Product Monograph

Including Patient Medication Information

PrALYFTREK™

vanzacaftor / tezacaftor / deutivacaftor
Film-coated Tablets
For Oral Use

vanzacaftor (as vanzacaftor calcium) 4 mg / tezacaftor 20 mg / deutivacaftor 50 mg
vanzacaftor (as vanzacaftor calcium) 10 mg / tezacaftor 50 mg / deutivacaftor 125 mg

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

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

Part 1: Healthcare Professional Information

1. Indications

ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [see *10.1 Mechanism of Action*].

1.1. Pediatrics

Pediatrics (< 6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for children less than 6 years of age.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of ALYFTREK did not include a sufficient number of CF patients aged 65 years and older to determine whether they respond differently from younger CF patients.

2. Contraindications

- ALYFTREK 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

Elevated transaminases have been observed in some patients treated with ALYFTREK. Cases of liver failure leading to transplantation and death have been reported in patients with and without a history of liver disease taking a fixed dose combination drug containing elexacaftor, tezacaftor, and ivacaftor, which contains one same (tezacaftor) and one similar (ivacaftor) active ingredient as ALYFTREK. Liver injury has primarily been reported within the first 6 months following initiation of elexacaftor/tezacaftor/ivacaftor [see *7 Warnings and Precautions*].

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating ALYFTREK, every 3 months during the first year of treatment, then annually thereafter. Consider more frequent monitoring during the first 6 months of treatment for patients who had no prior treatment with elexacaftor, tezacaftor and ivacaftor. Consider more frequent monitoring for patients with a history of liver disease or elevated liver function tests [see *4 Dosage and Administration*, *7 Warnings and Precautions*, *8 Adverse Reactions*].

Interrupt ALYFTREK 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 ALYFTREK [see *7 Warnings and Precautions*].

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

(Child-Pugh Class B) and should only be considered when there is a clear medical need, and the benefits outweigh the risks. If used, use with caution and monitor patients closely [see *4 Dosage and Administration*].

4. Dosage and Administration

4.1. Dosing Considerations

ALYFTREK should only be administered to patients with CF who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene [see *10 Clinical Pharmacology* and *14 Clinical Trials*]. Treatment with ALYFTREK should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of CF. ALYFTREK is only indicated for adults and children aged 6 years and older with CF who have an indicated mutation and a diagnosis of CF.

If the CF patient has an unknown genotype, an accurate and validated genotyping method should be performed to confirm the presence of at least one *F508del* mutation or another responsive *CFTR* mutation [see *10 Clinical Pharmacology*].

ALYFTREK dosing may be impacted in the following patient groups:

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

4.2. Recommended Dose and Dosage Adjustment

Adults and pediatric patients aged 6 years and older should be dosed according to Table 1.

Table 1: Dosing Recommendation for Adults and Pediatric Patients Aged 6 Years and Older

Age	Weight	Daily Dose (once daily)
≥ 6 years	< 40 kg	Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
	≥ 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg

Each dose should be taken in its entirety with fat-containing food once daily at approximately the same time each day [see *4.4 Administration*].

Health Canada has not authorized an indication for pediatric use in children aged less than 6 years [see *7.1 Special Populations* and *10.3 Pharmacokinetics*].

Hepatic Impairment

- Mild Hepatic Impairment (Child-Pugh Class A): No dose adjustment is recommended for patients with mild hepatic impairment. Liver function tests should be closely monitored [see *7 Warnings and Precautions*, *8 Adverse Reactions*, and *10.3 Pharmacokinetics*].
- Moderate Hepatic Impairment (Child-Pugh Class B): **Use not recommended**. Use of ALYFTREK should only be considered for patients with moderate hepatic impairment when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, no dose adjustment is required and the recommended dose is the same as for patients with normal hepatic function. Liver function tests should be closely monitored [see *7 Warnings and Precautions*, *8 Adverse Reactions*, and *10.3 Pharmacokinetics*].
- Severe Hepatic Impairment (Child-Pugh Class C): **Should not be used**. ALYFTREK has not been studied in patients with severe hepatic impairment [see *7 Warnings and Precautions*, *8 Adverse Reactions*, and *10.3 Pharmacokinetics*].

Rash Events

The incidence of rash events was higher in females than in males. A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, interrupting treatment with ALYFTREK and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming ALYFTREK without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered.

Elevated Transaminases

Assessments of transaminases (ALT and AST), alkaline phosphatase and total bilirubin are recommended for all patients prior to initiating ALYFTREK. Assess liver function tests every 3 months during the first year of treatment, then annually thereafter. Consider more frequent monitoring during the first 6 months of treatment for patients who had no prior treatment with elexacaftor, tezacaftor and ivacaftor. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt ALYFTREK 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 bilirubin > 2 x ULN. Follow laboratory tests closely until the abnormalities resolve.

Following resolution, consider the benefits and risks of resuming treatment [see *7 Warnings and Precautions* and *8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data*]. Patients who resume treatment after interruption should be monitored closely.

In patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), ALYFTREK should be used with caution 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*].

Concomitant Use of Moderate or Strong CYP3A inhibitors

When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin) or

strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, or clarithromycin), the dose of ALYFTREK should be reduced as recommended in Table 2 [see *7 Warnings and Precautions* and *9.4 Drug-Drug Interactions*].

No dose adjustment is recommended with concomitant use of ciprofloxacin [see *9.4 Drug-Drug Interactions*].

Table 2: Dosing Schedule for Concomitant Use of ALYFTREK with Moderate and Strong CYP3A Inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
≥ 6 years	< 40 kg	Two tablets of vanzacaftor 4 mg/ tezacaftor 20 mg/ deutivacaftor 50 mg every other day	Two tablets of vanzacaftor 4 mg/ tezacaftor 20 mg/ deutivacaftor 50 mg once a week
	≥ 40 kg	One tablet of vanzacaftor 10 mg/ tezacaftor 50 mg/ deutivacaftor 125 mg every other day	One tablet of vanzacaftor 10 mg/ tezacaftor 50 mg/ deutivacaftor 125 mg once a week

Concomitant Use of Moderate or Strong CYP3A Inducers

Co-administration with moderate or strong CYP3A inducers [e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*), and efavirenz] is not recommended [see *7 Warnings and Precautions* and *9.4 Drug-Drug Interactions*].

Renal Impairment

No dose adjustment is recommended for patients who have mild (estimated glomerular filtration rate [eGFR] 60 to < 90 mL/min/1.73 m^2) or moderate (eGFR 30 to < 60 mL/min/1.73 m^2) renal impairment. Caution is recommended for patients who have severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or end-stage renal disease [see *7 Warnings and Precautions* and *10.3 Pharmacokinetics*].

4.4. Administration

For oral use. Tablets should be swallowed whole.

ALYFTREK should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, peanut butter, cheeses, nuts, whole milk, or meats [see *10.3 Pharmacokinetics*].

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

4.5. Missed Dose

- If 6 hours or less have passed since the missed dose, the missed dose should be taken as soon as possible and the original schedule should be continued the next day.
- If more than 6 hours have passed since the missed dose, the missed dose should be skipped, and the original schedule should be continued the next day.

5. Overdose

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

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 3: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated Tablets • vanzacaftor 4 mg (as 4.24 mg of vanzacaftor calcium dihydrate)/ tezacaftor 20 mg/ deutivacaftor 50 mg (fixed-dose combination) • vanzacaftor 10 mg (as 10.6 mg of vanzacaftor calcium dihydrate)/ tezacaftor 50 mg/ deutivacaftor 125 mg (fixed-dose combination)	*Tablet core* Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate *Tablet film coat* Brilliant Blue FCF aluminum lake/FD&C Blue #1, carmine, hydroxypropyl cellulose, hypromellose, iron oxide red, talc, titanium dioxide

Description

*Vanzacaftor 4 mg/tezacaftor 20 mg/*deutivacaftor *50 mg*
Purple, round-shaped tablet debossed with "V4" on one side and plain on the other (7.35 mm diameter).

*Vanzacaftor 10 mg/tezacaftor 50 mg/*deutivacaftor *125 mg*
Purple, capsule-shaped tablet debossed with "V10" on one side and plain on the other (15 mm x 7 mm).

Nature and Contents of Container

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

Pack Size

ALYFTREK Pack size of 84 tablets (4 weekly wallets, each with 21 tablets):

- Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets

ALYFTREK Pack size of 56 tablets (4 weekly wallets, each with 14 tablets):

- Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

Patients who Discontinued or Interrupted Treatment with Drugs Containing Tezacaftor and/or Ivacaftor Due to Adverse Reactions

There are no available safety data for ALYFTREK in patients who previously discontinued or interrupted treatment with drugs containing tezacaftor and/or ivacaftor due to adverse reactions. Consider the benefits and risks before using ALYFTREK in these patients. If ALYFTREK is used in these patients, monitor closely, as clinically appropriate.

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 taking a drug containing elexacaftor, tezacaftor, and ivacaftor, which contains one same (tezacaftor) and one similar (ivacaftor) active ingredient as ALYFTREK [see *3 Serious Warnings and Precautions Box*].

In patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), ALYFTREK should be used with caution and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment [see *4.2 Recommended Dose and Dosage Adjustment*, *8.2 Clinical Trial Adverse Reactions*, and *10.3 Pharmacokinetics*].

Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with ALYFTREK. Treatment of patients with moderate hepatic impairment is not recommended and should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, liver function tests should be monitored (see Table 2). [see *4.2 Recommended Dose and Dosage Adjustment*, *8 Adverse Reactions*, and *10.3 Pharmacokinetics*].

Concomitant Use with CYP3A Inducers

Exposures to vanzacaftor, tezacaftor and deutivacaftor are expected to decrease with the concomitant use of moderate or strong CYP3A inducers, which may reduce ALYFTREK efficacy; therefore, co-administration with moderate or 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 vanzacaftor, tezacaftor and deutivacaftor are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose of ALYFTREK should be reduced when used concomitantly with strong or moderate CYP3A inhibitors [see *4.2 Recommended Dose and Dosage Adjustment* and *9.4 Drug-Drug Interactions*].

Monitoring and Laboratory Tests

Elevated Transaminases

Elevated transaminases are common in CF patients and have been observed in some patients treated with ALYFTREK.

Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating ALYFTREK, every 3 months during the first year of treatment, then annually thereafter. Consider more frequent monitoring during the first 6 months of treatment for patients who had no prior treatment with elexacaftor, tezacaftor and ivacaftor. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt ALYFTREK 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 bilirubin > 2 x ULN. Follow laboratory tests closely until the abnormalities resolve.

Following resolution, consider the benefits and risks of resuming treatment [see *4.2 Recommended Dose and Dosage Adjustment*, *8.2 Clinical Trial Adverse Reactions* and *8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data*]. Patients who resume treatment after interruption should be monitored closely.

Ophthalmologic

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in CF patients aged less than 18 years 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. As deutivacaftor is a deuterated isotopologue of ivacaftor, baseline and follow-up ophthalmological examinations are recommended in pediatric patients treated with ALYFTREK [see *16 Non-Clinical Toxicology*].

Reproductive Health: Female and Male Potential

- **Fertility**

There are no data available on the effect of vanzacaftor, tezacaftor, and deutivacaftor on fertility in humans. Vanzacaftor and tezacaftor had no effect on fertility and reproductive performance indices in male and female rats at doses up to 12.5 mg/kg/day in males and 10 mg/kg/day for females (approximately 19 times and 30 times in males and females respectively, based on the AUC for vanzacaftor at the maximum recommended human dose [MRHD]) for vanzacaftor and 200 mg/kg/day for males (approximately 3 times the MRHD) and 100 mg/kg/day for females (approximately 3 times the MRHD) for tezacaftor. The effects of deutivacaftor on fertility have not been evaluated; however, ivacaftor had an effect on fertility in male and female rats [see *16 Non-Clinical Toxicology*].

7.1. Special Populations

7.1.1. Pregnancy

No adequate and well-controlled studies of ALYFTREK have been conducted in pregnant women. Animal studies in pregnant animals were not conducted with concomitant administration of vanzacaftor, tezacaftor, and deutivacaftor. Animal studies have assessed

reproductive and developmental toxicity of vanzacaftor and tezacaftor separately in pregnant rats and rabbits. Deutivacaftor is a deuterated isotopologue of ivacaftor with a toxicity profile similar to ivacaftor. The safety profile of ivacaftor is established in pregnant rats and rabbits. Animal studies with the individual components of ALYFTREK do not indicate direct or indirect harmful effects with respect to reproductive toxicity [see *16 Non-Clinical Toxicology*]. Because animal reproduction studies are not always predictive of human response, ALYFTREK 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 ALYFTREK (vanzacaftor, tezacaftor, deutivacaftor), or their metabolites are excreted in human milk. ALYFTREK 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. Vanzacaftor and tezacaftor are excreted into the milk of lactating female rats. The effect of deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats. Exposure of ^{14}C-vanzacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.2, 3, and 1.5 times, respectively, the value observed in plasma (based on AUC).

7.1.3. Pediatrics

Pediatrics (< 6 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in children less than 6 years of age.

7.1.4. Geriatrics

Clinical studies of ALYFTREK did not include a sufficient number of CF patients aged 65 years and older to determine whether they respond differently from younger CF patients.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety profile of ALYFTREK is based on data from 480 participants aged 12 years and older in two randomized, active-controlled (elexacaftor/tezacaftor/ivacaftor-controlled), phase 3 studies (Study 121-102 and Study 121-103) with 52 weeks of treatment duration. In both studies, all subjects received a fixed-dose combination of elexacaftor/tezacaftor/ivacaftor (ELX/TEX/IVA) in a 4-week run-in period prior to randomization. Patients with a prior intolerance to ELX/TEZ/IVA (i.e., patients who discontinued or interrupted treatment due to adverse reactions) were excluded from the studies. Studies 121-102 and 121-103 were not designed to evaluate meaningful comparisons of the incidence of adverse reactions between the ALYFTREK and ELX/TEZ/IVA treatment groups. For additional information regarding ELX/TEZ/IVA adverse reactions, refer to the ELX/TEZ/IVA Product Monograph.

In Studies 121-102 and 121-103, the proportion of CF patients who discontinued ALYFTREK prematurely due to adverse events was 3.8% in the ALYFTREK treatment group, and 3.7% in the ELX/TEZ/IVA treatment group.

Serious adverse drug reactions that occurred with ALYFTREK in 2 or more participants (≥ 0.4%) were ALT increased (0.4%) and AST increased (0.4%).

The most common (≥ 10%) adverse drug reactions in patients treated with ALYFTREK were headache (15.8%) and diarrhea (12.1%).

The safety profile of ALYFTREK was generally similar across all subgroups of participants, including analysis by age, sex, baseline percent predicted Forced Expiratory Volume in one second ($ppFEV_1$), and geographic regions.

8.2. Clinical Trial Adverse Reactions

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

Table 4 shows overall incidence of adverse drug reactions in patients with CF aged 12 years and older in the 52-week, active-controlled trials (Study 121-102 and 121-103) treated with ALYFTREK.

Table 4: Incidence of Adverse Drug Reactions in CF Patients Aged 12 Years and Older Treated with ALYFTREK (Studies 121-102 and 121-103)*

System Organ Class (SOC)	Adverse Drug Reactions (Preferred Term)	ALYFTREK N=480 n (%)	ELX/TEZ/IVA† N=491 n (%)
Nervous System Disorders	Headache	76 (15.8)	63 (12.8)
Gastrointestinal Disorders	Diarrhea	58 (12.1)	59 (12.0)
Skin and Subcutaneous Tissue Disorders	Rash	37 (7.7)	22 (4.5)
Investigations	Blood creatine phosphokinase increased	43 (9.0)	41 (8.4)
	Alanine aminotransferase increased	38 (7.9)	29 (5.9)
	Aspartate aminotransferase increased	33 (6.9)	27 (5.5)

Abbreviations: ELX/TEZ/IVA: Elexacaftor/tezacaftor/ivacaftor fixed-dose combination.

* Patients were treated with ELX/TEZ/IVA during a 4-week run-in period prior to randomization to ALYFTREK or ELX/TEZ/IVA for the 52-week treatment period.

† Studies 121-102 and 121-103 were not designed to evaluate comparisons of safety between ALYFTREK and ELX/TEZ/IVA treatments. For additional information regarding ELX/TEZ/IVA adverse reactions, refer to the ELX/TEZ/IVA Product Monograph.

Safety data from the following studies were generally consistent with the safety data observed in Studies 121-102 and 121-103:

- A 24-week, open-label, study (Study 121-105, Cohort B1) in 78 CF patients aged 6 to less than 12 years.

Rash Events

In Studies 121-102 and 121-103, the incidence of rash events (e.g., rash, rash pruritic) was 11.0% with ALYFTREK and 7.7% with ELX/TEZ/IVA. The rash events were generally mild to

moderate in severity. The incidence of rash events was higher in females (13.0%) than in males (9.4%) treated with ALYFTREK. The incidence of rash events was 7.9% in females and 7.6% in males in the ELX/TEZ/IVA treatment group.

A role for hormonal contraceptives in the occurrence of rash cannot be excluded [see *4.2 Recommended Dose and Dosage Adjustment* and *9.4 Drug-Drug Interactions*].

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

The safety profile is generally consistent among children, adolescent, and adults. Children under the age of 6 years have not been studied.

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

Transaminase Elevations

The incidence of adverse reactions of transaminase elevations was 9.0% with ALYFTREK and 7.1% with ELX/TEZ/IVA. Of the ALYFTREK-treated participants, 1.5% discontinued treatment for elevated transaminases. Table 5 shows the incidence of maximum transaminase (ALT or AST) elevations in Studies 121-102 and 121-103.

