PDL DRUG REVIEW

Proprietary Name: Alyftrek®
Common Name: vanzacaftor, tezacaftor, and deutivacaftor
PDL Category: Cystic Fibrosis Agents

Comparable Products	Preferred Drug List Status
Orkambi	Non-Preferred with Conditions
Trikafta	Non-Preferred with Conditions

Pharmacology/Usage: Alyftrek® (vanzacaftor, tezacaftor, and deutivacaftor) is a fixed-dose combination (FDC) tablet. Vanzacaftor and tezacaftor bind to different sites on the cystic fibrosis transmembrane conductance regulator (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 medicated chloride transport in vitro and by sweat chloride in patients with CF.

Indication: For the treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on the use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population younger than 6 years of age have not been established.

Dosage Form: Tablets, Film-Coated:

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

Recommended Dosage: Prior to starting treatment, 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, and 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.

Administer Alyftrek® orally (swallow the tablets whole) with fat-containing food, once daily, at about the same time each day. 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. The recommended dosage is presented in the table below, which was adapted from the prescribing information.

Age	Weight	Once daily oral dosage
6 to <12 yrs	<40kg	Three tablets of vanzacaftor 4mg/tezacaftor 20mg/deutivacaftor 50mg
	≥40kg	Two tablets of vanzacaftor 10mg/tezacaftor 50mg/deutivacaftor 125mg
12 yrs and older	Any weight	Two tablets of vanzacaftor 10mg/tezacaftor 50mg/deutivacaftor 125mg

If 6 hours or less have passed since a missed dose, take the missed dose as soon as possible and continue on the original schedule. If more than 6 hours have passed since a missed dose, skip the missed dose, and continue on the original schedule the next day.

Dose adjustments are not required with mild hepatic impairment; however, liver function tests should be closely monitored. The use of Alyftrek® in patients with moderate hepatic impairment is not recommended. Use should only be considered in patients with moderate hepatic impairment when there is a clear medical need, and the benefit outweighs the risk. If used, the recommended dosage in patients with moderate hepatic impairment is the same as for patients with normal hepatic impairment, and liver function tests should be closely monitored. Alyftrek® should not be used in patients with severe hepatic impairment.

Clinically significant differences in the pharmacokinetics of vanzacaftor, tezacaftor, or deutivacaftor were not observed in patients with mild to moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics is not known. The recommended Alyftrek® dosage with mild to moderate renal impairment is the same as those with normal kidney function. Use in patients with severe renal impairment or end-stage renal disease is recommended only if the benefits are expected to outweigh the risks.

Drug Interactions: Vanzacaftor, tezacaftor, and deutivacaftor are substrates of CYP3A. Concomitant use of Alyftrek® with strong or moderate CYP3A inducers is not recommended.

Reduce the Alyftrek® dosage when used concomitantly with a strong or moderate CYP3A inhibitor. Refer to the prescribing information for additional information.

Food or drink containing grapefruit should be avoided during treatment with Alyftrek®.

Tezacaftor and deutivacaftor are P-gp inhibitors. 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.

Vanzacaftor and deutivacaftor are inhibitors of breast cancer resistance protein (BCRP). Unless otherwise recommended in the BCRP substrate prescribing information, monitor more frequently for adverse reactions with concomitant use of Alyftrek® with BCRP substrate where minimal concentrations may lead to serious adverse reactions related to BCRP 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.

A role for hormonal contraceptives contributing to rash cannot be excluded. 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.

Box Warning: Alyftrek® has a box warning regarding 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 FDC 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 after starting elexacaftor/tezacaftor/ivacaftor.
- Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to starting 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.
- 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®.
- 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.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Alyftrek®) minus reported % incidence for elexacaftor/tezacaftor/ivacaftor in patients aged 12 years and older. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included cough (1%), nasopharyngitis (2%), upper respiratory tract infection (1%), headache (3%), oropharyngeal pain (2%), influenza (6%), fatigue (2%), ALT increased (2%), rash (4%), AST increased (2%), and sinus congestion (4%).

Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the post marketing setting of drugs containing elexacaftor, tezacaftor and/or ivacaftor (the same or similar active ingredients in Alyftrek®). If signs or symptoms of serious hypersensitivity reactions develop during Alyftrek® treatment, discontinue Alyftrek® and start appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with Alyftrek®.

