Kaftrio (ivacaftor / tezacaftor / elexacaftor)
An overview of Kaftrio and why it is authorised in the EU

What is Kaftrio and what is it used for?

Kaftrio is a medicine used to treat patients aged 6 years and above who have cystic fibrosis, an inherited disease that has severe effects on the lungs, the digestive system and other organs.

Cystic fibrosis can be caused by various mutations (changes) in the gene for a protein called ‘cystic fibrosis transmembrane conductance regulator’ (CFTR). People have two copies of this gene, one inherited from each parent and the disease only occurs when there is a mutation in both copies.

Kaftrio is used in combination with ivacaftor in patients whose cystic fibrosis is due to at least one F508del mutation in the CFTR gene.

Cystic fibrosis is rare, and Kaftrio was designated an ‘orphan medicine’ (a medicine used in rare diseases) on 14 December 2018. Further information on the orphan designation can be found here: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182117

Kaftrio contains the active substances ivacaftor, tezacaftor and elexacaftor.

How is Kaftrio used?

The medicine can only be obtained with a prescription. Kaftrio should only be prescribed by a healthcare professional with experience in the treatment of cystic fibrosis.

Kaftrio is available as tablets, which come in two different strengths. For patients aged 12 years or more, or weighing at least 30 kg each tablet contains 75 mg ivacaftor, 50 mg tezacaftor and 100 mg elexacaftor. For younger or smaller patients, each tablet contains 37.5 mg ivacaftor, 25 mg tezacaftor and 50 mg elexacaftor. Kaftrio should be taken together with another medicine containing ivacaftor alone. The recommended daily dose is two tablets of Kaftrio of the appropriate strength in the morning with fat-containing food and one ivacaftor tablet (150 mg in those on the higher dose of Kaftrio, 75 mg in those on the lower dose) in the evening, about 12 hours later.

The doses of Kaftrio and ivacaftor may need to be reduced if the patient is also taking a type of medicine called a ‘moderate or strong CYP3A inhibitor’, such as certain antibiotics or medicines for fungal infections, as they may affect the way Kaftrio and ivacaftor work in the body. The doctor may need to adjust the dose in patients with reduced liver function.
For more information about using Kaftrio, see the package leaflet or contact your doctor or pharmacist.

**How does Kaftrio work?**

Cystic fibrosis is caused by mutations in the CFTR gene. This gene leads to the production of the CFTR protein, which works on the surface of cells to regulate the production of mucus in the lungs and digestive juices in the gut. The mutations reduce the number of CFTR proteins on the cell surface or affect the way the protein works, resulting in mucus and digestive fluids being too thick, which leads to blockages, inflammation, increased risk of lung infections, and poor digestion and growth.

Two of the active substances in Kaftrio, elexacaftor and tezacaftor, increase the number of CFTR proteins on the cell surface, while the other, ivacaftor, improves the activity of the defective CFTR protein. These actions combine to make lung mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease.

**What benefits of Kaftrio have been shown in studies?**

Kaftrio taken together with ivacaftor was effective at improving lung function in three main studies in patients with cystic fibrosis aged 12 years and above. The main measure of effectiveness was ppFEV1, which is the maximum amount of air a person can breathe out in one second compared with values from an average person with similar characteristics (such as age, height and sex). In these studies, patients started off (baseline) with average ppFEV1 values that were only 60 to 68% of the values seen in an average healthy person.

The first study involved 403 patients with an F508del mutation and another type of mutation known as a 'minimal function' mutation. After 24 weeks of treatment, patients who took Kaftrio and ivacaftor had an average increase in ppFEV1 of 13.9 percentage points compared with a reduction of 0.4 percentage points in patients who took placebo (a dummy treatment).

In the second study involving 107 patients with an F508del mutation from both parents, patients who took Kaftrio with ivacaftor had an average increase in ppFEV1 of 10.4 percentage points compared with an increase of 0.4 percentage points in patients who took a combination of ivacaftor and tezacaftor alone.

A third study involved 258 patients with an F508del mutation plus either a gating or residual CFTR activity mutation (two other types of mutations). Patients who took Kaftrio with ivacaftor had an average increase in ppFEV1 of 3.7 percentage points compared with an increase of 0.2 percentage points in patients who took ivacaftor alone or a combination of ivacaftor and tezacaftor alone.

Treatment with Kaftrio for 24 weeks has also been shown to produce an average increase in ppFEV1 of 10.2 percentage points in a fourth study involving 66 patients aged 6 to less than 12 years; these patients had an F508del mutation from both parents or an F508del mutation and a 'minimal function' mutation. The company also provided evidence to support the use of lower doses in this group, which showed that the medicine was distributed in the body to a similar extent as in older children and adults.

**What are the risks associated with Kaftrio?**

The most common side effects with Kaftrio (which may affect more than 1 in 10 people) are headache, diarrhoea and upper respiratory tract infection (nose and throat infection). Rashes may occur and sometimes be serious.

For the full list of side effects and restrictions of Kaftrio, see the package leaflet.
Why is Kaftrio authorised in the EU?

Kaftrio is an effective treatment for patients with cystic fibrosis who have at least one F508del mutation in the CFTR gene. These patients have a high unmet medical need. In terms of safety, Kaftrio was well tolerated. Therefore, the European Medicines Agency decided that Kaftrio’s benefits are greater than its risks and it can be authorised for use in the EU.

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

The company that markets Kaftrio will carry out a study on the long-term safety of Kaftrio including in pregnant women.

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

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

Other information about Kaftrio

Kaftrio received a marketing authorisation valid throughout the EU on 21 August 2020.

Further information on Kaftrio can be found on the Agency’s website: https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio

This overview was last updated in 12-2021.