3272-26A>G, D1152H, P67L, L206W.* Patients aged 12 years and older and with a $ppFEV_1$ between 40 to 90% at screening received either ivacaftor (F/Gating) or tezacaftor/ivacaftor (F/RF) during a 4-week open label run-in period. Patients with the F/R117H genotype received ivacaftor during the run-in period. A total of 258 patients were then randomized and dosed to receive TRIKAFTA or remained on the CFTR modulator therapy received during the run-in period. The mean age at baseline, following the run-in period, was 37.7 years, and the mean $ppFEV_1$ at baseline was 67.6% (range: 29.7%, 113.5%).

Patients in Trials 1, 2, and 3 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies, except for study drugs. Patients had a confirmed diagnosis of CF and at least one *F508del* mutation.

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 Trials 1, 2 and 3 were eligible to roll over into an open-label extension study.

14.2 Study Results

Trial 1

In Trial 1 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24. Treatment with TRIKAFTA 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 12). 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 ppFEV1, sex and geographic region. A total of 18 patients receiving TRIKAFTA had $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population. See Table 12 for a summary of primary and key secondary outcomes.

Table 12: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 1)

Analysis	Statistic	Placebo N=203	TRIKAFTA N=200
Primary			
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
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 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 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)
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)
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)

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; 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.

Trial 2

In Trial 2 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with Trikafta compared to the regimen of 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 13). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ and geographic region. See Table 13 for a summary of primary and key secondary outcomes.

Table 13: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 2)			
Analysis*	**Statistic**	**Tezacaftor/ Ivacaftor# N=52**	**TRIKAFTA N=55**
Primary			
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			
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)
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; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. # Regimen of tezacaftor/ivacaftor and ivacaftor. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor run-in period.			

Trial 3

Following a 4-week tezacaftor/ivacaftor or ivacaftor run-in period, the primary endpoint for Trial 3 of within group mean absolute change in $ppFEV_1$ from baseline through week 8 resulted in statistically significant improvement in $ppFEV_1$ from baseline of 3.7 percentage points (95% CI: 2.8, 4.6; P<0.0001) for the TRIKAFTA-treated group (See Table 14). Overall improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ geographic region and genotype groups (F/Gating or F/RF).

See Table 14 for a summary of primary and secondary outcomes in the overall trial population. In a subgroup analysis of patients with an F/Gating genotype, the treatment difference of TRIKAFTA (N=50) compared with ivacaftor (N=45) for mean absolute change in $ppFEV_1$ was 5.8 percentage points (95% CI: 3.5, 8.0). In a subgroup analysis of patients with an F/RF genotype, the treatment difference of TRIKAFTA (N=82) compared with tezacaftor/ivafator (N=81) for mean absolute change in $ppFEV_1$ was 2.0 percentage points (95% CI: 0.5, 3.4). The results of the F/Gating and the F/RF genotype subgroups for improvement in sweat chloride and CFQ-R respiratory domain score were consistent with the overall results.

Table 14: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 3)			
Analysis*	**Statistic**	**Control Group# N=126**	**TRIKAFTA N=132**
Primary			
Absolute change in ppFEV$_1$ from baseline through week 8 (percentage points)	Within-group change (95% CI) *P* value	0.2 (-0.7, 1.1) NA	3.7 (2.8, 4.6) *P*<0.0001
Key and other secondary			
Absolute change in sweat chloride from baseline through week 8 (mmol/L)	Within-group change (95% CI) *P* value	0.7 (-1.4, 2.8) NA	-22.3 (-24.5, -20.2) *P*<0.0001
Absolute change in ppFEV$_1$ from baseline through week 8 compared to the control group (percentage points)	Treatment difference (95% CI) *P* value	NA NA	3.5 (2.2, 4.7) *P*<0.0001
Absolute change in sweat chloride from baseline through week 8 compared to the control group (mmol/L)	Treatment difference (95% CI) P value	NA NA	-23.1 (-26.1, -20.1) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through week 8 (points)	Within-group change (95% CI)	1.6 (-0.8, 4.1)	10.3 (8.0, 12.7)
Absolute change in CFQ-R respiratory domain score from baseline through week 8 (points) compared to the control group	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)
ppFEV$_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SD: Standard Deviation; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and secondary endpoints is defined as the end of the 4-week run-in period of ivacaftor or tezacaftor/ivacaftor. # ivacaftor group or tezacaftor/ivacaftor group.			

