

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALYFTREK safely and effectively. See full prescribing information for ALYFTREK.

ALYFTREK (vanzacaftor, tezacaftor, and deutivacaftor tablets), for oral use

Initial U.S. Approval: 2024

WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE

See full prescribing information for complete boxed warning.

- Elevated transaminases have been observed in patients treated with ALYFTREK (5.1, 6).
- Cases of serious and potentially fatal drug-induced liver injury and liver failure leading to transplantation and death were reported in patients who were taking ELX/TEZ/IVA, a drug containing the same or similar active ingredients as ALYFTREK (5.1).
- Assess liver function tests (ALT, AST, alkaline phosphatase, bilirubin) in all patients prior to initiating ALYFTREK, every month for first 6 months, every 3 months for next 12 months, then at least annually (2.1, 5.1).
- Interrupt ALYFTREK for significant elevations in LFTs or signs or symptoms of liver injury. Follow patients closely with clinical and laboratory monitoring until abnormalities resolve (5.1).
- Resume ALYFTREK if abnormalities resolve and only if the benefit is expected to outweigh the risk (5.1).
- 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) (2.4, 5.1, 8.7, 12.3).

RECENT MAJOR CHANGES

Indications and Usage (1)	03/2026
Warnings and Precautions, Intracranial Hypertension (5.4)	09/2025
Warnings and Precautions, Neuropsychiatric Events, Including Suicidal Thoughts and Behaviors (5.5)	03/2026

INDICATIONS AND USAGE

ALYFTREK is a combination of deutivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor indicated for the treatment of cystic fibrosis (CF) in adult and pediatric patients aged 6 years and older who have a clinical diagnosis of CF and who have at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of CFTR protein. (1, 12.1)

If the patient's genotype is unknown, an FDA-cleared CF genetic test should be used to confirm the presence of at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of CFTR protein. (1)

DOSAGE AND ADMINISTRATION

Prior to initiating ALYFTREK obtain liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients. Monitor liver function tests every month during the first 6 months of treatment, then every 3 months during the next 12 months, then at least annually thereafter. (2.1, 5.1)

Recommended Dosage for Adult and Pediatric Patients Aged 6 Years and Older (with fat-containing food) (2.2)		
Age	Weight	Once Daily Oral Dosage
6 to less than 12 years old	Less than 40 kg	Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
	Greater than or equal to 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg
12 years and older	Any Weight	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg

- Should not be used in patients with severe hepatic impairment. Use not recommended in patients with moderate hepatic impairment unless the benefit outweighs the risk. If used, no dose adjustment is recommended. Liver function tests should be closely monitored. (2.4, 5.1, 6.1, 8.7)

- See full prescribing information for dosage modifications for concomitant use of ALYFTREK with strong or moderate CYP3A inhibitors. (2.3, 5.7, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- Fixed-dose combination containing vanzacaftor 4 mg, tezacaftor 20 mg, and deutivacaftor 50 mg. (3)
- Fixed-dose combination containing vanzacaftor 10 mg, tezacaftor 50 mg, and deutivacaftor 125 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Drug-Induced Liver Injury and Liver Failure:** Elevated transaminases have been observed in patients treated with ALYFTREK. Cases of serious and potentially fatal drug-induced liver injury and liver failure have been reported with a drug that contains the same or similar active ingredients as ALYFTREK. Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating and throughout treatment with ALYFTREK. Interrupt ALYFTREK in the event of significant elevations in liver function tests or signs or symptoms of liver injury. 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). (2.4, 5.1, 8.7)
- Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing setting for drugs containing elxacaftor, tezacaftor, and/or ivacaftor. If signs or symptoms of serious hypersensitivity reactions develop during ALYFTREK treatment, discontinue ALYFTREK and initiate appropriate therapy. (5.2)
- Patients Who Discontinued or Interrupted Elxacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions:** Consider benefits and risks before using ALYFTREK in patients who discontinued or interrupted elxacaftor-, tezacaftor-, or ivacaftor-containing drugs due to adverse reactions. If ALYFTREK is used, closely monitor for adverse reactions as clinically appropriate. (5.3)
- Intracranial Hypertension:** Intracranial hypertension (IH) has been reported in the postmarketing setting with use of drugs containing the same or similar active ingredients as ALYFTREK. If an unusual headache or visual disturbances occur during treatment, and IH is suspected, interrupt ALYFTREK and refer for prompt medical evaluation. (5.4)
- Neuropsychiatric Events, Including Suicidal Thoughts and Behaviors:** Serious neuropsychiatric events, including symptoms of anxiety, depression, suicidal ideation and behavior, and sleep disturbances, have been reported in the postmarketing setting for ALYFTREK or drugs containing the same or similar active ingredients. Monitor patients closely for new or worsening symptoms. Consider the risks and benefits for the individual patient to determine if therapy with ALYFTREK should be interrupted at the occurrence of neuropsychiatric symptoms. (5.5)
- Reduced Effectiveness in Patients with Concomitant Use with CYP3A Inducers:** Concomitant use with strong and moderate CYP3A inducers decreased vanzacaftor, tezacaftor, and deutivacaftor exposure, which may reduce ALYFTREK efficacy. Therefore, concomitant use is not recommended. (5.6, 7.1)
- Adverse Reactions with Concomitant Use with CYP3A Inhibitors:** Concomitant use with strong or moderate CYP3A inhibitors increased vanzacaftor, tezacaftor, and deutivacaftor exposure, which may increase the risk of ALYFTREK associated adverse reactions. Reduce the ALYFTREK dosage with concomitant use. (2.3, 5.7, 7.1)
- Cataracts:** Non-congenital lens opacities/cataracts have been reported in patients with CF aged 18 years or less treated with drugs containing ivacaftor. Baseline and follow up ophthalmological examinations are recommended in pediatric patients treated with ALYFTREK. (5.8, 8.4)

ADVERSE REACTIONS

Most common adverse reactions to ALYFTREK ($\geq 5\%$ of patients and at a frequency higher than ELX/TEZ/IVA by $\geq 1\%$) were cough, nasopharyngitis, upper respiratory tract infection, headache, oropharyngeal pain, influenza, fatigue, increased ALT, rash, increased AST, and sinus congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**DRUG INTERACTIONS**-----

- **Strong or moderate CYP3A inducers:** Concomitant use with ALYFTREK is not recommended. (5.6, 7.1)
- **Strong or moderate CYP3A inhibitors:** Reduce ALYFTREK dosage with concomitant use. Avoid food or drink containing grapefruit. (2.3, 5.7, 7.1)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Revised: 03/2026

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FULL PRESCRIBING INFORMATION

WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE

Elevated transaminases have been observed in patients treated with ALYFTREK. Cases of serious and potentially fatal drug-induced liver injury and liver failure were reported in patients who were taking a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor, which contains the same or similar active ingredients as ALYFTREK. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of elexacaftor/tezacaftor/ivacaftor [see *Warnings and Precautions (5.1) and Adverse Reactions (6)*].

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating ALYFTREK, every month during the first 6 months of treatment, then every 3 months for the next 12 months, then at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or elevated liver function tests at baseline [see *Dosage and Administration (2.1), Warnings and Precautions (5.1), Adverse Reactions (6), and Use in Specific Populations (8.7)*].

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 *Warnings and Precautions (5.1)*].

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 benefit outweighs the risk. If used, monitor patients closely [see *Dosage and Administration (2.4), Warnings and Precautions (5.1), Adverse Reactions (6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)*].

1 INDICATIONS AND USAGE

ALYFTREK is indicated for the treatment of cystic fibrosis (CF) in adult and pediatric patients 6 years of age and older who have a clinical diagnosis of CF and who have at least one variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is either responsive based on clinical and/or in vitro data (see Table 5) or results in production of *CFTR* protein [see *Clinical Pharmacology (12.1)*].

If the patient's genotype is unknown, an FDA-cleared CF genetic test should be used to confirm the presence of at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of *CFTR* protein.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Laboratory Testing Prior to ALYFTREK Initiation and During Treatment

Prior to initiating ALYFTREK, obtain liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) for all patients. Monitor liver function tests every month during the first 6 months of treatment, then every 3 months for the next 12 months, then at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease, elevated liver function tests at baseline, or a history of elevated liver function tests with drugs containing elexacaftor, tezacaftor, and/or ivacaftor [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.7)*].

2.2 Recommended Dosage

The recommended ALYFTREK dosage in adult and pediatric patients aged 6 years and older is provided in Table 1. Administer ALYFTREK orally (swallow the tablets whole) with fat-containing food, once daily, at approximately the same time each day [see *Clinical Pharmacology (12.3)*]. 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.

Age	Weight	Once Daily Oral Dosage
6 to less than 12 years old	Less than 40 kg	Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg (total dose of vanzacaftor 12 mg/tezacaftor 60 mg/ deutivacaftor 150 mg)
	Greater than or equal to 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg)
12 years and older	Any weight	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg)

2.3 Dosage Modification for Strong or Moderate CYP3A Inhibitors

Table 2 describes the recommended dosage modification for ALYFTREK when used concomitantly with strong or moderate CYP3A inhibitors [see *Warnings and Precautions* (5.7)]. Administer ALYFTREK orally (swallow the tablets whole) with fat-containing food, once daily, at approximately the same time each day [see *Clinical Pharmacology* (12.3)].

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
6 to less than 12 years old	Less than 40 kg	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg every other day (total dose of vanzacaftor 8 mg/tezacaftor 40 mg/deutivacaftor 100 mg)	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg once a week (total dose of vanzacaftor 8 mg/tezacaftor 40 mg/deutivacaftor 100 mg)
	Greater than or equal to 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
12 years and older	Any weight	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

2.4 Recommended Dosage for Patients with Hepatic Impairment

- **Severe Hepatic Impairment (Child-Pugh Class C):** ALYFTREK should not be used in patients with severe hepatic impairment (HI) (Child-Pugh Class C).
- **Moderate Hepatic Impairment (Child-Pugh Class B):** The use of ALYFTREK in patients with moderate HI (Child-Pugh Class B) is not recommended. Use of ALYFTREK should only be considered in patients with moderate HI when there is a clear medical need, and the benefit outweighs the risk. If used, the recommended dosage in patients with moderate HI is the same as for patients with normal hepatic function. Liver function tests should be closely monitored [see *Dosage and Administration* (2.1, 2.2)].
- **Mild Hepatic Impairment (Child-Pugh Class A):** The recommended dosage of ALYFTREK in patients with mild HI (Child-Pugh Class A) is the same as in patients with normal hepatic function. Liver function tests should be closely monitored [see *Dosage and Administration* (2.1, 2.2)].

