New drugs

Ivacaftor

Approved indication: cystic fibrosis
Kalydeco (Vertex)
150 mg film-coated tablets
Australian Medicines Handbook Appendix A

The prognosis of patients with cystic fibrosis has improved, but most treatments are dealing with the consequences of the disease. In contrast, ivacaftor is aimed at the cause of the disease.

Patients with cystic fibrosis have a mutation in a gene which codes for a specific protein called the cystic fibrosis transmembrane conductance regulator (CFTR). The mutation results in defective transport of water and chloride leading to thickened mucus and salty sweat. Ivacaftor enhances chloride transport by potentiating the action of the CFTR protein. Early research showed ivacaftor had its greatest effect on cells with a particular mutation identified as G551D. This is found in 4–5% of patients with cystic fibrosis.

A range of doses of ivacaftor were studied in 39 adults with the G551D mutation. Compared to placebo, there was a significant reduction in the sweat chloride concentration after 14 and 28 days of treatment. Ivacaftor also resulted in small improvements in lung function. The median increase from baseline in the forced expiratory volume in one second (FEV_1) after 28 days was 0.2 L with placebo and 0.25 L with ivacaftor 150 mg twice daily.[1] This dose was used in the later phase III trials of patients with the G551D mutation.

One trial enrolled patients aged 12 years or older (mean age 25.5 years) and randomised 161 to take ivacaftor or a placebo for 48 weeks. The primary end point of the study was the change in FEV_1 as a percentage of the predicted value at week 24. At that time the increase from baseline was 10.4% with ivacaftor versus a decrease of 0.2% in the placebo group. The mean increase in FEV_1 was 0.367 L with ivacaftor and 0.006 L with placebo. This statistically significant difference was maintained at the end of the study. At week 48, 67% of the ivacaftor group had not had a pulmonary exacerbation compared with 41% of the placebo group. The patients taking ivacaftor put on an average of 3.1 kg during the trial while the placebo group gained 0.4 kg.[2]

A similar trial randomised 52 children aged 6–11 years. After 24 weeks the change from baseline in the percentage of predicted FEV_1 was 12.6% with ivacaftor and 0.1% with placebo. FEV_1 had increased by 0.303 L with ivacaftor and by 0.067 L with placebo. This difference was still statistically significant after 48 weeks. There was only a small number of exacerbations with no difference between the groups. The children taking ivacaftor gained 5.9 kg in weight over 48 weeks compared with a weight gain of 3.1 kg in the placebo group.[3]

During the trials the common adverse events with ivacaftor included headache (24%), upper respiratory tract infections (23%), abdominal pain (16%), diarrhoea (13%), rash (13%) and dizziness (9%). Although some patients interrupted their treatment because of adverse events, more patients in the placebo group discontinued completely.[2,3] Some patients discontinued ivacaftor because of altered liver function, so liver function tests are recommended before treatment and then every three months during the first year of treatment.

Ivacaftor is metabolised mainly by cytochrome P450 3A. Concentrations of ivacaftor will therefore be increased by enzyme inhibitors such as ketoconazole and grapefruit juice and decreased by enzyme inducers such as carbamazepine, phenytoin and St John's wort. Ivacaftor may also interact with digoxin and benzodiazepines. The terminal half-life of ivacaftor is 12 hours with most of the metabolites being excreted in the faeces. As fat increases the absorption of ivacaftor the tablets should be taken with fatty food.

Some of the patients in the clinical trials continued to take ivacaftor. The improvements in FEV_1 were maintained, but as cystic fibrosis is a lifelong disease ongoing evaluation is required. There is also a need to investigate whether starting treatment at the time of diagnosis will prevent organ damage. Although ivacaftor is an advance, most patients with cystic fibrosis will not benefit as they do not have the G551D mutation. A phase II trial involving patients with the most common mutation found that ivacaftor was no better than placebo.[4]

T T T manufacturer provided clinical evaluation

REFERENCES *†A

1. Accurso FJ, Rowe SM, Clancy JP, Boyle MP, Dunitz JM, Durie PR, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med 2010;363:1991-2003.
2. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663-72.

A Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

3. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. 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.
4. Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordoñez CL, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest 2012;142:718-24.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)