Product Monograph

Including Patient Medication Information

PrTRIKAFTA®

Elexacaftor / Tezacaftor / Ivacaftor

Elexacaftor 100 mg / Tezacaftor 50 mg / Ivacaftor 75 mg Tablets and Ivacaftor 150 mg Tablets
Elexacaftor 50 mg / Tezacaftor 25 mg / Ivacaftor 37.5 mg Tablets and Ivacaftor 75 mg Tablets
For Oral Use

Elexacaftor 100 mg / Tezacaftor 50 mg / Ivacaftor 75 mg Granules and Ivacaftor 75 mg Granules
Elexacaftor 80 mg / Tezacaftor 40 mg / Ivacaftor 60 mg Granules and Ivacaftor 59.5 mg Granules
For Oral Use

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

ATC R07AX32

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Date of Authorization:
2025-05-13

Control Number: 293416

Recent Major Label Changes

1. Indications	2024-07
1. Indications, 1.1. Pediatrics	2023-10
3. Serious Warnings and Precautions Box	2025-05
4. Dosage and Administration, 4.2. Recommended Dose and Dosage Adjustment	2025-05
4. Dosage and Administration, 4.4. Administration	2023-10
7. Warnings and Precautions	2025-05

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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PART 1: Healthcare Professional Information

1. Indications

TRIKAFTA (elexacaftor/tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data [see *10.1 Mechanism of Action* and *14 Clinical Trials*].

1.1. Pediatrics

Pediatrics (< 2 years of age): No data in patients less than 2 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 2 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*].

3. Serious Warnings and Precautions Box

TRIKAFTA has been associated with serious and potentially fatal drug-induced liver injury.

Cases of liver failure leading to transplantation and death have been reported in patients with and without a history of liver disease taking TRIKAFTA, in both clinical trials and the post-marketing setting (see 8 Adverse Reactions). Liver injury has primarily been reported within the first 6 months following initiation of TRIKAFTA.

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating TRIKAFTA. Assess liver function tests every month during the first 6 months of treatment, every 3 months for the next 6 months, then at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or liver function test elevations at baseline (see 4 Dosage and Administration, 7 Warnings and Precautions, 8 Adverse Reactions).

Interrupt TRIKAFTA for significant elevations in liver function tests or in the event of signs or symptoms of liver injury. Consider referral to a hepatologist. Follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If abnormalities resolve, resume treatment only if the benefit is expected to outweigh the risk. Closer monitoring is advised after resuming TRIKAFTA (see 7 Warnings and Precautions).

TRIKAFTA should not be used in patients with severe hepatic impairment (Child-Pugh Class C). TRIKAFTA is not recommended in patients with moderate hepatic impairment (Child-Pugh

Class B). If used, use with caution at a reduced dosage and monitor patients closely (see 4 Dosage and Administration).

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, or another mutation that is responsive based on clinical and/or *in vitro* data [see *10 Clinical Pharmacology* and *14 Clinical Trials*]. Treatment with TRIKAFTA should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of CF. TRIKAFTA is only indicated for adults and children aged 2 years and older with CF who have an indicated mutation and a diagnosis of CF.

If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of at least one *F508del* mutation or a mutation that is responsive based on clinical and/or *in vitro* data.

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 and pediatric patients aged 2 years and older should be dosed according to Table 1.

Table 1: Dosage by Age and Weight in Patients aged 2 Years and Older

Age	Body Weight (kg)	Morning Dose	Evening Dose
2 to < 6 years	< 14 kg	One packet of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules	One packet of ivacaftor 59.5 mg granules
	≥ 14 kg	One packet of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules	One packet of ivacaftor 75 mg granules
6 to < 12 years	< 30 kg	Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
	≥ 30 kg	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
≥ 12 years	-	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

The morning and evening dose should be taken with fat-containing food, approximately 12 hours apart.

Health Canada has not authorized an indication for use in pediatric patients less than 2 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 2).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with TRIKAFTA. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see Table 2) [see *7 Warnings and Precautions*, *8 Adverse Reactions*, and *10.3 Pharmacokinetics*].

Table 2: Recommendation for Use in Patients with Hepatic Impairment

Age	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
2 to < 6 years	No dose adjustment	**Use 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, as follows: • Days 1-3: one packet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 4: no dose • Days 5-6: one packet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 7: no dose Repeat above dosing schedule each week. The evening dose of the ivacaftor granules should not be taken.	Should not be used
6 years and older	No dose adjustment	**Use 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, as follows: • Day 1: two elexacaftor/tezacaftor/ivacaftor tablets in the morning • Day 2: one elexacaftor/tezacaftor/ivacaftor tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. The evening dose of the ivacaftor tablet should not be taken.	Should not be used

Concomitant use of CYP3A inhibitors

The dose of TRIKAFTA should be adjusted when co-administered with moderate and strong

CYP3A inhibitors [see *7 Warnings and Precautions* and *9.4 Drug-Drug Interactions*].

Concomitant use of Moderate CYP3A inhibitors
When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the dose should be reduced as in Table 3.

