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
Orkambi 200 mg/125 mg film coated tablets

Each film coated tablet contains:
Orkambi 100mg/125mg film coated tablets
100 mg lumacaftor
125 mg ivacaftor

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

The list of the inactive ingredients in the product is shown in section 6 ("Additional information") in this leaflet.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have further questions, contact 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.

1. What is the medicine intended for?

Orkambi (lumacaftor and ivacaftor) 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 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 the 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.

Worsening of liver function has been seen in patients with severe liver disease. The worsening of liver function can be serious or fatal.

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 under 6 years old:
Orkambi tablets should not be used in children under 6 years of age.

Examinations that have to be performed before and during the use of the medicine:
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** 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 or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Especially tell your doctor if you take any of the following medicines:

- Antibiotic medicines (used for the treatment of bacterial infections) such as: telithromycin, clarithromycin, rifampicin, rifabutin, rifapentine, erythromycin
- Anticonvulsant medicines (used for the treatment of epileptic seizures) such as: phenobarbital, carbamazepine, phenytoin
- Benzodiazepines (used for the treatment of anxiety or sleeplessness, agitation) such as: midazolam, triazolam
- Antifungal medicines (used for the treatment of fungal infections) such as: fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
- Immunosuppressants (used after an organ transplantation) such as: ciclosporin, everolimus, sirolimus, 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, fexofenadine
- Antidepressant medicines (used for the treatment of depression) such as: citalopram, escitalopram, sertraline, 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, 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 hypoglycemics (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 think that you are pregnant, planning to have a child or are breast-feeding, consult a doctor or pharmacist before taking this medicine. It is 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, so it is essentially 'sodium-free'.

3. How to use this medicine?

Always use this medicine exactly as your doctor has told you. 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** of Orkambi for patients aged 6 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

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 every 12 hours.

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.

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

If you have taken a higher dosage by mistake you may feel side-effects including those shown in section 4 below. If you have taken an overdose or if a child has swallowed some of the medicine by accident, attend a doctor or a hospital's A&E department at once and bring with you the medicine's packaging and this leaflet.

If you forgot to take this medicine at the required time and less than 6 hours have passed since the time when you were supposed to take the medicine, take the dose. 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.

You should carry on with the treatment as recommended by the doctor.
If you stop taking the medicine, inform the doctor. Before stopping you should discuss the implications with the doctor or the pharmacist.

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

If you have further questions about using the medicine, consult a 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

Very common side-effects (occur in more than one user in ten):

- 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 users out of 100):
- Chest tightness
- 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)
- 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 users out of 1000):
- 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 the 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/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:
ivacaftor SDD contains also hypromellose acetate succinate USP/NF, and sodium lauryl sulfate Ph.Eur.

Core tablet Intra-granular:
Microcrystalline cellulose
hypromellose acetate succinate
Povidone K30
Croscarmellose sodium
Sodium lauryl sulfate
Core tablet Extra-granular:
Microcrystalline cellulose
Croscarmellose sodium
Magnesium Stearate
Film Coat:
Opadry II (Pink) 85F140026
Printing Ink:
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.

Orkambi 100 mg/125 mg film coated tablets is available in the following pack size:
- Pack containing 112 film-coated tablets (4 packs of 28 film-coated tablets).

Orkambi 200 mg/125 mg film coated tablets is available in the following pack size:
- Packs 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 November 2020

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