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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 1 month and above who weigh at least 3 kg and who have certain mutations (changes) in the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR).
- together with a medicine containing tezacaftor / 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 from one parent and have certain other mutations in the *CFTR* gene;
- together with another medicine containing ivacaftor / tezacaftor / elexacaftor to treat patients aged 2 years and above who have at least one non-class I mutation in the *CFTR* gene.

Kalydeco contains the active substance ivacaftor.

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. If the patient's specific mutations are unknown, these should be confirmed using appropriate genetic tests.

More information on the specific *CTFR* mutations for the different treatments is available in the package leaflet. Some mutations are not included in this list but may still respond to treatment with Kalydeco. For these mutations, doctors can prescribe Kalydeco plus ivacaftor / tezacaftor / elexacaftor when the benefits of treatment are expected to outweigh its risks, and under close supervision.

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 Kalydeco together with ivacaftor / tezacaftor / elexacaftor.

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

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; children aged 1 to 6 months who are taking this type of medicine should not use Kalydeco.

The dose may also need to be adjusted in patients over 6 months old with reduced liver function. Infants aged 1 to 6 months with reduced liver function should not use Kalydeco.

For more information about using Kalydeco, including information about mutations that are responsive to 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 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 in turn leads to blockages, inflammation, increased risk of lung infections and poor digestion and growth.

The active substance in Kalydeco, ivacaftor, improves 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?

Kalydeco on its own

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 in FEV_1 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, an average improvement in FEV_1 of around 5 percentage points was seen in those who took Kalydeco compared with those 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 their 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 2 to 5 years 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 digesting food.

Positive results in terms of a decrease in sweat chloride were also shown with Kalydeco granules in a study involving 7 children aged 1 month to less than 4 months, 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.

Kalydeco in combination with tezacaftor / ivacaftor

Kalydeco taken together with tezacaftor plus 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 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.

Kalydeco in combination with ivacaftor / tezacaftor / elexacaftor

Kalydeco taken together with ivacaftor, tezacaftor and elexacaftor was effective at improving lung function in four main studies in patients with cystic fibrosis aged 6 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 88.8% of the values for an average healthy person.

The first study involved 403 patients aged 12 years and older with an *F508del* mutation (a non-class I 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 aged 12 years and older 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 aged 12 years and older with an *F508del* mutation plus either a gating or residual CFTR activity mutation (two other types of mutations). Patients who took Kalydeco with ivacaftor / tezacaftor / elexacaftor had an average increase in $ppFEV_1$ of 3.7 percentage points compared with an average increase of 0.2 percentage points in patients who took Kalydeco alone or a combination of Kalydeco and tezacaftor.

The fourth study involved 66 children aged 6 to 11 years with either an *F508del* mutation from both parents or an *F508del* mutation and a 'minimal function' mutation. Kalydeco with ivacaftor / tezacaftor / elexacaftor was not compared with other treatments. Patients had an increase in $ppFEV_1$ and a decrease in sweat chloride levels, similar to previous observations in adults and adolescents taking Kalydeco with ivacaftor / tezacaftor / elexacaftor.

An additional study involved 75 children aged 2 to 5 years of age with either an *F508del* mutation from both parents or an *F508del* mutation and a 'minimal function' mutation, who were treated with Kalydeco plus ivacaftor / tezacaftor / elexacaftor. The combination treatment was not compared with other treatments. Treatment with Kalydeco plus ivacaftor / tezacaftor / elexacaftor reduced the level of chloride in patients' sweat. This decrease in sweat chloride levels was similar to that seen in older patients. Other data also showed that the medicine behaves in the same way in the body of younger children as in that of older children and adults. Taken together, the data suggest that the medicine will be as effective in children aged 2 to 5 years as in older children.

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 ivacaftor / tezacaftor / elexacaftor. In this study, patients received Kalydeco plus ivacaftor / tezacaftor / elexacaftor or placebo for 24 weeks. Patients who took the Kalydeco combination 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 ivacaftor / tezacaftor / elexacaftor based on laboratory data. This study showed that, after an average of 16 months of treatment, patients taking the combination 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 ivacaftor / tezacaftor / elexacaftor in patients who harbour at least one non-class I mutation in the *CFTR* gene.

What are the risks associated with Kalydeco?

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

The most common side effects with Kalydeco (which may affect more than 1 in 10 people) include headache, sore throat, upper respiratory tract infection (nose and throat infection), nasal congestion (blocked nose), 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.

Why is Kalydeco authorised in the EU?

Kalydeco used on its own or together with tezacaftor plus ivacaftor or with ivacaftor, tezacaftor and elexacaftor has been shown to improve lung function or sweat chloride levels in patients with cystic fibrosis who have certain mutations in the *CFTR* gene. 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?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Kalydeco have 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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