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Cystic Fibrosis Agents

Updated: December 5, 2018.

OVERVIEW

Introduction

Ivacaftor, lumacaftor and tezacaftor are orally available potentiators or correctors of the cystic fibrosis transmembrane conductance regulator (CFTR) that are used to treat patients with cystic fibrosis with specific mutations of the CFTR. Ivacaftor alone or in combination with lumacaftor or tezacaftor has been associated with transient serum enzyme elevations during treatment, but neither agent has been convincingly implicated in cases of clinically apparent acute liver injury with jaundice.

Background

Cystic fibrosis (CF) is a severe inherited disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator gene, which results in impaired clearance of mucous secretions leading to progressive pancreatic and pulmonary dysfunction, considerable disability and early mortality. CF is considered the most common, fatal genetic disorder among Caucasians, affecting approximately 1:2000 persons of European descent. Disease manifestations generally arise in childhood and include pancreatic insufficiency, poor nutrition, failure to thrive and progressive lung disease with frequent respiratory infections and pulmonary exacerbations. Survival is poor, but has improved greatly with medical interventions and attention to maintenance of rigorous pulmonary hygiene, preventive or rapid treatment of respiratory infections and proper nutritional management. The discovery that the disease was caused by mutations in the CFTR gene led to a focused search for small molecules that might improve, correct or potentiate abnormal CFTR function. A major problem was the diversity of mutations found in CF and the variability in how these mutations affected gene function (proper folding of the mature CFTR protein, trafficking of the protein to the proper place in the plasma membrane, channel opening and maintenance of the open configuration). Nevertheless, several agents were identified that were potentiators or correctors ("tor") of the CFTR ("caf") and could improve respiratory function, sense of well being and nutrition and decrease pulmonary exacerbations in patients with CF who had agent-specific mutations in the CFTR gene. Currently, three such agents are available clinically – ivacaftor, lumacaftor and tezacaftor. Several other CFTR potentiators are in various stages of development.

Ivacaftor (eye" va kaf' tor) was the first CFTR modulator to become available for use in the United States. It potentiates the opening of the CFTR channel in patients who harbor at least one mutation in the CFTR gene that is responsive to invacaftor based upon clinical or in vitro assay data, such as the Gly551Asp (also abbreviated as G551D) CFTR mutation. Ivacaftor was approved in the United States for use in patients with the CFTR Gly551Asp mutation in 2012 and is available as monotherapy in tablets of 150 mg and as oral granules in packets of 50 and 75 mg under the brand name Kalydeco. The recommended dose in adults and children above 6 years

of age is 150 mg orally every 12 hours. The dose in children less than 6 years of age is based upon body weight. The Gly551Asp mutation is found in approximately 5% of patients with CF.

Lumacaftor (loo" ma kaf' tor) is a "corrector" of the CFTR and was the second agent to gain approval as therapy of CF, but only in combination with ivacaftor, and specifically for patients who are homozygous for the Phe508del (F508del) mutation in the CFTR. Phen508del is the most frequent mutation in CFTR found in patients with CF and is associated with a lack of trafficking of the transporter to the cell surface. In vitro, lumacaftor was found to partially correct this trafficking error. Lumacaftor combined with ivacaftor was approved for use in patients homozygous for Phe508del CFTR in 2015 and is available as tablets consisting of 200 mg of lumacaftor and 125 mg of ivacaftor under the brand name Orkambi. Side effects of these agents are generally mild, but can include headache, nasal congestion, abdominal pain, diarrhea, nausea, dizziness and rash.

Tezacaftor (tez" a kaf' tor) is a "corrector" of the CFTR and was the third agent to gain approval, but only in combination with ivacaftor, and specifically for patients who are homozygous for the Phe508Del (F508del) mutation in the CFTR or are heterozygous and have another mutation in CFTR found in patients with CF and is associated with a lack of trafficking of the transporter to the cell surface. In vitro, tezacaftor was found to partially correct this trafficking error. Tezacaftor combined with ivacaftor was approved for use in the United States as therapy for patients with cystic fibrosis in 2018 and is available as tablets of fixed dose of 100 mg tezacaftor with 150 mg of ivacaftor co-packaged with tablets of 150 mg of ivacaftor alone under the brand name Symdeko. Side effects of these agents are generally mild but can include headache, nasal congestion, abdominal pain, diarrhea, nausea, dizziness and rash.