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

Fertility and Pregnancy
Elexacaftor was associated with lower male and female fertility, male copulation, and female conception indices in males at 75 mg/kg/day [6 times the maximum recommended human dose (MRHD) based on summed AUCs of elexacaftor and its metabolite] and in females at 35 mg/kg/day (7 times the MRHD based on summed AUCs of elexacaftor and its metabolite).

The No Observed Adverse Effect Level (NOAEL) for fertility findings was 55 mg/kg/day (2 times the 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 fetal body weight at ≥25 mg/kg/day. Placental transfer of elexacaftor was observed in pregnant rats.

Carcinogenicity
Elexacaftor was shown to be non-carcinogenic in a 6-month study in Tg.rasH2 mice.

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

Fertility and Pregnancy
Ivacaftor was associated with a reduction in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the estrous cycle in females at 200 mg/kg/day dose (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites). Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day dose (approximately 7 times the MRHD based on summed AUCs of ivacaftor and its metabolites).

In pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day, ivacaftor resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights. 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 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 fetuses derived from rat dams treated with ivacaftor on gestation Days 7 to 17, in rat pups exposed to ivacaftor to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 3.5- to 5-month-old dogs treated with ivacaftor. The potential relevance of these findings in humans is unknown.

Elexacaftor/tezacaftor/ivacaftor
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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTRIKAFTA®
Elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg tablets
and
Ivacaftor 150 mg tablets

Read this carefully before you start taking **TRIKAFTA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TRIKAFTA**.

What is TRIKAFTA used for?

TRIKAFTA is used for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who have at least one *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene.

It is not known if TRIKAFTA is safe and effective in children under 12 years of age.

How does TRIKAFTA work?

- The CFTR gene provides instructions to your cells to make the CFTR protein. This protein helps take chloride ions in and out of the cells in many organs of your body.
- People with CF have a lower amount of the CFTR protein and/or reduced function of the CFTR protein.
- TRIKAFTA contains 3 ingredients:
  - Elexacaftor and tezacaftor: These are CFTR Correctors. They increase the amount of CFTR protein on the surface of the cell.
  - Ivacaftor: This is a CFTR Potentiator. It makes CFTR protein at the cell surface work better by allowing chloride ions to pass through.

What are the ingredients in TRIKAFTA?

Medicinal ingredients: elexacaftor / tezacaftor/ ivacaftor

Non-medicinal ingredients:

Elexacaftor/Tezacaftor/Ivacaftor tablet:

Tablet core:	Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate
Tablet film coat:	Hydroxypropyl cellulose, hypromellose, Iron oxide red, iron oxide yellow, talc, titanium dioxide

Ivacaftor tablet:

Tablet core:	Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate
Tablet film coat:	Carnauba wax, indigo carmine aluminum lake, PEG 3350, polyvinyl alcohol, talc, titanium dioxide
Printing ink:	Ammonium hydroxide, iron oxide black, propylene glycol, shellac

TRIKAFTA comes in the following dosage forms:
Orange tablet (marked with “T100”): elexacaftor 100 mg / tezacaftor 50 mg / ivacaftor 75 mg
Light blue tablet (marked with “V 150”): ivacaftor 150 mg

Do not use TRIKAFTA if:
- You are allergic to:
  - elexacaftor
  - tezacaftor
  - ivacaftor
  - any of the non-medicinal ingredients (listed in **What are the ingredients in TRIKAFTA?**)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRIKAFTA. Talk about any health conditions or problems you may have, including if you:
- Have problems with your liver or liver disease (such as cirrhosis).
- Have kidney disease.
- Are a woman and taking hormonal contraceptives.
- Are pregnant or plan to become pregnant. It is not known if TRIKAFTA will harm your unborn baby. You and your doctor should decide if you will take TRIKAFTA while you are pregnant.
- Are breastfeeding or planning to breastfeed. It is not known if TRIKAFTA can pass into your breast milk. You and your doctor should decide if you should take TRIKAFTA while you are breastfeeding.

Other warnings you should know about:
Cataracts: Cloudiness of the eye lens (cataract) with no changes to vision has been seen in some children and adolescents taking TRIKAFTA. Your doctor may perform eye exams before you start treatment and while you are taking TRIKAFTA to look for cataracts.

Abnormal liver test results: Abnormal liver blood tests results have been seen in some people taking TRIKAFTA.
Your doctor will order some blood tests to check your liver:
- before you start treatment with TRIKAFTA,
- every 3 months during the first year of treatment and
- every year while you are taking TRIKAFTA.

If you have had abnormal liver blood test results in the past or you have a history of problems with your liver or liver disease, your doctor may order blood tests to check your liver more often.