Table 3: Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate CYP3A Inhibitors

Age	Dosing
2 to < 6 years	Alternate each day: • One packet of elexacaftor/tezacaftor/ivacaftor granules on the first day • One packet of ivacaftor granules on the next day No evening packet of ivacaftor granules.
6 years and older	Alternate each day: • Two elexacaftor/tezacaftor/ivacaftor tablets on the first day • One ivacaftor tablet on the next day No evening ivacaftor tablet dose.

Concomitant use of Strong CYP3A Inhibitors

When co-administered with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin), the dose should be reduced. See Table 4 for dosing adjustments.

Table 4: Dosing Schedule for Concomitant Use of TRIKAFTA with Strong CYP3A Inhibitors

Age	Dosing
2 to < 6 years	One packet of elexacaftor/tezacaftor/ivacaftor granules twice a week, approximately 3 to 4 days apart. No evening packet of ivacaftor granules.
6 years and older	Two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.

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 Warnings 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 month during the first 6 months of treatment, every 3 months during the next 6 months, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt TRIKAFTA and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms suggestive of liver injury (e.g., jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain, or anorexia). Interrupt dosing in the event of ALT or AST > 5 x the upper limit of normal (ULN), or ALT or AST > 3 x ULN with total bilirubin > 2 x ULN. Follow laboratory tests closely until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely [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

TRIKAFTA tablets and granules 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, peanut butter, cheeses, nuts, whole milk, or meats [see *9.5 Drug-Food Interactions* and *10.3 Pharmacokinetics*].

Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA [see *9.5 Drug-Food Interactions*].

Granules

- For oral use.
- The entire contents of each packet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed.
- Food or liquid should be at room temperature or below.
- Each packet is for single use only. Once mixed, the product has been shown to be stable for 1 hour, and therefore should be ingested during this period.
- Some examples of soft food or liquids include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice (except for grapefruit juice).
- A fat-containing meal or snack should be consumed just before or after dosing.

Tablets

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

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. Overdose

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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition and Packaging

Table 5: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Granules • elexacaftor 80 mg/ tezacaftor 40 mg/	Elexacaftor/tezacaftor/ivacaftor Colloidal silicon dioxide, croscarmellose sodium, hypromellose, hypromellose

	ivacaftor 60 mg (fixed-dose combination) and ivacaftor 59.5 mg • elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg (fixed-dose combination) and ivacaftor 75 mg	acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose <u>Ivacaftor</u> Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose
Oral	Film-coated Tablets • elexacaftor 50 mg/ tezacaftor 25 mg/ ivacaftor 37.5 mg (fixed-dose combination) and ivacaftor 75 mg • elexacaftor 100 mg/ tezacaftor 50 mg/ ivacaftor 75 mg (fixed-dose combination) and ivacaftor 150 mg	<u>Elexacaftor/tezacaftor/ivacaftor</u> *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 <u>Ivacaftor</u> *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

Description

<u>Granules</u>

80 mg/40 mg/60 mg granules and 59.5 mg granules

Morning dose
White to off-white, unflavored, sweetened granules in a sealed packet containing 80 mg of elexacaftor, 40 mg of tezacaftor and 60 mg of ivacaftor.

Evening dose
White to off-white, unflavored, sweetened granules in a sealed packet containing 59.5 mg of ivacaftor.

100 mg/50 mg/75 mg granules and 75 mg granules

Morning dose
White to off-white, unflavored, sweetened granules in a sealed packet containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor.

Evening dose
White to off-white, unflavored, sweetened granules in a sealed packet containing 75 mg of ivacaftor.

Tablets

50 mg/25 mg/37.5 mg tablets and 75 mg tablets

Morning dose
Light orange, capsule-shaped tablet debossed with “T50” on one side and plain on the other (6.4 mm x 12.2 mm). Contains 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor as a fixed-dose combination tablet.

Evening dose
Light blue, capsule-shaped tablet printed with “V 75” in black ink on one side and plain on the other (12.7 mm x 6.8 mm). Contains 75 mg of ivacaftor.

100 mg/50 mg/75 mg tablets and 150 mg tablets

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

Granules
Biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE) printed foil laminate packet.

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

Pack Size

TRIKAFTA Granules: 56 unit-dose packets (4 weekly wallets, each with 14 packets)
- Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules in packets co-packaged with ivacaftor 75 mg granules in packets.
- Elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules in packets co-packaged with ivacaftor 59.5 mg granules in packets.

