

Package leaflet: Information for the patient

Orkambi 100 mg/125 mg film-coated tablets
Orkambi 200 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orkambi is and what it is used for
2. What you need to know before you take Orkambi
3. How to take Orkambi
4. Possible side effects
5. How to store Orkambi
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1. What Orkambi is and what it is used for

Orkambi contains two active substances, lumacaftor and ivacaftor. It is a medicine used for long-term treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a specific change (called *F508del* mutation) affecting the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR), which plays an important role in regulating the flow of mucus in the lungs. People with the mutation will produce an abnormal CFTR protein. Cells contain two copies of the *CFTR* gene; Orkambi is used in patients in whom both copies are affected by the *F508del* mutation (homozygotes).

Lumacaftor and ivacaftor work together to improve the function of the abnormal CFTR protein. Lumacaftor increases the amount of CFTR available and ivacaftor helps the abnormal protein to work more normally.

Orkambi may help your breathing by improving your lung function. You may also notice that it is easier to gain weight.

2. What you need to know before you take Orkambi

Do not take Orkambi

- if you are allergic to lumacaftor, ivacaftor, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Orkambi.

Orkambi should not be used in patients other than those **who have two copies of the *F508del* mutation** in their *CFTR* gene.

Talk to your doctor before taking Orkambi if you have been told you have **liver or kidney** disease as your doctor may need to adjust the dose of Orkambi.

Abnormal blood tests of the liver have been commonly seen in some people receiving Orkambi. Tell your doctor straight away if you have any of these symptoms, which may be a sign of liver problems:

- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of your skin or the white part of your eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine
- Confusion

Your doctor should do some blood tests to check your liver before and while you are taking Orkambi, particularly during the first year.

Respiratory events such as **shortness of breath or chest tightness or narrowing of the airways** were seen in patients when starting Orkambi, especially in patients who have poor lung function. If you have poor lung function your doctor may monitor you more closely when you start Orkambi.

An **increase in blood pressure** has been seen in some patients treated with Orkambi. Your doctor may monitor your blood pressure during treatment with Orkambi.

Abnormality of the lens of the eye (cataract) without any effect on vision has been noted in some children and adolescents treated with Orkambi and ivacaftor alone (one of the components of Orkambi). Your doctor may perform some eye examinations prior to and during treatment with Orkambi.

Orkambi is not recommended in patients who have undergone **an organ transplant**.

Children under 6 years old

Orkambi tablets should not be used in children under the age of 6 years. Other forms of this medicine (granules in a sachet) are more suitable for children under 6 years of age, ask your doctor or pharmacist.

Other medicines and Orkambi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially tell your doctor if you take any of the following medicines:

- Antibiotic medicines (used for the treatment of bacterial infections) for example: telithromycin, clarithromycin, rifampicin, rifabutin, rifapentine, erythromycin
- Anticonvulsant medicines (used for the treatment of fits [epileptic seizures]) for example: phenobarbital, carbamazepine, phenytoin
- Benzodiazepines (used for the treatment of anxiety or sleeplessness [insomnia], agitation, etc.) for example: midazolam, triazolam
- Antifungal medicines (used for the treatment of fungal infections) for example: fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole

- Immunosuppressants (used after an organ transplantation) for example: ciclosporin, everolimus, sirolimus, tacrolimus
- Herbal medicines, for example: St. John's wort (*Hypericum perforatum*)
- Anti-allergic medicines (used for the treatment of allergies and/or asthma) for example: montelukast, fexofenadine
- Antidepressant medicines (used for the treatment of depression) for example: citalopram, escitalopram, sertraline, bupropion
- Anti-inflammatory medicines (used for the treatment of inflammation) for example: ibuprofen
- H2 Antagonist medicines (used to reduce stomach acid) for example: ranitidine
- Cardiac glycosides (used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation) for example: digoxin
- Anticoagulants (used to prevent blood clots from forming or growing larger in blood and blood vessels) for example: warfarin, dabigatran
- Contraceptive medicines (used for the prevention of pregnancy): oral, injectable, and implantable contraceptives as well as contraceptive skin patches; that may include ethinyl estradiol, norethindrone, and other progestogens. These should not be relied upon as an effective method of birth control when given with Orkambi
- Corticosteroid medicines (used to treat inflammation): methylprednisolone, prednisone
- Proton pump inhibitor medicines (used to treat acid reflux disease and ulcers): omeprazole, esomeprazole, lansoprazole
- Oral hypoglycaemics (used for the management of type 2 diabetes): repaglinide

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC - an active component in cannabis) in patients receiving Orkambi. Your doctor may request another test to verify results.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. It may be better to avoid using Orkambi during pregnancy, if possible, and your doctor will help you decide what is best for you and your child.

It is unknown if lumacaftor or ivacaftor are found in human milk. If you plan to breast-feed, ask your doctor for advice before taking Orkambi. Your doctor will decide whether to recommend that you stop breast-feeding or for you to stop lumacaftor/ivacaftor therapy. Your doctor will take into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines

Dizziness has been reported in patients receiving ivacaftor, a component of Orkambi, which could influence the ability to drive or use machines. If you experience dizziness, you should not drive or use machines until these symptoms disappear.

If a child experiences dizziness while taking Orkambi, it is advised that the child does not ride a bike or do anything else that needs their full attention, until their symptoms disappear.