Hepatotoxicity

In large randomized controlled trials of ivacaftor with or without lumacaftor or tezacaftor, up to 25% of subjects had some degree of serum aminotransferase elevations during therapy. The elevations, however, were generally transient and mild and were above 3 times the upper limit of normal (ULN) in only 2% to 5% of patients. The abnormalities were usually asymptomatic and often resolved spontaneously without dose adjustment. Furthermore, in several studies, similar rates of serum enzyme elevations were noted in the placebo treated groups. Nevertheless, serum aminotransferase elevations resulted in dose modification or interruption in 1% to 2% of patients on ivacaftor. In prelicensure clinical trials of the combination of ivacaftor and lumacaftor, a higher rate of serum enzyme elevations was reported, and 3 patients had concurrent bilirubin elevations (above 2 times ULN). The clinical features of the liver injury such as the timing of onset, height of bilirubin or serum enzyme elevations, response to discontinuation or dose modification and outcomes were not described. Since approval of these agents and their more widescale use, there have no published case reports of clinically apparent liver injury attributed to ivacaftor or its combination with lumacaftor, but both have been available for a short time only and used in a limited number of patients. Complicating the issue is that patients with CF often have mild serum enzyme elevations that can be transient and intermittent, but are sometimes persistent and even accompanied by bilirubin elevations. A proportion of patients with CF develop severe liver disease with portal hypertension and marked hepatic dysfunction.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which ivacaftor, lumacaftor and tezacaftor might cause liver injury is not known. Ivacaftor is extensively metabolized by the liver by the cytochrome P450 system (largely CYP 3A) and liver injury might be caused by a toxic or immunogenic product of their metabolism. In contrast, lumacaftor is not extensively metabolized and the majority is excreted unchanged in the feces. Tezacaftor is also metabolized by CYP 3A and with ivacaftor is susceptible to drug-drug interactions, particularly with strong inducers (such as rifampin and

St. John's wort) or strong inhibitors (such as ketoconazole) of CYP 3A and with other drugs that are metabolized and are substrates of CYP 3A.

Outcome and Management

While chronic therapy with ivacaftor with or without lumacaftor or tezacaftor can be associated with mild-to-moderate serum aminotransferase elevations, they have not been convincingly linked to cases of clinically apparent liver injury. Monitoring of serum aminotransferase levels is recommended for patients taking ivacaftor with or without lumacaftor or tezacaftor every 3 months for the first year and intermittently thereafter. Patients who develop aminotransferase elevations on therapy should be monitored more carefully and dosing should be interrupted if values rise above 5 times ULN, with caution in restarting if they then fall into the normal range. The safety and efficacy of these agents in patients with CF and significant liver disease has not been demonstrated.

Drug Class: Genetic Disorder Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ivacaftor – Kalydeco®

Tezacaftor/Ivacaftor – Symdeko®

DRUG CLASS

Cystic Fibrosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

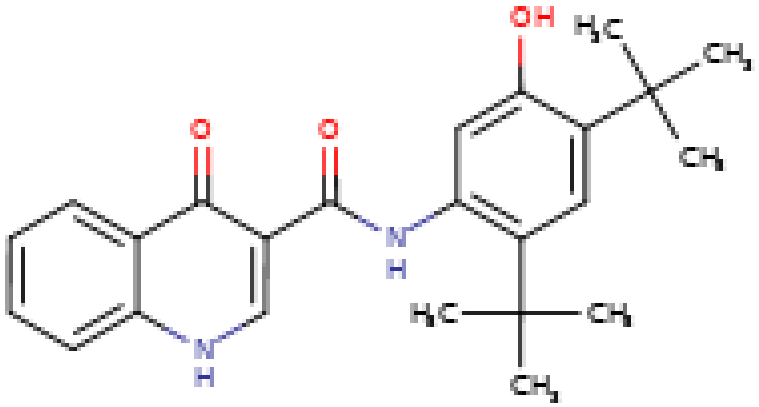
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ivacaftor	873054-44-5	C24-H28-N2-O3	

Table continued from previous page.