TRIKAFTA Tablets: 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.
- Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg film-coated tablets co-packaged with ivacaftor 75 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 *8.3 Less Common 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

Cases of liver failure leading to transplantation have been reported within the first 6 months of treatment in patients with and without pre-existing advanced liver disease. 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*, *7 Monitoring and Laboratory Tests*, *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 2). Patients with severe hepatic impairment should not be treated with TRIKAFTA [see *4.2 Recommended Dose and Dosage Adjustment*, *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 3* and *4* 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 month during the first 6 months of treatment, every 3 months during the next 6 months, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt TRIKAFTA and promptly measure serum transaminases and total bilirubin if a patient

develops clinical signs or symptoms suggestive of liver injury (e.g., jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain, or anorexia). Interrupt dosing in the event of ALT or AST > 5 x ULN, or ALT or AST > 3 x ULN with total bilirubin > 2 x ULN. Follow laboratory tests closely until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely [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. Pregnancy

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. Breastfeeding

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 benefits outweigh 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

Pediatrics (< 2 years of age): No data in patients less than 2 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication of pediatric use in patients less than 2 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 (Study 445-102, Study 445-103, and Study 445-104), 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 Study 445-102, 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

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in 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 6 shows adverse drug reactions occurring in ≥ 5% of TRIKAFTA-treated patients and at a frequency higher than placebo by ≥ 1% in Study 445-102.

Table 6: 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 *	32 (16)	25 (12)
	Influenza	14 (7)	3 (1)
Nervous System Disorders	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 †	29 (14)	18 (9)
Skin and Subcutaneous Tissue disorders	Rash ‡	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)

* Includes upper respiratory tract infection and viral upper respiratory tract infection
† Includes abdominal pain, abdominal pain upper, abdominal pain lower
‡ 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 Study 445-102:

- a 4-week, randomized, double-blind, active-controlled study in 107 patients aged 12 years and older (Study 445-103)
- an 8-week, randomized, double-blind, active-controlled study in 258 patients aged 12 years and older (Study 445-104)
- a 24-week, open-label study in 66 patients aged 6 to less than 12 years (Study 445-106)
- a 24-week, open-label study in 75 patients aged 2 to less than 6 years (Study 445-111)
- a 24-week, randomized, double-blind, placebo-controlled study in 307 patients aged 6 years and older (Study 445-124)

Rash Events

In Study 445-102, 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 contraceptives and 13.6% in females not taking hormonal contraceptives. 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 pediatrics and adult patients. Pediatric patients under the age of 2 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 Study 445-102, 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 7: 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

During Study 445-106, in patients aged 6 to less than 12 years, no TRIKAFTA-treated patients had transaminase elevations > 3 x ULN associated with elevated total bilirubin > 2 x ULN, and no patients discontinued treatment due to transaminase elevations.

Table 8: Threshold Analysis of Liver Function Tests During Overall Treatment-emergent Period: Study 445-106 Safety Set	
Threshold Analysis Criteria	**TRIKAFTA N = 66 n/N1 (%)**
ALT or AST	
> 3 × ULN	7/66 (10.6)
> 5 × ULN	1/66 (1.5)
> 8 × ULN	0
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal	

During Study 445-111, in patients aged 2 to less than 6 years, no TRIKAFTA-treated patients had transaminase elevations > 3 x ULN associated with elevated total bilirubin > 2 x ULN or discontinued treatment due to transaminase elevations.

Table 9: Threshold Analysis of Liver Function Tests During Overall Treatment-emergent Period: Study 445-111 Safety Set	
Threshold Analysis Criteria	**TRIKAFTA N = 75 n/N1 (%)**
ALT or AST	
> 3 × ULN	6/75 (8.0)
> 5 × ULN	2/75 (2.7)
> 8 × ULN	1/75 (1.3)
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal	

Increased Creatine Phosphokinase

In Study 445-102, 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 Study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for 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 patients with and without pre-existing advanced liver disease (e.g., cirrhosis, 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 10 and 11 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 10: 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 [*] 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 [†] CT [†,‡]	↑ 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 4]
Ketoconazole	CT [*] T	↑ 8.5-fold in ivacaftor AUC ↑ AUC of tezacaftor and elexacaftor	
Moderate CYP3A Inhibitors			
Fluconazole	CT [*] 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 3]

↑ = increase, ↓ = decrease
Legend: CT = Clinical Trial; T = Theoretical; M = Modeling; AUC = Area Under the Curve
[*] data derived from a trial conducted with ivacaftor alone
[†] data derived from a trial conducted with ivacaftor + tezacaftor
[‡] 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 Warnings 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 4* in *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings* 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 3* in *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

The effects of elexacaftor/tezacaftor/ivacaftor (or ivacaftor alone) on the exposure of co-administered drugs are shown in Table 11.

Effect of TRIKAFTA on Other Drugs

Table 11: 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 †	↔ Midazolam	No dose adjustment for midazolam or CYP3A substrates is recommended
CYP2D6 Substrates			
Desipramine	CT *	↔ Desipramine	No dose adjustment for desipramine or CYP2D6 substrates is recommended
CYP2C8 Substrates			
Rosiglitazone	CT *	↔ Rosiglitazone	No dose adjustment for rosiglitazone or CYP2C8 substrates is recommended
P-glycoprotein Substrates			
Digoxin	CT †	↑ 1.3-fold in digoxin AUC	Caution is warranted and therapeutic concentration monitoring of sensitive p-gp substrate is recommended
OATP1B1 Substrates			
Pitavastatin	CT †	↑ 1.2-fold in pitavastatin AUC	Caution and appropriate monitoring is recommended
Hormonal Contraceptives			
Oral Contraceptive Ethinyl estradiol/ Levonorgestrel	CT ‡	↑ 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
* data derived from a trial conducted with ivacaftor alone
† data derived from a trial conducted with ivacaftor + tezacaftor
‡ 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 Study 445-102, mild increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX.

