PDL DRUG REVIEW

Proprietary Name: Trikafta®
Common Name: elexacaftor, tezacaftor, & ivacaftor
PDL Category: Cystic Fibrosis Agents

Comparable Products	Preferred Drug List Status
Kalydeco	Non-Preferred with Conditions
Orkambi	Non-Preferred with Conditions
Symdeko	Non- Preferred with Conditions

Summary

Pharmacology/Usage: Trikafta® is a co-package of elexacaftor, tezacaftor, and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Elexacaftor and tezacaftor bind to different sites of the cystic fibrosis transmembrane conductance regulator (CFTR) protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

Indication: For the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation.

There is no pregnancy category for this medication; however, the risk summary indicates that there are limited and incomplete human data from clinical trials on the use of Trikafta® or its individual components in pregnant women to inform a drug-associated risk. The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

Dosage Form: Co-package of fixed-dose combination tablets containing elexacaftor 100mg/tezacaftor 50mg/ivacaftor 75mg, and ivacaftor 150mg tablets. Swallow tablets whole.

Recommended Dosage: Take 2 of the combination tablets QAM and one ivacaftor tablet 150mg QPM, about 12 hours apart. Take with fat-containing food, such as meals or snacks prepared with butter or oils or those containing eggs, cheese, nuts, whole milk, or meats. If 6 hours or less have passed since the missed AM or PM dose, the patient should take the missed dose as soon as possible and continue on the original schedule. If more than 6 hours have passed since the missed AM dose, the patient should take the missed dose as soon as possible and should NOT take the PM dose. The next scheduled morning dose should be taken at the usual time. If more than 6 hours have passed since the missed PM dose, the patient should NOT take the missed dose. The next scheduled AM dose should be taken at the usual time.

Dose adjustments are not required with mild hepatic impairment. Trikafta® has not been studied in patients with moderate or severe hepatic impairment. Patients with severe hepatic impairment should not be treated with Trikafta®. Use of Trikafta® is not recommended in patients with moderate hepatic impairment unless the benefit exceeds the risk. If used in patients with moderate hepatic impairment, Trikafta® should be used with caution and at a reduced dose. Furthermore, liver function tests should be closely monitored. Refer to the table below, which was adapted from the prescribing information.

	Mild hepatic	Moderate hepatic	Severe hepatic
AM	No dose adjustment	2 combination tablets	Should not be used
PM	No dose adjustment	No ivacaftor dose	Should not be used

Dose adjustments are not required with mild or moderate renal impairment. Trikafta® has not been studied in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with severe renal impairment (eGFR <30ml/min/1.73m^2) or end-stage renal disease.

Drug Interactions: Co-administration of Trikafta® with strong CYP3A inducers (e.g. rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort) is not recommended.

The dosage of Trikafta® should be reduced when co-administered with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin). The dosage of Trikafta® should also be reduced when co-administered with moderate CYP3A inhibitors (e.g. fluconazole, erythromycin). The co-administration of Trikafta® with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor, and ivacaftor; thus, food or drink containing grapefruit should be avoided during treatment with Trikafta®. Refer to the table below for further dosing information, which was adapted from the prescribing information.

	Day 1	Day 2	Day 3	Day 4
Moderate CYP3A Inhibitors				
AM dose*	2 combination tabs	1 ivacaftor tab	2 combination tabs	1 ivacaftor tab
PM dose	No dose			
Strong CYP3A Inhibitors				
AM dose^	2 combination tabs	No dose	No dose	2 combination tabs
PM dose	No dose			

*Continue dosing with 2 combination tabs and 1 ivacaftor tab on alternate days

^Continue dosing with 2 combination tabs twice a week, approximately 3 to 4 days apart

Ivacaftor may inhibit CYP2C9 substrates. Thus, monitoring of the INR during co-administration of Trikafta® with warfarin is recommended. Other medicinal products for which exposure may be increased by Trikafta® include glimepiride and glipizide. These medicinal products should be used with caution.

When Trikafta® is used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used.

Box Warning: There are no box warnings listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Trikafta®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (2%), upper respiratory tract infection (4%), abdominal pain (5%), diarrhea (6%), rash (5%), alanine aminotransferase increased (7%), nasal congestion (2%), blood creatine phosphokinase increased (5%), aspartate aminotransferase increased (7%), rhinorrhea (5%), rhinitis (2%), influenza (6%), sinusitis (1%), and blood bilirubin increased (4%).

Additional adverse reactions that occurred in Trikafta®-treated patients at a frequency of 2% to <5% and higher than placebo by ≥1% include the following: flatulence, abdominal distension, conjunctivitis, pharyngitis, respiratory tract infection, tonsillitis, urinary tract infection, c-reactive protein increased, hypoglycemia, dizziness, dysmenorrhea, acne, eczema, and pruritus.

Elevated transaminases have been observed in patients with CF treated with Trikafta®. Bilirubin elevations have also been seen with Trikafta® treatment. Assessments of liver function tests (ALT, AST, and bilirubin) are recommended for all patients prior to starting Trikafta®, every 3 months during the first year of treatment, and annually thereafter. For patients with a

history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered. With significant elevations in liver function tests, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve.

Cases of non-congenital lens opacities have been reported in pediatric patients treated with ivacaftor-containing regimens. While other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological exams are recommended in pediatric patients starting Trikafta® treatment.

