

Package leaflet: Information for the patient

Orkambi 100 mg/125 mg granules in sachet
Orkambi 150 mg/188 mg granules in sachet
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 your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child starts 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 child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's 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 your child takes Orkambi
3. How to take Orkambi
4. Possible side effects
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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 2 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.

2. What you need to know before your child takes Orkambi

Do not use Orkambi

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

Warnings and precautions

Talk to your child's 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 child's doctor before taking Orkambi if you have been told your child has **liver or kidney** disease as the 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 child's doctor straight away if your child has any of these symptoms, which may be a sign of liver problems:

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

Your child's doctor should do some blood tests to check your child's liver before and while she/he is 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 your child has poor lung function your child's doctor may monitor your child more closely when she/he starts Orkambi.

An **increase in blood pressure** has been seen in some patients treated with Orkambi. Your child's doctor may monitor your child's 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 child's 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 2 years old

It is not known if Orkambi is safe and effective in children under 2 years of age. Therefore, Orkambi should not be used in children under the age of 2 years.

Other medicines and Orkambi

Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

Especially tell the doctor if your child takes 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 child's doctor may request another test to verify results.

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 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 give your child this medicine exactly as your child's doctor has told you. Check with the doctor if you are not sure.

Your child's doctor will determine the correct dose for your child. Your child must keep using all other medicines, unless your child's doctor tells you to stop using any.

Recommended dose

The recommended dose for patients aged 2 years and over is indicated in the table below. Orkambi has to be taken in the morning and in the evening (12 hours apart) with food containing fat.

There are different strengths of Orkambi according to a child's age and weight. Check your child has been given the right dose (below).

Age, weight	Product	Dose
2 to 5 years and weighing less than 14 kg	Orkambi 100 mg/125 mg granules in sachet	One sachet in the morning; One sachet in the evening
2 to 5 years and weighing 14 kg or greater	Orkambi 150 mg/188 mg granules in sachet	One sachet in the morning; One sachet in the evening

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

- **Moderate liver problems:** the dose may be reduced on alternate days: two sachets on one day (morning and evening), one sachet the next (morning only).
- **Severe liver problems:** the dose may be reduced to one sachet per day, or less often.

Method of administration

Orkambi is for oral use.

Each sachet is for single use only.

You may start giving your child Orkambi on any day of the week.

Giving Orkambi granules to your child:

- Hold sachet of granules with cut line on top.
- Shake sachet gently to settle contents.
- Tear or cut sachet open along the line.
- Mix the entire contents of a sachet with one teaspoon (5 mL) of age-appropriate soft food or liquid. Food or liquid should be at room temperature or below. Some examples of age-appropriate soft foods and liquids include puréed fruits, flavoured yogurt, and milk or juice.
- Once mixed, give the product to your child immediately. If this is not possible, give it within the hour after mixing. Make sure that the mixture is consumed immediately and completely.
- Food containing fat should be given to your child just before or just after dosing (some examples are provided below).

Taking Orkambi with fat-containing food is important to get the right levels of medicine in the body. 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 your child takes more Orkambi than he/she should

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

If you forget to give your child Orkambi

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

If you stop giving your child Orkambi

Give Orkambi to your child for as long as your child's doctor recommends. Do not stop unless your child's doctor advises you to. You should keep giving the medicine as the doctor directs even if the child feels well.

If you have any further questions on the use of this medicine, ask your child's 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 child's doctor straight away if he/she gets any of these:

- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of the skin or the white part of the 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 the 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 your child gets any side effects, talk to your child's 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/sachet 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 child's pharmacist how to throw away medicines your child no longer uses. 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 granules in sachet:

Each sachet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 150 mg/188 mg granules in sachet:

Each sachet contains 150 mg of lumacaftor and 188 mg of ivacaftor.

The other ingredients are: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone (K30); and sodium laurilsulfate (see section 2 “Orkambi contains sodium”).

What Orkambi looks like and contents of the pack

Orkambi 100 mg/125 mg granules in sachet are white to off-white granules.

Orkambi 150 mg/188 mg granules in sachet are white to off-white granules.

The granules are supplied in sachets.

- Pack size of 56 sachets (contains 4 individual wallets with 14 sachets per wallet)

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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.