Trikafta: A novel triple therapy for Cystic Fibrosis

Summary: Cystic fibrosis is a lethal, inherited autosomal recessive disorder that affects approximately 80,000 people worldwide. The disease affects many systems within the body and the treatment historically has focused on symptomatic management. A combination product of elexacaftor, tezacaftor, and ivacaftor (Trikafta) was approved on October 21, 2019. It is indicated for cystic fibrosis treatment in patients who are ≥12 years of age and who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene. The objective of this article is to review the pertinent properties of this triple therapy medication for cystic fibrosis, to summarize the clinical trial efficacy and safety data, and to evaluate the appropriate use of elexacaftor/tezacaftor/ivacaftor.

Learning Objectives:

1. Review the pathophysiology of cystic fibrosis and mechanism of action of current treatment options.
2. Discuss the results of two phase 3 clinical trials that evaluated the safety and efficacy of elexacaftor, tezacaftor, and ivacaftor (Trikafta).
3. Describe relevant clinical considerations when prescribing, dispensing, and monitoring therapy.

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Introduction

Cystic fibrosis (CF) is a lethal, inherited autosomal recessive disorder that affects approximately 80,000 people worldwide.[1] The disease is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein that leads to reduced CFTR function. The CFTR protein works on the cell surface to allow chloride out of the cell surface. When the CFTR protein is mutated, the CFTR proteins display several dysfunctions including absence from the cell surface and not opening properly to allow the flow of chloride outside of the cell. Without chloride to attract water to the cell surface, the mucus on the cell surface in various organs becomes thick and sticky. This thick and sticky mucus becomes hard to clear. In the lungs, this can lead to increased infections and complications from the thick mucus.[1] There are hundreds of different disease-causing mutations in CF, though nearly 90% of patients have at least one copy of the most common mutation, Phe508del CFTR mutation, and almost 50% have two copies.[1,2] This article reviews the pharmacology, efficacy, safety, dosing, and administration of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) and focuses on the role of the drug in the treatment of CF in patients aged 12 years and older who have at least one Phe508del mutation in the CFTR gene.

Cystic fibrosis affects many systems within the body and treatment historically has focused on symptomatic management. These therapies include: CFTR modulators, airway clearance techniques (acapella, mucolytics, hypertonic saline, inhaled dornase alfa, inhaled mannitol, etc.), and the use of pancreatic enzymes replacement. The CFTR modulators treat the actual cause of CF by improving intracellular processing and/or functioning of the CFTR protein and depending on the patient's CFTR genotype and age, specific CFTR modulators can be utilized.[3,4] Within the last decade, the utilization of CFTR modulators has expanded and has become a mainstay of CF treatment. CFTR modulator treatment approved for CF treatment includes ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor. With the addition of elexacaftor to tezacaftor and ivacaftor, the first triple therapy CFTR treatment, ELX/TEZ/IVA, has been approved.

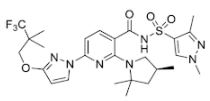
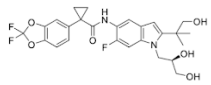
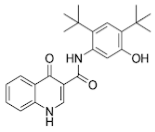
A combination product of ELX/TEZ/IVA (Trikafta) was approved on October 21, 2019, and is prepared as a package with tablets containing fixed-doses of elexacaftor, tezacaftor, and ivacaftor. To understand the benefit of the triple therapy, a quick look at the history of CF treatment is provided. A short description of agents utilized in the treatment of CF, including the newly approved triple therapy, is shown below and summarized in Table 1:

- **ivacaftor (Kalydeco) -** Ivacaftor was the first CFTR modulator to receive FDA approval and is a CFTR potentiator. IVA increases chloride transport by increasing the likelihood that the channel remains open on the CFTR protein at the cell surface. IVA does not correct mutations independently; it is coupled with a CFTR corrector. It is indicated for cystic fibrosis treatment in patients who are ≥ 4 months of age and who have only one mutation in the CFTR gene (heterozygous).[5,6] FDA approval was received on January 31, 2012.[6]
- **lumacaftor/ivacaftor (Orkambi)** - Lumacaftor is a CFTR correctors that aids in the processing and trafficking of the protein to the cell surface. It is never utilized as monotherapy. It is added to ivacaftor for cystic fibrosis treatment in patients who are ≥ 2 years of age and who have two mutations for the F508del mutation in the CFTR gene (homozygous).[7,8] FDA approval was received on July 2, 2015.[8]
- **tezacaftor/ivacaftor (Symdeko)** - Tezacaftor is never utilized as monotherapy; it is also a CFTR corrector. It is added to ivacaftor for cystic fibrosis treatment in patients who are ≥ 6 years of age and who have two mutations for the F508del mutation in the CFTR gene (homozygous).[9,10] It is also approved for patients who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor (heterozygous).[9,10] FDA approval was received on February 12, 2018.[10]
- **elexacaftor/tezacaftor/ivacaftor (Trikafta)** - Elexacaftor is never utilized as monotherapy. ELX is considered a second-generation CFTR corrector and helps the cell to process and move CFTR to increase the amount of mature CFTR protein that is delivered to the cell surface. It is added to tezacaftor and ivacaftor as the first triple therapy CFTR treatment. It is indicated for cystic fibrosis treatment in patients who are ≥12 years of age and who have at

least one F508del mutation in the CFTR gene (heterozygous and homozygous F508del mutation).[11,12] FDA approval was received on October 21, 2019.[12]

It is recommended that patients have their genotype tested to determine which CFTR modulator is most appropriate for their specific type of cystic fibrosis. Beyond CFTR genotyping, some specific recommendations exist for appropriate CFTR modulator use based on additional patient characteristics such as FEV1 and patient age. That being said, current CFTR therapy guidelines provide further guidance around the use of some of these agents in various subsets of patients based upon their age and ppFEV1.[4]

Table 1. Chemistry and pharmacologic properties of Trikafta components[11,12]

	Elexacaftor	**Tezacaftor**	**Ivacaftor**
Chemistry			
Chemical formula	$C_{26}H_{34}N_7O_4SF_3$	$C_{26}H_{27}N_2F_3O_6$	$C_{24}H_{28}N_2O_3$
Chemical structure			
Absorption			
Bioavailability	80%	Not determined	Not determined
Average AUC, mcg*h/mL	162	94.5	11.7
Effect of food	AUC increased 1.9-2.5x with a moderate-fat meal	No significant effect from food	Food increases exposure 2.5-4x
Average time to peak (hr)	6	3	4
Time to steady-state	Within 14 days	Within 8 days	Within 3-5 days
Distribution			
Average Volume of Distribution ± SD (L)	53.7 ± 17.7	82 ± 22.3	293 ± 89.8
Protein binding	> 99%	~99%	~99%
Metabolism			
Average Half-life ± SD (hr)	29.8 ± 10.6	17.4 ± 3.7	15 ± 3.9
Average Clearance (L/hr)	1.18	0.79	10.2
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active Metabolite	M23-ELX	M1-TEZ	M1-IVA
Metabolite Potency Relative to Parent	Similar	Similar	~1/6th of parent

Excretion			
Excretion in urine	0.23%	6.6%	14%
Excretion in feces	87.3% (as metabolites)	87.8%	72% (unchanged or M2-TEZ)

Clinical Trials

Two separate phase 3 clinical trials were conducted that evaluated the efficacy and safety of ELX/TEZ/IVA for the treatment of CF.[1,13] A comparison of these two trials is provided in Table 2.

Table 2. Summary of Primary Endpoints of Phase 3 Clinical Trials

	Middleton PG, et al.[1]		**Heijerman HGM, et al.[13]**	
CF genotype	Phe508del-MF		Phe508del-Phe508del	
Treatment group	PBO for 24 weeks	ELX/TEZ/IVA for 24 weeks	TEZ/IVA run-in for 4 weeks followed by PBO/TEZ/IVA for 4 weeks	TEZ/IVA run-in for 4 weeks followed by ELX/TEZ/IVA for 4 weeks
Number of patients (received ≥ one dose)	203	200	52	55
Absolute change in $ppFEV_1$[a] (95% CI)	-0.2 (-1.3 to 1.0)	13.6 (12.4 to 14.8)	0.4 (-1.4 to 2.3)	10.4 (8.6 to 12.2)
Difference (95% CI)	13.8 (12.1 to 15.4)		10.0 (7.4 to 12.6)	
P value	<0.001		<0.0001	

CI=confidence interval; MF=minimal function; PBO=placebo; $ppFEV_1$=percentage of predicted forced expiratory volume in 1 second; [a]$ppFEV_1$ was evaluated at 4 weeks after treatment initiation[1,13]

Middleton PG, et al.[1]