2.5 Recommendations Regarding Missed Dose(s)

If 6 hours or less have passed since the missed dose, take the missed dose as soon as possible and continue on the original schedule.

If more than 6 hours have passed since the missed dose, skip the missed dose, and continue on the original schedule the next day.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- Fixed-dose combination containing vanzacaftor 4 mg (equivalent to 4.24 mg of vanzacaftor calcium dihydrate), tezacaftor 20 mg, and deutivacaftor 50 mg. Each tablet is purple, round-shaped, film-coated, debossed with “V4” on one side and plain on the other.
- Fixed-dose combination containing vanzacaftor 10 mg (equivalent to 10.6 mg of vanzacaftor calcium dihydrate), tezacaftor 50 mg, and deutivacaftor 125 mg. Each tablet is purple, oblong-shaped, film-coated, debossed with “V10” on one side and plain on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Drug-Induced Liver Injury and Liver Failure

Elevated transaminases have been observed in patients treated with ALYFTREK [see *Adverse Reactions* (6.1)]. Cases of serious and potentially fatal drug-induced liver injury and liver failure have been reported in patients with and without a history of liver disease who were taking a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA), which contains the same or similar active ingredients as ALYFTREK. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of ELX/TEZ/IVA.

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating ALYFTREK. Assess liver function tests every month during the first 6 months of treatment, then every 3 months for the next 12 months, then at least annually thereafter. Consider more frequent monitoring in patients with a history of liver disease, elevated liver function tests at baseline, or a history of elevated liver function tests with drugs containing ELX, TEZ and/or IVA. [see *Dosage and Administration (2.4) and Use in Specific Populations (8.7)*].

Interrupt ALYFTREK in the event of signs or symptoms of liver injury. These may include:

- Significant elevations in liver function tests (e.g., ALT or AST $>5\times$ the upper limit of normal (ULN) or ALT or AST $>3\times$ ULN with bilirubin $>2\times$ ULN)
- Clinical signs or symptoms suggestive of liver injury (e.g., jaundice, right upper quadrant pain, nausea, vomiting, altered mental status, ascites)

Consider referral to a hepatologist and follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If abnormalities resolve and if the benefit is expected to outweigh the risk, resume ALYFTREK treatment with close monitoring.

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 benefit outweighs the risk. If used, monitor patients closely [see *Dosage and Administration (2.4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)*].

5.2 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the postmarketing setting of drugs containing ELX, TEZ, and/or IVA (the same or similar active ingredients in ALYFTREK). If signs or symptoms of serious hypersensitivity reactions develop during ALYFTREK treatment, discontinue ALYFTREK and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ALYFTREK.

5.3 Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions

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

5.4 Intracranial Hypertension

Cases of intracranial hypertension (IH) have been reported in the postmarketing setting with the use of drugs containing the same or similar active ingredients as ALYFTREK [see *Adverse Reactions (6.2)*]. Clinical manifestations of IH include headache, blurred vision, diplopia, and potential vision loss; papilledema can be found on fundoscopy. If an unusual headache or visual disturbances occur during treatment, and IH is suspected, interrupt ALYFTREK and refer for prompt medical evaluation. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ALYFTREK. Patients should be monitored until IH resolution and for recurrence. Patients with elevated vitamin A levels may be at increased risk.

5.5 Neuropsychiatric Events, Including Suicidal Thoughts and Behaviors

Serious neuropsychiatric events, including symptoms of anxiety, depression, suicidal ideation and behavior, and sleep disturbances, have been reported in the postmarketing setting in patients taking ALYFTREK or drugs containing the same or similar active ingredients [see *Adverse Reactions (6.2)*]. The events were reported in adult and pediatric patients with and without a previous history of neuropsychiatric symptoms. Symptoms may occur within the first three months of treatment initiation.

Assess patients for baseline neuropsychiatric symptoms and monitor for new or worsening symptoms of anxiety, depression, suicidal ideation or behavior, or sleep disturbances. Consider the benefits and risks for the individual patient to determine if therapy with ALYFTREK should be interrupted at the occurrence of neuropsychiatric symptoms and whether to resume therapy with symptom improvement.

5.6 Reduced Effectiveness with Concomitant Use with CYP3A Inducers

Following concomitant use of strong or moderate CYP3A inducers with ALYFTREK, exposures of vancacaftor, tezacaftor, and deutivacaftor were decreased, which may reduce ALYFTREK effectiveness. Concomitant use with strong or moderate CYP3A inducers is not recommended [see *Drug Interactions (7.1)*].

5.7 Adverse Reactions with Concomitant Use with CYP3A Inhibitors

Following concomitant use of strong or moderate CYP3A inhibitors with ALYFTREK, exposures of vancacaftor, tezacaftor, and deutivacaftor were increased, which may increase the risk of ALYFTREK-associated adverse reactions. Reduce the ALYFTREK

dosage with concomitant use of strong or moderate CYP3A inhibitors [see *Dosage and Administration (2.3)* and *Drug Interactions (7.1)*].

5.8 Cataracts

Cases of non-congenital lens opacities have been reported in pediatric patients treated with drugs containing ivacaftor (which is similar to an active ingredient in ALYFTREK). Although other risk factors were present (such as corticosteroid use, exposure to radiation) in some cases, a possible risk attributable to ivacaftor treatment cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients treated with ALYFTREK [see *Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

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

- Drug-Induced Liver Injury and Liver Failure [see *Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions, Including Anaphylaxis [see *Warnings and Precautions (5.2)*]
- Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions [see *Warnings and Precautions (5.3)*]
- Intracranial Hypertension [see *Warnings and Precautions (5.4)*]
- Neuropsychiatric Events, Including Suicidal Thoughts and Behaviors [see *Warnings and Precautions (5.5)*]
- Cataracts [see *Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

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

The adverse reactions data below are from clinical trials of ALYFTREK in patients 6 years of age and older with CF with at least one responsive *CFTR* variant who were able to tolerate ELX/TEZ/IVA. Adverse reactions data in patients who previously discontinued or interrupted ELX/TEZ/IVA due to adverse reactions are not available.

Adverse Reactions in Patients Aged 12 Years and Older with CF

The safety of ALYFTREK is based on 480 patients with CF aged 12 years and older who have at least one *F508del* variant or another responsive variant in the *CFTR* gene in two, 52-week, active-controlled trials (Trials 1 and 2) [see *Clinical Studies (14)*]. In both trials, patients received a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA) in a 4-week run-in period and then were subsequently randomized to continue ELX/TEZ/IVA (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening) or receive ALYFTREK (vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg) once daily. Patients with a history of prior intolerance to ELX/TEZ/IVA (i.e., patients who discontinued or interrupted treatment due to adverse reactions) were excluded. Trials 1 and 2 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 ELX/TEZ/IVA Prescribing Information.

In Trial 1 and Trial 2 combined, the proportion of patients who discontinued treatment prematurely due to adverse reactions were 3.8% and 3.7% in ALYFTREK and ELX/TEZ/IVA treatment groups, respectively.

Serious adverse reactions that occurred more frequently with ALYFTREK treatment than with ELX/TEZ/IVA treatment that occurred in 2 or more patients ($\geq 0.4\%$) were influenza (1.5%), increased AST (0.4%), increased GGT (0.4%), depression (0.4%), and syncope (0.4%).

Table 3: Adverse Reactions Occurring in $\geq 5\%$ of ALYFTREK-Treated Patients and $\geq 1\%$ Higher than ELX/TEZ/IVA-Treated Patients Aged 12 Years and Older with CF Who Had at Least One <i>F508del</i> Variant or Responsive Variant in the <i>CFTR</i> Gene (Trials 1 and 2)		
Adverse Reactions	ALYFTREK N=480	ELX/TEZ/IVA N=491
Cough*	120 (25%)	116 (24%)
Nasopharyngitis	102 (21%)	95 (19%)
Upper respiratory tract infection†	101 (21%)	97 (20%)
Headache	76 (16%)	63 (13%)
Oropharyngeal pain	69 (14%)	60 (12%)
Influenza	52 (11%)	26 (5%)

Fatigue	51 (11%)	46 (9%)
ALT increased	38 (8%)	29 (6%)
Rash	37 (8%)	22 (4%)
AST increased	33 (7%)	27 (5%)
Sinus congestion	32 (7%)	15 (3%)
* Cough is composed of several similar terms including productive cough.		
† Upper respiratory tract infection is composed of several similar terms including viral upper respiratory tract infection.		
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELX, elxacaftor; IVA, ivacaftor; TEZ, tezacaftor		

Adverse events that occurred in $\geq 5\%$ of ELX/TEZ/IVA-treated patients at a similar or higher incidence than the ALYFTREK-treated patients included: infective pulmonary exacerbation of CF, COVID-19, diarrhea, abdominal pain, pyrexia, nasal congestion, increased sputum, increased blood creatinine phosphokinase, rhinorrhea, hemoptysis, nausea, back pain, arthralgia, constipation, sinusitis, dyspnea, and vomiting.

Liver Function Test Elevations

The incidence of adverse reactions of transaminase elevations was 9% in ALYFTREK-treated patients and 7.1% in ELX/TEZ/IVA-treated patients in Trials 1 and 2. In these trials, 1.5% of ALYFTREK-treated patients and 0.6% of ELX/TEZ/IVA-treated patients discontinued treatment for elevated transaminases. Table 4 shows the incidence of maximum transaminase (ALT or AST) elevations in Trials 1 and 2.

Table 4: Number and Incidence of Maximum Transaminase Elevation in Patients Aged 12 Years and Older with CF Who Had at Least One <i>F508del</i> Variant or Responsive Variant in the <i>CFTR</i> Gene (Trials 1 and 2)		
Maximum ALT or AST Elevation	ALYFTREK N=480	ELX/TEZ/IVA* N=491
>3 × ULN	29 (6%)	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, elxacaftor; IVA, ivacaftor; TEZ, tezacaftor.		
* Trials 1 and 2 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.		