Table 5: Threshold Analysis of Liver Function Tests in Patients Aged 12 Years and Older (Studies 121-102 and 121-103)*

Maximum ALT or AST Elevation	ALYFTREK N=480	ELX/TEZ/IVA† N=491
>3 × ULN	29 (6.0)	15 (3.1)
>5 × ULN	12 (2.5)	6 (1.2)
>8 × ULN	6 (1.3)	1 (0.2)

Abbreviations: ALT: alanine aminotransferase; AST, aspartate aminotransferase; ELX/TEZ/IVA: Elexacaftor/tezacaftor/ivacaftor fixed-dose combination

* Patients were treated with ELX/TEZ/IVA during a 4-week Run-in period prior to randomization to ALYFTREK or ELX/TEZ/IVA during the 52-week treatment period.

† Studies 121-102 and 121-103 were not designed to evaluate meaningful comparisons of safety between the ALYFTREK and ELX/TEZ/IVA treatment groups. For additional information regarding ELX/TEZ/IVA transaminase elevations, refer to ELX/TEZ/IVA Prescribing Information.

In Study 121-105 Cohort B1 in CF patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and > 3 × ULN were 0%, 1.3%, and 3.8%, respectively.

Increased Creatine Phosphokinase

In Studies 121-102 and 121-103, the incidence of maximum creatine phosphokinase > 5 x the ULN was 7.9% with ALYFTREK and 6.5% with ELX/TEZ/IVA. Of the ALYFTREK-treated participants, 0.2% discontinued treatment for increased creatine phosphokinase.

9. Drug Interactions

9.2. Drug Interactions Overview

Based on *in vitro* results, vanzacaftor, tezacaftor, and deutivacaftor are mainly metabolized by

CYP3A. Concomitant use of CYP3A inducers may result in reduced exposures of vanzacaftor, tezacaftor, and deutivacaftor and thus reduced efficacy. Co-administration of ALYFTREK with moderate or strong CYP3A inducers is not recommended [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

Co-administration with strong and moderate CYP3A inhibitors may increase vanzacaftor, tezacaftor, and deutivacaftor exposures. The dose of ALYFTREK should be reduced when co-administered with strong and moderate CYP3A inhibitors [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

Co-administration of ALYFTREK may increase exposure of P-gp sensitive substrates. When used concomitantly with P-gp substrates with a narrow therapeutic index, caution and appropriate monitoring should be used.

Concomitant use of ALYFTREK with BCRP substrates may increase exposure of these substrates. When administered concomitantly with substrates of BCRP, caution and appropriate monitoring should be used.

Deutivacaftor may inhibit CYP2C9. Administration of ALYFTREK may increase the exposure of CYP2C9 substrates. Caution and appropriate monitoring should be used.

9.4. Drug-Drug Interactions

The drugs listed in Table 6 and Table 7 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 ALYFTREK

Table 6: Established or Potential Drug-Drug Interactions - Effect of Other Drugs on Vanzacaftor/Tezacaftor/Deutivacaftor

Drug	Source of evidence	Effect	Clinical comment
Strong CYP3A Inducers			
Rifampin	M	↓ AUC of VNZ, TEZ and D-IVA	Co-administration of ALYFTREK with strong CYP3A inducers is not recommended. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced efficacy.
Moderate CYP3A Inducers			
Efavirenz	M	↓ AUC of VNZ, TEZ and D-IVA	Co-administration of ALYFTREK with moderate CYP3A inducers is not recommended. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced efficacy.

Strong CYP3A Inhibitors			
Itraconazole	CT*	↑ 10.5-fold in VNZ AUC	Reduction in dose of ALYFTREK is recommended with co-administration of strong CYP3A inhibitors [see Table 2].
	CT†‡	↑ 4.0-4.5-fold in TEZ AUC	
	CT‡	↑ 11.1-fold in D-IVA AUC	
Moderate CYP3A Inhibitors			
Fluconazole Verapamil Erythromycin	M	↑ 2.4-3.9-fold in VNZ AUC	Reduction in dose of ALYFTREK is recommended with co-administration of moderate CYP3A inhibitors [see Table 2].
	M	↑ 2.1-fold in TEZ AUC	
	M	↑ 2.9-4.8-fold in D-IVA AUC	

↑ = increase, ↓ = decrease, ↔ = no change
Legend: CT = Clinical Trial; T = Theoretical; M = Modeling; AUC = Area Under the Curve; IVA = ivacaftor; TEZ = tezacaftor; VNZ = vanzacaftor; D-IVA = deutivacaftor; ELX = elexacaftor
* Data derived from a trial conducted with VNZ and modeling
† Data derived from a trial conducted with IVA + TEZ
‡ Data derived from a trial conducted with ELX + TEZ + D-IVA

CYP3A Inducers:
Vanzacaftor, tezacaftor and deutivacaftor are substrates of CYP3A. Vanzacaftor and deutivacaftor are sensitive substrates of CYP3A. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced ALYFTREK efficacy. Co-administration of ALYFTREK with moderate or strong CYP3A inducers is not recommended [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

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

CYP3A Inhibitors:
Co-administration with itraconazole, a strong CYP3A inhibitor, increased vanzacaftor AUC by 10.5-fold, tezacaftor AUC by 4.0- to 4.5-fold and deutivacaftor AUC by 11.1-fold. The dose of ALYFTREK should be reduced when co-administered with strong CYP3A inhibitors [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

Examples of strong CYP3A inhibitors include ketoconazole, itraconazole, posaconazole, and voriconazole, and clarithromycin.

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase vanzacaftor, tezacaftor, and deutivacaftor AUC by approximately 2.4- to 3.9-fold, 2.1-fold, and 2.9- to 4.8-fold, respectively. The dose of ALYFTREK should be reduced when co-administered with moderate CYP3A inhibitors [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

Examples of moderate CYP3A inhibitors include fluconazole, erythromycin, and verapamil.

Ciprofloxacin:
Vanzacaftor/tezacaftor/deutivacaftor was not evaluated for concomitant use with ciprofloxacin.

However, ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor when co-administered, and is not expected to have a clinically relevant effect on the exposure of vanzacaftor or deutivacaftor. Therefore, no dose adjustment is necessary during concomitant administration of ALYFTREK with ciprofloxacin [see *4.2 Recommended Dose and Dosage Adjustment*].

Effect of ALYFTREK on Other Drugs

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

Drug	Source of evidence	Effect	Clinical comment
CYP2C9 Substrates			
Warfarin	T	↑ Warfarin exposure potential	Caution is warranted; monitoring the international normalized ratio (INR) during co-administration with warfarin is recommended.
P-glycoprotein Substrates			
Digoxin	CT *	↑ 1.3-fold in digoxin AUC	Caution and appropriate monitoring should be used.
OATP1B1 Substrates			
Pitavastatin	CT *	↑ 1.2-fold in pitavastatin AUC	No dose adjustment of pitavastatin or other OATP1B1 substrates is recommended
Hormonal Contraceptives			
Oral Contraceptive	CT * †	↔ Ethinyl estradiol ↔ Norethindrone	No dose adjustment of the hormonal contraceptives is recommended

↑ = increase, ↓ = decrease, ↔ = no change
Legend: CT = Clinical Trial; T = Theoretical; M = Modeling; AUC = Area Under the Curve; IVA = ivacaftor; TEZ = tezacaftor
* Data derived from a trial conducted with IVA + TEZ
† Data derived from a trial conducted with IVA alone

CYP2C9 Substrates:

Deutivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of ALYFTREK with warfarin is recommended. Other medicinal products for which exposure may be increased by ALYFTREK include glimepiride and glipizide; these medicinal products should be used with caution.

Potential for Interaction with Transporters:

ALYFTREK was not evaluated for concomitant use with P-glycoprotein (P-gp) substrates. However, co-administration of tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold. Administration of ALYFTREK 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.

Based on *in vitro* data, vanzacaftor, tezacaftor, and deutivacaftor have low potential to inhibit OATP1B1 at clinically relevant concentrations. Deutivacaftor has a similar OATP1B1 inhibition potential to ivacaftor *in vitro*. Co-administration of tezacaftor / ivacaftor with pitavastatin, an OATP1B1 substrate, had no clinically relevant effect on the exposure of pitavastatin.

Breast Cancer Resistance Protein (BCRP) Substrates:

Vanzacaftor and deutivacaftor are inhibitors of BCRP *in vitro*. Concomitant use of ALYFTREK with BCRP substrates may increase exposure of these substrates; however, this has not been studied clinically. When administered concomitantly with substrates of BCRP, caution and appropriate monitoring should be used.

Hormonal Contraceptives:

ALYFTREK is not expected to have an impact on the efficacy of oral contraceptives. Vanzacaftor and ALYFTREK were not evaluated for concomitant use with oral contraceptives. Tezacaftor in combination with ivacaftor and ivacaftor alone have been studied with ethinyl estradiol/norethindrone and were found to have no clinically relevant effect on the exposures of the oral hormonal contraceptive. Vanzacaftor, tezacaftor, and deutivacaftor have low potential to induce or inhibit CYP3A based on *in vitro* data.

