

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**PrORKAMBI[®]
lumacaftor / ivacaftor tablets
lumacaftor / ivacaftor granules**

Read this carefully before you start taking ORKAMBI and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ORKAMBI.

What is ORKAMBI used for?

- ORKAMBI is for the chronic treatment of cystic fibrosis (CF). It is used for patients aged 2 years and older who have two copies of the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene (*F508del/F508del*).
- ORKAMBI should not be used in patients other than those who have two copies of the *F508del* mutation in their *CFTR* gene.

It is not known if ORKAMBI is safe and effective in children under 2 years of age.

How does ORKAMBI work?

- The CFTR gene provides instructions to your cells to make the CFTR protein. This protein helps take chloride ions in and out of the cells in many organs of your body.
- People with CF have a lower amount of the CFTR protein and/or reduced function of the CFTR protein.
- ORKAMBI has two ingredients:
 - Lumacaftor, a CFTR corrector, increases the amount of the CFTR proteins at the cell surface.
 - Ivacaftor, a CFTR potentiator, makes the CFTR protein at the cell surface work better.

What are the ingredients in ORKAMBI?

Medicinal ingredients: lumacaftor and ivacaftor

Non-medicinal ingredients:

Lumacaftor/ivacaftor tablets

Tablet core: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate.

Tablet film coat: carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Printing ink: ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

Non-medicinal ingredients in lumacaftor/ivacaftor granules

cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone; sodium lauryl sulfate.

ORKAMBI comes in the following dosage forms:

Tablet: 100 mg lumacaftor/125 mg ivacaftor

Tablet: 200 mg lumacaftor/125 mg ivacaftor

Granules: 100 mg lumacaftor/125 mg ivacaftor

Granules: 150 mg lumacaftor/188 mg ivacaftor

Do not use ORKAMBI if:

- You are hypersensitive (allergic) to this drug or to any ingredient in the formulation or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ORKAMBI. Talk about any health conditions or problems you may have, including if you:

- have liver disease. Taking ORKAMBI when you already have severe liver disease can cause serious life-threatening problems. Your doctor should closely monitor you and may adjust your dose of ORKAMBI.
- have had an organ transplant.
- have high blood pressure, a low heart rate, or other heart conditions.
- have kidney disease.
- are using birth control (hormonal contraceptives including oral, injectable, transdermal, or implantable forms). Hormonal contraceptives should not be used as a method of birth control when taking ORKAMBI.
- are pregnant or plan to become pregnant. It is not known if ORKAMBI will harm your unborn baby. You and your doctor should decide if you will take ORKAMBI while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if ORKAMBI passes into your breast milk. You and your doctor should decide if you will take ORKAMBI while you are breastfeeding.

Other warnings you should know about:

Cataracts

Cloudiness of the eye lens (cataract) has been seen in some children and adolescents while taking ORKAMBI. Your doctor may perform an eye exam before you start taking ORKAMBI and during treatment with ORKAMBI to look for cataracts.

Abnormal test results

Abnormal blood tests of the liver have been seen in some people receiving ORKAMBI. Your doctor will order some blood tests to check your liver:

- before you take ORKAMBI,
- every 3 months of the first year while you are taking ORKAMBI, and
- every year while you are taking ORKAMBI.

If you have had abnormal blood tests of the liver in the past, your doctor may order blood tests to check your liver more often.

Tell your doctor right 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
- Pale stools

Menstrual Irregularities

Women taking ORKAMBI may have irregular or abnormal periods. They may also have more bleeding during their periods. This happened mainly in women taking hormonal birth control.

Children

ORKAMBI is not for use in children under the age of 2 years. It is not known if ORKAMBI is safe and effective in children under 2 years of age.

Respiratory

You may experience shortness of breath or tightness in your chest when you first start taking ORKAMBI, especially if you have poor lung function. Your doctor may monitor you more closely if you have poor lung function.

Blood Pressure and Heart Rate (number of heart beats per minute)

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

A decrease in heart rate has been seen in some patients treated with ORKAMBI.

Tell your doctor if you are taking medicines that affect your blood pressure or heart rate.