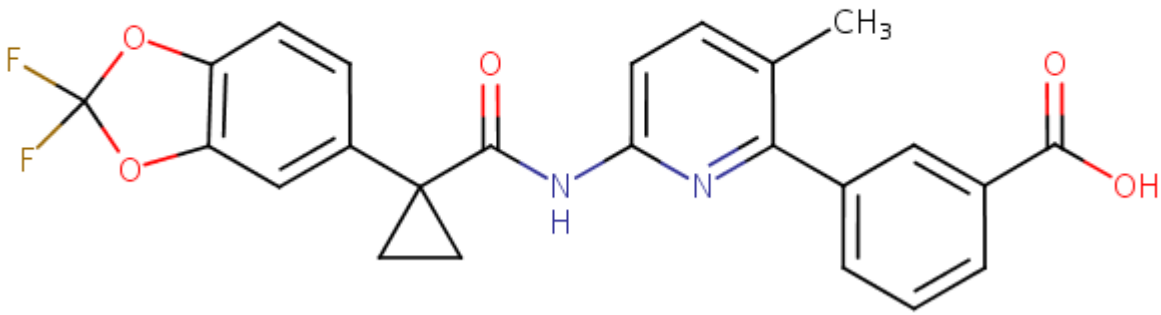
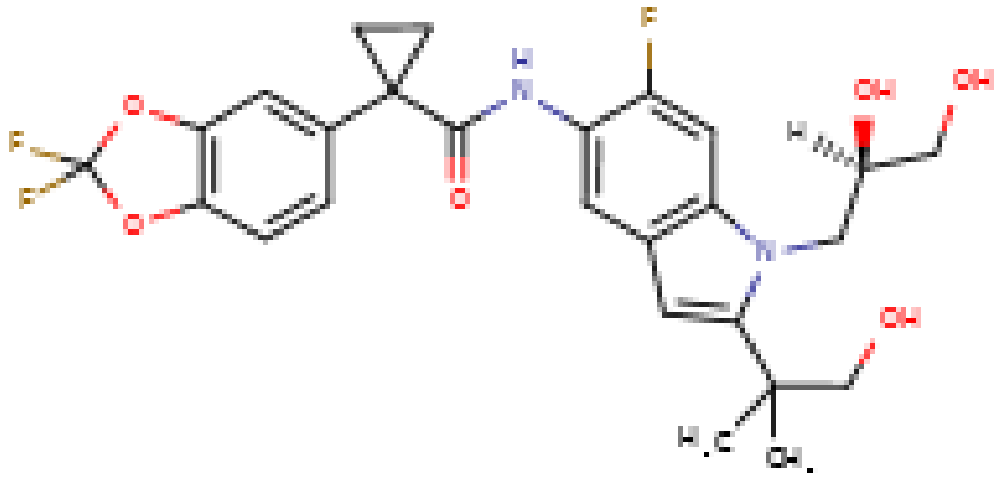
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Lumacaftor	936727-05-8	C24-H18-F2-N2-O5	

Table continued from previous page.

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tezacaftor	1152311-62-0	C26-H27-F3-N2-O6	

ANNOTATED BIBLIOGRAPHY

References updated: 05 December 2018

Abbreviatiions used: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevínek P, Griese M, et al.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365: 1663-72. PubMed PMID: 22047557.