9.5. Drug-Food Interactions

Co-administration of ALYFTREK with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of vanzacaftor, tezacaftor and deutivacaftor. Food or drink containing grapefruit should be avoided during treatment with ALYFTREK [see *4.2 Recommended Dose and Dosage Adjustment*].

When ALYFTREK is administered with food, there is an increase in the rate (C_{max}) and extent (AUC_T) of absorption for vanzacaftor and deutivacaftor. Food increases the extent of absorption for tezacaftor but has no effect on the rate of absorption of tezacaftor. As a result, ALYFTREK should be administered with fat-containing 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 vanzacaftor, tezacaftor and deutivacaftor, which may reduce the therapeutic effectiveness of ALYFTREK [see *4.2 Recommended Dose and Dosage Adjustment* and *7 Warnings and Precautions*].

10. Clinical Pharmacology

10.1. Mechanism of Action

Vanzacaftor 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 select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Deutivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of vanzacaftor, tezacaftor, and deutivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured both by CFTR-mediated chloride transport *in vitro* and by sweat chloride (SwCl) in patients with CF.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) Cells Expressing Mutant CFTR

The chloride transport response of mutant CFTR protein to vanzacaftor/tezacaftor/deutivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines stably expressing CFTR protein with individual mutations. Vanzacaftor/tezacaftor/deutivacaftor increased chloride transport in FRT cells expressing select *CFTR* mutations.

The *in vitro* treatment-induced increase in CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is 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 generally consistent with *in vitro* results and indicate that a single responsive allele (including the *F508del* mutation) is sufficient to result in a clinical response [see *14 Clinical Trials*].

Table 8 lists *CFTR* mutations responsive to ALYFTREK based on clinical data and/or *in vitro* data in FRT cells indicating that vanzacaftor/tezacaftor/deutivacaftor increases chloride transport by at least 10% of normal over baseline, or *in vitro* data derived from human bronchial epithelial (HBE) cells. The occurrence of *CFTR* mutations listed in Table 8 in a patient should not be used in lieu of a diagnosis of CF, nor as a sole determinant for prescribing purposes.

Table 8:List of *CFTR* Gene Mutations that are Responsive to ALYFTREK*

Based on Clinical Data†							
A455E	*G1244E*	*H1054D*	*L1077P*	*R1066H*	*S1159F*	*S549R*	*W1282R*
D1152H	*G551D*	*I336K*	*L206W*	*R347P*	*S1251N*	*S945L*	*Y563N*
F508del	*G85E*	*I502T*	*M1101K*	*R352Q*	*S549N*	*W1098C*	
Based on *in vitro* Data‡							
1507_1515del9	*D443Y;G576A;R668C§*	*F587I*	*H1085R*	*L137P*	*Q1313K*	*R347L*	*T1086I*
2183A->G	*D513G*	*G1047R*	*H1375P*	*L1480P*	*Q237E*	*R352W*	*T1246I*
3141del9	*D565G*	*G1061R*	*H139R*	*L15P*	*Q237H*	*R516G*	*T1299I*
3195del6	*D579G*	*G1069R*	*H199R*	*L165S*	*Q359R*	*R516S*	*T338I*
3199del6	*D614G*	*G1123R*	*H199Y*	*L333F*	*Q372H*	*R555G*	*T351I*
546insCTA	*D924N*	*G1247R*	*H609R*	*L333H*	*Q452P*	*R560S*	*T604I*
A1006E	*D979V*	*G1249R*	*H620P*	*L346P*	*Q493R*	*R560T*	*V1153E*
A1067P	*D993Y*	*G126D*	*H939R;H949L§*	*L441P*	*Q552P*	*R74Q*	*V1240G*
A1067T	*E116K*	*G1349D*	*I105N*	*L453S*	*Q98R*	*R74W*	*V1293G*
A107G	*E116Q*	*G149R*	*I1139V*	*L619S*	*R1048G*	*R74W;D1270N§*	*V201M*

A120T	*E193K*	*G178R*	*I1234Vdel 6aa*	*M1101R*	*R1066C*	*R74W;V2 01M;D127 0N*§	*V232D*
A234D	*E292K*	*G194R*	*I1269N*	*M1137V*	*R1066L*	*R74W;V2 01M*§	*V392G*
A309D	*E474K*	*G194V*	*I1366N*	*M150K*	*R1066M*	*R751L*	*V456A*
A349V	*E56K*	*G27E*	*I1398S*	*M265R*	*R1070Q*	*R75L*	*V456F*
A46D	*E588V*	*G27R*	*I148N*	*M952I*	*R1070W*	*R933G*	*V520F*
A554E	*E60K*	*G314E*	*I331N*	*M952T*	*R117C*	*S1045Y*	*V603F*
A559T	*E822K*	*G424S*	*I506L*	*N1088D*	*R117C;G 576A;R66 8C*§	*S108F*	*W361R*
A559V	*E92K*	*G463V*	*I506T*	*N1303I*	*R117G*	*S1118F*	*Y1014C*
A561E	*F1016S*	*G480C*	*I601F*	*N1303K*¶	*R117H*	*S1159P*	*Y1032C*
A613T	*F1052V*	*G480S*	*I618T*	*N186K*	*R117L*	*S1255P*	*Y109N*
A62P	*F1074L*	*G551A*	*I980K*	*N187K*	*R117P*	*S13F*	*Y161D*
A72D	*F1099L*	*G551S*	*K1060T*	*P205S*	*R1283M*	*S341P*	*Y161S*
C491R	*F1107L*	*G576A;R6 68C*§	*K162E*	*P574H*	*R1283S*	*S364P*	*Y569C*
D110E	*F191V*	*G622D*	*K464E*	*P5L*	*R258G*	*S492F*	*Y913C*
D110H	*F200I*	*G628R*	*L1011S*	*P67L*	*R297Q*	*S549I*	
D1270N	*F311del*	*G91R*	*L102R*	*P750L*	*R31L*	*S737F*	
D1445N	*F311L*	*G970D*	*L1065P*	*P99L*	*R334L*	*S912L*	
D192G	*F508C;S1 251N*§	*G970S*	*L1324P*	*Q1100P*	*R334Q*	*S977F*	
D443Y	*F575Y*	*H1085P*	*L1335P*	*Q1291R*	*R347H*	*T1036N*	
Based on Extrapolation#							
1898+3A →G	*2789+5G →A*	*3272-26A→G*	*3849+10kbC→T*	*3849+4A →G*	*4005+2T →C*	*5T;TG13*	*711+3A→ G*
2789+2insA	*3041-15T→G*	*3600G→A*	*3849+40A →G*	*3850-3T→G*	*5T;TG12*	*621+3A→ G*	*E831X*

Abbreviations: IVA: ivacaftor; TEZ: tezacaftor

* Based on the mechanism of action of vanzacaftor/tezacaftor/deutivacaftor, *CFTR* gene mutations that do not allow for the production of CFTR protein are not expected to respond to ALYFTREK.

† Clinical data is obtained from Studies 121-102 and 121-103.

‡ *CFTR* mutations were responsive to ALYFTREK or were responsive to IVA and/or TEZ/IVA *in vitro* in the FRT cell lines and response to ALYFTREK is therefore expected.

§ 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.

¶ The *N1303K* mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with *in vitro* data are supported by FRT assay.

[#] Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

10.2. Pharmacodynamics

Effects on Sweat Chloride

Sweat chloride levels were evaluated in Phase 3 clinical trials in CF patients, who were treated with elexacaftor/tezacaftor/ivacaftor for 4 weeks prior to randomized treatment with ALYFTREK or elexacaftor/tezacaftor/ivacaftor (Studies 121-102 and 121-103) during the treatment periods.

In Study 121-102 (CF patients 12 years and older heterozygous for a *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor [minimal function mutation]), the treatment difference of ALYFTREK compared to elexacaftor/tezacaftor/ivacaftor for mean absolute change in SwCl from baseline through Week 24 was -8.4 mmol/L (95% CI: -10.5, -6.3; P < 0.0001).

In Study 121-103 (CF patients 12 years and older homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation), the treatment difference of ALYFTREK compared to elexacaftor/tezacaftor/ivacaftor for mean absolute change in SwCl from baseline through Week 24 was -2.8 mmol/L (95% CI: -4.7, -0.9; *P* = 0.0034).

In Study 121-105, Cohort B1 (an open-label clinical study in patients aged 6 to less than 12 years with at least one mutation that is responsive to elexacaftor/tezacaftor/ivacaftor), the mean absolute change in SwCl from baseline through Week 24 was -8.6 mmol/L (95% CI: -11.0, -6.3).

Cardiovascular Effects

Cardiac Electrophysiology

Vanzacaftor: In a randomized, double-blind, placebo- and positive-controlled study in healthy adult subjects, vanzacaftor doses with exposures corresponding up to 6 times over those observed with the vanzacaftor maximum recommended dose, the QTc interval was not prolonged to any clinically relevant extent.

