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Orkambi (*lumacaftor / ivacaftor*)

An overview of Orkambi and why it is authorised in the EU

What is Orkambi and what is it used for?

Orkambi is a medicine used to treat cystic fibrosis in patients aged 1 year and above. Cystic fibrosis is an inherited disease that has severe effects on the lungs, the digestive system (gut) and other organs.

Orkambi is used in patients who have a genetic mutation (change) called the *F508del* mutation. This mutation affects the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR). Orkambi is used in patients who have inherited the mutation from both parents.

Orkambi contains the active substances lumacaftor and ivacaftor.

How is Orkambi used?

Orkambi can only be prescribed by a doctor with experience in the treatment of cystic fibrosis.

Orkambi is available as tablets and granules to be taken by mouth. It is taken every 12 hours with fat-containing foods.

For more information about using Orkambi, see the package leaflet or contact your doctor or pharmacist.

How does Orkambi work?

Cystic fibrosis is caused by mutations in the *CFTR* gene. This gene makes the CFTR protein, which is involved in regulating the production of mucus and digestive juices. The mutations reduce the amount of CFTR protein on the cell surface or affect the way the protein works.

One of the active substances in Orkambi, lumacaftor, increases the amount of CFTR protein on the cell and the other, ivacaftor, increases the activity of the defective CFTR protein. These actions make mucus and digestive juices less thick.

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What benefits of Orkambi have been shown in studies?

Orkambi improved lung function in two main studies involving 1,108 cystic fibrosis patients aged 12 years and above, and one study involving 204 children aged 6 to 11 years. All patients had the *F508del* mutation in the *CFTR* gene. In these three studies, Orkambi was compared with placebo (a dummy treatment), both added to patients' usual therapy.

In the two studies in patients aged 12 years and above, the main measure of effectiveness was based on improvement in patients' predicted FEV_1 which is a measure of how well the lungs work. Results from the first study showed that after 24 weeks of treatment patients who took Orkambi had an average improvement in FEV_1 of 2.41 percentage points more than those who took placebo; this figure was 2.65 in the second study. Treatment with Orkambi also reduced the number of exacerbations (flare-ups) requiring hospital admission or antibiotic therapy. Overall the number of exacerbations was reduced by 39% when compared with placebo.

In the study in children aged 6 to 11 years, the main measure of effectiveness was a decrease in the lung clearance index ($LCI_{2.5}$), which indicates an improvement in lung ventilation. After 24 weeks of treatment, $LCI_{2.5}$ decreased by 1.01 in patients treated with Orkambi compared with an increase of 0.08 in patients treated with placebo.

Additional studies have investigated the effects of Orkambi in children aged 1 to 5 years.

One study involved 60 children aged 2 to 5 years with cystic fibrosis who had the *F508del* mutation in both copies of the *CFTR* gene. All children were treated with Orkambi. There was improvement in CFTR protein activity, as measured by a decrease in the amount of chloride in sweat after 24 weeks of treatment. Patients with cystic fibrosis have high levels of chloride in sweat due to CFTR not working properly. Stopping treatment with Orkambi caused chloride levels to rise again. The children's growth (measured in terms of the body mass index, weight and height) also improved.

A second study involved 46 children aged 12 to 23 months with cystic fibrosis who had the F508del mutation in both copies of the CFTR gene. All children were treated with Orkambi. The study showed a decrease in the amount of chloride in sweat after 24 weeks of treatment, which was comparable to that seen in older children treated with Orkambi in separate studies.

What are the risks associated with Orkambi?

For the full list of side effects and restrictions with Orkambi, see the package leaflet.

The most common side effects with Orkambi (which may affect more than 1 in 10 people) include dyspnoea (shortness of breath), diarrhoea and nausea (feeling sick). Serious side effects (which may affect up to 1 in 100 people) include liver problems such as raised liver enzymes, cholestatic hepatitis (build-up of bile leading to inflammation of the liver) and hepatic encephalopathy (a brain disease caused by liver problems).

Why is Orkambi authorised in the EU?

Orkambi has been shown to improve lung function and lung ventilation in patients with cystic fibrosis from 6 years of age. The effects of Orkambi in children aged 1 to 5 years were considered to be similar to those in older children and a long-term study will be carried out to confirm this.

The beneficial effects of Orkambi were smaller than expected for a medicine that treats the mechanism of the disease rather than its symptoms. However, as cystic fibrosis caused by *F508del* mutation is particularly severe, the observed effects were considered clinically relevant for patients with no other

treatment options. Orkambi's side effects mainly affected the gut and breathing and were generally considered mild to moderate and manageable.

The European Medicines Agency decided that Orkambi's benefits are greater than its risks and recommended that it be approved for use in the EU.

What measures are being taken to ensure the safe and effective use of Orkambi?

The company that markets Orkambi is required to conduct a long-term study in children aged 1 to 5 years with cystic fibrosis who have the *F508del* mutation in both copies of the CFTR gene. The study is to evaluate how the disease progresses in children who are treated with Orkambi compared to children who are not treated with Orkambi. As part of this study, the long-term safety of Orkambi in children aged 12 to 23 months will be further assessed.

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Orkambi have also been included in the summary of product characteristics and the package leaflet.

As for all medicines, data on the use of Orkambi are continuously monitored. Side effects reported with Orkambi are carefully evaluated and any necessary action taken to protect patients.

Other information about Orkambi

Orkambi received a marketing authorisation valid throughout the EU on 19 November 2015.

Further information on Orkambi can be found on the Agency's website: ema.europa.eu/medicines/human/EPAR/Orkambi.

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