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 Warnings 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.

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 select *CFTR* mutations.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical 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. Not all mutations can be tested in the FRT system, but patients harboring some mutations not amenable to testing in this system may demonstrate clinical benefit.

Clinical outcomes were consistent with *in vitro* results and indicate that a single elexacaftor/tezacaftor/ivacaftor-responsive mutation is sufficient to result in a significant clinical response.

Table 12 lists responsive *CFTR* mutations based on clinical response and/or *in vitro* data in FRT cells indicating that elexacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline. The occurrence of *CFTR* mutations listed in Table 12 in a patient should not be used in lieu of a diagnosis of cystic fibrosis, nor as a sole determinant for prescribing purposes.

Table 12: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA

3141del9	*E588V*	*H139R*	*P574H*	*S341P*
546insCTA	*E822K*†	*H199Y*	*Q98R*	*S364P*
711+3A→G	*F191V*	*H1054D*	*Q237E*†	*S492F*
2789+5G→A	*F311del*†	*H1085P*	*Q237H*†	*S549N*†
3272-26A→G	*F311L*†	*H1085R*	*Q359R*†	*S549R*†
3849+10kbC→T	*F508C; S1251N**†	*H1375P*†	*Q1291R*†	*S737F*†
A46D	*F508del*	*I336K*	*R74Q*	*S912L*
A120T†	*F575Y*	*I502T*	*R74W*†	*S945L*†
A234D†	*F1016S*	*I601F*	*R74W;D1270N**	*S977F*†
A349V†	*F1052V*†	*I618T*	*R74W;V201M**	*S1159F*†
A455E	*F1074L*†	*I980K*	*R74W;V201M; D1270N**	*S1159P*†
A554E	*F1099L*	*I1269N*	*R117C*†	*S1251N*†
A1006E	*G27R*	*I1366N*	*R117G*†	*S1255P*†
A1067T†	*G85E*	*L15P*	*R117H*†	*T338I*†
D110E†	*G126D*	*L165S*	*R117L*†	*T1036N*
D110H†	*G178R*†	*L206W*	*R117P*†	*V201M*
D192G†	*G194R*†	*L346P*	*R258G*	*V232D*†
D443Y	*G194V*	*L453S*	*R334L*	*V456A*

D443Y;G576A; R668C[*]	*G314E*[†]	*L967S*[†]	*R334Q*	*V456F*
D579G[†]	*G463V*	*L1077P*	*R347H*[†]	*V1153E*
D614G	*G480C*	*L1324P*	*R347L*[†]	*V1240G*
D924N[†]	*G551D*[†]	*L1335P*	*R347P*	*W361R*
D979V	*G551S*[†]	*L1480P*[†]	*R352Q*[†]	*W1098C*
D1152H[†]	*G622D*	*M265R*	*R352W*	*W1282R*[†]
D1270N[†]	*G628R*	*M952I*[†]	*R933G*[†]	*Y109N*
E56K	*G970D*[†]	*M952T*[†]	*R1066H*	*Y161D*
E60K	*G1061R*	*M1101K*	*R1070Q*[†]	*Y161S*
E92K	*G1069R*[†]	*N1303K*	*R1070W*[†]	*Y563N*
E116K	*G1244E*[†]	*P5L*	*R1283M*[†]	*Y1032C*[†]
E193K[†]	*G1249R*[†]	*P67L*	*R1283S*	
E474K	*G1349D*[†]	*P205S*	*S13F*	

CFTR mutations with significant clinical evidence of efficacy for elexacaftor/tezacaftor/ivacaftor, independent of the mutation on the second allele, are underscored.

[*] 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.

[†] *CFTR* mutations for which an *in vitro* response was also demonstrated for ivacaftor alone.

10.2. Pharmacodynamics

Effects on sweat chloride

In Study 445-102 [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 (patients heterozygous for the *F508del* mutation and a minimal function mutation)], 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 Study 445-103 (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 Study 445-104 (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).

In Study 445-106 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2).

In Study 445-111 (patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -57.9 mmol/L

(95% CI: -61.3, -54.6).

In Study 445-124 (patients aged 6 years and older with a qualifying non-*F508del,* elexacaftor/tezacaftor/ivacaftor-responsive mutation [see Table 21]), the mean absolute change in sweat chloride from baseline through Week 24 compared to placebo was -28.3 mmol/L (95% CI: -32.1, -24.5 mmol/L; P < 0.0001).

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 13.