Orkambi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to take Orkambi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Recommended dose

The recommended dose for patients aged 6 years and over is two tablets in the morning, and two tablets in the evening (12 hours apart). That is a total of four tablets per day, to be taken with food containing fat.

There are different strengths of Orkambi tablet for different age groups. Check you have been given the right tablet (below).

Age	Tablets	Dose
6 to 11 years	Orkambi 100 mg/125 mg	2 tablets in the morning 2 tablets in the evening
12 years and older	Orkambi 200 mg/125 mg	2 tablets in the morning 2 tablets in the evening

You may start taking Orkambi on any day of the week.

If you have moderate or severe problems with liver function, your doctor may need to reduce the dose of Orkambi as your liver will not clear Orkambi as fast as in people who have normal liver function.

- **Moderate liver problems:** the dose may be reduced to two tablets in the morning and one tablet in the evening.
- **Severe liver problems:** the dose may be reduced to one tablet in the morning and one tablet in the evening.

Method of administration

Orkambi is for oral use. Swallow the tablets whole. Do not chew, break, or dissolve the tablets.

Taking Orkambi with fat-containing food is important to get the right levels of medicine in your body. A fat-containing meal or snack should be consumed just before or just after taking Orkambi. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs. Examples of other fat-containing foods are:

- Cheese, whole milk, whole-milk dairy products
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nutritional bars or drinks

If you take more Orkambi than you should

Contact your doctor or pharmacist for advice. If possible, have your medicine and this leaflet with you. You may experience side effects, including those mentioned in section 4 below.

If you forget to take Orkambi

Take the missed dose with fat-containing food if less than 6 hours have passed since the time you missed the dose. Otherwise, wait until your next scheduled dose as you normally would. Do not take a double dose to make up for the forgotten tablets.

If you stop taking Orkambi

You should keep taking the medicine as your doctor directs even if you feel well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them. The side effects reported with Orkambi and ivacaftor alone (one of the active substances of Orkambi) are listed below and may occur with the use of Orkambi.

Serious side effects for Orkambi include raised levels of liver enzymes in the blood, liver injury, and worsening of pre-existing severe liver disease. The worsening of liver function can be fatal. These serious side effects are uncommon (may affect up to 1 in 100 people).

Tell your doctor straight away if you have any of the following symptoms:

- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of your skin or the white part of your eyes
- Loss of appetite
- Nausea or vomiting
- Confusion
- Dark urine

Other side effects

Very common (may affect more than 1 in 10 people)

- Cough with sputum
- Nasal congestion
- Shortness of breath
- Headache
- Abdominal pain (stomach ache)
- Diarrhoea
- Increase in sputum
- Nausea
- Common cold*
- Dizziness*
- Changes in the type of bacteria in mucus*

Common (may affect up to 1 in 10 people)

- Chest tightness
- Narrowing of the airways
- Sinus congestion*
- Stuffy or runny nose
- Upper respiratory tract infection
- Sore throat
- Redness in the throat*
- Rash

- Passing gas
- Vomiting
- Increase of an enzyme in your blood (blood creatine phosphokinase)
- high levels of liver enzymes, shown by blood test
- Irregular periods (menses) or pain with menses
- Ear pain, ear discomfort*
- Ringing in the ears*
- Redness inside the ear*
- Inner ear disorder (feeling dizzy or spinning)*
- Breast mass*

Uncommon (may affect up to 1 in 100 people)

- Abnormal periods, including the absence or infrequent menses, or more frequent or heavier menstrual bleeding
- Increase in blood pressure
- Ear congestion*
- Breast inflammation*
- Enlargement of the breast in males*
- Nipple changes or pain*

*Side effects seen for ivacaftor alone.

Side effects in children

Side effects seen in children are similar to those seen in adults and adolescents. However, increased liver enzymes in the blood have been seen more frequently in younger children than in adults.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, website: www.hpra.ie.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orkambi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton/blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Orkambi contains

The active substances are lumacaftor and ivacaftor.

Orkambi 100 mg/125 mg film-coated tablets:

Each film-coated tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 200 mg/125 mg film-coated tablets:

Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 100 mg/125 mg film-coated tablets and Orkambi 200 mg/125 mg film-coated tablets:

The other ingredients are:

- Tablet core: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone (K30); sodium laurilsulfate; and magnesium stearate (see section 2 “Orkambi contains sodium”).
- Tablet coating: polyvinyl alcohol; titanium dioxide (E171); macrogol 3350; talc; carmine (E120); brilliant blue FCF aluminium lake (E133); and indigo carmine aluminium lake (E132).
- Printing ink: shellac; iron oxide black (E172); propylene glycol; and ammonium hydroxide.

What Orkambi looks like and contents of the pack

Orkambi 100 mg/125 mg film-coated tablets

Orkambi 100 mg/125 mg film-coated tablets (tablets) are pink, oval-shaped tablets (dimensions 14 × 7.6 × 4.9 mm) printed with “1V125” in black ink on one side.

Orkambi 100 mg/125 mg is available in packs containing 112 film-coated tablets (4 packs of 28 film-coated tablets).

Orkambi 200 mg/125 mg film-coated tablets

Orkambi 200 mg/125 mg film-coated tablets (tablets) are pink, oval-shaped tablets (dimensions 14 × 8.4 × 6.8 mm) printed with “2V125” in black ink on one side.

Orkambi 200 mg/125 mg is available in packs containing 28 film-coated tablets and in multipacks containing 112 film-coated tablets (4 packs of 28 film-coated tablets).

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.