Rash

In Trials 1 and 2, the incidence of rash (e.g., rash, rash pruritic) was 11% in ALYFTREK-treated patients and 7.7% in ELX/TEZ/IVA-treated patients. The rashes were generally mild to moderate in severity. The incidence of rash was 9.4% in males and 13% in females with ALYFTREK treatment and 7.6% in males and 7.9% in females with ELX/TEZ/IVA treatment. A role of hormonal contraceptives in the occurrence of rash cannot be excluded [see *Drug Interactions (7.3)*].

Increased Creatine Phosphokinase

In Trials 1 and 2, the incidence of maximum creatine phosphokinase $> 5 \times$ the ULN was 7.9% with ALYFTREK treatment and 6.5% with ELX/TEZ/IVA treatment. Discontinuation due to increased creatinine phosphokinase was 0.2% for ALYFTREK-treated patients and 0.2% for ELX/TEZ/IVA-treated patients. Cases of rhabdomyolysis without renal involvement have been reported in patients who had recently exercised taking a fixed-dose combination drug containing ELX/TEZ/IVA (the same or similar active ingredients as ALYFTREK).

Increased Blood Pressure

Elevations in mean systolic and diastolic blood pressure have been reported in patients taking a fixed-dose combination drug containing ELX/TEZ/IVA (the same or similar active ingredients as ALYFTREK). The proportion of patients who had systolic blood pressure > 140 mmHg and > 10 mmHg increase from baseline on at least two occasions was 3.5% in ALYFTREK-treated patients and 3.3% in ELX/TEZ/IVA-treated patients. The proportion of patients who had diastolic blood pressure > 90 mmHg and > 5 mmHg increase from baseline on at least two occasions was 1.7% in ALYFTREK-treated patients and 1.8% in ELX/TEZ/IVA-treated patients. The mean systolic and diastolic blood pressures remained in the normal range from both ALYFTREK and ELX/TEZ/IVA treatment arms.

Adverse Reactions in Pediatric Patients Aged 6 to Less Than 12 Years with CF

A 24-week, open-label trial of ALYFTREK was conducted in 78 patients with CF aged 6 to less than 12 years with at least one variant responsive to ELX/TEZ/IVA (Trial 3). In Trial 3, patients who weighed less than 40 kg received ALYFTREK (vanzacaftor 12 mg/tezacaftor 60 mg/deutivacaftor 150 mg once daily) and patients who weighed 40 kg or more received ALYFTREK (vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg once daily). Adverse reactions for these patients were generally

similar to those reported in Trial 1 and Trial 2. In Trial 3, the incidence of maximum transaminase (ALT or AST) >3×, >5×, and >8× ULN were 3.8%, 1.3%, and 0%, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ALYFTREK or drugs containing the same or similar active ingredients as ALYFTREK. 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.

Nervous System Disorders: intracranial hypertension

Psychiatric Disorders: anxiety, depression, suicidal ideation and behavior, insomnia

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs and Grapefruit on ALYFTREK

Strong or Moderate CYP3A Inducers

Concomitant use of ALYFTREK with strong or moderate CYP3A inducers is not recommended.

Vanzacaftor, tezacaftor, and deutivacaftor are substrates of CYP3A. Concomitant use of ALYFTREK with a strong or moderate CYP3A inducer decreases vanzacaftor, tezacaftor, and deutivacaftor exposure [see *Clinical Pharmacology (12.3)*] which may reduce ALYFTREK effectiveness [see *Warnings and Precautions (5.6)*].

Strong or Moderate CYP3A Inhibitors

Reduce the ALYFTREK dosage when used concomitantly with a strong or moderate CYP3A inhibitor [see *Dosage and Administration (2.3)*].

Vanzacaftor, tezacaftor, and deutivacaftor are CYP3A substrates. Concomitant use with a strong CYP3A inhibitor increases vanzacaftor, tezacaftor, and deutivacaftor exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of ALYFTREK adverse reactions [see *Warnings and Precautions (5.7)*]. Concomitant use with a moderate CYP3A inhibitor is predicted to increase vanzacaftor, tezacaftor, and deutivacaftor exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of ALYFTREK adverse reactions [see *Warnings and Precautions (5.7)*].

Grapefruit

Food or drink containing grapefruit should be avoided during treatment with ALYFTREK. Concomitant use of ALYFTREK with grapefruit juice which contains one or more components that moderately inhibit CYP3A may increase exposure of vanzacaftor, tezacaftor and deutivacaftor.

7.2 Effect of ALYFTREK on Other Drugs

P-glycoprotein (P-gp) Substrates

Unless otherwise recommended in the P-gp substrate Prescribing Information, monitor more frequently for adverse reactions with concomitant use of ALYFTREK with P-gp substrates where minimal concentration changes may lead to serious adverse reactions related to P-gp substrates.

Tezacaftor and deutivacaftor (components of ALYFTREK) are P-gp inhibitors. Administration of tezacaftor/ivacaftor increases exposure of P-gp substrates [see *Clinical Pharmacology (12.3)*], which may increase the risk of adverse reactions related to these substrates.

Breast Cancer Resistance Protein (BCRP) Substrates

Unless otherwise recommended in the BCRP substrate Prescribing Information, monitor more frequently for adverse reactions with concomitant use of ALYFTREK with BCRP substrates where minimal concentration changes may lead to serious adverse reactions related to BCRP substrates.

Vanzacaftor (VNZ) and deutivacaftor (D-IVA) (components of ALYFTREK) 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 [see *Clinical Pharmacology (12.3)*].

CYP2C9 Substrates

Use caution when ALYFTREK is used concomitantly with CYP2C9 substrates. Monitor the international normalized ratio (INR) more frequently with concomitant use of ALYFTREK with warfarin.

This recommendation is based upon a mechanistic understanding of deutivacaftor pharmacokinetics (it is an inhibitor of CYP2C9 *in vitro*) [see *Clinical Pharmacology (12.3)*]. Concomitant use of ALYFTREK with CYP2C9 substrates may increase exposure of these substrates; however, this has not been studied clinically.

7.3 Drugs with No Clinically Significant Interactions with ALYFTREK

Ciprofloxacin

No clinically relevant effect on the exposure of tezacaftor was observed when tezacaftor/ivacaftor was used concomitantly with ciprofloxacin [see *Clinical Pharmacology (12.3)*].

Hormonal Contraceptives

No clinically significant differences in the pharmacokinetics of ethinyl estradiol/norethindrone containing hormonal contraceptives were observed when used concomitantly with tezacaftor in combination with ivacaftor and ivacaftor alone [see *Clinical Pharmacology (12.3)*]. No clinically significant differences in the pharmacokinetics of ethinyl estradiol/norethindrone containing hormonal contraceptives are expected when used in combination with ALYFTREK based upon a mechanistic understanding of vanzacaftor, tezacaftor, and deutivacaftor pharmacokinetics [see *Clinical Pharmacology (12.3)*]; however, this has not been studied clinically.

A role for hormonal contraceptives contributing to rash cannot be excluded [see *Adverse Reactions (6.1)*]. For patients with CF taking hormonal contraceptives who develop rash, consider interrupting ALYFTREK and hormonal contraceptives. Following the resolution of rash, consider resuming ALYFTREK without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on ALYFTREK use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although there are no animal reproduction studies with the concomitant administration of vanzacaftor, tezacaftor, and deutivacaftor, separate reproductive and developmental studies were conducted with vanzacaftor and tezacaftor in pregnant rats and rabbits. Deutivacaftor is a deuterated isotopologue of ivacaftor with a toxicity profile similar to ivacaftor. Reproductive and development studies were conducted with ivacaftor in pregnant rats and rabbits.

In animal embryo fetal development (EFD) studies, oral administration of vanzacaftor to pregnant rats and rabbits during organogenesis demonstrated no adverse developmental effects at doses that produced maternal exposures up to approximately 30 times the exposure at the maximum recommended human dose (MRHD) in rats and 22 times the MRHD in rabbits. Oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the MRHD in rats and 0.2 times the MRHD in rabbits (based on summed AUCs of tezacaftor and the metabolite M1-TEZ). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no adverse developmental effects at doses that produced maternal exposures up to approximately 8 and 9 times the exposure at the MRHD, respectively (based on AUC of ivacaftor for rats and rabbits). No adverse developmental effects were observed after oral administration of vanzacaftor, tezacaftor, or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 18 times, 1 time, and 8 times the exposures at the MRHD, respectively (based on AUCs of vanzacaftor, tezacaftor and M1-TEZ, and ivacaftor) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Vanzacaftor: In an EFD study, pregnant rats were administered vanzacaftor at oral doses of 2.5, 5, and 10 mg/kg/day during the period of organogenesis from gestation Days 6-17. Vanzacaftor did not cause adverse effects to the fetus at exposures up to 30 times the MRHD (based on AUC for vanzacaftor at maternal doses up to 10 mg/kg/day). In an EFD study, pregnant rabbits were administered vanzacaftor at oral doses of 10, 40, and 70 mg/kg/day during the period of organogenesis from gestation Days 7-20. Vanzacaftor did not cause adverse effects to the fetus at exposures up to 22 times the MRHD (based on AUC of vanzacaftor at maternal doses up to 40 mg/kg/day). The high dose of 70 mg/kg/day (71 times the exposure at the MRHD) produced maternal toxicity (i.e., mortality, abortion, decreased mean body weight or body weight gains) and was associated with findings of increased post-implantation loss, decreased live fetuses, decreased fetal body weight, and increased kidney malformations. In a pre- and postnatal development (PPND) study in pregnant rats administered vanzacaftor at oral doses of 2.5, 5, and 10 mg/kg/day from gestation Day 6 through lactation Day 18, vanzacaftor did not cause adverse developmental effects in pups at maternal doses up to

10 mg/kg/day (approximately 18 times the exposure at the MRHD). Placental transfer of vanzacaftor was observed in pregnant rats.