Table 13: 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)	$AUC_{0\text{-}24h}$ or $AUC_{0\text{-}12h}$ (mcg·h/mL)*	Apparent Clearance (L/hr)	Apparent Volume of Distribution (L)
Elexacaftor 200 mg and	Elexacaftor	9.15 (2.09)	24.7 (4.87)	162 (47.5)	1.18 (0.29)	53.7 (17.7)

Table 13: 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)**
tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	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 hours (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 (< 18 years of age): Elexacaftor, tezacaftor and ivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group and dose administered in Table 14. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 2 to less than 18 years are within the range observed in patients aged 18 years and older.

Table 14: Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures Observed at Steady State by Age Group and Dose Administered

Age group (N)	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)

Patients aged 2 to < 6 years, < 14 kg (N = 16)	elexacaftor 80 mg qd/ tezacaftor 40 mg qd/ ivacaftor 60 mg qAM and ivacaftor 59.5 mg qPM	128 (24.8)	87.3 (17.3)	11.9 (3.86)
Patients aged 2 to < 6 years, ≥ 14 kg (N = 59)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	138 (47.0)	90.2 (27.9)	13.0 (6.11)
Patients aged 6 to < 12 years, < 30 kg (N = 36)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to < 12 years, ≥ 30 kg (N = 30)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)
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)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	168 (49.9)	89.5 (23.7)	12.1 (4.17)
qd = once daily, qAM = once every morning, qPM = once every evening, q 12h= every 12 hours, SD = Standard Deviation, AUC = Area Under the Curve				

Pediatrics (< 2 years of age): No data in patients less than 2 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 2 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 breastfeeding: 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 benefits outweigh 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 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 < 30 mL/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.

Disposal of unused/expired medicines:

No special requirements for disposal.

Part 2 : Scientific Information

13. Pharmaceutical Information

Drug Substance

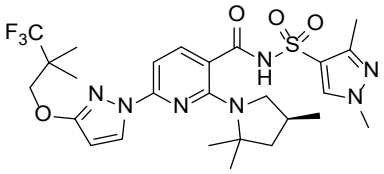
Non-proprietary name of the drug substance(s): elexacaftor/tezacaftor/ivacaftor

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

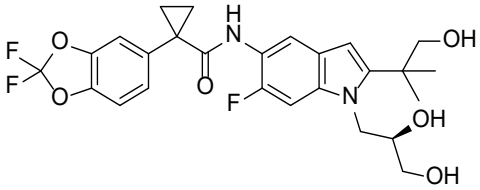
Molecular formula and molecular mass: elexacaftor: $C_{26}H_{34}N_7O_4SF_3$; 597.66
tezacaftor: $C_{26}H_{27}N_2F_3O$; 520.50
ivacaftor: $C_{24}H_{28}N_2O_3$; 392.49

Structural formula:

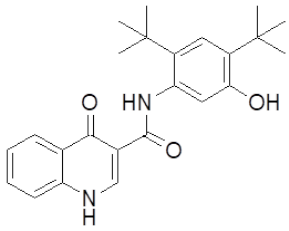
elexacaftor



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. Clinical Trials by Indication

The efficacy of TRIKAFTA (elexacaftor/tezacaftor/ivacaftor; ivacaftor) in patients with CF was demonstrated in six Phase 3 trials. Studies 445-102 and 445-124 were randomized, double-blind, placebo-controlled trial, Studies 445-103 and 445-104 were randomized, double-blind, active-controlled trials and Studies 445-106 and 445-111 were open-label trials. These studies enrolled CF patients with at least one *F508del* mutation or a mutation responsive to TRIKAFTA listed in Table 21. Not all *F508del* heterozygotes have been clinically evaluated with TRIKAFTA.

Patients with CF Aged 12 Years and Older with at Least One *F508del* Mutation in the *CFTR* Gene

Table 15: Summary of Patient Demographics for Clinical Trials in CF Patients with *CFTR* Mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 445-102 (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%
Study 445-103 (homozygous for the *F508del* mutation [F/F])	Randomized, active-controlled, parallel-group, multicenter	Run-in with 4 weeks: Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h. Randomized to: Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h or Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h Oral 4 weeks	107	28.4 years (12 to 61)	Male: 45% Female: 55%
Study 445-104 (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%

Study 445-102

Study 445-102 was a 24-week, randomized, double-blind, placebo-controlled trial in patients who had an *F508del* mutation on one allele and a minimal function 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%).

In Study 445-102 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) (see Table 16). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15 and sustained through the 24-week treatment period. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex and geographic region. A total of 18 patients receiving 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 16 for a summary of primary and key secondary outcomes.

Table 16: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)			
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.			

Study 445-103

Study 445-103 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%).

In Study 445-103 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with 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) (see Table 17). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ and geographic region. See Table 17 for a summary of primary and key secondary outcomes.

Table 17: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103)			
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.			

Study 445-104

Study 445-104 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.* A total of 258 patients aged 12 years and older received either ivacaftor (F/Gating) or tezacaftor/ivacaftor (F/RF) during a 4-week open-label run-in period and were dosed during the treatment period. Patients with the F/R117H genotype received ivacaftor during the run-in period. The mean age at baseline, following the run-in period, was 37.7 years. Patients were then randomized and dosed to receive TRIKAFTA or remained on the CFTR modulator therapy received during the run-in period. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 67.6% (range: 29.7%, 113.5%).