Contraindications: There are currently no contraindications for this product.

Manufacturer: Vertex Pharmaceuticals Inc.

Analysis: The safety and efficacy of Trikafta® were assessed in 2 phase 3, double-blind controlled trials that included patients 12 years and older with CF. Patients in both trials had a confirmed diagnosis of CF and at least one *F508del* mutation. Patients discontinued any previous CFTR modulator therapies but continued on their standard-of-care CF therapies (e.g. bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline). Furthermore, patients had a percent predicted forced expiratory volume in 1 second (ppFEV1) at screening between 40-90%. Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 X upper limit of normal (ULN) or total bilirubin ≥2 X ULN) were excluded from the trials.

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. An interim analysis was planned when at least 140 patients completed week 4 and at least 100 patients completed week 12.

Trial 2 was a 4-week, randomized, double-blind, active-controlled study that included patients who are homozygous for the *F508del* mutation. Patients received tezacaftor 100mg QD/ivacaftor 150mg BID during a 4-week open-label run-in period and were then randomized and dosed to receive Trikafta® or tezacaftor 100mg QD/ivacaftor 150mg BID during the double-blind period.

Trial 1 included patients (N=403) with a mean ppFEV1 at baseline that was 61.4% and a mean age of 26.2 years. The primary endpoint assessed at the time of the interim analysis was mean absolute change in ppFEV1 from baseline at week 4. The final analysis tested all key secondary endpoints in the patients who completed the 24-week study participation.

Of the 403 patients included in the interim analysis, the treatment difference between Trikafta® and placebo for the mean absolute change from baseline in ppFEV1 at week 4 was 13.8 percentage points (p<0.0001). The treatment difference between Trikafta® and placebo for mean absolute change in ppFEV1 from baseline through week 24 was 14.3 percentage points, also statistically significant (p<0.0001). Mean improvement in ppFEV1 was seen at the first assessment on day 15 and sustained through the 24-week treatment period. Results of the primary and secondary outcomes can be seen in the table below, which was adapted from the prescribing information. Note that the CFQ-R is the Cystic Fibrosis Questionnaire-Revised. The rate ratio is provided as the outcome measure for the number of pulmonary exacerbations.

Analysis	Statistic	Treatment Difference for Trikafta® (N=200) vs placebo (N=203)
Primary (Interim Full Analysis Set)		
Absolute change in ppFEV1 from baseline at week 4 (% points)	Treatment difference p-value	13.8 p<0.0001
Key Secondary (Full Analysis Set)		
Absolute change in ppFEV1 from baseline through week 24 (% points)	Treatment difference p-value	14.3 p<0.0001
# of pulmonary exacerbations from baseline through week 24	Rate Ratio p-value	0.37 p<0.0001
Absolute change in Sweat Chloride from	Treatment difference	-41.8

Analysis	Statistic	Treatment Difference for Trikafta® (N=200) vs placebo (N=203)
baseline through week 24 (mmol/L)	p-value	p<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through week 24 (points)	Treatment difference p-value	20.2 p<0.0001
Absolute change in BMI from baseline at week 24 (kg/m^2)	Treatment difference p-value	1.04 p<0.0001
Absolute change in Sweat Chloride from baseline at week 4 (mmol/L)	Treatment difference p-value	-41.2 p<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference p-value	20.1 p<0.0001

Trial 2 included patients (N=107) with CF who had a mean ppFEV1 at baseline, following the 4-week open-label run-in period with tezacaftor/ivacaftor of 60.9% and a mean age of 28.4 years. The primary endpoint was the mean absolute change in ppFEV1 from baseline at week 4 of the double-blind period. Key secondary efficacy endpoints were also assessed. Treatment with Trikafta® compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in ppFEV1 of 10 percentage points (p<0.0001). Mean improvement in ppFEV1 was seen at the first assessment on day 15. Results of the primary and key secondary endpoints can be seen in the table below, which was adapted from the prescribing information.

Analysis	Statistic	Treatment Difference for Trikafta® (N=55) vs tezacaftor/ivacaftor (N=52)
Primary		
Absolute change in ppFEV1 from baseline at week 4 (% points)	Treatment difference p-value	10.0 p<0.0001
Key Secondary		
Absolute change in Sweat Chloride from baseline at week 4 (mmol/L)	Treatment difference p-value	-45.1 p<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at week 4 (points)	Treatment difference p-value	17.4 p<0.0001

Place in Therapy: Trikafta® is a fixed-dose combination product containing elexacaftor, tezacaftor and ivacaftor co-packaged with ivacaftor 150mg tablets indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene. If the patient's genotype is not known, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation. In clinical trials, Trikafta® resulted in a statistically significant treatment difference from placebo for the mean absolute change from baseline in ppFEV1 at week 4 in an interim analysis. All secondary outcomes at week 24 were statistically significantly in favor of Trikafta® when compared with placebo. In a second study with an active-comparator, treatment with Trikafta® compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in ppFEV1.

There is some evidence at this time to suggest that Trikafta® may be more effective than tezacaftor/ivacaftor. It is recommended that Trikafta® 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]Trikafta [package insert]. Boston, MA: Vertex Pharmaceuticals Inc; 2019.