Tezacaftor: In a randomized, double-blind, placebo- and positive-controlled, ECG assessment study in healthy adult subjects, at tezacaftor doses up to 3 times the maximum recommended dose of 100 mg once daily, the QTcF interval was not prolonged to any clinically relevant extent.

Deutivacaftor: In a randomized, double-blind, placebo- and positive-controlled, ECG assessment study of ivacaftor in healthy adult subjects, at ivacaftor doses up to 3 times the maximum recommended dose of 150 mg twice daily, the QTcF interval was not prolonged to any clinically relevant extent. Based on the similarity between deutivacaftor and ivacaftor, and the exposures at the high concentrations, these results support an expected similar risk of QTc prolongation for deutivacaftor.

10.3. Pharmacokinetics

The pharmacokinetics of vanzacaftor, tezacaftor and deutivacaftor are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of

vanzacaftor/tezacaftor/deutivacaftor, plasma concentrations reach steady state within 20 days for vanzacaftor, and within 8 days for tezacaftor and deutivacaftor.

Upon dosing vanzacaftor/tezacaftor/deutivacaftor to steady state, the accumulation ratio based on AUC is approximately 6.09 for vanzacaftor, 1.92 for tezacaftor, and 1.74 for deutivacaftor. Key pharmacokinetic parameters for vanzacaftor/tezacaftor/deutivacaftor at steady state in patients with CF aged 12 years and older are shown in Table 9.

Table 9: Mean (SD) Pharmacokinetic Parameters of Vanzacaftor, Tezacaftor and Deutivacaftor at Steady State in Patients with CF Aged 12 Years and Older

Dose	Drug	C_{max} (mcg/mL)	Effective $t_{½}$ (h)	AUC_{0-24h} (mcg·h/mL)	Apparent Clearance* (L/hr)	Apparent Volume of Distribution (L)
Vanzacaftor 20 mg/ tezacaftor 100 mg/ deutivacaftor 250 mg once daily	Vanzacaftor	0.812 (0.344)	92.8 (30.2)	18.6 (8.08)	1.34 (0.819)	121 (28.6)
	Tezacaftor	6.77 (1.24)	22.5 (5.85)	89.5 (28.0)	1.22 (0.390)	73.1 (13.3)
	Deutivacaftor	2.33 (0.637)	19.2 (8.71)	39.0 (15.3)	7.29 (2.68)	159 (26.1)

SD= Standard Deviation, AUC = Area Under the Curve; C_{max} = peak maximum concentration.

Absorption

Vanzacaftor, tezacaftor, and deutivacaftor are absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 7.80 hours (3.70 to 11.9 hours), 1.60 hours (1.40 to 1.70 hours), and 3.7 hours (2.7 to 11.4 hours), respectively.

Following administration of ALYFTREK tablets (2 x 10 mg/50 mg/125 mg) under low fat, low calorie and high fat, high calorie fed conditions there was an increase in vanzacaftor and deutivacaftor AUC_T and C_{max} up to approximately 497% and 534%, and 320% and 437%, respectively when compared to administration under fasting conditions. The effect of food (both meal types) resulted in an increase in tezacaftor AUC_T by approximately 13-21% but did not have an effect on tezacaftor C_{max} when compared to administration under fasting conditions. As a result, ALYFTREK should be administered with fat-containing food [see *4.2 Recommended Dose and Dosage Adjustment*].

Distribution

Vanzacaftor and deutivacaftor are > 99% bound to plasma protein primarily to albumin and alpha-1-acid glycoprotein. Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin.

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent volume of distribution of vanzacaftor, tezacaftor and deutivacaftor was 121 L (28.6), 73.1 L (13.3), and 159 L (26.1), respectively. Vanzacaftor, tezacaftor and deutivacaftor do not partition preferentially into human red blood cells.

Metabolism

Vanzacaftor is metabolized extensively in humans, mainly by CYP3A4/5. Vanzacaftor has no major circulating metabolites.

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 three 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.

Deutivacaftor is primarily metabolized by CYP3A4/5 to form the 2 major circulating metabolites, M1-D-IVA and M6-D-IVA. Relative to ivacaftor, deutivacaftor exhibited more metabolic stability and formed less M1-D-IVA, the deuterated equivalent of M1-IVA. M1-D-IVA has approximately one-fifth the potency of deutivacaftor, and is considered pharmacologically active. M6-D-IVA is the other major metabolite of deutivacaftor, the deuterated equivalent of M6-IVA, and is not considered pharmacologically active.

Elimination

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent clearance values of vanzacaftor, tezacaftor and deutivacaftor were 1.34 (0.819) L/h, 1.22 (0.390) L/h and 7.29 (2.68) L/h, respectively. The mean (SD) terminal half-lives of vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor fixed-dose combination tablets are approximately 54.0 (10.1) hours, 92.4 (23.1) hours and 17.3 (2.67) hours, respectively. The mean (SD) effective half-lives of vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor fixed-dose combination tablets are approximately 92.8 (30.2) hours, 22.5 (5.85) hours and 19.2 (8.71) hours, respectively.

Excretion

Following oral administration of ^{14}C-vanzacaftor alone (91.6%), the majority of radioactivity was eliminated in 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 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.

Preclinical data indicate that the majority of ^{14}C-deutivacaftor and ^{14}C-ivacaftor are excreted in the feces. Major excreted metabolites of deutivacaftor were M1-D-IVA and M6-D-IVA, and major excreted metabolites for ivacaftor were M1-IVA and M6-IVA. The excretion of deutivacaftor in humans is expected to be similar to that of ivacaftor, based on similar structure (deuterated isotopologue) and non-clinical data.

After oral administration of ^{14}C-ivacaftor alone, the majority of ivacaftor (87.8%) was eliminated in feces after metabolic conversion. There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of ivacaftor was recovered in the urine).

Special populations and conditions

- **Pediatrics (6 to < 18 years of age):**

Vanzacaftor, tezacaftor and deutivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 10. Vanzacaftor, tezacaftor and deutivacaftor exposures in CF patients aged 6 to less than 18 years are within

the range observed in adults with CF.

Table 10. Mean (SD) Vanzacaftor, Tezacaftor and Deutivacaftor Exposures by Age Group					
Age group	**Weight (N)**	**Dose**	**Vanzacaftor AUC_{0-24h} (mcg·h/mL)**	**Tezacaftor AUC_{0-24h} (mcg·h/mL)**	**Deutivacaftor AUC_{0-24h} (mcg·h/mL)**
6 to < 12 years	< 40 kg (N=70)	vanzacaftor 12 mg qd/ tezacaftor 60 mg qd/ deutivacaftor 150 mg qd	13.0 (4.90)	69.1 (20.7)	30.2 (11.6)
	≥ 40 kg (N=8)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 250 mg qd	18.6 (7.49)	101 (33.7)	48.5 (18.7)
12 to < 18 years	(N=66)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 250 mg qd	15.8 (6.52)	93.0 (32.5)	37.1 (15.3)
≥ 18 years	(N=414)		19.0 (8.22)	89.0 (27.2)	39.3 (15.3)
SD: Standard Deviation; AUC_{0-24h}: area under the concentration versus time curve at steady state; qd: once daily					

- **Pediatrics (< 6 years of age):**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for children less than 6 years of age [see *7.1 Special Populations*].

- **Geriatrics:**

Clinical studies of ALYFTREK did not include a sufficient number of patients aged 65 years and older to determine whether they respond differently from younger CF patients. [see *7.1 Special Populations*].

- **Sex:**

Based on population PK analysis, there are no clinically relevant differences in exposures of vanzacaftor, tezacaftor and deutivacaftor between males and females.

- **Pregnancy and breastfeeding:**

No adequate and well-controlled studies of ALYFTREK in pregnant women have been conducted. Animal studies assessing the reproductive and developmental toxicity in pregnant rats and rabbits were not conducted with concomitant administration of vanzacaftor, tezacaftor, and deutivacaftor. Animal studies conducted using vanzacaftor or tezacaftor did not demonstrate harmful effects with respect to reproductive toxicity in pregnant rats and rabbits. Because animal reproduction studies are not always predictive of human response, ALYFTREK should be used during pregnancy only if the potential benefits outweigh the potential risks [see *7.1 Special Populations*].

It is unknown if the components of ALYFTREK (vanzacaftor, tezacaftor, deutivacaftor), or their metabolites are excreted in human milk. Vanzacaftor and tezacaftor are excreted into the milk of lactating female rats. The effect of deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats. ALYFTREK should be used during breastfeeding only if the potential benefits outweigh the potential risks to the infant [see *7.1 Special Populations*].

- **Hepatic Insufficiency:**

Vanzacaftor/tezacaftor/deutivacaftor have not been studied in subjects with severe hepatic impairment (Child-Pugh Class C). Following a single dose of vanzacaftor/tezacaftor/deutivacaftor, subjects with moderate hepatic impairment had an approximately 30% lower total vanzacaftor exposures, comparable total tezacaftor exposures, and 20% lower total deutivacaftor exposures compared to healthy subjects matched for demographics.