Following a 4-week tezacaftor/ivacaftor or ivacaftor run-in period, the primary endpoint for Study 445-104 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 18). 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 18 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/ivacaftor (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 18: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-104)			
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.

Patients with CF Aged 6 to Less Than 12 Years Old with at Least One *F508del* Mutation in The *CFTR* Gene

Table 19: Summary of Patient Demographics for Clinical Trials in CF Patients with *CFTR* Mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 445-106 (homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation [F/F or F/MF])	Open-label, multicenter	Elexacaftor 100 mg qd / Tezacaftor 50 mg qd / Ivacaftor 75 mg q12h or Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h according to weight Oral 24 weeks	66	9.3 years (6.1, 12.1)	Male: 40.9% Female: 59.1%

Study 445-106

Study 445-106 was a 24-week, open-label study in patients who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation. A total of 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) were dosed according to weight. Patients weighing < 30 kg at baseline were administered elexacaftor 100 mg once daily (qd)/tezacaftor 50 mg qd/ivacaftor 75 mg every 12 hours (q12h), and patients weighing ≥ 30 kg at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients had a $ppFEV_1$ ≥ 40% and weighed ≥ 15 kg at screening. The mean $ppFEV_1$ at baseline was 88.8% (range: 39.0%, 127.1%).

The pharmacokinetic profile, safety and efficacy of TRIKAFTA in patients aged 6 to less than 12 years are supported by evidence from studies of TRIKAFTA in patients aged 12 years and older (Studies 445-102, 445-103 and 445-104), with additional data from patients aged 6 to less than 12 years (Study 445-106).

The primary endpoint of safety and tolerability was evaluated through 24 weeks. The safety profile of patients in this trial was similar to that observed in Studies 445-102, 445-103 and 445-104 (see *8 Adverse Reactions*). The effectiveness of TRIKAFTA in patients aged 6 to less than 12 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing elexacaftor, tezacaftor and ivacaftor exposure levels in patients aged 6 to less than 12 years within the range of exposures observed in patients aged 12 years and older (see *10 Clinical Pharmacology*).

Patients with CF Aged 6 Years and Older with at Least One Qualifying Non-*F508del*, elexacaftor/tezacaftor/ivacaftor-responsive Mutation

Table 20: Summary of Patient Demographics for Clinical Trials in CF Patients with non-*F508del*, ELX/TEZ/IVA-responsive mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 445-124 (qualifying non-F508del, ELX/TEZ/IVA-responsive	Randomized, double-blind, placebo-	Elexacaftor 100 mg qd / Tezacaftor 50 mg qd / Ivacaftor 75 mg q12h	307	33.5 years (6.3,	Male: 46.3%

mutation and did not have an exclusionary [other ELX/TEZ/IVA-responsive] mutation)	controlled, parallel-group	or Elexacaftor 200 mg qd / Tezacaftor 100 mg qd / Ivacaftor 150 mg q12h according to weight and age Oral 24 weeks		87.3)	Female: 53.7%

Study 445-124

Study 445-124 was a 24 week, randomized, placebo-controlled, double-blind, parallel group study in patients aged 6 years and older. Patients who had at least one qualifying non-*F508del*, elexacaftor/tezacaftor/ivacaftor-responsive mutation (see Table 21) and did not have an exclusionary (other elexacaftor/tezacaftor/ivacaftor-responsive) mutation were eligible for the study. A total of 307 patients were enrolled and dosed according to age and weight. Patients 6 to <12 years weighing <30 kg at baseline were administered elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h. Patients 6 to <12 years weighing ≥30 kg at baseline were administered elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h. Patients ≥12 years at baseline were administered elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h. Patients had a ppFEV$_1$ ≥40% and ≤100% and aged 6 years or older at screening. The mean ppFEV$_1$ at baseline was 67.7% (range: 34.0%, 108.7%)].

Table 21: Eligible *CFTR* Mutations				
2789+5G>A	*D1152H*	*L997F*	*R117C*	*T338I*
3272-26A>G	*G85E*	*M1101K*	*R347H*	*V232D*
3849+10kbC>T	*L1077P*	*P5L*	*R347P*	
A455E	*L206W*	*R1066H*	*S945L*	

The safety and efficacy of TRIKAFTA in patients with CF aged 6 years and older without an *F508del* mutation were evaluated (Study 445-124).

In Study 445-124, the primary endpoint of efficacy was ppFEV$_1$. Secondary endpoints were absolute change in sweat chloride, CFQ-R respiratory domain score, growth parameters (BMI, weight), and number of PEx. See Table 22 for a summary of primary and secondary efficacy outcomes.