In the first double-blind, multicenter, randomized, placebo-controlled trial 403 participants were enrolled, meeting the following criteria: 12 years of age or older, FEV_1 of 40-90%, stable disease during a 28 day screening period, and eligible residual functional mutation of the Phe508del-MF genotype.[1] Participants were randomly assigned the triple combination of ELX 200 mg once daily, TEZ 100 mg once daily, and IVA 150 mg every 12 hours for 24 weeks or matching placebos.[14] The primary outcome was an absolute change from baseline $ppFEV_1$ at week 4 of the trial and was also measured using the mixed-effects model. Key secondary outcome variables included the absolute change from baseline in sweat chloride concentration, $ppFEV_1$, CFQ-R respiratory domain score, and body mass index, and the number of pulmonary exacerbation events. Primary outcomes are displayed in Table 2.

In patients with CF, the concentration of chlorine in sweat is higher than in healthy individuals due to defective CFTR function in the CF patients.[15,16] Because of that, a statistically significant decrease in sweat chloride concentration further supports that the triple therapy combination of ELX/TEZ/IVA could improve CFTR function.[1] Of note, there was a 63% (0.37 difference between both groups, confidence interval 0.25 to 0.55) lower annualized rate of pulmonary exacerbations in patients receiving ELX/TEZ/IVA compared to placebo. Serious adverse events, most commonly infective pulmonary

exacerbations, occurred in 13.9% (n=13.9) of the ELX/TEZ/IVA group, whereas 29% (n=42) of the placebo group experienced serious adverse events.[1] However, only 1% (n=2) of participants in the ELX/TEZ/IVA group discontinued their medications due to the severity of the side effects. The three most common adverse effects seen in patients receiving the triple therapy regimen included increased sputum production (19.8%, n=40), headache (17.3%, n=35), cough (16.8%, n=34).

Heijerman HGM, et al.[13]

In a second phase 3, multicenter, randomized, double-blind, active-controlled trial, patients 12 years of age or older, confirmed diagnosis of CF, homozygous for the Phe508del-Phe508del mutation, $ppFEV_1$ of 40-90%, and stable disease as judged by the investigators were studied.[13] Patients either took standard of care TEZ/IVA or ELX/TEZ/IV. The primary outcome variable under investigation in this study was an absolute change from baseline in $ppFEV_1$ at week 4 of the intervention. Key secondary outcomes included absolute change from baseline in sweat chloride, CFQ-R respiratory domain score, safety, and tolerability. Results were similar to the previous trial and shown in Table 2. Secondary outcomes of absolute change in sweat chloride concentration at week 4 in patients taking ELX/TEZ/IVA was -43.4 mmol/L compared to 1.7 mmol/L in the TEZ/IVA group. As mentioned previously, this decrease in sweat chloride concentration shows that the addition of ELX to the traditional TEZ/IVA regimen can improve CFTR function.[13,15,16]
In the TEZ/IVA arm, 2% (n=1) of patients reported a severe adverse event, while zero patients in the ELX/TEZ/IVA arm reported a severe adverse event.[13] Otherwise, both treatment arms tolerated the treatments, reporting only mild or moderate adverse effects as shown in Table 3. The authors state that the majority of the adverse events resolved during the 8-week study. The most common adverse event observed in the ELX/TEZ/IVA group was cough (15%, n=8) in contrast to the TEZ/IVA which was pulmonary exacerbation (12%, n=6). A mild rash was reported in two (4%) participants from each treatment group; all happened in females and did not interfere with maintaining the trial regimen.

Table 3. Frequently reported adverse events occurring in patients given elexacaftor/tezacaftor/ivacaftor and comparators in the Phase 3 trials[1,13]