- **Renal Insufficiency:**

Urinary excretion of vanzacaftor, tezacaftor, and deutivacaftor is negligible [see *Elimination* section].

Vanzacaftor alone or in combination with tezacaftor and deutivacaftor has not been studied in CF patients with severe renal impairment (eGFR less than 30 mL/min) or in CF patients with end-stage renal disease. Based on population pharmacokinetic (PK) analysis, exposure of vanzacaftor was similar in patients with mild renal impairment (N = 126; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 580; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of tezacaftor was similar in patients with mild renal impairment (N = 172; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 8; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 637; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of deutivacaftor was similar in patients with mild (N = 132; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 577; eGFR 90 mL/min/1.73 m^2 or greater) [see *4.2 Recommended Dose and Dosage Adjustment*].

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.

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Use established “collection systems” if available.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substances: vanzacaftor calcium dihydrate/tezacaftor/deutivacaftor

Chemical name: vanzacaftor calcium dihydrate: calcium bis((14*S*)-8-[3-(2-{dispiro[2.0.2⁴.1³]heptan-7-yl}ethoxy)pyrazol-1-yl]-12,12-dimethyl-2,2,4-trioxo-2λ⁶-thia-3,9,11,18,23-pentaazatetracyclo[17.3.1.1¹¹,¹⁴.0⁵,¹⁰]tetracosa-1(23),5,7,9,19,21-hexaen-3-ide) dihydrate

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

deutivacaftor: *N*-(2-(*tert*-butyl)-5-hydroxy-4-(2-(methyl-d_3)propan-2-yl-1,1,1,3,3,3-d_6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

Molecular formula and molecular mass:

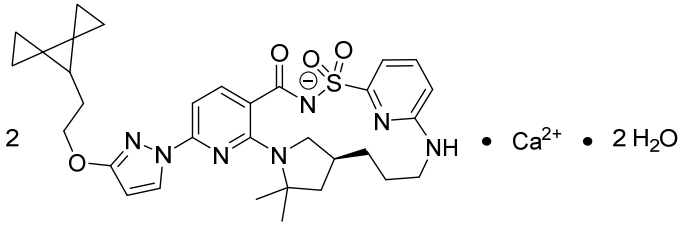
vanzacaftor calcium dihydrate: $C_{32}H_{38}N_7O_4S \cdot Ca_{0.5} \cdot H_2O$; 654.82

tezacaftor: $C_{26}H_{27}N_2F_3O$; 520.50

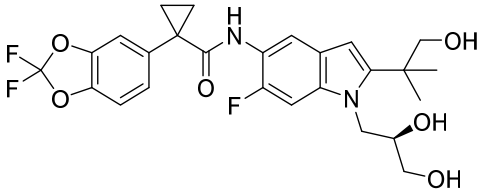
deutivacaftor: $C_{24}H_{19}D_9N_2O_3$; 401.55

Structural formula:

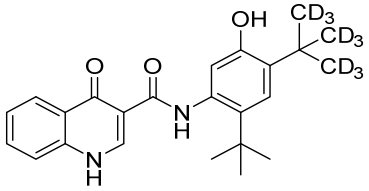
vanzacaftor calcium dihydrate



tezacaftor



deutivacaftor



Physicochemical properties: vanzacaftor calcium dihydrate is a white solid that is practically insoluble in water (< 0.1 mg/mL).

tezacaftor is a white to off-white powder that is practically

insoluble in water (< 5 µg/mL).

deutivacaftor is a white to off-white powder that is practically insoluble in water (< 0.1 µg/mL).

14. Clinical Trials

14.1. Clinical Trials by Indication

CF Patients Aged 6 years and Older

The efficacy of ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) in patients with CF aged 12 years and older who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene was evaluated in two Phase 3, randomized, double-blind, active-controlled studies (Study 121-102 and Study 121-103) comparing ALYFTREK and a fixed-dose combination of elexacaftor/tezacaftor/ivacaftor. The pharmacokinetic profile, safety, and efficacy of ALYFTREK in patients aged 6 to less than 12 years are supported with evidence from studies of ALYFTREK in CF patients aged 12 years and older (Study 121-102 and Study 121-103) with additional data from patients aged 6 to less than 12 years in an open-label, phase 3 study (Study 121-105, Cohort B1).

A summary of demographic data for clinical trials with ALYFTREK is presented in Table 11.

Table 11: Summary of Demographics for Clinical Trials in CF Patients

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 121-102 (patients heterozygous for the *F508del* mutation and a minimal function mutation [F/MF])	Randomized, double-blind, active-controlled, parallel-group, multicentre	Run-in for 4 weeks: Elexacaftor 200 mg qd/ Tezacaftor 100 mg qd/ Ivacaftor 150 mg q12h Randomized 1:1 to: Vanzacaftor 20 mg qd/ Tezacaftor 100 mg qd/ Deutivacaftor 250 mg qd or Elexacaftor 200 mg qd/ Tezacaftor 100 mg qd/ Ivacaftor 150 mg q12h Oral 52 weeks	398	30.8 years (12 to 72)	Male: 59% Female: 41%

Study 121-103 (patients homozygous for the *F508del* mutation [F/F], heterozygous for *F508del* mutation and a gating or residual function [F/G or F/RF] mutation, or have at least 1 triple combination responsive [TCR] *CFTR* mutation without *F508de*l [TCR/non-F])	Randomized, double-blind, active-controlled, parallel-group, multicentre	Run-in for 4 weeks: Elexacaftor 200 mg qd/ Tezacaftor 100 mg qd/ Ivacaftor 150 mg q12h Randomized 1:1 to: Vanzacaftor 20 mg qd/ Tezacaftor 100 mg qd/ Deutivacaftor 250 mg qd or Elexacaftor 200 mg qd/ Tezacaftor 100 mg qd/ Ivacaftor 150 mg q12h Oral 52 weeks	573	33.7 years (12 to 71)	Male: 51% Female: 49%
Study 121-105, Cohort B1 (patients with at least one TCR mutation [including *F508del*] in the *CFTR* gene)	Open-label, 2-part, multicohort, multicentre	Run-in for 4 weeks (for subjects not on stable elexacaftor/tezacaftor/ivacaftor): < 30 kg Elexacaftor 100 mg qd/ Tezacaftor 50 mg qd/ Ivacaftor 75 mg q12h ≥ 30 kg Elexacaftor 200 mg qd/ Tezacaftor 100 mg qd/ Ivacaftor 150 mg q12h Assigned to: < 40 kg Vanzacaftor 12 mg qd/ Tezacaftor 60 mg qd/ Deutivacaftor 150 mg qd ≥ 40 kg Vanzacaftor 20 mg qd/ Tezacaftor 100 mg qd/ Deutivacaftor 250 mg qd Oral 24 weeks	78	9.1 years (6 to 12)	Male: 56% Female: 44%

Studies 121-102 and 121-103

Study 121-102 was a 52-week, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled study in patients with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function [MF] mutation). A total of 398 CF patients aged 12 years and older received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive ALYFTREK or elexacaftor/tezacaftor/ivacaftor during the 52-week treatment period. Patients had a mean age of 30.8 years, 59% were male, 97.5% were White and 14% were aged 12 to < 18 years. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 67.1 percentage points (range: 28.0, 108.6), and the mean SwCl at baseline was 53.9 mmol/L (range: 10.0 mmol/L, 113.5 mmol/L).

Study 121-103 was a 52-week, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled study in 573 patients with CF aged 12 years and older who had one of the following genotypes: homozygous for the *F508de*l mutation (F/F; n=446 [78%]), heterozygous for the *F508del* mutation and either a gating (F/G; n=39 [6.8%]) or a residual function mutation (F/RF; n=46 [8.0%]), or at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation (triple-combination responsive [TCR]/non-F; n=42 [7.3%]). Patients had a mean age of 33.7 years, 51% were male, 92.8% were White and 14% were aged 12 to < 18 years. Patients received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive ALYFTREK or elexacaftor/tezacaftor/ivacaftor during the 52-week treatment period. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 66.8 percentage points (range: 36.4, 112.5) and the mean SwCl at baseline was 42.8 mmol/L (range: 10.0 mmol/L, 113.3 mmol/L).

Patients with a history of intolerance to elexacaftor/tezacaftor/ivacaftor were excluded from Studies 121-102 and 121-103 because all patients were to receive elexacaftor/tezacaftor/ivacaftor during the run-in period.

In both studies, the primary endpoint evaluated non-inferiority in mean absolute change in $ppFEV_1$ from baseline through Week 24. A key secondary endpoint evaluated superiority in mean absolute change from baseline in SwCl through Week 24.

In Study 121-102, treatment with ALYFTREK resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.7, 1.1) in absolute change in $ppFEV_1$ from baseline through Week 24 compared to elexacaftor/tezacaftor/ivacaftor. In Study 121-103, treatment with ALYFTREK resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.5, 0.9) in absolute change in $ppFEV_1$ from baseline through Week 24 compared to elexacaftor/tezacaftor/ivacaftor.