Tezacaftor: In an EFD study, pregnant rats were administered tezacaftor at oral doses of 25, 50, and 100 mg/kg/day during the period of organogenesis from gestation Days 6-17. Tezacaftor did not cause adverse effects to the fetus at exposures up to 3 times the MRHD (based on summed AUCs of tezacaftor and M1-TEZ). Maternal toxicity in rats was observed at ≥ 50 mg/kg/day (approximately ≥ 1 time the MRHD). In an EFD study, pregnant rabbits were administered tezacaftor at oral doses of 10, 25, and 50 mg/kg/day during the period of organogenesis from gestation Days 7-20. Tezacaftor did not cause adverse effects to the fetus at exposures up to 0.2 times the MRHD (based on summed AUCs of tezacaftor and M1-TEZ). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 1 time the MRHD (based on summed AUCs of tezacaftor and M1-TEZ at a maternal dose of 50 mg/kg/day). In a PPND study, pregnant rats were administered tezacaftor at oral doses of 25, 50, and 100 mg/kg/day from gestation Day 6 through lactation Day 18. Tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening, and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 2 times the exposure at the MRHD (based on summed AUCs for tezacaftor and M1-TEZ). Placental transfer of tezacaftor was observed in pregnant rats.

Deutivacaftor: Animal reproduction studies have not been conducted with deutivacaftor. However, as a deuterated isotopologue of ivacaftor with a toxicity profile similar to ivacaftor based on a 13-week single-agent repeat dose toxicity study, the reproductive and developmental toxicity data from ivacaftor can inform the developmental and reproductive risks associated with deutivacaftor.

In an EFD study, pregnant rats were administered ivacaftor at oral doses of 50, 100, and 200 mg/kg/day during the period of organogenesis from gestation Days 7-17. Ivacaftor did not cause adverse effects to the fetus at exposures up to 8 times the MRHD for deutivacaftor (based on AUC of ivacaftor in animal studies up to 200 mg/kg/day). In an EFD study, pregnant rabbits were administered ivacaftor at oral doses of 25, 50, and 100 mg/kg/day during the period of organogenesis from gestation Days 7-19. Ivacaftor did not cause adverse effects to the fetus at exposures up to 9 times the MRHD for deutivacaftor (based on AUC of ivacaftor in animal studies). Maternal toxicity (i.e., death, decreased food consumption, decreased mean body weight and body weight gain, decreased clinical condition, abortions) was observed at doses greater than or equal to 50 mg/kg/day (approximately 3 times the MRHD). In a PPND study, pregnant rats were administered ivacaftor at oral doses of 50, 100, and 200 mg/kg/day from gestation Day 7 through lactation Day 20. Ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 8 times the MRHD (based on AUC for ivacaftor at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose (200 mg/kg/day, 13 times the exposure at MHRD). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There are no data on the presence of vanzacaftor, tezacaftor, or deutivacaftor or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Vanzacaftor and tezacaftor are excreted into the milk of lactating female rats. Deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ALYFTREK and any potential adverse effects on the breastfed child from ALYFTREK or from the underlying maternal condition.

Data

The concentration of vanzacaftor, tezacaftor, or deutivacaftor in animal milk does not necessarily predict the concentration of drug in human milk.

Vanzacaftor: Lactal excretion of vanzacaftor in rats was demonstrated following a single oral dose (10 mg/kg) of ^{14}C -vanzacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C -vanzacaftor in milk was approximately 0.2 times the value observed in plasma (based on $\text{AUC}_{0-72\text{h}}$).

Tezacaftor: Lactal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C -tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C -tezacaftor in milk was approximately 3.0 times higher than in plasma (based on $\text{AUC}_{0-72\text{h}}$).

Deutivacaftor: Deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats. Lactal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ¹⁴C-ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ¹⁴C-ivacaftor in milk was approximately 1.5 times higher than in plasma (based on AUC_{0-24h}).

8.4 Pediatric Use

The safety and effectiveness of ALYFTREK for the treatment of CF have been established in pediatric patients aged 6 years and older who have a clinical diagnosis of CF and who have at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of CFTR protein. Use of ALYFTREK for this indication was supported by evidence from two adequate and well-controlled trials (Trials 1 and 2) in patients with CF aged 12 years and older who had at least one *F508del* variant or another responsive variant in the *CFTR* gene and additional pharmacokinetic and safety data in pediatric patients with CF aged 6 to less than 12 years who had at least one *F508del* variant or another responsive variant in the *CFTR* gene (Trial 3). In these trials, a total of 145 patients with CF aged 6 to less than 18 years received ALYFTREK including:

- In Trial 1, 26 adolescents aged 12 to less than 18 years who were heterozygous for *F508del* and a *CFTR* variant that is not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function variant) [see *Adverse Reactions (6.1) and Clinical Studies (14)*].
- In Trial 2, 41 adolescents aged 12 to less than 18 years who were homozygous for *F508del* variant, heterozygous for *F508del* variant and either a gating or a residual function variant, or with at least one variant responsive to ELX/TEZ/IVA with no *F508del* variant [see *Adverse Reactions (6.1) and Clinical Studies (14)*].
- In Trial 3, 78 pediatric patients with CF aged 6 to less than 12 years (mean age 9.1 years) with at least one variant that is responsive to ELX/TEZ/IVA [see *Adverse Reactions (6.1)*]. In Trial 3, patients who weighed less than 40 kg patients received ALYFTREK (vanzacaftor 12 mg/tezacaftor 60 mg/deutivacaftor 150 mg once daily) and patients who weighed 40 kg or more received ALYFTREK (vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg once daily).

The efficacy of ALYFTREK in patients aged 6 to less than 12 years for this indication 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 to be within the range of exposures observed in patients aged 12 years and older [see *Clinical Pharmacology (12.3)*].

Safety of ALYFTREK in patients aged 6 to less than 12 years for this indication was based on Trial 3. The overall safety profile of patients in Trial 3 was generally similar to the safety data in adult and pediatric patients 12 years of age and older observed in Trials 1 and 2 [see *Adverse Reactions (6.1)*].

There is a risk of cataracts in pediatric patients treated with ALYFTREK. Perform baseline and follow-up ophthalmological examination in pediatric patients prior to and during treatment with ALYFTREK [see *Warnings and Precautions (5.8)*].

The safety and effectiveness of ALYFTREK in patients younger than 6 years of age have not been established.

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.21 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals [see *Warnings and Precautions (5.8)*].

Studies were conducted with tezacaftor in juvenile rats starting at postnatal day (PND) 21 and ranging up to PNDs 35 to 49. Findings of convulsions and death were observed in juvenile rats that received a tezacaftor dose level of 100 mg/kg/day (approximately equivalent to 1.9 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). A no effect dose level was identified at 30 mg/kg/day (approximately equivalent to 0.8 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period (PND 7, which would be approximately equivalent to a human neonate). 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 6 to 11 years of age, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.

8.5 Geriatric Use

Clinical studies of ALYFTREK did not include a sufficient number of patients with CF aged 65 years and older (n=2, 0.4% of patients treated with ALYFTREK in Trials 1 and 2) to determine whether they respond differently from younger adult patients with CF.

8.6 Renal Impairment

The recommended ALYFTREK dosage in patients with CF with mild to moderate renal impairment (RI) (eGFR 30 to < 90 mL/min/1.73 m²) is the same in patients with CF with normal kidney function. Use of ALYFTREK in patients with CF with severe RI (eGFR <30 mL/min/1.73 m²) or end-stage renal disease is recommended only if the benefits are expected to outweigh the risks.

No clinically significant differences in the pharmacokinetics of vanzacaftor, tezacaftor, or deutivacaftor were observed in patients with mild to moderate RI (eGFR 30 to <90 mL/min/1.73 m²) [see *Clinical Pharmacology* (12.3)]. The effect of severe RI (eGFR <30 mL/min/1.73 m²) on vanzacaftor, tezacaftor, or deutivacaftor pharmacokinetics is unknown [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

Severe Hepatic Impairment

ALYFTREK should not be used in patients with severe hepatic impairment (HI) (Child-Pugh Class C). ALYFTREK has not been studied in patients with CF with severe HI [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

Moderate Hepatic Impairment

The use of ALYFTREK is not recommended in patients with moderate HI (Child-Pugh Class B). Use of ALYFTREK should only be considered in patients with HI when there is a clear medical need, and the benefit outweighs the risk. If used, the recommended dosage in patients with moderate HI is the same as for patients with normal hepatic function. Liver function tests should be closely monitored [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

Mild Hepatic Impairment

The recommended dosage of ALYFTREK in patients with mild HI (Child-Pugh Class A) is the same as in patients with normal hepatic function. Liver function tests should be closely monitored [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

10 OVERDOSAGE

Treatment of overdosage consists of general supportive measures including monitoring of vital signs and observation of the clinical status.

11 DESCRIPTION

ALYFTREK (vanzacaftor, tezacaftor, and deutivacaftor tablets) are fixed-dose combination tablets for oral use available as:

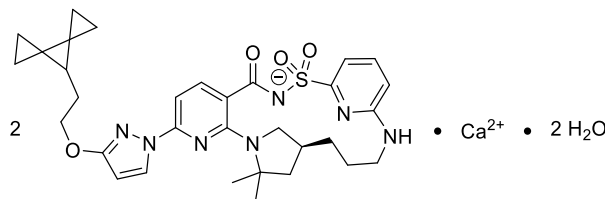
- 10 mg of vanzacaftor (equivalent to 10.6 mg of vanzacaftor calcium dihydrate), 50 mg of tezacaftor, 125 mg of deutivacaftor or
- 4 mg of vanzacaftor (equivalent to 4.24 mg of vanzacaftor calcium dihydrate), 20 mg of tezacaftor, 50 mg of deutivacaftor.

The tablets contain the following inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coating contains Brilliant Blue FCF aluminum lake/FD&C Blue #1, carmine, hydroxypropyl cellulose, hypromellose, iron oxide red, talc, and titanium dioxide.