Table 22: Primary and Secondary Efficacy Analyses, Full Analysis Set (Study 445-124)			
Analysis	**Statistic**	**Placebo N = 102**	**TRIKAFTA N = 205**
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 (0.8)	9.2 (7.2, 11.3) P < 0.0001 8.9 (0.6)
Secondary			
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.5 (1.6)	-28.3 (-32.1, -24.5) P < 0.0001 -27.8 (1.1)
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 -2.0 (1.6)	19.5 (15.5, 23.5) P < 0.0001 17.5 (1.2)
Absolute change from baseline in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.35 (0.09)	0.47 (0.24, 0.69) P < 0.0001 0.81 (0.07)
Absolute change from baseline in weight at Week 24 (kg)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.2 (0.3)	1.3 (0.6, 1.9) P < 0.0001 2.4 (0.2)
Number of PEx through Week 24	Rate ratio (95% CI) *P* value Number of events Estimated event rate per year	NA NA 40 0.63	0.28 (0.15, 0.51) P < 0.0001 21 0.17
BMI: Body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; IV: intravenous; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor			

Patients with CF aged 2 to Less Than 6 Years Old With at Least One *F508del* Mutation in The *CFTR* Gene

Table 23: Summary of Patient Demographics for Clinical Trials in CF Patients with *CFTR* Mutations					
Study #	**Study design**	**Dosage, route of administration and duration**	**Study subjects (n)**	**Age (Range)**	**Sex**
Study 445-111 (homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation [F/F or F/MF])	Open-label, multicenter	Elexacaftor 80 mg qd / Tezacaftor 40 mg qd / Ivacaftor 60 mg qAM and Ivacaftor 59.5 mg qPM or Elexacaftor 100 mg qd / Tezacaftor 50 mg qd / Ivacaftor 75 mg q12h according to weight Oral 24 weeks	75	4.1 years (2.1, 6.0)	Male: 45.3% Female: 54.7%

Study 445-111

Study 445-111 was a 24-week, open-label study in patients aged 2 to less than 6 years (mean age at baseline 4.1 years). Patients who had at least one *F508del* mutation or a mutation known

to be responsive to elexacaftor/tezacaftor/ivacaftor were eligible for the study. A total of 75 patients who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation were enrolled and dosed according to weight. Patients weighing 10 kg to < 14 kg at baseline were administered elexacaftor 80 mg once daily (qd)/tezacaftor 40 mg qd/ivacaftor 60 mg once every morning and ivacaftor 59.5 mg once every evening. Patients weighing ≥ 14 kg at baseline were administered elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h.

The pharmacokinetic profile, safety, and efficacy of TRIKAFTA in patients with CF aged 2 to less than 6 years are supported by evidence from studies of TRIKAFTA in patients aged 12 years and older (Studies 445-102, 445-103 and 445-104), with additional data from a 24-week, open-label, phase 3 study in 75 patients aged 2 to less than 6 years (Study 445-111).

In Study 445-111, the primary endpoint of safety and tolerability was evaluated through 24 weeks. The safety profile of patients in this study was similar to that observed in Studies 445-102, 445-103, 445-104 and 445-106 (see *8 Adverse Reactions*). Secondary endpoints were an evaluation of pharmacokinetics, and efficacy endpoints of absolute change in sweat chloride (see *10.2 Pharmacodynamics*) and $LCI_{2.5}$ from baseline through Week 24. The effectiveness of TRIKAFTA in patients aged 2 to less than 6 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing elexacaftor, tezacaftor and ivacaftor exposure levels in patients aged 2 to less than 6 years within the range of exposures observed in patients aged 12 years and older.

Patients in all trials 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 diagnosis of CF and met study eligibility criteria.

In Studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124, 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. In Study 445-111, patients who had ALT or AST ≥ 2 x ULN were also excluded. Patients in Studies 445-102, 445-103, 445-104, 445-106, 445-111, and 445-124 were eligible to roll over into separate open-label extension studies.

16. Non-Clinical Toxicology

Elexacaftor

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

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.

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.

Juvenile toxicity studies in rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are not relevant for the indicated pediatric population 2 years of age and older, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.

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 / tezacaftor / ivacaftor tablets
and
ivacaftor tablets

elexacaftor / tezacaftor / ivacaftor granules
and
ivacaftor granules

This Patient Medication Information is written for the person who will be taking **TRIKAFTA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TRIKAFTA**, talk to a healthcare professional.

Serious warnings and precautions box

Liver disorder: TRIKAFTA may worsen your liver function, even if you have no prior liver disease. This can lead to serious liver problems. This includes a liver transplant, and even death.

Your healthcare professional will order some blood tests to check your liver:
- before you start treatment with TRIKAFTA,
- every month during the first 6 months of treatment,
- every 3 months during the next 6 months, and
- every year thereafter while you are taking TRIKAFTA.

If you have had abnormal liver blood test results in the past or have a history of liver problems and you are prescribed TRIKAFTA, your healthcare professional may order blood tests to check your liver more often.

If you have any of these symptoms while taking TRIKAFTA, **stop** taking it and tell your healthcare professional **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

What TRIKAFTA is used for:
TRIKAFTA is used for the treatment of cystic fibrosis (CF) in patients 2 years of age and older who have at least one *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene or another mutation in the *CFTR* gene that is responsive to TRIKAFTA.

