**Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986**
This medicine is dispensed with a doctor's prescription only

# Orkambi 100 mg/125 mg film coated tablets
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**Active ingredients and their quantities**
Orkambi 100mg/125mg film coated tablets
Each film coated tablet contains:
100 mg lumacaftor
125 mg ivacaftor

Orkambi 200mg/125mg film coated tablets
Each film coated tablet contains:
200 mg lumacaftor
125 mg ivacaftor

Inactive ingredients - See section 6 **"Additional information"**. See also **"Important information about some of this medicine's ingredients"** in section 2.

**Read the entire leaflet carefully before you start using this medicine.** This leaflet contains concise information about this medicine. If you have further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

## 1. What is this medicine intended for?

Orkambi (lumacaftor and ivacaftor) is 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 has an important role in regulating the flow of mucus in the lungs. People with the mutation will produce an abnormal CFTR protein. Orkambi is used in patients in whom both copies of the CFTR gene in the cell are affected by the *F508del* mutation.

Orkambi is a single tablet that contains two active substances, lumacaftor and ivacaftor. These two 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 properly.

**Therapeutic group:** Lumacaftor – CFTR corrector
Ivacaftor – Potentiator of the CFTR protein

## 2. Before using this medicine

**Do not use this medicine if:**
- You are sensitive (allergic) to the active ingredients (lumacaftor or ivacaftor) or to any of the other ingredients in this medicine (see section 6 **"Additional information"**).

**Special warnings about using this medicine**
Talk to your doctor or pharmacist before taking Orkambi.

Orkambi is designated only to patients 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

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

**Children**
Orkambi tablets are not intended for use in children under 6 years of age.

**Tests and follow-up**
Your doctor will do some blood tests to check your liver function 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.

**Drug interactions**
**If you are taking, have recently taken or might take other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.** Particularly if you are taking:

- Antibiotic medicines (used for the treatment of bacterial infections) such as telithromycin, clarithromycin, rifampicin, rifabutin, rifapentine and erythromycin
- Anticonvulsant medicines (used for the treatment of epileptic seizures) such as phenobarbital, carbamazepine and phenytoin
- Benzodiazepines (used for the treatment of anxiety or sleeplessness, agitation) such as midazolam and triazolam
- Antifungal medicines (used for the treatment of fungal infections) such as fluconazole, ketoconazole, itraconazole, posaconazole and voriconazole
- Immunosuppressants (used after an organ transplantation) such as ciclosporin, everolimus, sirolimus and tacrolimus
- Herbal medicines, such as St. John's wort (*Hypericum perforatum*)
- Anti-allergic medicines (used for the treatment of allergies and/or asthma) such as montelukast and fexofenadine
- Antidepressant medicines (used for the treatment of depression) such as citalopram, escitalopram, sertraline and bupropion
- Anti-inflammatory medicines (used for the treatment of inflammation) such as ibuprofen
- H2 Antagonist medicines (used to reduce stomach acid) such as ranitidine
- Cardiac glycosides (used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation) such as digoxin
- Anticoagulants (used to prevent blood clots from forming or growing larger in blood and blood vessels) such as warfarin and 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) such as methylprednisolone and prednisone

- Proton pump inhibitor medicines (used to treat acid reflux disease and ulcers) such as omeprazole, esomeprazole and lansoprazole
- Oral hypoglycemics (used for the management of type 2 diabetes) such as 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.

**Using this medicine and food**
**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 eaten 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

**Pregnancy and breastfeeding**
If you are pregnant or breastfeeding, 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. The doctor will help you decide what is best for you and your child.

It is unknown if lumacaftor or ivacaftor are secreted in mother's 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, do 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.

**Important information about some of this medicine's ingredients**
This medicine contains less than 23 mg sodium per dose, that is to say essentially 'sodium-free'.

## 3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Only your doctor will determine your dose and how you should take this medicine. **The recommended dosage** for patients aged 6 and over is 2 tablets in the morning, and 2 tablets in the evening (12 hours apart). That is a total of 4 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<br>2 tablets in the evening |
| **12 years and older** | Orkambi 200 mg/125 mg | 2 tablets in the morning<br>2 tablets in the evening |

**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.

**Do not exceed the recommended dose.**

Swallow the tablets whole. Do not chew, break, or dissolve the tablets.
You may start taking Orkambi on any day of the week.

**If you have accidentally taken a higher dosage** you may experience side effects, including those mentioned in section 4 below. If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

**If you forgot to take this medicine** at the scheduled time and less than 6 hours have passed since the time when you were supposed to take the medicine, take the missed dose with fat containing food. Otherwise skip the forgotten dose. Take the next dose at the usual time. Do not take a double dose in order to compensate for the forgotten dose.

Adhere to the treatment as recommended by your doctor. Even if your health improves, do not stop taking this medicine without consulting your doctor.

**Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.**

**If you have further questions about using this medicine, consult your doctor or pharmacist.**

## 4. <u>Side effects</u>

Like with all medicines, using Orkambi may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them. The side effects reported with Orkambi and ivacaftor alone (one of the active substances of Orkambi) are listed below and may occur when using 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 right away** if you have any of the following symptoms:

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

**Additional side effects**
<u>Very common side effects (occur in more than one in ten users)</u>

- Cough with sputum
- Nasal congestion
- Shortness of breath
- Headache
- Abdominal pain
- Diarrhoea
- Increase in sputum
- Nausea
- Common cold*

- Dizziness*
- Changes in the type of bacteria in mucus*

Common side effects (occur in 1-10 in 100 users)
- 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 side effects (occur in 1-10 in 1,000 users)
- Abnormal periods, including the absence of 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.

**If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.**

**Reporting side effects**
You can report side effects to the Ministry of Health by following the link "Reporting side effects of drug treatment" on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

## 5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use Orkambi after the expiry date (exp. date) which is stated on the carton and blister. The expiry date refers to the last day of that month.

**Storage conditions**
Store below 30°C.

## 6. Additional information

In addition to the active ingredients, this medicine also contains:

- Tablet core contains:
  microcrystalline cellulose, hypromellose acetate succinate USP/NF, croscarmellose sodium, povidone K30, magnesium stearate, sodium lauryl sulfate.
- Tablet coating contains opadry II (pink) 85F140026
- Printing ink contains opacode black, S-1-17823

**What the medicine looks like and contents of the pack**

Orkambi 100 mg/125 mg film coated tablets
pink oval-shaped tablet with “1V125” printed in black on one face and plain on the other.

Orkambi 200 mg/125 mg film coated tablets
pink oval-shaped tablet with “2V125” printed in black on one face and plain on the other.

Each of the strengths of Orkambi is available in a pack containing 112 film coated tablets (4 packs of 28 film coated tablets).

**Registration holder's name and address**

Vertex Pharmaceuticals (U.K.) Limited
7 Rival Street, Tel Aviv-Yafo, Israel

**Manufacturer's name and address**

Vertex Pharmaceuticals (Europe) Limited
2 Kingdom Street, London, W2 6BD, United Kingdom

Revised in January 2021 according to the MOH guidelines.

**Registration number of the medicine in the Ministry of Health's National Drug Registry**

Orkambi 100 mg/125 mg film coated tablets: 161-99-35506
Orkambi 200 mg/125 mg film coated tablets: 157-84-34839