The active ingredients of ALYFTREK are described below:

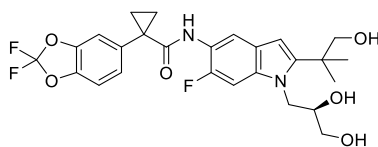
Vanzacaftor

Vanzacaftor is provided as a calcium salt. Vanzacaftor calcium dihydrate is a white solid that is practically insoluble in water (< 0.1 mg/mL). Its chemical name is 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[17.3.1.1^{11,14}.0^{5,10}]tetracos-1(23),5,7,9,19,21-hexaen-3-ide) dihydrate. Its molecular formula is C₃₂H₃₈N₇O₄S·Ca_{0.5}·H₂O and its molecular weight is 654.82. Vanzacaftor calcium dihydrate has the following structural formula:



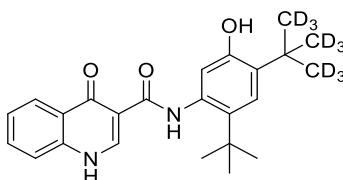
Tezacaftor

Tezacaftor is a white to off-white solid that is practically insoluble in water (< 5 microgram/mL). Its chemical name is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is C₂₆H₂₇N₂F₃O₆ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Deutivacaftor

Deutivacaftor is a white to off-white solid that is practically insoluble in water (< 0.1 mg/mL). Pharmacologically, it is a CFTR potentiator. Its chemical name is *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. Its molecular formula is C₂₄H₁₉D₉N₂O₃ and its molecular weight is 401.55. Deutivacaftor has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vanzacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. 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 in patients with CF.

CFTR Chloride Transport Assay in Fischer Rat Thyroid Cells Expressing Mutant CFTR Protein

Effects of vanzacaftor/tezacaftor/deutivacaftor on chloride transport for mutant CFTR protein was determined in Ussing chamber electrophysiology studies using a panel of Fischer Rat Thyroid (FRT) cell lines stably expressing CFTR protein from individual variants. Vanzacaftor/tezacaftor/deutivacaftor increased chloride transport in FRT cells expressing select *CFTR* variants, as identified in Table 5.

The threshold that the treatment-induced increase in chloride transport must exceed for the mutant CFTR protein to be considered responsive is $\geq 10\%$ of normal over baseline. This threshold was used because it is expected to predict clinical benefit. For individual variants, the magnitude of the net change over baseline in CFTR-mediated chloride transport in vitro is not correlated with the magnitude of clinical response.

CFTR Chloride Transport Assay in Human Bronchial Epithelial Cells Expressing Mutant CFTR Protein

Homozygous and heterozygous *N1303K*- Human Bronchial Epithelial (HBE) cells showed greater chloride transport in the presence of vanzacaftor/tezacaftor/deutivacaftor than *F508del/F508del*-HBE cells treated with tezacaftor/ivacaftor which has shown clinical benefit in people homozygous for *F508del*.

Patient Selection

Select adult and pediatric patients 6 years of age and older for the treatment of CF with ALYFTREK based on a clinical diagnosis of CF and the presence of at least one variant in the *CFTR* gene that is either responsive based on clinical and/or in vitro data or results in production of CFTR protein [see *Indications and Usage (1)*].

ALYFTREK should only be used in patients with a clinical diagnosis of CF. The presence of eligible *CFTR* variant(s) should not be the sole determinant for using ALYFTREK.

Table 5 lists *CFTR* variants responsive to ALYFTREK based on clinical and/or in vitro data in FRT or HBE cells [see *Clinical Studies (14)*].

Table 5: List of <i>CFTR</i> Gene Variants Responsive to ALYFTREK						
Based on Clinical Data*						
A455E	G551D [†]	L1077P [†]	R352Q	S1251N	S945L	W1098C [†]
D1152H	G85E [†]	L206W	R75Q	S549N	V562I	W1282R
F508del [†]	H1054D	M1101K [†]	S1159F	S549R	V754M	Y563N [†]
G1244E	I336K	R1066H				
Based on in vitro Data[‡]						
1140-1151dup	D443Y	G1265V	I1398S	M150R	R1283M	S977F
1461insGAT	D443Y;G576A;R668C [§]	G126D	I148L	M152L	R1283S	S977F;R1438W [§]
1507 1515del9	D513G	G1298V	I148N	M152V	R1438W	T1036N
2055del9	D529G	G1349D	I148T	M265R	R170H	T1053I
2183A→G	D565G	G149R	I148T;H609R [§]	M348K	R248K	T1057R
2851A/G	D567N	G149R;G576A;R668C [§]	I175V	M394L	R258G	T1086A
293A→G	D572N	G178E	I331N	M469V	R297Q	T1086I
3007del6	D579G	G178R	I336L	M498I	R31C	T1246I
3131del15	D58H	G194R	I444S	M952I	R31L	T1299I
3132T→G	D58V	G194V	I497S	M952T	R334L	T1299K
3141del9	D614G	G213E	I502T	M961L	R334Q	T164P
3143del9	D651H	G213E;R668C [§]	I506L	N1088D	R347H	T338I
314del9	D651N	G213V	I506T	N1195T	R347L	T351I
3195del6	D806G	G226R	I506V	N1303I	R347P	T351S
3199del6	D836Y	G239R	I506V;D1168G [§]	N1303K [‡]	R352W	T351S;R851L [§]
3331del6	D924N	G253R	I521S	N186K	R516G	T388M
3410T→C	D979A	G27E	I530N	N187K	R516S	T465I
3523A→G	D979V	G27R	I556V	N396Y	R553Q	T465N
3601A→C	D985H	G314E	I586V	N418S	R555G	T501A
3761T→G	D985Y	G314R	I601F	N900K	R560S	T582S
3791C/T	D993A	G424S	I601T	P1013H	R560T	T604I
3850G→A	D993G	G437D	I618N	P1013L	R600S	T908N
3978G→C	D993Y	G451V	I618T	P1021L	R668C	T990I
4193T→G	E1104K	G461R	I807M	P1021T	R709Q	V1008D
546insCTA	E1104V	G461V	I86M	P111L	R74Q	V1010D
548insTAC	E1126K	G463V	I980K	P1372T	R74Q;R297Q [§]	V1153E
A1006E	E116K	G480C	K1060T	P140S	R74Q;V201M;D1270N [§]	V111
A1025D	E116Q	G480D	K162E	P205S	R74W	V1240G
A1067P	E1221V	G480S	K464E	P439S	R74W;D1270N [§]	V1293G
A1067T	E1228K	G500D	K464N	P499A	R74W;R1070W;D1270N [§]	V1293I
A1067V	E1409K	G545R	K522E	P574H	R74W;S945L [§]	V1415F
A107G	E1433K	G551A	K522Q	P5L	R74W;V201M [§]	V201M
A1081V	E193K	G551R	K951E	P67L	R74W;V201M;D1270N [§]	V232A
A1087P	E217G	G551S	L1011S	P750L	R74W;V201M;L997F [§]	V232D
A120T	E264V	G576A	L102R	P798S	R751L	V317A
A1319E	E282D	G576A;R668C [§]	L102R;F1016S [§]	P988R	R75L	V322M
A1374D	E292K	G576A;S1359Y [§]	L1065P	P99L	R75Q;L1065P [§]	V392G
A141D	E384K	G622D	L1065R	Q1012P	R75Q;N1088D [§]	V456A
A1466S	E403D	G622V	L1227S	Q1100P	R75Q;S549N [§]	V456F

A155P	E474K	G628A	L1324P	Q1209P	R792G	V520F
A234D	E527G	G628R	L1335P	Q1291H	R792Q	V520I
A234V	E56K	G85V	L137P	Q1291R	R810G	V562I;A1006E [§]
A238V	E588V	G91R	L137R	Q1313K	R851L	V562L
A309D	E60K	G930E	L1388P	Q1352H	R933G	V591A
A349V	E822K	G970D	L1480P	Q151K	S1045Y	V603F
A357T	E92K	G970S	L159S	Q179K	S108F	V920L
A455V	F1016S	G970V	L15P	Q237E	S1118F	V920M
A457T	F1052V	H1079P	L15P;L1253F [§]	Q237H	S1159P	V93D
A462P	F1074L	H1085P	L165S	Q237P	S1188L	W1282G
A46D	F1078S	H1085R	L167R	Q30P	S1235R	W202C
A534E	F1099L	H1375N	L210P	Q359K/T360K [§]	S1255P	W361R
A554E	F1107L	H1375P	L293P	Q359R	S13F	W496R
A559T	F191V	H139L	L320V	Q372H	S13P	Y1014C
A559V	F200I	H139R	L327P	Q452P	S158N	Y1032C
A561E	F311del	H146R	L32P	Q493L	S182R	Y1032N
A566D	F311L	H147del	L333F	Q493R	S18I	Y1073C
A613T	F312del	H147P	L333H	Q552P	S18N	Y1092H
A62P	F433L	H199Q	L346P	Q98P	S308P	Y109C
A72D	F508C	H199R	L441P	Q98R	S341P	Y109H
A872E	F508C;S1251N [§]	H199Y	L453S	R1048G	S364P	Y109N
c.1367_1369dup TTG	F508del;R1438 W [§]	H609L	L467F	R1066C	S434P	Y122C
C225R	F575Y	H609R	L558F	R1066G	S492F	Y1381H
C491R	F587I	H620P	L594P	R1066L	S50P	Y161C
C590Y	F587L	H620Q	L610S	R1066M	S519G	Y161D
C866Y	F693L(TTG)	H939R	L619S	R1070P	S531P	Y161S
D110E	F87L	H939R;H949L [§]	L633P	R1070Q	S549I	Y301C
D110H	F932S	H954P	L636P	R1070W	S557F	Y517C
D110N	G1047D	I1023R	L88S	R1162L	S589I	Y569C
D1152A	G1047R	I1027T	L927P	R1162Q	S589N	Y89C
D1270N	G1061R	I105N	L967F;L1096R [§]	R117C	S624R	Y913C
D1270Y	G1069R	I1139V	L967S	R117C;G576A;R 668C [§]	S686Y	Y913S
D1312G	G1123R	I1203V	L973F	R117G	S737F	Y919C
D1377H	G1173S	I1234L	L997F	R117H	S821G	
D1445N	G1237V	I1234Vdel6aa	M1101R	R117L	S898R	
D192G	G1244R	I125T	M1137R	R117L;L997F [§]	S912L	
D192N	G1247R	I1269N	M1137V	R117P	S912L;G1244V [§]	
D373N	G1249E	I1366N	M1210K	R1239S	S912T	
D426N	G1249R	I1366T	M150K	R1283G	S955P	

The list of responsive *CFTR* variants is non-exhaustive. There may be protein-producing *CFTR* variants not listed that respond to treatment with ALYFTREK.