	Middleton PG, et al		Heijerman HGM, et al	
	Phe508del-MF		Phe508del-Phe508del	
	Placebo N=201 (%)	ELX/TEZ/IVA N=202 (%)	TEZ/IVA N=52 (%)	ELX/TEZ/IVA N=55 (%)
Any AE	193 (96.0)	188 (93.1)	33 (63.0)	32 (58.0)
AE, according to maximum severity:				
Mild	53 (26.4)	67 (33.2)	21 (40.0)	23 (42.0)
Moderate	125 (62.2)	102 (50.5)	11 (21.0)	9 (16.0)
Severe	14 (7.0)	19 (9.4)	1 (2.0)	0
Life Threatening	1 (0.5)	0	0	0
Most common AE:				
Cough	77 (38.3)	34 (16.8)	4 (8.0)	8 (15.0)
Diarrhea	14 (7.0)	26 (12.9)	—	—
Fatigue	20 (10.0)	9 (4.5)	—	—
Headache	30 (14.9)	35 (17.3)	4 (8.0)	3 (5.0)
Hemoptysis	28 (13.9)	11 (5.4)	5 (10.0)	2 (4.0)
Infective pulmonary exacerbation of CF	95 (47.3)	44 (21.8)	6 (12.0)	1 (2.0)
Nasopharyngitis	26 (12.9)	22 (10.9)	2 (4.0)	4 (7.0)
Oropharyngeal Pain	25 (12.4)	20 (9.9)	0	4 (7.0)
Sputum Increased	39 (19.4)	40 (19.8)	—	—
URI	22 (10.9)	24 (11.9)	2 (4.0)	4 (7.0)

AE=adverse event; MF=minimal function; URI=upper respiratory tract infection

Clinical Considerations

The Trikafta Oral Tablet Therapy Pack is a carton containing 84 tablets which have been packaged as four, weekly, 21 tablet-containing, blister cards (figure 1).[11,12,17] Each weekly pack includes 3 total tablets per day. The average wholesale price (AWP) for one Trikafta Oral Tablet Therapy Pack, 84 tablets, is $28,675.36. This is $341.37 per tablet.[11,18] In regards to the storage of this medication, the medication packs should be stored at controlled room temperature, 68 - 77ºF (20 - 25ºC).

In regards to dosing and administration, three total tablets should be administered each day. Every morning, two of the light-orange, fixed-dose tablets containing 100 mg ELX, 50 mg TEZ, and 75 mg IVA should be administered orally. In the evening, roughly 12 hours later, one of the light-blue 150 mg IVA tablets should be administered orally. Tablets should be swallowed whole and administered with fat-containing foods for best absorption. If a patient misses either the morning or evening dose, but less than 6 hours have gone by, the missed dose should be immediately administered and the patient should stay on track to their original dosing schedule. For patients with mild or moderate renal impairment, no dosing change is recommended. There are recommendations regarding dose adjustments in patients with hepatic impairment and is based on the Child-Pugh Class. Additional dosing adjustments are recommended when coadministered with certain medications, such as strong or moderate inhibitors of CYP3A.

Drug interactions between ELX, TEZ, IVA and concomitant medications, as well as the effects between these three ingredients, enzymes, and transporters have been investigated. Some of the various interactions and pharmacokinetic effects identified and described within the package insert[11] are further summarized and discussed below. Due to the potential for increased exposure of ELX, TEZ, and IVA through moderate CYP3A4 inhibition, Grapefruit foods and grapefruit juices should be avoided. A summary of clinically relevant drug interactions has been compiled in Table 4.

Table 4. Select, Notable Drug Interactions for ELX/TEZ/IVA[11]

Interacting Group	Examples of Interacting Agent	Select, Notable Interactions
CYP3A Inducers	Strong Inducers ● carbamazepine ● phenobarbital ● phenytoin ● rifabutin ● rifampin ● St. John's wort	When administered with rifampin, its area under the curve (AUC) fell by 89%, demonstrating a substantial drop in exposure. Similarly, ELX and TEZ would likely have a drop in exposure with concomitant use of a strong inducer.
CYP3A Inhibitors	Strong Inhibitors ● clarithromycin ● itraconazole ● ketoconazole ● posaconazole ● telithromycin ● voriconazole Moderate Inhibitors ● erythromycin ● fluconazole	The AUC of ELX and TEZ were approximately increased by 2.8-fold and 4 to 4.5-fold, respectively, when given with itraconazole. The AUC for each, respectively, was simulated to approximately increase by 1.9 to 2.3-fold and 2.1-fold with co-use of a moderate inhibitor. The AUC of IVA rose by 15.6-fold when given with itraconazole, approximately 8.5-fold when given with ketoconazole, and 2.95-fold when given with fluconazole.
Transporters	P-gp Substrate ● digoxin ● cyclosporine ● everolimus ● sirolimus ● tacrolimus OATP1B1 or OATP1B3 Substrate ● glyburide ● HMG-CoA inhibitors ● nateglinide ● repaglinide	There was a rise in AUC by 1.3-fold for digoxin when administered with IVA or TEZ/IVA.