(Among 161 patients with CF and the Gly551Asp mutation of CFTR, pulmonary function improved more and respiratory exacerbations were less in those who were treated with ivacaftor compared to placebo; serum ALT levels above 2 times ULN occurred in 9.6% of ivacaftor vs 11.6% of placebo recipients, and were above 5 times ULN in 3.6% vs 1.3%).

Davis PB. Therapy for cystic fibrosis--the end of the beginning? N Engl J Med 2011; 365: 1734-5. PubMed PMID: 22047565.

(Editorial in response to Ramsey [2011]).

Hebestreit H, Sauer-Heilborn A, Fischer R, Käng M, Mainz JG. Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation. J Cyst Fibros 2013; 12: 599-603. PubMed PMID: 23757359.

(Among 14 patients with severe lung disease due to CF who were treated with ivacaftor for up to 1 year, 1 developed ALT elevations of 3 to 4 times ULN, 1 had AST elevations and 1 bilirubin elevations, but all resolved spontaneously without drug discontinuation).

Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, Mainz JG, et al.; VX08-770-103 (ENVISION) Study Group. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med 2013; 187: 1219-25. PubMed PMID: 23590265.

(Among 52 children with CF and CFTR mutation Gly551Asp treated with ivacaftor or placebo for 48 weeks, FEV1 improved significantly in ivacaftor, but not placebo recipients [12.6% vs 0.1%], while adverse event rates were similar and there were "no clinically important trends attributable to ivacaftor" in liver test results).

Wood ME, Smith DJ, Reid DW, Masel PJ, France MW, Bell SC. Ivacaftor in severe cystic fibrosis lung disease and a G551D mutation. Respirol Case Rep 2013; 1: 52-4. PubMed PMID: 25473543.

(Among 3 adults with CF, CFTR Gly551Asp mutations and severe lung disease who were treated with ivacaftor for 24 weeks, one developed "elevated liver enzymes" which required drug withdrawal, but later tolerated restarting ivacaftor without recurrence of liver injury).

Holmes D. False dawn for cystic fibrosis disease modifiers? Nat Rev Drug Discov 2014; 13: 713-4. PubMed PMID: 25270946.

(Editorial on the results of trials of ivacaftor/lumacaftor combination therapy focusing on the modest effects achieved [2.6-4% increase in FEV1] and recent in vitro data suggesting that ivacaftor may reverse the effects of lumacaftor on the Phe508del mutant CFTR).

McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, Ratjen F, et al.; VX08-770-105 (PERSIST) Study Group. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). Lancet Respir Med 2014; 2: 902-10. PubMed PMID: 25311995.

(Among 192 adults and children with CF and Gly551Asp mutant CFTR who were treated in an extension study after the 48 week-controlled trials of ivacaftor [Ramsey 2011, Davies 2013], efficacy was maintained and there

were no new safety concerns, although 9 patients [5%] developed ALT elevations above 5 times ULN [without bilirubin elevations] and required dose interruptions).

Boyle MP, Bell SC, Konstan MW, McColley SA, Rowe SM, Rietschel E, Huang X, et al.; VX09-809-102 study group. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. Lancet Respir Med 2014; 2: 527-38. PubMed PMID: 24973281.

(In a dose finding study of lumacaftor alone and in combination with ivacaftor vs placebo in 188 patients with CF and the Phe508del mutant CFTR, there was little change in lung function [FEV1] and one patient developed ALT elevations, but before starting active therapy).

Hayes D Jr, Warren PS, McCoy KS, Sheikh SI. Improvement of hepatic steatosis in cystic fibrosis with ivacaftor therapy. J Pediatr Gastroenterol Nutr 2015; 60: 578-9. PubMed PMID: 25688481.

(17 year old girl with Gly551Asp mutant CFTR and hepatic steatosis was treated with ivacaftor for 2 years and was found to have resolution of the steatosis by MR imaging, but had also received ursodiol which was associated temporarily with improvements in serum enzyme elevations).

Taylor-Cousar J, Niknian M, Gilmartin G, Pilewski JM; for the VX11-770-901 investigators. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: Safety and efficacy in an expanded access program in the United States. J Cyst Fibros 2016; 15 (1): 116-22. PubMed PMID: 25682022.