* Clinical data is obtained from Trials 1 and 2.
[†] This variant is also predicted to be responsive by FRT assay with ALYFTREK.
[‡] The N1303K variant is predicted to be responsive only by HBE assay. All other variants predicted to be responsive with in vitro data are supported by FRT assay.
[§] Complex/compound variants where a single allele of the *CFTR* gene has multiple variants; these exist independent of the presence of variants on the other allele.

12.2 Pharmacodynamics

Effects on Sweat Chloride

- In patients with CF heterozygous for *F508del* and a *CFTR* variant that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor [minimal function variant] (Trial 1) the treatment difference of ALYFTREK compared to ELX/TEZ/IVA for mean absolute change in sweat chloride from baseline through Week 24 was -8.4 mmol/L (95% CI: -10.5, -6.3; $P < 0.0001$).
- In patients with CF homozygous for the *F508del* variant, heterozygous for the *F508del* variant and either a gating or a residual function variant, or at least one variant responsive to ELX/TEZ/IVA with no *F508del* variant (Trial 2), the treatment difference of ALYFTREK compared to ELX/TEZ/IVA for mean absolute change in sweat chloride from baseline through Week 24 was -2.8 mmol/L (95% CI: -4.7, -0.9; $P = 0.0034$).
- In an open-label trial in patients with CF aged 6 to less than 12 years with at least one variant that is responsive to ELX/TEZ/IVA (Trial 3) [see Adverse Reactions (6.1)], the mean absolute change in sweat chloride from baseline through Week 24 was -8.6 mmol/L (95% CI: -11.0, -6.3).

The clinical relevance of these differences in sweat chloride has not been established in interventional clinical trials.

Cardiac Electrophysiology

At approximately 6 times the maximum recommended dose of vanzacaftor, clinically significant QTc interval prolongation was not observed. Similarly, in separate studies of tezacaftor and ivacaftor evaluating up to 3 times the respective maximum recommended doses, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

The pharmacokinetic parameters for vanzacaftor, tezacaftor, and deutivacaftor in patients with CF aged 12 years and older are provided in Table 6 as mean (SD) unless otherwise specified. No clinically significant differences in the pharmacokinetics of vanzacaftor, tezacaftor, and deutivacaftor were observed between healthy adult subjects and patients with CF.

Table 6: Pharmacokinetics Parameters of ALYFTREK Components			
	Vanzacaftor	Tezacaftor	Deutivacaftor
Exposure			
C _{max,ss} (mcg/mL)	0.812 (0.344)	6.77 (1.24)	2.33 (0.637)
AUC _{0-24h,ss} (mcg·h/mL)	18.6 (8.08)	89.5 (28.0)	39.0 (15.3)
Time to steady state	within 20 days	within 8 days	within 8 days
AUC Accumulation Ratio	6.09 (1.81)	1.92 (0.337)	1.74 (0.497)
Absorption			
T _{max} * (hours)	7.80 (3.70, 11.9)	1.60 (1.40, 1.70)	3.7 (2.7, 11.4)
<i>Effect of food</i>			
AUC _{inf} †	Increase 4- (low-fat meal) to 6- (high-fat meal) fold	No clinically significant change	Increase 3- (low-fat meal) to 4- (high-fat meal) fold
Distribution‡			
Apparent (oral) volume of distribution (L)	121 (28.6)	73.1 (13.3)	159 (26.1)
Protein Binding§	> 99%	Approximately 99%	> 99%
Elimination			
Effective Half-life (hours)¶	92.8 (30.2)	22.5 (5.85)	19.2 (8.71)
Apparent (oral) Clearance (L/hours)	1.34 (0.819)	1.22 (0.390)	7.29 (2.68)
<i>Metabolism</i>			
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active metabolites	None	M1-TEZ	M1-D-IVA
Metabolite potency (relative to parent)	Not applicable	Similar	Approximately 20%
<i>Excretion #</i>			
Feces	91.6% (primarily metabolites)	72% (unchanged or M2-TEZ) [0.79% as unchanged drug]	Not available
Urine	0.50%	13.7%	Not available
<i>Abbreviations:</i> AUC: area under the concentration versus time curve; SD: Standard Deviation; C _{max} : maximum observed concentration; T _{max} : time of maximum concentration; ss: steady state * Median (range) † When administered with fat-containing meals relative to fasted conditions. Note: The high-fat meal was approximately 800-1000 calories with 50% fat. The low-fat meal was approximately 400-500 calories with 25% fat. ‡ Vanzacaftor, tezacaftor, deutivacaftor do not partition preferentially into human red blood cells. § Vanzacaftor and deutivacaftor bind primarily to albumin and alpha 1-acid glycoprotein. Tezacaftor binds primarily to albumin. ¶ The mean (SD) terminal half-lives of vanzacaftor, tezacaftor, and deutivacaftor are 54.0 (10.1) hours, 92.4 (23.1) hours and 17.3 (2.67) hours, respectively based on a single dose of vanzacaftor/tezacaftor/deutivacaftor tablets in healthy subjects in the fed state. # Following radiolabeled doses.			

Specific Populations

No clinically significant differences in the pharmacokinetics of vanzacaftor, tezacaftor, or deutivacaftor were observed based on age, sex, race, *CFTR* genotype, or mild to moderate renal impairment (eGFR 30 to <90 mL/min/1.73 m² as estimated by modification of diet in renal disease (MDRD) equation). The effect of severe renal impairment (eGFR less than 30 mL/min/1.73 m²) on vanzacaftor, tezacaftor, or deutivacaftor pharmacokinetics is unknown.

Weight was identified as the key covariate having a clinically meaningful impact on pharmacokinetics of vanzacaftor, tezacaftor, and deutivacaftor.

Pediatric Patients Aged 6 to Less Than 18 Years

Vanzacaftor, tezacaftor and deutivacaftor exposures observed in clinical trials are presented by age group and dosage administered in Table 7. No clinically significant differences in vanzacaftor, tezacaftor, and deutivacaftor exposures were observed in patients with CF aged 6 to less than 18 years compared to adults following the recommended dosages.

Age Group	Weight	Dosage (once daily)	AUC _{0-24h} (mcg·h/mL)		
			Vanzacaftor	Tezacaftor	Deutivacaftor
6 to <12 years	<40 kg (N = 70)	vanzacaftor 12 mg tezacaftor 60 mg deutivacaftor 150 mg	13.0 (4.90)	69.1 (20.7)	30.2 (11.6)
	≥40 kg (N = 8)	vanzacaftor 20 mg tezacaftor 100 mg deutivacaftor 250 mg	18.6 (7.49)	101 (33.7)	48.5 (18.7)
12 to <18 years	- (N = 66)	vanzacaftor 20 mg tezacaftor 100 mg deutivacaftor 250 mg	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)

Abbreviations: SD: Standard Deviation; AUC_{0-24h}: Area Under the Concentration versus time curve at steady state

Patients with Hepatic Impairment

Vanzacaftor AUC was approximately 30% lower, tezacaftor AUC was comparable, and deutivacaftor AUC was approximately 20% lower in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal liver function matched for demographics [see Use in Specific Populations (8.7)].

The effect of mild hepatic impairment (Child-Pugh Class A) or severe hepatic impairment (Child-Pugh Class C) on vanzacaftor, tezacaftor, or deutivacaftor pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Exposure changes associated with concomitant use of vanzacaftor, tezacaftor, ivacaftor and/or deutivacaftor with other drugs are shown in Table 8.

Dosage		Effected Drug	Geometric Mean Ratio (90% CI)	
			No Effect = 1.0	
			AUC	C _{max}
Itraconazole 200 mg q12h on Day 1, followed by 200 mg daily	TEZ 25 mg daily + IVA 50 mg daily	Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
Itraconazole 200 mg daily	ELX 20 mg + TEZ 50 mg + D-IVA 50 mg single dose	Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
		Deutivacaftor	11.1 (8.72, 14.1)	1.96 (1.70, 2.26)
Itraconazole 200 mg daily*	VNZ 5 mg single dose	Vanzacaftor	6.37 (5.53, 7.35)	1.55 (1.41, 1.70)
Ciprofloxacin [†] 750 mg twice daily	TEZ 50 mg q12h + IVA 150 mg q12h	Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
Digoxin 0.5 mg single dose	TEZ 25 mg daily + IVA 50 mg daily	Digoxin	1.3 (1.17, 1.45)	1.32 (1.07, 1.64)

Table 8: Observed or Predicted Exposure Changes Associated with Concomitant Use of Vanzacaftor, Tezacaftor, Ivacaftor and/or Deutivacaftor with Other Drugs

Dosage		Effected Drug	Geometric Mean Ratio (90% CI)	
			No Effect = 1.0	
			AUC	C _{max}
Fluconazole 200 mg daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	2.55 (2.12, 3.12) [‡]	2.48 (2.04, 3.01) [‡]
		Deutivacaftor	3.13 (2.44, 3.95) [‡]	2.27 (1.82, 2.93) [‡]
Erythromycin 500 mg four times daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	3.29 (1.62, 7.55) [‡]	3.19 (1.60, 7.29) [‡]
		Deutivacaftor	4.13 (1.80, 9.73) [‡]	2.89 (1.52, 6.97) [‡]
Verapamil 80 mg three times daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	3.93 (1.84, 8.75) [‡]	3.80 (1.78, 8.33) [‡]
		Deutivacaftor	5.11 (2.06, 12.5) [‡]	3.43 (1.64, 7.65) [‡]
Rifampin 600 mg daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	0.18 (0.10, 0.34) [‡]	0.22 (0.12, 0.38) [‡]
		Deutivacaftor	0.10 (0.04, 0.26) [‡]	0.20 (0.08, 0.44) [‡]
Carbamazepine 400 mg twice daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	0.44 (0.28, 0.61) [‡]	0.46 (0.31, 0.64) [‡]
		Deutivacaftor	0.24 (0.11, 0.47) [‡]	0.32 (0.17, 0.57) [‡]
Efavirenz 600 mg daily	VNZ 20 mg qd + TEZ 100 mg + D-IVA 250 mg qd	Vanzacaftor	0.31 (0.16, 0.57) [‡]	0.35 (0.19, 0.59) [‡]
		Deutivacaftor	0.27 (0.11, 0.50) [‡]	0.44 (0.23, 0.68) [‡]

Abbreviations: CI = Confidence Interval; ELX = elexacaftor; VNZ = vanzacaftor; TEZ = tezacaftor; IVA = ivacaftor; D-IVA = deutivacaftor; PK = Pharmacokinetics; qd = once daily

* The itraconazole dosing (200 mg qd for 14 days) did not fully cover the elimination of vanzacaftor. A 10.5-fold increase in vanzacaftor AUC is predicted by physiologically based pharmacokinetic modeling and simulations when itraconazole fully covers the elimination.