A tolerable spectrum of adverse events, with few reports of severe events, were identified in clinical trials.[1,13] A summary of common side effects in the two phase 3 have been summarized in Table 3. Due to these known adverse reactions, specific monitoring parameters are recommended.[11,12] Liver function tests (LFTs) should be assessed at baseline prior to therapy initiation, every 3 months during the first 12 months of use, and then annually. Frequency of monitoring can be increased in patients with a history of hepatobiliary disease or elevated LFTs. It is recommended that pediatric patients undergo baseline and follow-up ophthalmologic examinations. Other reported laboratory abnormalities include increased creatinine phosphokinase and blood pressure, however, no specific monitoring parameters have been recommended concerning these.[11]

Conclusion

ELX/TEZ/IVA is a novel triple therapy medication regimen used for patients with CF aged 12 years and older who have at least one Phe508del mutation in the CFTR gene. The most recent CFTR guidelines from the Cystic Fibrosis Foundation were published in March 2018, and as ELX/TEZ/IVA was approved in 2019, it has not been discussed in any treatment guidelines currently.[4] However, based on clinical trials outlined above, ELX/TEZ/IVA is superior to the current standard of care in the current recommendations. Although it has only been studied in children > 12 years of age at this time, trials are ongoing to show efficacy in various other populations which could support additional indications for CFTR modulators.[19] As more clinical trial is reported, it will be interesting to follow where this novel triple therapy option falls in the treatment recommendations for patients with cystic fibrosis.

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Trikafta Home Study MTC Questions

1. What is the drug class of elexacaftor?
    a. Second-generation CFTR corrector
    b. First-generation CFTR corrector
    c. CFTR modulator
    d. Mucolytic

2. The combination of elexacaftor, tezacaftor, and ivacaftor (Trikafta) is approved for the use in individuals with at least one of which of the following cystic fibrosis transmembrane conductance regulator gene mutations?
    a. Phe508del
    b. G542X
    c. I507del
    d. R347D

3. In the phase 3 clinical trials completed by Middleton PG, et al. and Heijerman HGM, et al. that evaluated elexacaftor/tezacaftor/ivacaftor (Trikafta), what was the primary outcome studied?
    a. Sweat chloride concentration change from baseline
    b. Frequency of pulmonary exacerbations
    c. Number of antibiotics utilized in exacerbations
    d. ppFEV$_1$ change from baseline at 4 weeks

4. What was the minimum age requirement for participation in the two phase 3 clinical trials that studied elexacaftor/tezacaftor/ivacaftor (Trikafta)?
    a. 12 years old
    b. 18 years old
    c. 6 years old
    d. 21 years old

5. How many total tablets are taken each day of therapy with Trikafta in someone without drug interactions or interacting conditions?
    a. 3 each morning, 2 each evening
    b. 1 each morning, 1 each evening
    c. 2 each morning, 1 each evening
    d. 1 each morning, 3 each evening

6. Elexacaftor/tezacaftor/ivacaftor (Trikafta) has a notable interaction with which of the following CYP isoenzyme inhibitors?
    a. CYP3A4 inhibitors
    b. CYP2C19 inhibitors
    c. CYP2D6 inhibitors
    d. CYP2E1 inhibitors

7. Which of the following is **not** one of the top 3 common adverse events seen in patients treated with elexacaftor/tezacaftor/ivacaftor (Trikafta)?
    a. Increased sputum production
    b. Bleeding
    c. Cough
    d. Headache

8. For adult patients who have been treated with elexacaftor/tezacaftor/ivacaftor (Trikafta), what lab value should be assessed prior to therapy initiation, every 3 months during the first 12 months of use, and then annually?
    a. Liver Function Test
    b. Renal Function Test
    c. Fasting Lipid Panel
    d. Thyroid Function Panel

9. Which individual agent in elexacaftor/tezacaftor/ivacaftor (Trikafta) is taken both in the morning and in the evening doses because of its shorter half-life?
    a. Elexacaftor
    b. Tezacaftor
    c. Ivacaftor
    d. None of the above

10. Which of the following counseling points is true and should be provided to patients who are taking elexacaftor/tezacaftor/ivacaftor (Trikafta)?
    a. It should be taken with a full glass of grapefruit juice every morning.
    b. It should be stored in the refrigerator.
    c. The blue tablet should be taken exactly 1 hour after the orange tablets.
    d. It should be administered with fat-containing food for the best absorption.