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.

Cases of non-congenital lens opacities have been reported in pediatric patients treated with drugs containing ivacaftor (which is similar to an active ingredient of Alyftrek®). While 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®.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Vertex Pharmaceuticals

Analysis: The efficacy of Alyftrek® was assessed in two 52-week, randomized, double-blind, active-controlled trials that included patients aged 12 years and older with CF (N=971) who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene. Patients were randomized to Alyftrek® or a FDC containing elexacaftor, tezacaftor and ivacaftor (ELX/TEZ/IVA). As 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* mutation that results in a protein that was not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function mutation). Patients (N=398) aged

12 years and older received a daily oral dosage of ELX/TEZ/IVA (200mg/100mg/150mg in the AM) and ivacaftor (150mg in the PM) during a 4-week run-in period and were then randomized to Alyftrek® or ELX/TEZ/IVA during the 52 week treatment period. Patients included in this trial had a mean age of 30.8 years (range 12.2 to 71.6), while 59% were make and 97.5% were white. After the 4-week run-in, the mean percent predicted (pp) FEV1 at baseline was 67.1 percentage points and the mean sweat chloride at baseline was 53.9mmol/L.

- Trial 2 enrolled patients with CF who had one of the following genotypes: homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to ELX/TEZ/IVA with no *F508del* mutation. Patients (N=573) aged 12 years and older received a daily oral dosage of ELX/TEZ/IVA (200mg/100mg/150mg in the AM) and ivacaftor (150mg in the PM) during a 4-week run-in period and were then randomized to receive Alyftrek® or ELX/TEZ/IVA during the 52-week treatment period. Included patients had a mean age of 33.7 years (range 12.2 to 71.2), while 51.1% were male and 92.8% were white. After the 4-week run-in, the mean ppFEV1 at baseline was 66.8 percentage points and the mean sweat chloride at baseline was 42.8mmol/L.
- 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 assessed 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.

In Trial 1, treatment with Alyftrek® resulted in an least square (LS) mean difference of 0.2 percentage points 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 in absolute change in ppFEV1 from baseline through week 24 compared to ELX/TEZ/IVA.

As the lower bounds of the 95% confidence interval 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. Results are presented in the table below, which was adapted from the prescribing information.

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 ppFEV1 through week 24 (percentage points)				
n	187	193	268	276
LS mean	05	0.3	0.2	0.0
LS mean difference	0.2		0.2	
Key Secondary Endpoint- Absolute change from baseline in sweat chloride through week 24 (mmol/L)				
n	185	194	270	276
LS mean	-7.5	0.9	-5.1	-2.3
LS mean difference; p-value (2-sided)	-8.4; p<0.0001		-2.8; p=0.0034	

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 in 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.

Place in Therapy: Alyftrek® is a combination of deutivacaftor, tezacaftor, and vanzacaftor indicated for the treatment of CF in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation. A noted reference recommends the use of triple therapy (ELX/TEZ/IVA) instead of dual therapy or ivacaftor in patients ≥2 years of age with any disease severity and who have two F508del mutations (homozygotes). In addition, ELX/TEZ/IVA is recommended over no therapy and over dual therapy or ivacaftor in patients ≥2 years of age with any disease severity and who have one F508del mutation (heterozygotes).[2] (Note that this reference has not been updated with Alyftrek® drug information.)

Alyftrek® has a box warning regarding drug-induced liver injury and liver failure; Alyftrek® should not be used in patients with severe hepatic impairment while use is not recommended in patients with moderate hepatic impairment. Liver function tests should be assessed regularly. The efficacy of Alyftrek® was assessed in two randomized, double-blind, active-controlled trials that included patients aged 12 years and older with CF who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene. The primary endpoint in both studies evaluated non-inferiority in mean absolute change in ppFEV1 from baseline through week 24, and results for this primary endpoint demonstrated non-inferiority of Alyftrek® to ELX/TEZ/IVA.

Summary

It is recommended that Alyftrek® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:

☐ **Preferred**

☒ **Non-Preferred with Conditions**

References

[1] Alyftrek® [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2025.

[2] UpToDate online. Cystic fibrosis: Treatment with CFTR modulators. Accessed February 2025.

Prepared By: Iowa Medicaid Date: 02/17/2025