[†] Effect is not clinically significant [see Drug Interactions (7.3)].

[‡] Predicted by physiologically based pharmacokinetic modeling and simulations. Data presented as geometric mean ratio and 5th to 95th percentiles of individuals in the simulated population [see Drug Interactions (7.1)].

Other Drugs: No clinically significant differences in tezacaftor pharmacokinetics were observed when tezacaftor/ivacaftor was used concomitantly with ciprofloxacin. No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with tezacaftor/ivacaftor: midazolam (CYP3A4 substrate) or ethinyl estradiol/norethindrone containing hormonal contraceptives.

In Vitro Studies

CYP450 Enzymes: Vanzacaftor, tezacaftor, and deutivacaftor are CYP3A substrates. Deutivacaftor inhibits CYP2C8, CYP2C9, and CYP3A4. Vanzacaftor and tezacaftor do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Vanzacaftor, tezacaftor, and deutivacaftor do not induce CYP3A4.

Transporter Systems: Tezacaftor and deutivacaftor are substrates of P-gp, but vanzacaftor is not a substrate of P-gp. Tezacaftor is a substrate of BCRP, OATP1B1, but not OATP1B3. Vanzacaftor and deutivacaftor are not substrates for OATP1B1 or OATP1B3. Vanzacaftor and deutivacaftor are BCRP inhibitors. Vanzacaftor, tezacaftor and deutivacaftor are P-gp inhibitors. Vanzacaftor, tezacaftor, and deutivacaftor do not inhibit OATP1B1 nor OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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, deutivacaftor, and ivacaftor are described below.

Vanzacaftor

A 6-month study in Tg.rash2 mice showed no evidence of tumorigenicity at 30 mg/kg/day dose, the highest dose tested.

Vanzacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene variant, in vitro micronucleus assay in TK6 cells, and in vivo rat micronucleus assay.

Administration of oral vanzacaftor had no effects on fertility and early embryonic development in male and female rats at up to 12.5 and 10 mg/kg/day, respectively (approximately 19 times for males and 30 times for females the exposure at the MRHD based on AUCs of vanzacaftor).

Tezacaftor

A two-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 2 and 4 times the MRHD based on summed AUCs of tezacaftor and M1-TEZ in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

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

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

Deutivacaftor

Deutivacaftor is a deuterated isotopologue of ivacaftor with an established 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 equivalent to deutivacaftor.

Ivacaftor

Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 3 and 11 times the MRHD, respectively, based on summed AUCs of ivacaftor).

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

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 15 and 13 times, respectively, the MRHD based on AUCs of ivacaftor). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations and viable embryos in rats at 200 mg/kg/day when dams were dosed prior to and during early pregnancy. Slight decreases of the seminal vesicle weights were observed in males at 200 mg/kg/day dose (approximately 15 times the MRHD based on summed AUCs of ivacaftor). These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.

14 CLINICAL STUDIES

The efficacy of ALYFTREK in patients aged 12 years and older with cystic fibrosis (CF) who have at least one *F508del* variant or a responsive variant in the *CFTR* gene was evaluated in two 52-week randomized, double-blind, active-controlled trials comparing ALYFTREK and a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA) (Trial 1, NCT05033080 and Trial 2, NCT05076149). The two trials enrolled a total of 971 patients aged 12 years and older with CF who have at least one *F508del* variant or other ELX/TEZ/IVA-responsive variants in the *CFTR* gene. Because patients in Trial 1 and Trial 2 would receive ELX/TEZ/IVA, patients with a history of intolerance to ELX/TEZ/IVA were excluded from these trials.

- Trial 1 enrolled patients with CF heterozygous for *F508del* and a *CFTR* variant that results in a protein that was not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function variant). A total of 398 patients with CF aged 12 years and older received a daily oral dosage of ELX/TEZ/IVA (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening) during a 4-week run-in period and were then randomized to receive ALYFTREK (total once daily oral dosage of vanzacaftor 20 mg/tezacaftor 100 mg/deutivacaftor 250 mg) or ELX/TEZ/IVA (same dosage as in the run-in period) during the 52-week treatment period. Patients had a mean age of 30.8 years (range: 12.2 to 71.6 years), were 59% male, 97.5% White, 1.3% Black/African American, 0.3% Asian, 0.3% Other race, and 6% Hispanic or Latino ethnicity. After the 4-week run-in, the mean ppFEV₁ at baseline was 67.1 percentage points (range: 28.0, 108.6) and the mean sweat chloride at baseline was 53.9 mmol/L (range: 10.0 mmol/L, 113.5 mmol/L).

- Trial 2 enrolled patients with CF who had one of the following genotypes: homozygous for the *F508del* variant, heterozygous for the *F508del* variant and either a gating or a residual function variant, or at least one variant responsive to ELX/TEZ/IVA with no *F508del* variant. A total of 573 patients with CF aged 12 years and older received a daily oral dosage of ELX/TEZ/IVA (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening) during a 4-week run-in period and were then randomized to receive ALYFTREK (total once daily oral dosage of vanzacaftor 20 mg/tezacaftor 100 mg/ deuterivacaftor 250 mg) or ELX/TEZ/IVA (same dosage as during the run-in period) during the 52-week treatment period. Patients had a mean age of 33.7 years (range: 12.2 to 71.2 years), were 51.1% male, 92.8% White, 0% Black/African American, 0.3% Asian, 0.2% American Indian or Alaska Native, 0.3% Other race, and 1.6% Hispanic or Latino ethnicity. After the 4-week run-in, the mean ppFEV₁ at baseline was 66.8 percentage points (range: 36.4, 112.5) and the mean sweat chloride at baseline was 42.8 mmol/L (range: 10.0 mmol/L, 113.3 mmol/L).

Efficacy Endpoints

In both trials, the primary endpoint evaluated non-inferiority in mean absolute change in ppFEV₁ from baseline through Week 24 and a key secondary endpoint evaluated the mean absolute change from baseline in sweat chloride through Week 24 in the ALYFTREK and ELX/TEZ/IVA treatment groups.

Trials 1 and 2 also assessed other secondary endpoints including pulmonary exacerbation rate and change in Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) score from baseline.

Efficacy Results

- In Trial 1, treatment with ALYFTREK resulted in an LS mean difference of 0.2 percentage points (95% CI: -0.7, 1.1) in absolute change in ppFEV₁ from baseline through Week 24 compared to ELX/TEZ/IVA.
- In Trial 2, treatment with ALYFTREK resulted in an LS mean difference of 0.2 percentage points (95% CI: -0.5, 0.9) in absolute change in ppFEV₁ from baseline through Week 24 compared to ELX/TEZ/IVA.

As the lower bounds of the 95% CI of the LS mean difference in absolute change from baseline in ppFEV₁ through Week 24 were greater than -3.0 percentage points (the pre-specified non-inferiority margin) in Trial 1 and Trial 2, these results demonstrate non-inferiority of ALYFTREK to ELX/TEZ/IVA.

Table 9 provides the primary and key secondary efficacy endpoints results for Trials 1 and 2.

Table 9: Efficacy Results in Patients Aged 12 Years and Older with CF Who Had at Least One <i>F508del</i> Variant or Responsive Variant in the <i>CFTR</i> Gene (Trials 1 and 2)					
Analysis*	Statistic	Trial 1		Trial 2	
		ALYFTREK N = 196	ELX/TEZ/IVA N = 202	ALYFTREK N = 284	ELX/TEZ/IVA N = 289
Primary Endpoint					
Absolute change from baseline in ppFEV ₁ 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)	
Key Secondary Endpoint					
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; SE: Standard Error; SwCl: sweat chloride Note: Analyses were based on the full analysis set (FAS). FAS was defined as all randomized subjects who carry the intended CFTR allele variant 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.					

The trials were not designed to demonstrate a difference between the treatment groups or to support non-inferiority of the other secondary endpoints. In Trial 1 and Trial 2, mean absolute change from baseline ppFEV₁ through Week 52, the rate in pulmonary

exacerbations through Week 52, and the absolute change from baseline in the CFQ-R RD through Week 24 were similar between the ALYFTREK-treated and the ELX/TEZ/IVA-treated patients. The results were not tested for statistical significance as they were not in the pre-specified multiple testing procedure.

16 HOW SUPPLIED/STORAGE AND HANDLING

ALYFTREK (vanzacaftor, tezacaftor, and deutivacaftor) tablets are supplied as follows:

Strengths	Tablet Description	Package Configuration	NDC
4 mg of vanzacaftor/ 20 mg of tezacaftor / 50 mg of deutivacaftor	purple, round-shaped, film-coated, debossed with “V4” on one side and plain on the other	84-count carton containing 4 wallets, each wallet containing 21 tablets in blister packs	NDC 51167-135-01
10 mg of vanzacaftor/ 50 mg of tezacaftor / 125 mg of deutivacaftor	purple, oblong-shaped, film-coated, debossed with “V10” on one side and plain on the other	56-count carton containing 4 wallets, each wallet containing 14 tablets in blister packs	NDC 51167-121-01

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug-Induced Liver Injury and Liver Failure

Inform patients that elevations of transaminases have occurred in patients with CF treated with ALYFTREK and that cases of drug-induced liver injury and failure have been observed with fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor, which contains the same or similar active ingredients as ALYFTREK.