If you have any of these symptoms, tell your doctor **right away**. It may be a sign of liver problems:
- pain or discomfort in the upper right part of your stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark urine
- pale stools
- itchy skin

Worsening of liver function: worsening of liver function in patients with severe liver disease can be serious and may require a liver transplant.

Driving and using machines: You may get dizzy when you take TRIKAFTA. Wait to see how you feel after taking TRIKAFTA before you drive or use machines. **For children**: you or your child's caregiver should supervise your child when they take TRIKAFTA. Wait to see if your child is dizzy after taking TRIKAFTA before they ride their bikes or do anything else that needs their full attention.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
The following may interact with TRIKAFTA:

- Medicines used to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole and fluconazole).
- Medicines used to treat bacterial infections (such as clarithromycin, erythromycin, rifampin and rifabutin).
- Medicines used to treat seizures (such as phenobarbital, carbamazepine and phenytoin).
- Warfarin (a medicine used to prevent blood clots from forming or growing bigger).
- Medicines used to treat diabetes (such as repaglinide, glimepiride and glipizide).
- Digoxin (a medicine used to treat congestive heart failure or a heart rhythm problem called atrial fibrillation).
- Medicines used after an organ transplant (such as cyclosporine, everolimus, sirolimus and tacrolimus).
- St. John's wort (*Hypericum perforatum*).
- Grapefruit, grapefruit juice or products that contain grapefruit. You should avoid food and beverages containing grapefruit while you are taking TRIKAFTA.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How to take TRIKAFTA:

- TRIKAFTA should **always be taken** with fat-containing food. Examples of meals that contain fat are:
  - meals that have been prepared with butter or oils.
  - meals that have eggs, nuts, whole-milk dairy products (such as whole-milk, cheese, yogurt) or meats.
- Swallow the tablets **whole. Do NOT** chew, break or dissolve the tablets.

Follow the instructions below and on the blister card. To remove the tablets <u>push</u> it through the blister strip.
Morning Dose: Take **2** orange tablets marked with "T100".
Evening Dose: Take **1** light-blue tablet marked with "V 150" <u>12 hours</u> after your morning dose.

Take TRIKAFTA exactly how your doctor tells you, even if you feel well. Contact your doctor if you are not sure about how to take TRIKAFTA.

Refilling your prescription:
Remember to get a new prescription from your doctor or a refill from your pharmacy 7-10 days before taking your last dose of TRIKAFTA.

Overdose:

If you think you, or a person you are caring for, have taken too much TRIKAFTA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you have taken too much TRIKAFTA, the symptoms of an overdose include:

- nausea
- headache
- feeling dizzy
- diarrhea

Missed Dose:

If you:

Missed taking a **morning dose** (orange tablets) or an **evening dose** (light blue tablet) and it has been less than **6 hours:**	• **Take the missed dose** with fat-containing food as soon as you can. • Then take your next morning dose (orange tablets) or evening dose (light-blue tablet) at your usual time with fat-containing food.
Missed taking a **morning dose** (orange tablets) and it has been **more than 6 hours:**	• **Take the missed morning dose** (orange tablets) with fat-containing food as soon as you can. • **Do NOT take the evening dose (light-blue tablet) that day**. • Then take your next **morning dose** (orange tablets) at your usual time with fat-containing food.
Missed taking an **evening dose** (light-blue tablet) and it has been **more than 6 hours:**	• **Do NOT take the missed evening dose (light-blue tablet).** • Then take your next **morning dose** (orange tablets) at your usual time with fat-containing food.

Do NOT take a morning and evening doses together at the same time to make up for a dose that you missed.

What are possible side effects from using TRIKAFTA?

These are not all the possible side effects you may have when taking TRIKAFTA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- upper respiratory tract infection (common cold)
- flu (influenza)
- headache
- blocked nose (nasal congestion)
- runny nose
- swelling of the sinuses
- diarrhea
- stomach (abdominal) pain
- rash, affecting more women than men and women taking hormonal contraceptives
- changes in blood tests results: increased phosphokinase (sign of muscle breakdown), increased liver enzymes

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Liver disorder:** yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite Worsening of liver function in patients with severe liver disease can be serious and may require a liver transplant.			√
UNKNOWN **Allergic reaction:** difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use this medicine after the expiry date ("EXP") that is stated on the package. The expiry date refers to the last day of that month.

Store at or below 30°C.

Keep out of reach and sight of children.

If you want more information about TRIKAFTA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.vrtx.ca, or by calling 1-877-634-8789.

This leaflet was prepared by Vertex Pharmaceuticals (Canada) Incorporated.

Last Revised June-17-2021