(Among 44 adults and children with CF [Gly551Asp mutant CFTR] and severe lung disease who were treated with ivacaftor for 24 weeks, FEV1 improved by an average of 5.5% and most patients gained weight; liver test abnormalities were noted in 1 patient [2%], but no details were provided).

Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, et al.; TRAFFIC and TRANSPORT Study Groups. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373: 220-31. PubMed PMID: 25981758.

(Among 1108 adult and adolescent patients with CF who were homozygous for the Phe508del CFTR mutant allele and were treated with the combination of lumacaftor and ivacaftor for 24 weeks, ALT elevations above 3 times ULN occurred in 5.2% of patients on the drug combination vs 5.1% on placebo; drug discontinuations for liver test elevations occurred in 7 patients on the drug combination vs none on placebo, and concurrent ALT and bilirubin elevations occurred only in drug-treated patients [n=3]).

Jones AM, Barry PJ. Lumacaftor/ivacaftor for patients homozygous for Phe508del-CFTR: should we curb our enthusiasm? Thorax 2015; 70: 615-6. PubMed PMID: 26071414.

(Commentary on the safety and efficacy of the combination of lumacaftor with ivacaftor in patients with CF [with the Phe508del mutation in the CFTR] mentions the rather modest improvements in lung function found in the controlled trials of the combination [Wainwright 2015], and the finding of significant elevations in both ALT and bilirubin levels in 3 treated patients raising the issue of interaction between the two agents).

Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, et al.; VX11-770-110 (KONDUCT) Study Group. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med 2015; 3: 524-33. PubMed PMID: 26070913.

(Among 69 adults and children with CF and the Arg117His mutant CFTR treated with ivacaftor or placebo for 24 weeks, sweat chloride levels decreased with treatment, but FEV1 results did not improve significantly; no mention of ALT elevations or clinically apparent liver injury).

Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G, Waltz D, et al.; VX-809 TRAFFIC and TRANSPORT study groups. Efficacy and safety of lumacaftor/ ivacaftor combination therapy in patients

with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. Lancet Respir Med 2016; 4: 617-26. PubMed PMID: 27298017.

(Pooled analysis of two placebo controlled trials of lumacaftor/ivacaftor in 1108 patients with CF [and Phe508del CFTR mutation], focuses on improvements in pulmonary function test results; no mention of ALT elevations, hepatotoxicity or non-pulmonary serious adverse events).

Hubert D, Dehillotte C, Munck A, David V, Baek J, Mely L, Dominique S, et al. Retrospective observational study of French patients with cystic fibrosis and a Gly551Asp-CFTR mutation after 1 and 2 years of treatment with ivacaftor in a real-world setting. J Cyst Fibros 2017 Jul 12. pii: S1569-993. PubMed PMID: 28711222.

(Among 57 patients with CF [and Gly551Asp-CFTR mutation] treated with ivacaftor for 1-2 years, "no significant adverse events were reported", although therapy was discontinued in 2 patients because of abnormal liver enzyme levels or cirrhosis).

Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, Milla CE, et al; VX14-809-109 investigator group. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med 2017; 5: 557-67. PubMed PMID: 28606620.

(Among 204 children with CF [homozygous for Phen508del CFTR mutation] treated with lumacaftor/ ivacaftor or placebo, pulmonary function tests improved more frequently in drug treated children, while overall adverse event rates were similar; ALT or AST elevations above 3 times ULN occurred in 13% vs 8%, and above 5 times in 5% vs 3%, although all liver enzyme elevations were self-limited and not accompanied by jaundice or symptoms).

Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med 2017; 5: 107-18. PubMed PMID: 28011037.

(Among 340 patients with CF [Phen508del CFTR mutation] who continued lumacaftor/ivacaftor therapy after participation in randomized controlled trials [Wainwright 2015; Elborn 2016], the beneficial effects of therapy appeared to be maintained while ALT or AST elevations above 3 times ULN arose in 8% of patients, but all elevations were self-limited and none were accompanied by bilirubin elevations; one subject developed acute hepatitis E).

