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Kalydeco (*ivacaftor*)

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

What is Kalydeco and what is it used for?

Kalydeco is a medicine used to treat cystic fibrosis, an inherited disease that has severe effects on the lungs, the digestive system and other organs. Cystic fibrosis affects the cells that produce mucus and digestive juices. As a result, these secretions become thick and cause blockage. Build-up of thick and sticky secretions in the lungs causes inflammation and long-term infection. In the gut, blockage of the tubes from the pancreas slows down the digestion of food and causes poor growth.

Kalydeco is used on its own to treat cystic fibrosis in patients aged 1 year and above who have one of nine mutations (changes) in the gene for a protein called 'cystic fibrosis transmembrane conductance regulator' (CFTR). The mutations are: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* and *S549R* (also known as gating mutations).

Kalydeco is also used on its own to treat patients with cystic fibrosis aged 18 years and above who have the *R117H* mutation in the *CFTR* gene.

Kalydeco is also used together with another cystic fibrosis medicine containing the active substances tezacaftor and ivacaftor to treat patients with cystic fibrosis aged 12 years and above who have a mutation called *F508del* in the *CFTR* gene. The two medicines are used in patients who have inherited the *F508del* mutation from both parents and therefore have the mutation in both copies of the *CFTR* gene. They are also used in patients who have inherited the *F508del* mutation from one parent and also have one of the following mutations in *CFTR*: *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272 26A→G*, or *3849+10kbC→T*.

Kalydeco contains the active substance ivacaftor.

Cystic fibrosis is 'rare', and Kalydeco was designated an 'orphan medicine' (a medicine used in rare diseases) on 8 July 2008. Further information on the orphan designation can be found here: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

How is Kalydeco used?

Kalydeco can only be obtained with a prescription. It should only be prescribed by a doctor with experience in the treatment of cystic fibrosis, and only in patients confirmed to have the mutations mentioned above.

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Kalydeco is available as tablets (150 mg) and as granules (50 mg and 75 mg) in a sachet. For children aged 1 year and above and weighing 7 to 25 kg, the granules should be used. They should be mixed with 5 ml of soft food or liquid to make a suspension to be taken by mouth.

The tablets are used in adults and children aged 6 years and above and weighing 25 kg or more.

The dose and frequency depends on whether Kalydeco is used alone or together with tezacaftor / ivacaftor.

The doses of Kalydeco may need to be adjusted 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. The doses may also need to be adjusted in patients with reduced liver function.

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

How does Kalydeco work?

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

The active substance in Kalydeco, ivacaftor, increases the activity of the defective CFTR protein. This makes mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease.

What benefits of Kalydeco have been shown in studies?

G551D, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, *R117H* mutations

Kalydeco was shown to be effective at improving lung function in 4 main studies involving patients with cystic fibrosis who had various mutations. The main measure of effectiveness in these studies was based on improvements in patients' FEV_1. FEV_1 is the maximum amount of air a person can breathe out in one second and is a measure of how well the lungs work. In the studies, Kalydeco was compared with placebo (a dummy treatment).

Two of the studies involved 219 patients with cystic fibrosis who had the *G551D* mutation. One of the studies was in patients aged over 12 years, while the other was in patients aged between 6 and 11 years. After 24 weeks of treatment, patients aged 12 years and older who took Kalydeco had an average improvement in FEV_1 of 10.6 percentage points more than those who took placebo. Similar results were seen in patients aged between 6 and 11 years, where Kalydeco treatment led to an improvement of 12.5 percentage points more than with placebo.

The third study involved 39 patients over 6 years of age with cystic fibrosis due to several mutations other than *G551D*. After 8 weeks of treatment patients who took Kalydeco had an average improvement of 10.7 percentage points more than those who took placebo.

The fourth study involved 69 patients aged 6 years and above with cystic fibrosis who had the *R117H* mutation. No difference was seen between placebo and Kalydeco for children aged 6 years and above. However, when analysing the subset of patients aged 18 years and above alone, an average improvement of around 5.0 percentage points was seen in patients who took Kalydeco compared with patients who took placebo.

Another study investigated Kalydeco granules in 34 patients aged between 2 and 5 years of age who had cystic fibrosis due to a *G551D* or *S549N* mutation. The study found that Kalydeco granules resulted in increased bodyweight and a decreased amount of chloride contained in sweat. Patients with cystic fibrosis have low bodyweight due to problems with digestion of food and high levels of chloride in sweat due to CFTR not working properly.

Positive results have also been shown with Kalydeco granules in a study involving 19 children aged 1 to 2 years.

***F508del* mutation from both parents or *F508del* mutation from one parent and *P67L*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272 26A→G* or *3849+10kbC→T* mutations**

Kalydeco taken together with tezacaftor / ivacaftor was shown to be effective at improving lung function in two main studies of patients with cystic fibrosis aged 12 years and above with the the *F508del* mutation. The main measure of effectiveness was based on improvement in patients' FEV_1.

The first study involved 510 patients with cystic fibrosis who have inherited the *F508del* mutation from both parents. Kalydeco, taken with tezacaftor / ivacaftor, was compared with placebo. After 24 weeks of treatment, patients who took the medicines had an average increase in FEV_1 of 3.4 percentage points compared with a reduction of 0.6 percentage points in patients who took placebo.

The second study involved 248 patients with cystic fibrosis who have inherited the *F508del* mutation from one parent and who also have another *CFTR* mutation. Kalydeco, taken with tezacaftor / ivacaftor, was compared with Kalydeco taken alone and with placebo. Lung function was measured after 4 weeks and 8 weeks of treatment. Patients who took Kalydeco and tezacaftor / ivacaftor had an average increase in FEV_1 of 6.5 percentage points compared with an increase of 4.4 percentage points in patients who took Kalydeco alone and a reduction of 0.3 percentage points in patients who took placebo.

What are the risks associated with Kalydeco?

The most common side effects with Kalydeco (which may affect more than 1 in 10 people) are headache, sore throat, upper respiratory tract infection (nose and throat infection), nasal congestion, abdominal (belly) pain, nasopharyngitis (inflammation of the nose and throat), diarrhoea, dizziness, rash, bacteria in sputum (phlegm) and an increase in certain liver enzymes. Serious side effects include abdominal pain and increased liver enzymes.

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

Why is Kalydeco authorised in the EU?

Kalydeco used on its own or together with tezacaftor / ivacaftor has been shown to improve lung function in patients with specific mutations. The medicine was also shown to have an acceptable safety profile. The European Medicines Agency therefore decided that the benefits of Kalydeco are greater than its risks and it can be authorised for use in the EU. The Agency also noted, however, that there were limited data on the longer-term effects of the medicine and that further data should be provided by the company.

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

The company that markets Kalydeco is conducting a study in children who were aged 2 to 5 years at the start of treatment to assess long-term effects of early treatment.

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

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

Other information about Kalydeco

Kalydeco received a marketing authorisation valid throughout the EU on 23 July 2012.

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

This overview was last updated in 11-2018.