As the lower bounds of the 95% CI of the absolute change in $ppFEV_1$ from baseline through Week 24 were greater than -3.0 percentage points (the pre-specified non-inferiority margin) in Study 121-102 and Study 121-103, these results demonstrate non-inferiority of ALYFTREK compared to elexacaftor/tezacaftor/ivacaftor.

In both studies, the mean absolute change from baseline in $ppFEV_1$ through Week 24 was maintained through Week 52.

In Study 121-102 and Study 121-103, ALYFTREK was superior to elexacaftor/tezacaftor/ivacaftor on all key secondary endpoints. On the first key secondary endpoint, when compared to elexacaftor/tezacaftor/ivacaftor, treatment with ALYFTREK resulted in a reduction of -8.4 mmol/L (95% CI: -10.5, -6.3; $P < 0.0001$) and -2.8 mmol/L (95% CI: -4.7, -0.9; $P = 0.0034$) in SwCl through Week 24, in Studies 121-102 and 121-103, respectively.

Other secondary endpoints (pulmonary exacerbation rate, change in CFQ-R RD score from baseline) demonstrated consistent benefit between ALYFTREK and elexacaftor/tezacaftor/ivacaftor.

The results for other secondary endpoints not controlled for multiplicity evaluated in Studies 121-102 and 121-103, including the rate of pulmonary exacerbations through Week 52 and absolute change from baseline in CFQ-Revised respiratory domain score through Week 24, were similar between ALYFTREK and elexacaftor/tezacaftor/ivacaftor treatment groups. The difference in the rate of pulmonary exacerbations through Week 52 was -0.10 (95%: CI 0.24, 0.04) in Study 102 and 0.03 (95% CI: 0.07, 0.13) in Study 103. The absolute change from baseline in CFQ-R respiratory domain score through Week 24 was 2.3 (95%: CI 0.6, 5.2) in Study 102) and was 0.1 (95% CI: 2.3, 2.1) in Study 103.

See Table 12 for a summary of key efficacy outcomes for Studies 121-102 and 121-103.

Table 12: Efficacy Analyses from Study 121-102 and Study 121-103 in Patients 12 Years and Older

Analysis*	Statistic	Study 121-102		Study 121-103	
		ALYFTREK N = 196	ELX/TEZ/IVA N = 202	ALYFTREK N = 284	ELX/TEZ/IVA N = 289
Primary					
Baseline ppFEV$_1$	Mean (SD)	67.0 (15.3)	67.2 (14.6)	67.2 (14.6)	66.4 (14.9)
Absolute change in ppFEV$_1$ from baseline through Week 24 (percentage points)	n	187	193	268	276
	LS mean (SE)	0.5 (0.3)	0.3 (0.3)	0.2 (0.3)	0.0 (0.2)
	LS mean difference, 95% CI	0.2 (-0.7, 1.1)		0.2 (-0.5, 0.9)	
	P-value (1-sided) for Non-Inferiority#	< 0.0001		< 0.0001	
Key Secondary					
Baseline SwCl	Mean (SD)	53.6 (17.0)	54.3 (18.2)	43.4 (18.5)	42.1 (17.9)
Absolute change from baseline in SwCl through Week 24 (mmol/L)	n	185	194	270	276
	LS mean (SE)	-7.5 (0.8)	0.9 (0.8)	-5.1 (0.7)	-2.3 (0.7)
	LS mean difference, 95% CI	-8.4 (-10.5, -6.3)		-2.8 (-4.7, -0.9)	
	P-value (2-sided)	< 0.0001		0.0034	

ppFEV$_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SD: Standard Deviation; SE: Standard Error; SwCl: Sweat Chloride; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.
Note: Analyses were based on the full analysis set (FAS). FAS was defined as all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug.
* A 4-week ELX/TEZ/IVA run-in-period was performed to establish an on-treatment baseline.
# The pre-specified non-inferiority margin was -3.0 percentage points.

Study 121-105

Study 121-105 was a 24-week, multicenter, open-label study in CF patients aged 6 to less than 12 years with at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor (genotypes: F/F [47% of patients], F/MF [31%], F/G [3.8%]. F/RF [1.3%], TCR/F [6.4%] and TCR/non-F [7.7%]). Cohort B1 evaluated the safety, tolerability, and efficacy of ALYFTREK. A total of 78 patients aged 6 to less than 12 years were dosed according to weight. All patients were treated with elexacaftor/tezacaftor/ivacaftor (dosed according to weight) for at least 4 weeks prior to baseline and receiving ALYFTREK in the 24-week treatment period (see Table 11). Patients had a mean age at baseline of 9.1 years and a mean weight of 30.2 kg, 56% were

male, and 91% were White. The mean $ppFEV_1$ at baseline, on elexacaftor/tezacaftor/ivacaftor treatment, was 99.7 percentage points (range: 29, 146.0), and the mean SwCl at baseline was 40.4 mmol/L (range: 11.5 mmol/L, 109.5 mmol/L).

Patients with a history of intolerance to elexacaftor/tezacaftor/ivacaftor were excluded from Study 121-105.

Safety, pharmacokinetics and tolerability were the primary endpoints. Secondary efficacy endpoints included: absolute change in $ppFEV_1$, absolute change in SwCl, absolute change in CFQ-R respiratory domain score, and number of pulmonary exacerbations (PEx) through Week 24. The results for ALYFTREK through Week 24 showed consistency with baseline values (following treatment with elexacaftor/tezacaftor/ivacaftor prior to the treatment period with ALYFTREK) in $ppFEV_1$. The absolute change from baseline in SwCl through Week 24 was -8.6 mmol/L (95% CI -11.0, -6.3) and the absolute change in CFQ-R Respiratory Domain score was 3.9 (95% CI 1.5, 6.3) points.

The effectiveness of ALYFTREK in patients aged 6 to less than 12 years of age was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing vanzacaftor, tezacaftor and deutivacaftor exposure levels in patients aged 6 to less than 12 years within the range of exposures observed in patients aged 12 years and older.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

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

Vanzacaftor

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

Repeat dose toxicity:

Animal studies evaluated once daily oral administration of vanzacaftor in male and female rats and dogs for 26 weeks and 39 weeks respectively. No adverse effects were noted in male and female rats up to doses of 12 mg/kg/day and 12.5 mg/kg/day respectively (yielding a safety margin of approximately 21-fold and 59-fold in male and female rats respectively based on AUC of vanzacaftor at MRHD) and 10 mg/kg/day dose in male and female dogs (safety margin of approximately 103-fold based on AUC of vanzacaftor at MRHD).

Carcinogenicity:

Vanzacaftor was non-mutagenic and non-clastogenic in the *in vitro* bacterial gene mutation assay- Ames test, *in vitro* micronucleus assay in TK6 cells, and *in vivo* rat micronucleus assay. A 6-month carcinogenicity study conducted in Tg.rasH2 mice demonstrated no evidence of tumorigenicity at the highest dose evaluated in the study of 30 mg/kg/day dose (a safety margin of approximately 27 times the AUC measured at the MRHD).

Reproductive and Developmental Toxicology:

Vanzacaftor had no effects on fertility and early embryonic development in rats at oral doses up

to 12.5 mg/kg/day in males and 10 mg/kg/day for females (approximately 19 times for males and 30 times for females the maximum recommended human dose [MRHD] based on AUC of vanzacaftor).

In the embryo-fetal developmental studies conducted in pregnant rats, administration of vanzacaftor during the period of organogenesis from gestational day 6-17 did not demonstrate any adverse effects to the fetus at doses up to 10 mg/kg/day in rats (an exposure approximately 30 times higher based on the AUC of vanzacaftor at MRHD). Embryo-fetal developmental study conducted in pregnant rabbits during gestational days 6-20 did not demonstrate adverse effects on either does or offspring at doses up to 40 mg/kg/day (approximately 22 times the MRHD based on the AUC of vanzacaftor).

In a pre-natal and post-natal development study in female rats, administration of vanzacaftor at oral doses of up to 10 mg/kg/day (approximately 18 times the exposure measured at the MRHD) from gestational day 6 to post natal day 18, did not cause any adverse effects in the pups. Vanzacaftor was detected in the plasma of lactating pups suggestive of transfer of vanzacaftor through breast milk.

Placental transfer of vanzacaftor was observed in pregnant rats.

Juvenile study:

Administration of vanzacaftor to male and female juvenile rats from post-natal days 7 to 70 was well tolerated and showed no adverse effects at doses up to 25 mg/kg/day in male and 12.5 mg/kg/day in females (28 times and 58 times the exposure measured at the MRHD for males and females, respectively).

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.

Carcinogenicity:

Tezacaftor was shown to be non-carcinogenic in a 6-month trial in Tg.rasH2 transgenic mice up to the oral dose of 500 mg/kg/day (approximately 2.6 times the MRHD based on the sum of AUCs of tezacaftor and M1-TEZ). No evidence of tumorigenicity was observed in a 2-year trial in Sprague-Dawley rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 2 and 4 times the MRHD based on the sum of AUCs of tezacaftor and M1-TEZ).