How TRIKAFTA works:
- 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.

The ingredients in TRIKAFTA are:
Medicinal ingredient(s): elexacaftor / tezacaftor / ivacaftor

Non-medicinal ingredients:
- elexacaftor/tezacaftor/ivacaftor granules:
  Colloidal silicon dioxide, croscarmellose sodium, hypromellose, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose

- ivacaftor granules:
  Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose

- 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:
Granules:
- 80 mg elexacaftor / 40 mg tezacaftor / 60 mg ivacaftor (in a white and blue packet) and 59.5 mg ivacaftor (in a white and green packet)
- 100 mg elexacaftor / 50 mg tezacaftor / 75 mg ivacaftor (in a white and orange packet)

and 75 mg ivacaftor (in a white and pink packet)

Tablets:

- 50 mg elexacaftor / 25 mg tezacaftor / 37.5 mg (light orange and marked with “T50”) and 75 mg ivacaftor (light blue and marked with “V 75”)
- 100 mg elexacaftor / 50 mg tezacaftor / 75 mg ivacaftor (orange and marked with “T100”) and 150 mg ivacaftor (light blue and marked with “V 150”)

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 healthcare professional 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 healthcare professional 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 healthcare professional may perform eye exams before you start treatment and while you are taking TRIKAFTA to look for cataracts.

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:** children should be supervised after 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 healthcare professional and pharmacist when you get a new medicine.

How to take TRIKAFTA:

- Take TRIKAFTA exactly as your healthcare professional tells you to, even if you feel well. Check with your healthcare professional if you are not sure. Do not change the dose or stop taking TRIKAFTA without first talking to your healthcare professional.
- **Always take TRIKAFTA with a fat-containing food**. This helps ensure that you get the right amount of medicine in your body. Examples of meals that contain fat are:
    - meals that have been prepared with butter or oils.
    - meals that have eggs, peanut butter, nuts, whole-milk dairy products (such as whole milk, cheese, and yogurt) or meats.
- Take each morning and evening doses approximately 12 hours apart.

TRIKAFTA tablets:

1. To remove the tablet(s) push it through the blister strip.

2. Swallow the tablet(s) whole with food that contains fat. Do NOT chew, break or dissolve the tablet(s).

TRIKAFTA granules:

1. Do not remove packet from the wallet until ready to give dose.

2. Shake the packet gently to settle the granules to the bottom of the packet.

3. Tear or cut packet completely open along cut line.

4. Pour all the granules of the packet into 5 mL (1 teaspoon) of soft food or liquid that is between 5°C to 25°C and mix in a small container (like an empty bowl). Look inside the sachet to make sure there are no granules left inside. Some examples of soft foods or liquids include puréed fruits or vegetables, flavoured yogurt or pudding, applesauce, milk, or juice (except grapefruit).

5. **After mixing, give within 1 hour. Make sure all medicine is taken. This is very important for it to work properly and be effective.**

6. In addition to the granule mixture, fat-containing food must be ingested just before or just after the granules dose. This helps the body better absorb the medicine.

Usual dose:

Your healthcare professional will determine the right dose of TRIKAFTA tablets or TRIKAFTA granules for you. This may depend on your health condition, other medicines you are taking, your weight, your age and how you respond to TRIKAFTA.

The usual dose for TRIKAFTA is as follows:

Take each morning and evening dose approximately 12 hours apart.

Age	Body Weight (kg)	Morning Dose	Evening Dose
2 to < 6 years	**< 14 kg**	1 white and blue packet containing 80 mg elexacaftor / 40 mg tezacaftor / 60 mg ivacaftor granules	1 white and green packet containing 59.5 mg ivacaftor granules
	≥ 14 kg	1 white and orange packet containing 100 mg elexacaftor / 50 mg tezacaftor / 75 mg ivacaftor granules	1 white and pink packet containing 75 mg ivacaftor granules
6 to < 12 years	**< 30 kg**	2 light orange tablets, each containing 50 mg elexacaftor / 25 mg tezacaftor / 37.5 mg ivacaftor	1 light blue tablet of 75 mg ivacaftor
	≥ 30 kg	2 orange tablets, each containing 100 mg elexacaftor / 50 mg tezacaftor / 75 mg ivacaftor	1 light blue tablet of 150 mg ivacaftor
≥ 12 years	**Not applicable**	2 orange tablets, each containing 100 mg elexacaftor / 50 mg tezacaftor / 75 mg ivacaftor	1 light blue tablet of 150 mg ivacaftor

Refilling your prescription:
Remember to get a new prescription from your healthcare professional 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, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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** or an	• **Take the missed dose** with fat-containing food

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

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 with TRIKAFTA may 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

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this 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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
- Store at or below 30°C.
- 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.
- 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 the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website http://www.vrtx.ca; or by calling 1-877-634-8789.

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

Date of Authorization: 2025-05-13