EMEA/H/C/005269

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 2 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 non-class I 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. If the patient's specific mutations are unknown, the presence of two CFTR mutations that are not responsive to Kaftrio should be excluded using appropriate genetic tests.

Patients with two class I (null) mutations (mutations that are known not to produce CFTR protein and are therefore not expected to respond to treatment) should not take Kaftrio, as some CFTR protein is needed for Kaftrio to have an effect.

More information on *CFTR* mutations that are likely to be responsive is available in the product information. Not all mutations have been tested, therefore mutations are not included in this list but may still respond to treatment with Kaftrio. For patients with these mutations, doctors can prescribe Kaftrio when the benefits of treatment are expected to outweigh its risks, and under close supervision.

Kaftrio is available as tablets and granules in a sachet, both of which come in two different strengths. The dose and formulation depend on the patient's age and body weight. Kaftrio should be taken in the

morning with fat-containing food. It is used together with another medicine containing ivacaftor alone, which should be taken in the evening, about 12 hours after Kaftrio.

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, including information about mutations that are likely to be responsive to Kaftrio, see the product information 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, with at least one *F508del* mutation (a non-class I mutation). 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), who were already receiving ivacaftor (patients with a gating mutation) or ivacaftor and tezacaftor (patients with a residual activity mutation). 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.

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.

Another study involved 75 children aged 2 to 5 years with an *F508del* mutation from both parents or an *F508del* mutation and a 'minimal function' mutation. In this study, patients received Kaftrio granules for 24 weeks and the medicine was not compared with other treatments. The results showed that treatment with Kaftrio granules reduced the level of chloride in patients' sweat. Patients with cystic fibrosis have high levels of chloride in sweat due to the CFTR protein not working properly and a decrease in sweat chloride can indicate that the medicine is having an effect. The reduction in sweat chloride level was similar to that seen in older patients in previous studies.

The effectiveness of Kaftrio in children aged 2 to 5 years was also supported by evidence showing that the medicine behaves in the same way in the body of younger children as in that of older children and adults.

Another study involved 307 patients from six years of age who did not have an *F508del* mutation. These patients harboured at least one of 18 frequently reported non-F508del mutations that would likely respond to Kaftrio. In this study, patients received either Kaftrio plus ivacaftor or placebo for 24 weeks. Patients who took Kaftrio plus ivacaftor had an average increase in ppFEV1 of 8.9 percentage points, compared with a reduction of 0.4 percentage points in patients who took placebo. Data from a 4-week extension of this study supported these results.

Supportive data were obtained from a registry study involving 422 patients, who did not have an *F508del* mutation. These patients harboured at least one non-F508del mutation that would likely respond to Kaftrio based on laboratory data. This study showed that, after an average of 16 months of treatment, patients taking Kaftrio plus ivacaftor had an average increase in ppFEV1 of 4.5 percentage points. Literature data from a compassionate use programme involving 479 patients who harboured at least one non-class I mutation in the CFTR gene showed an overall improvement in ppFEV1 of around 7.8 percentage points. Finally, laboratory data and additional data from published literature support the use of Kaftrio in patients who harbour at least one non-class I mutation in the *CFTR* gene.

What are the risks associated with Kaftrio?

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

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

Why is Kaftrio authorised in the EU?

Kaftrio is an effective treatment for patients with cystic fibrosis who have at least one non-class I 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. It will also carry out a study based on a patient registry to provide data on the long-term effectiveness of Kaftrio in children aged 2 to 5 years who have an *F508del* mutation from one parent.

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 03-2025.