Rowe SM, McColley SA, Rietschel E, Li X, Bell SC, Konstan MW, Marigowda G, Waltz D, Boyle MP; VX09-809-102 Study Group. Lumacaftor/ivacaftor treatment of patients with cystic fibrosis heterozygous for F508del-CFTR. Ann Am Thorac Soc 2017; 14: 213-9. PubMed PMID: 27898234.

(Among 126 patients with CF [heterozygous for phe508del CFTR mutation] treated with lumacaftor/ivacaftor for 56 days, overall side effect rates were simillar in the two groups; one drug treated subject discontinued therapy because of ALT and AST elevations).

Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M; VX13-809-011 Part B Investigator Group *. Lumacaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for F508del-CFTR. Am J Respir Crit Care Med 2017; 195: 912-20. PubMed PMID: 27805836.

(Among 56 children with CF [homozygous for phe508del] treated with lumacaftor/ivacaftor for 24 weeks, ALT or AST elevations above 5 times ULN occurred in 5 patients [9%], and 3 stopped therapy because of enzyme elevations, but none developed jaundice or symptoms).

Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, et al. Tezacaftor-Ivacaftor in residual-function heterozygotes with cystic fibrosis. N Engl J Med 2017; 377: 2024-35. PubMed PMID: 29099333.

(Among 248 patients with cystic fibrosis heterozygous for the Phe508del mutation in CFTR treated in a cross over study of tezacaftor/ivacaftor vs ivacaftor alone vs placebo, improvements in lung function were greater with active treatment, but adverse event rates were similar in all 3 groups, ALT elevations above 3 times ULN occurring in 11.7% of tezacaftor/ivacaftor, 13.4% on ivacaftor alone and 8% on placebo, but none were accompanied by jaundice or led to early discontinuation).

Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, Wang LT, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for phe508del. N Engl J Med 2017; 377: 2013-23. PubMed PMID: 29099344.

(Among 509 patients with cystic fibrosis who were homozygous for phe508del who were treated with tezacaftor/ivacaftor or placebo for 24 weeks improvement in lung function was treated with the active drug than with placebo, while adverse event rates were similar, ALT elevations above 3 times ULN occurring in 4.7% vs 3.2% and leading to early discontinuation in 0.4% vs 0.2% of subjects).

Tezacaftor/Ivacaftor (Symdeko) for cystic fibrosis. Med Lett Drugs Ther 2018; 60 (1558): 174-6. PubMed PMID: 30335045.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of tezacaftor/ivacaftor; mentions that serum aminotransferase levels can occur and that monitoring of liver tests should be done before starting therapy followed by every 3 months for the first year and annually thereafter).

Davies JC, Moskowitz SM, Brown C, Horsley A, Mall MA, McKone EF, Plant BJ, et al.; VX16-659-101 Study Group. VX-659-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018; 379: 1599-611. PubMed PMID: 30334693.

(Among 117 selected patients with cystic fibrosis treated with tezacaftor/ivacaftor with or without VX-659 or placebo, improvements in lung function and sweat chloride were greatest with triple therapy, but that 3 of 49 patients receiving triple therapy developed ALT elevations above 3 times ULN, but the abnormalities resolved even without dose reduction).

Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, Ramsey BW, et al.; VX16-445-001 Study Group.VX-445-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. N Engl J Med 2018; 379: 1612-20. PubMed PMID: 30334692.

(Among 123 selected patients with cystic fibrosis treated with tezacaftor/ivacaftor with or without VX445 or placebo, improvements in lung function and sweat chloride were greatest with triple therapy and adverse event rates were similar in all groups, ALT or AST elevations occurring in 28% receiving VX445, 28% receiving tezacaftor/ivacaftor and 33% on placebo and were above 5 times ULN in only 1 subject).