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

Reproductive and Developmental Toxicology:

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

Placental transfer of tezacaftor was observed in pregnant rats.

Deutivacaftor

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

Deutivacaftor is a deuterated isotopologue of ivacaftor with a toxicity profile similar to ivacaftor based on a 13-week single-agent repeat-dose toxicity study; therefore, reproductive and developmental toxicity data and carcinogenicity data from ivacaftor are expected to be comparable to deutivacaftor.

Carcinogenicity:

Two-year studies in CD-1 mice and Sprague-Dawley rats to assess carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures of ivacaftor on an AUC basis in mice at the non-carcinogenic dose (200 mg/kg/day, the highest dose tested) were approximately 2 times the MHRD based on the sum of AUCs of ivacaftor and its metabolites). Plasma exposures of ivacaftor on an AUC basis in rats at the non-carcinogenic dose (50 mg/kg/day, the highest dose tested) were approximately 6 times (males) and 9 times (females) the MHRD based on the sum of the AUCs of ivacaftor and its metabolites).

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

Reproductive and Developmental Toxicology:

The effect of deutivacaftor on fertility and pregnancy has not been evaluated; however, 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 13 times the MRHD based on AUC of ivacaftor). Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day dose (approximately 15 times the MRHD based on AUC of ivacaftor).

In pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day (approximately 8 times the MRHD), 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 Toxicity:

Findings of cataracts were observed in juvenile rats dosed from post-natal Days 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.3 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 post-natal 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 [see *7 Warnings and Precautions*].

Vanzacaftor/tezacaftor/deutivacaftor

A 13-week repeat-dose toxicity study in rats involving the co-administration of vanzacaftor, tezacaftor and deutivacaftor to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions.

17. Supporting Product Monographs

KALYDECO (ivacaftor): Tablets 150 mg, Granules 13.4 mg, 25 mg, 50 mg and 75 mg per packet, Control number 273575, Product Monograph, Vertex Pharmaceuticals (Canada) Incorporated (November 27, 2023).

SYMDEKO (tezacaftor/ivacaftor): Tablets tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg, Control number 237289 Product Monograph, Vertex Pharmaceuticals (Canada) Incorporated (August 21, 2020).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrALYFTREK™

Vanzacaftor/tezacaftor/deutivacaftor tablets

This Patient Medication Information is written for the person who will be taking **ALYFTREK**. 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 **ALYFTREK**, talk to a healthcare professional.

Serious warnings and precautions box

Liver disorder: ALYFTREK may worsen your liver function, even if you have no prior liver disease. This can lead to serious liver problems. Serious liver problems, including liver transplant and even death have occurred in people taking elexacaftor/tezacaftor/ivacaftor, a medicine that has the same or similar ingredients to ALYFTREK.

Your healthcare professional will order some blood tests to check your liver:

- before you start treatment with ALYFTREK,
- every 3 months during the first year of treatment,
- every year thereafter while you are taking ALYFTREK.

Your healthcare professional may order blood tests to check your liver more often if you:

- have or ever had abnormal liver blood test results,
- have a history of liver problems, or
- have never taken elexacaftor, tezacaftor or ivacaftor.

If you have any of these symptoms while taking ALYFTREK, **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 ALYFTREK is used for:

ALYFTREK is used for the treatment of cystic fibrosis (CF) in patients 6 years 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 ALYFTREK.

How ALYFTREK works:

- The *CFTR* gene provides instructions to your cells to make CFTR protein. This protein helps take chloride ions in and out of the cells in many organs in your body.

- Patients with CF have a lower amount of the CFTR protein and/or reduced function of the CFTR protein.
- ALYFTREK contain three active substances:
    - vanzacaftor and tezacaftor: these are CFTR correctors. They increase the amount of CFTR protein at the surface of the cell.
    - deutivacaftor: 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 ALYFTREK are:

Medicinal ingredients: vanzacaftor calcium/tezacaftor/deutivacaftor

Non-medicinal ingredients:

Tablet core:	Croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate
Tablet film coat:	Brilliant Blue FCF aluminum lake/FD&C Blue #1, carmine, hydroxypropyl cellulose, hypromellose, iron oxide red, talc, titanium dioxide

ALYFTREK comes in the following dosage forms:

Film-coated Tablets:

- 4 mg vanzacaftor (as vanzacaftor calcium)/20 mg tezacaftor/50 mg deutivacaftor (purple, round-shaped tablet marked with “V4”)
- 10 mg vanzacaftor (as vanzacaftor calcium)/50 mg tezacaftor/125 mg deutivacaftor (purple, capsule-shaped tablet marked with “V10”)

Do not use ALYFTREK if:

- You are allergic to vanzacaftor, tezacaftor, deutivacaftor or any of the non-medicinal ingredients (listed in **The ingredients in ALYFTREK are**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALYFTREK. Talk about any health conditions or problems you may have, including if you:

- Have liver problems (including liver disease) or have had them previously.
- Have taken another medicine containing tezacaftor or ivacaftor before and temporarily or permanently stopped because of side effects. Your healthcare professional may want to see you more often.
- Have kidney problems, or you have previously had them.
- Are a woman and taking hormonal contraceptives.
- Are pregnant or plan to become pregnant. It is not known if ALYFTREK will harm your unborn baby. You and your healthcare professional should decide if you will take ALYFTREK while you are pregnant.
- Are breastfeeding or planning to breastfeed. It is not known if ALYFTREK can pass into your breast milk. You and your healthcare professional should decide if you should take ALYFTREK while you are breastfeeding.

Other warnings you should know about:

Cataracts: Cloudiness of the eye lens (cataract) without any effect on vision has been seen in some children and adolescents taking ivacaftor. Ivacaftor is similar to deutivacaftor, an ingredient in ALYFTREK. Your healthcare professional may perform eye exams before and

during treatment with ALYFTREK.

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 ALYFTREK:

- Medicines used to treat fungal infections (such as fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole).
- Medicines used to treat bacterial infections (such as clarithromycin, erythromycin, rifampin, and rifabutin).
- Medicines used to treat seizures (such as phenobarbital, carbamazepine, and phenytoin).
- St. John's wort (*Hypericum perforatum*), an herbal medicine.
- Medicines used after an organ transplant (such as cyclosporine, everolimus, sirolimus, and tacrolimus).
- Efavirenz (a medicine used for the treatment of HIV-1 infection).
- Digoxin (a medicine used to treat congestive heart failure or a heart rhythm problem called atrial fibrillation).
- Warfarin (a medicine used to prevent blood clots from forming or growing bigger).
- Medicines that are substrates of the breast cancer resistance protein (BCRP; such as methotrexate and glyburide).
- Medicines used to treat diabetes (such as glimepiride and glipizide).
- Medicines for lowering blood pressure (such as verapamil).
- Grapefruit, grapefruit juice or products that contain grapefruit. Avoid food and drinks containing grapefruit while taking ALYFTREK.

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 ALYFTREK:

- Always take ALYFTREK exactly as your healthcare professional tells you. Check with your healthcare professional if you are not sure.
- Do not change the dose or stop taking ALYFTREK without first talking to your healthcare professional.
- **Always take ALYFTREK 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.
- To remove the tablets, push it through the blister strip.
- **Swallow the tablets whole** with food that contains fat. Do NOT chew, crush, break or dissolve the tablets.
- Avoid food and drinks containing grapefruit while you are taking ALYFTREK.

Usual dose:

- Your healthcare professional will determine the correct dose for you. This may depend on your health condition, your weight and other medicines you are taking.
- The usual dose of ALYFTREK in patients aged 6 years and older is as follows:

Age	Weight	Daily Dose (once daily)
6 years and older	Less than 40 kg	**Three** vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg tablets
	40 kg or more	**Two** vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg tablets

- Take your medicine at approximately the same time each day.

Overdose:

If you think you, or a person you are caring for, have taken too much ALYFTREK, contact a healthcare professional, hospital emergency department, or 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.

Missed dose:

If you:

Missed taking a dose and it has been **less than 6 hours:**	• **Take the missed dose** with fat-containing food as soon as you can. • Then take your next dose at your usual time with fat-containing food.
Missed taking a dose and it has been **more than 6 hours:**	• **Skip the missed dose.** • Then take your next dose at your usual time with fat-containing food.

- **Do not** take 2 doses at the same time to make up for your missed dose.

Possible side effects from using ALYFTREK:

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

Very common side effects (may affect more than 1 in 10 people)
- Headache
- Diarrhea

Common side effects (may affect up to 1 in 10 people)
- Rash
- Changes in blood tests results:
  - Increased liver enzymes (signs of stress on the liver)
  - Increased creatine phosphokinase (sign of muscle breakdown)

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 problems			√

Pain or discomfort in the upper right area of the stomach (abdominal) area, yellowing of the skin or the white part of the eyes, loss of appetite, nausea or vomiting, dark urine, pale stool, itchy skin.			

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 ALYFTREK:

- 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.vrtx.ca; or by calling 1-877-634-8789.

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

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