NEW DRUGS

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Lumacaftor/ivacaftor

Approved indication: cystic fibrosis

Orkambi (Vertex)
film-coated tablets containing 100 mg/125 mg or 200 mg/125 mg
sachets of granules containing 100 mg/125 mg or 150 mg/188 mg

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These mutations affect the functioning of the CFTR protein which is a chloride channel that helps regulate the transport of water and chloride. Affected individuals have impaired chloride transport leading to thickened mucus which interferes with normal lung function.

Lumacaftor/ivacaftor is a new fixed-dose combination product for patients with cystic fibrosis from two years of age. It is specifically indicated for those who are homozygous for the F508del mutation, which accounts for about 45% of affected patients. This is a severe form of the disease as they have little or no CFTR protein on their cells. Lumacaftor is a newly approved chemical entity whereas ivacaftor is already available as monotherapy and in combination with tezacaftor.

The lumacaftor/ivacaftor combination works by improving CFTR activity in the lungs. Like tezacaftor, lumacaftor helps with cellular processing of the CFTR protein so more is present on the cell surface. Ivacaftor improves the function of CFTR and increases chloride transport.

The approval of the lumacaftor/ivacaftor combination is primarily based on two phase III trials (TRAFFIC and TRANSPORT)[1] of 1108 patients (aged ≥12 years) with the homozygous F508del mutation. At baseline, patients had a mean forced expiratory volume in one second that was 61% of the predicted normal value ($ppFEV_1$). Patients were randomised to ivacaftor (250 mg every 12 hours) plus lumacaftor (400 mg every 12 hours or 600 mg once daily), or placebo. After 24 weeks of treatment, both doses of lumacaftor/ivacaftor had produced statistically significant improvements in $ppFEV_1$ over placebo (2.6–4%) (see Table). Also, pulmonary exacerbations were less with combination treatment, including episodes that led to hospitalisation or the need for intravenous antibiotics.[1]

In a 96-week extension study of the TRAFFIC and TRANSPORT trials (PROGRESS trial), the mean absolute change in $ppFEV_1$ remained above baseline in patients continuing the lumacaftor 400 mg plus ivacaftor 250 mg dose. However, the difference from baseline was no longer statistically significant, presumably because lung function was deteriorating with age.[2] The annualised rate of pulmonary exacerbations in these patients remained lower than the placebo rate in the TRAFFIC and TRANSPORT trials (0.65 vs 1.14).

Lumacaftor/ivacaftor has also been assessed in children aged 6–11 years in a placebo-controlled phase III trial (204 patients).[3] After 24 weeks of treatment, those randomised to the combination had statistically significant changes in $ppFEV_1$ over those randomised to placebo (2.4%) (see Table).

Table **Efficacy of lumacaftor/ivacaftor in cystic fibrosis (homozygous F508del mutation)**

Drug regimen (patients)	Improvement in $ppFEV_1$ after 24 weeks of treatment*	Pulmonary exacerbations†
TRAFFIC trial (549 patients aged ≥12 years)[1]		
Lumacaftor 600 mg/day plus ivacaftor 250 mg vs placebo	4%	79 vs 112
Lumacaftor 400 mg every 12 hours plus ivacaftor 250 mg vs placebo	2.6%	73 vs 112
TRANSPORT trial (559 patients aged ≥12 years)[1]		
Lumacaftor 600 mg/day plus ivacaftor 250 mg vs placebo	2.6%	94 vs 139
Lumacaftor 400 mg every 12 hours plus ivacaftor 250 mg vs placebo	3%	79 vs 139
Paediatric trial (204 patients aged 6–11 years)[3]		
Lumacaftor 200 mg every 12 hours plus ivacaftor 250 mg vs placebo	2.4%	Not available

* mean difference versus placebo in absolute change from baseline in percentage of predicted forced expiratory volume in one second ($ppFEV_1$) from baseline
† number of pulmonary exacerbations recorded in 24 weeks

During the TRAFFIC and TRANSPORT studies, more patients in the treatment groups than in the placebo group discontinued because of an adverse event (4.2% vs 1.6%). Reasons for discontinuing included elevated creatine kinase (4 patients), haemoptysis (3), bronchospasm (2), dyspnoea (2), pulmonary exacerbation (2) and rash (2).[1] Adverse events that were more common with treatment than placebo included dyspnoea (14% vs 7.8%), diarrhoea (11% vs 8.4%) and nausea (10.2% vs 7.6%).

A similar safety profile was observed with longer term treatment,[2] and in children aged 6–11 years.[3,4] In an open-label trial of 60 children aged 2–5 years, the combination was generally well tolerated. Adverse events included cough (63%), vomiting (28%), fever (28%), diarrhoea (10%), constipation (12%), and elevated alanine aminotransferase (13%) and aspartate aminotransferase (10%).[5]

Chest tightness and abnormal breathing were more common at the beginning of treatment, particularly in patients with poorer lung function at baseline ($ppFEV_1$ <40%). These patients should be started on a lower dose (one tablet/12 hours for the first two weeks) and need additional monitoring.

Lumacaftor has the potential to cause many drug interactions. It is a strong inducer of cytochrome P450 (CYP) 3A and may decrease serum concentrations (and efficacy) of many drugs that are metabolised by this enzyme (e.g. corticosteroids, azole antifungals, clarithromycin, erythromycin, oral contraceptives). Lumacaftor also inhibits and induces P-glycoprotein, CYP2C8 and CYP2C9, and induces CYP2B6 and CYP2C19. The product information should be checked before prescribing lumacaftor/ivacaftor as co-administration of some drugs is not recommended and others may require dose adjustment.

The recommended lumacaftor/ivacaftor dose is two 200 mg/125 mg tablets every 12 hours for patients older than 12 years and two 100 mg/125 mg tablets every 12 hours for children aged 6–11 years. For those aged 2–5 years, the recommended dose is one 100 mg/125 mg sachet every 12 hours for children weighing less than 14 kg and one 150 mg/188 mg sachet every 12 hours for those weighing 14 kg and over. Granules should be taken in a teaspoon of soft food or liquid and tablets should be swallowed whole. This medicine should be taken with fatty foods.

Maximum serum concentrations of lumacaftor and ivacaftor are reached approximately four hours after administration. The half-life is around 26 hours and most of the dose is excreted in the faeces. Dose reductions are recommended in hepatic impairment and are outlined in the product information.

This fixed-dose combination for cystic fibrosis (homozygous F508del mutation) is associated with a slower rate of decline in pulmonary function in patients aged six years and over. Efficacy data in children aged 2–5 years old are limited. It is not clear how the efficacy of lumacaftor/ivacaftor will compare to the other recently approved combination for this indication – tezacaftor/ivacaftor – which is approved for those 12 years and older. However, prescribers should be aware the lumacaftor/ivacaftor combination is a strong inducer of the CYP3A enzyme so has more drug interactions.

TT manufacturer provided additional useful information

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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, the European Medicines Agency and the Therapeutic Goods Administration.