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Kalydeco (*ivacaftor*)

An overview of Kalydeco and why it is 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.

Kalydeco is used on its own to treat cystic fibrosis in patients aged 4 months and above who have one of the following mutations (changes) in the gene for a protein called 'cystic fibrosis transmembrane conductance regulator' (CFTR): *R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* and *S549R*.

Kalydeco is also used together with a medicine containing tezacaftor and ivacaftor to treat patients aged 6 years and above who have inherited the *F508del* mutation in the *CFTR* gene from both parents or who have inherited the *F508del* mutation plus 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 is also used together with another medicine containing ivacaftor, tezacaftor and elexacaftor to treat patients aged 12 years and above who have at least one *F508del* mutation in the *CFTR* gene

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/medicines/human/orphan-designations/eu308556.

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.

Kalydeco is available as tablets and as granules in a sachet. For infants and children aged 4 months and above and weighing 5 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.

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

The dose 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, and these medicines should not be taken with Kalydeco by patients aged 4–6 months. The dose 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 treatment 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. When analysing the subset of patients aged 18 years and above alone, an average improvement of FEV_1 of around 5 percentage points was seen in patients who took Kalydeco compared with patients who took placebo. However, no difference was seen between placebo and Kalydeco for children aged 6 years and above. The study also looked at changes in the level of chloride in patients' sweat. In all age groups, patients who took Kalydeco had a decrease in sweat chloride level compared with those who took placebo. Patients with cystic fibrosis have high levels of chloride in sweat due to CFTR not working properly and a decrease in sweat chloride can indicate that the medicine is having an effect.

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 decrease in sweat chloride. Patients with cystic fibrosis have low bodyweight due to problems with digestion of food.

Positive results were also shown with Kalydeco granules in a study involving 6 children aged 4 months to less than 6 months, 11 children aged 6 months to less than 12 months and 19 children aged 12 months to less than 24 months.

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 and one study of patients from 6 up to 12 years.

The first study involved 510 patients with cystic fibrosis who 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 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 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.

The study of patients aged from 6 up to 12 years involved 69 patients who had the *F508del* mutation from both parents or from one parent together with another mutation. The study looked at a measure of lung disease called the lung clearance index (LCI). After 8 weeks of treatment, patients who took Kalydeco together with tezacaftor / ivacaftor had a moderate decrease in LCI, which can indicate that the medicine is having an effect.

F508del mutation from both parents or *F508del* mutation from one parent

Kalydeco taken together with ivacaftor / tezacaftor / elexacaftor 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 $ppFEV_1$, which is a person's FEV_1 compared with that of an average person with similar characteristics (such as age, height and sex). In these studies, patients started off with average values of 60 to 68% of the values for an average healthy person.

The first study involved 403 patients who have an *F508del* mutation and another type of mutation known as a 'minimal function' mutation. After 24 weeks of treatment, patients who took Kalydeco and ivacaftor / tezacaftor / elexacaftor had an average increase in $ppFEV_1$ of 13.9 percentage points compared with a reduction of 0.4 percentage points in patients who took placebo.

In the second study involving 107 patients with an *F508del* mutation from both parents, patients who took Kalydeco and ivacaftor / tezacaftor / elexacaftor had an average increase in $ppFEV_1$ of 10.4 percentage points compared with an increase of 0.4 percentage points in patients who took a combination of Kalydeco and tezacaftor.

A third study involved 258 patients with an *F508del* mutation plus either a gating or residual CFTR activity mutation (two other mutations). Patients who took Kalydeco with ivacaftor / tezacaftor / elexacaftor had an average increase in ppFEV1 of 3.7 percentage points compared with an increase of

0.2 percentage points in patients who took Kalydeco alone or a combination of Kalydeco and tezacaftor.

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 increased liver enzymes, which can indicate liver damage, and abdominal pain.

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 or with ivacaftor / tezacaftor / elexacaftor has been shown to improve lung function or sweat chloride levels in patients with specific mutations. The medicine has 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 aged 2 to 5 years starting 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.

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