Advise all patients that liver function tests should be assessed prior to initiating ALYFTREK, and then assessed every month during the first 6 months of treatment, then every 3 months for the next 12 months, then at least annually thereafter. Inform patients with a history of liver disease or liver function test elevations at baseline that more frequent monitoring may be necessary. Instruct patients to interrupt treatment with ALYFTREK if symptoms of liver injury occur (e.g., jaundice, right upper quadrant pain, nausea, vomiting, altered mental status, ascites) and notify their healthcare provider immediately [see *Dosage and Administration (2.1)*, *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*, *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

Hypersensitivity Reactions, Including Anaphylaxis

Inform patients that hypersensitivity reactions including anaphylaxis have been reported in patients who received drugs containing elexacaftor, tezacaftor, and/or ivacaftor (the same or similar active ingredients as ALYFTREK). Instruct patients to discontinue ALYFTREK and notify their healthcare provider if they experience signs and symptoms of a hypersensitivity reaction, including rash, hives, itching, facial swelling, tightness of the chest and wheezing [see *Warnings and Precautions (5.2)*].

Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions

Inform patients that there is no available safety data for ALYFTREK in patients who previously discontinued or interrupted treatment with elexacaftor-, tezacaftor-, or ivacaftor-containing drugs due to adverse reactions. These patients who start treatment with ALYFTREK may require closer and more frequent monitoring [see *Warnings and Precautions (5.3)*].

Intracranial Hypertension

Inform patients that intracranial hypertension has occurred in patients who received drugs containing the same or similar active ingredients as ALYFTREK. Instruct patients to notify their healthcare provider right away if they experience signs and symptoms of intracranial hypertension, including headache, blurred vision, diplopia, and vision loss [see *Warnings and Precautions (5.4)*].

Neuropsychiatric Events, Including Suicidal Thoughts and Behaviors

Inform patients that neuropsychiatric symptoms, including anxiety, depression, suicidal thoughts and behaviors, and sleep disturbances (e.g., insomnia), have been reported with the use of ALYFTREK or drugs containing the same or similar active ingredients as ALYFTREK. The symptoms have been observed in patients with and without a history of similar symptoms and may occur within three months of ALYFTREK initiation. Instruct patients to contact their healthcare provider immediately if changes in behavior or thinking that are not typical for the patient occur, or if the patient develops suicidal ideation or behavior [see *Warnings and Precautions (5.5)*].

Drug Interactions with CYP3A Inducers and Inhibitors

Inform patients that certain medications, herbal supplements, or vitamins, when used concomitantly with ALYFTREK, may reduce the effectiveness of ALYFTREK or increase the risk of adverse reactions associated with ALYFTREK. Instruct patients to report all concomitant medications, herbal supplements, or vitamins, to their healthcare providers while taking ALYFTREK [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.6, 5.7)* and *Drug Interactions (7.1)*].

Instruct patients to avoid food or drink containing grapefruit when using ALYFTREK [see *Drug Interactions (7.1)*].

Cataracts

Inform patients that abnormality of the eye lens (cataract) has been noted in some pediatric patients receiving drugs containing ivacaftor (which is similar to an active ingredient in ALYFTREK) and baseline and follow-up ophthalmological examinations are needed in pediatric patients receiving ALYFTREK [see *Warnings and Precautions (5.8)* and *Nonclinical Toxicology (13.1)*].

Administration

Inform patients that ALYFTREK is best absorbed by the body when taken with food that contains fat. Examples include eggs, butter, peanut butter, whole-milk dairy products (such as whole milk, cheese and yogurt), etc. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

Inform patients of the following if they miss an ALYFTREK dose [see *Dosage and Administration (2.5)*]:

- If 6 hours or less have passed since the missed dose is usually taken, patients with CF should be instructed to take the prescribed dose with fat-containing food as soon as possible.
- If more than 6 hours have passed since the missed dose, patients with CF should be instructed to skip the missed dose and continue on the original schedule the next day.



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50 Northern Avenue
Boston, MA 02210

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MEDICATION GUIDE
ALYFTREK™ (ah-LIF-trek)
(vanzacaftor, tezacaftor, and deutivacaftor tablets), tablets for oral use

What is the most important information I should know about ALYFTREK?

Elevated liver enzymes have been observed in patients taking ALYFTREK. Cases of serious liver damage and liver failure leading to transplantation and death have been seen in some people with or without a history of liver problems taking elexacaftor/tezacaftor/ivacaftor (TRIKAFTA), a medicine which has the same or similar active ingredients as ALYFTREK.

Your healthcare provider will do blood tests to check your liver:

- before you start ALYFTREK
- every month during your first 6 months of taking ALYFTREK
- then every 3 months during the next 12 months of taking ALYFTREK
- then at least every year while you are taking ALYFTREK

Your healthcare provider may do blood tests to check the liver more often if you have had high liver enzymes in your blood in the past or are experiencing signs or symptoms of liver injury.

Stop taking ALYFTREK and call your healthcare provider right away if you have any of the following symptoms of liver problems:

- pain, swelling, or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- mental changes
- nausea or vomiting
- dark, amber-colored urine
- loss of appetite
- have fluid in your stomach area (ascites)

What is ALYFTREK?

- ALYFTREK is a prescription medicine for people aged 6 years and older who have a diagnosis of cystic fibrosis (CF) and who have at least one genetic change (variant) in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is either responsive to ALYFTREK or results in the production of protein.
- Talk to your healthcare provider to learn if you have an indicated CF gene variant.

It is not known if ALYFTREK is safe and effective in children under 6 years of age.

What should I tell my healthcare provider before taking ALYFTREK?

Before taking ALYFTREK, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems.
- are allergic to ALYFTREK or any ingredients in ALYFTREK. See the end of this medication guide for a complete list of ingredients in ALYFTREK.
- have taken another medicine with elexacaftor, tezacaftor, or ivacaftor before and temporarily or permanently stopped because of side effects. Your healthcare provider may want to see you more often.
- have kidney problems.
- have or have had mental health problems.
- are pregnant or plan to become pregnant. It is not known if ALYFTREK will harm your unborn baby. You and your healthcare provider should decide if you will take ALYFTREK while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if ALYFTREK passes into your breast milk. You and your healthcare provider should decide if you will take ALYFTREK while you are breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ALYFTREK may affect the way other medicines work and other medicines may affect how ALYFTREK works.

The dose of ALYFTREK may need to be adjusted when taken with certain medicines. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

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

How should I take ALYFTREK?

- Take ALYFTREK exactly as your healthcare provider tells you to take it.
- Take ALYFTREK by mouth only.
- **Always take ALYFTREK tablets with food that contains fat.** Examples of fat-containing foods include butter, oil, eggs, peanut butter, nuts, meat, and whole-milk dairy products such as whole milk, cheese, and yogurt.
- ALYFTREK tablets (age 6 to less than 12 years weighing less than 88 pounds (40 kg)):
 - The purple round-shaped tablet is marked with 'V4' and each tablet contains the medicines vanzacaftor, tezacaftor, and deutivacaftor. Take 3 tablets at the same time each day.
- ALYFTREK tablets (age 6 to less than 12 years weighing 88 pounds (40 kg) or more, or 12 years and older):
 - The purple oblong-shaped tablet is marked with 'V10' and each tablet contains the medicines vanzacaftor, tezacaftor, and deutivacaftor. Take 2 tablets at the same time each day.
- Take ALYFTREK tablets whole.
- Take the doses **about the same time** every day.
- If you miss a dose of ALYFTREK and:
 - it is **6 hours or less** from the time you usually take the dose, **take the missed dose** with food that contains fat as soon as you can. Then take your next dose at your usual time.
 - it is **more than 6 hours** from the time you usually take the dose, **do not take the missed dose**. Take your dose the next day at your usual time.
 - **Do not** take more than your usual dose of ALYFTREK to make up for a missed dose.

If you are not sure about your dosing, call your healthcare provider.

What should I avoid while taking ALYFTREK?

Avoid food or drink that contains grapefruit while you are taking ALYFTREK.

What are the possible or reasonably likely side effects of ALYFTREK?

ALYFTREK can cause serious side effects, including:

- See "**What is the most important information I should know about ALYFTREK?**"
- **Serious Allergic Reactions** can happen to people who are treated with ALYFTREK. Call your healthcare provider or go to the emergency room right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction may include:
 - rash or hives
 - tightness of the chest or throat or difficulty breathing
 - light-headedness or dizziness

- **Increased pressure around the brain (intracranial hypertension)** has happened in people treated with medicines containing the same or similar ingredients as ALYFTREK. If you experience an unusual headache, blurred vision, double vision, or vision loss, call your healthcare provider right away.
- **Serious mental health problems** such as anxiety, depression, suicidal thoughts and behaviors, and trouble sleeping have happened in people treated with ALYFTREK or medicines containing the same or similar ingredients as ALYFTREK. If you experience new or worsening mental health problems, call your healthcare provider right away.
- **Abnormality of the eye lens (cataract)** has happened in some children and adolescents treated with ALYFTREK. If you are a child or adolescent, your healthcare provider should perform eye examinations before and during treatment with ALYFTREK to look for cataracts.

The most common side effects of ALYFTREK include:

- cough
- pain or swelling of your nose or throat (nasopharyngitis)
- upper respiratory tract infection (common cold) including stuffy and runny nose
- headache
- mouth or throat pain
- flu (influenza)
- tiredness
- increase in liver enzymes
- rash
- sinus congestion

Your healthcare provider should monitor you during treatment with ALYFTREK. You may require additional monitoring if your treatment with a medicine that works like ALYFTREK has been previously stopped or interrupted because of side effects.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ALYFTREK. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALYFTREK?

- Store ALYFTREK at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ALYFTREK and all medicines out of the reach of children.

General information about the safe and effective use of ALYFTREK.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ALYFTREK for a condition for which it was not prescribed. Do not give ALYFTREK to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ALYFTREK that is written for health professionals.

What are the ingredients in ALYFTREK?

Active ingredients: vanzacaftor, tezacaftor, and deutivacaftor.

Inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains Brilliant Blue FCF aluminum lake/FD&C Blue #1, carmine, hydroxypropyl cellulose, hypromellose, iron oxide red, talc, and titanium dioxide.



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