

New drugs

Elexacaftor/tezacaftor/ivacaftor

Approved indication: cystic fibrosis

Trikafta (Vertex)

100 mg/75 mg/50 mg film-coated tablets

Cystic fibrosis is an autosomal recessive disorder caused by mutations in the genes encoding the cystic fibrosis transmembrane conductance regulator (CFTR). There are many possible mutations affecting the formation and function of the CFTR protein. The most common is the F508del mutation. These mutations result in defects in the transport of chloride ions. This leads to the formation of thick mucus which affects the lungs, pancreas and gut.

In the past decade several drugs have been developed to enhance the structure and activity of the CFTR protein. The first was *ivacaftor* and this is now available in combination with *lumacaftor* or *tezacaftor*. Elexacaftor is a new drug that acts at a different site on the CFTR protein. This increases the amount of CFTR protein delivered to the cell surface. The new combination of elexacaftor, tezacaftor and ivacaftor is intended to enhance the quantity and function of the protein. Patients will take two tablets of the combination in the morning and a separate dose of ivacaftor 150 mg in the evening.

The combination should be taken with a moderately fatty meal as this will increase the absorption of elexacaftor. As the drugs in the combination are extensively metabolised by cytochrome P450 (CYP) 3A4/5, there are many potential interactions including with grapefruit juice. Strong inducers such as carbamazepine, and inhibitors such as azole antifungals, of CYP3A should be avoided. The combination is also not recommended for patients with moderate or severe liver disease. Little drug is excreted in the urine so no dose adjustment is recommended in kidney disease, although there are no studies in patients with severe renal impairment. The pharmacokinetics of the combination in children aged 12 years and over are similar to adults. Treatment is not currently approved in younger children. Animal studies show the drugs in the combination cross the placenta and are excreted in breast milk.

A phase II trial studied the effect of different daily doses of elexacaftor in combination with tezacaftor and ivacaftor in 123 patients with cystic fibrosis who had F508del genotypes. After four weeks all doses had resulted in improvements in the percentage of

predicted forced expiratory volume in one second (FEV₁). There was no change in the patients given a placebo. Treatment with the combination also reduced the chloride concentration in sweat.¹

The triple combination therapy, containing elexacaftor 200 mg, was compared to placebo in a 24-week phase III trial. The 403 patients in the trial had an F508del mutation on one allele and a minimal function mutation on the other. At baseline their mean percentage of predicted FEV₁ was approximately 61%. By four weeks this had improved by an average of 13.6 percentage points in the 200 patients who took the combination. This change was sustained at week 24 while the FEV₁ of patients in the placebo group declined slightly. There were 41 pulmonary exacerbations in the treatment group compared with 113 in the placebo group. Treatment also reduced the sweat chloride concentration.²

Another phase III trial studied the combination in patients who were homozygous for the F508del mutation. This randomised 55 patients to take the combination and 52 to take ivacaftor and tezacaftor. The mean percentage of predicted FEV₁ was approximately 61% at the start of the study. After four weeks of treatment this had increased by 10.4 percentage points with the combination, but only by 0.4 percentage points with ivacaftor and tezacaftor. The combination also reduced the sweat chloride concentration.³

Most patients with cystic fibrosis will experience adverse events which may be unrelated to drug therapy. In the placebo-controlled phase III trial the most common adverse events were exacerbations of cystic fibrosis and increased sputum. Only two of the 202 patients in that trial discontinued the combination because of adverse effects.² Adverse events that have been reported more frequently with the combination than with placebo include headache, diarrhoea and rashes. Patients taking elexacaftor, tezacaftor and ivacaftor may develop increases in liver transaminases and creatine phosphokinase.

The three-drug combination is indicated for patients, aged 12 years and above, who have at least one F508del mutation. This increases the proportion of patients with cystic fibrosis who may benefit from therapy with CFTR modulators, but the combination is not a cure and it will be unsuitable for treating patients with different mutations. There is still a need

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for standard management such as airway clearance. Most of the trials were short term, but cystic fibrosis is lifelong so it will be important for the patients to adhere to treatment. Adding elexacaftor to tezacaftor and ivacaftor further improves FEV₁,³ but continuing follow-up is going to be needed to confirm that this leads to long-term clinical benefits.

T manufacturer provided the product information

REFERENCES

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The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.](#)

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA and the [European Medicines Agency](#).