Driving and using machines

It is not known if ORKAMBI causes dizziness. You should know how you react to ORKAMBI before driving or using heavy machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with ORKAMBI:

- Antifungal medicines (used for the treatment of fungal infections) such as ketoconazole, itraconazole, posaconazole, voriconazole, fluconazole
- Antibiotic medicines (used for the treatment of bacterial infections) such as clarithromycin, rifabutin, rifampicin, levofloxacin, erythromycin

- Anticonvulsant medicines (used for the treatment of epileptic seizures) such as phenobarbital, carbamazepine, phenytoin
- Ranitidine, a medication used to treat peptic ulcers and gastroesophageal reflux disease
- St. John's wort (*Hypericum perforatum*), an herbal medicine
- Benzodiazepines (used for the treatment of anxiety, insomnia, agitation, etc.) such as midazolam, triazolam
- Antidepressants such as citalopram, escitalopram, sertraline
- Anti-allergics such as montelukast
- Anti-inflammatories such as ibuprofen
- Immunosuppressants (used after an organ transplantation) such as cyclosporine, everolimus, sirolimus, tacrolimus
- 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
- Hormonal contraceptives (used to prevent pregnancy) such as oral, injectable, skin patches (transdermal), and implantable products. These should not be relied upon as an effective method of birth control when given with ORKAMBI.
- Glucocorticoids (used to treat inflammation) such as methylprednisolone, prednisone
- Proton pump inhibitors (used to treat acid reflux disease and ulcers) such as omeprazole, esomeprazole, lansoprazole

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How to take ORKAMBI:

In order to get the right amount of medicine in your body, ORKAMBI should always be taken with a fat-containing food. Meals and snacks recommended in CF guidelines contain acceptable amounts of fat. Examples of fat-containing food: meals that have been prepared with butter or oils, meals that have eggs, nuts, whole-milk dairy products (such as whole-milk, cheese, and yogurt), or meats.

- Take ORKAMBI exactly as your doctor tells you to take it, even if you feel well.
- Check with your doctor if you are not sure about your dose.
- Do not change the dose or stop taking ORKAMBI without first talking to your doctor.
- Your doctor may need to adjust your dose if you have liver disease or if you are taking medications that may interact with ORKAMBI.

ORKAMBI Tablets (for patients aged 6 years and older): The usual dose is to give 2 tablets every 12 hours by mouth with fat-containing food (see below).

- **Do not** break, crush, or chew the tablet. Swallow the tablet **whole**.
- Each ORKAMBI box contains 4 cartons, a 4-week supply.
- Each carton contains 7 blister strips, one for each day. Each blister strip contains 4 tablets - 2 morning doses and 2 evening doses.
- You may cut along the dotted line to separate your doses from the blister strip.

- **Morning dose:** unpeel the paper backing from a blister strip. Do not push the tablet through the paper backing because the tablet could break. Remove 2 ORKAMBI tablets and swallow them whole with food that contains fat.
- **Evening dose:** 12 hours after your first dose, unpeel the paper backing from another blister strip to remove 2 ORKAMBI tablets and swallow them whole with food that contains fat.

ORKAMBI Granules (for children aged 2 through 5 years and weighing less than 14 kg): Your doctor will prescribe the appropriate amount based on weight. The usual dose is to give 1 lumacaftor 100 mg/ivacaftor 125 mg packet of granules every 12 hours with fat-containing food.

ORKAMBI Granules (for children aged 2 through 5 years and weighing 14 kg or greater): Your doctor will prescribe the appropriate amount based on weight. The usual dose is to give 1 lumacaftor 150 mg/ivacaftor 188 mg packet of granules every 12 hours with fat-containing food.

How to prepare the granules:

- Each ORKAMBI box contains 4 individual wallets, a 4-week supply.
- There are 7 days of granules in each wallet. Each wallet contains 14 packets of granules – 7 morning doses and 7 evening doses.
- Use all 7 days' doses before starting a new wallet.
- Each packet is for single use only.

Morning dose: Remove the first dose from the wallet.

- Hold the packet with cut line on top.
- Shake the packet gently to settle the granules to the bottom of the packet.
- Tear or cut packet completely open along cut line.
- Pour all of the granules in the packet into 5 mL (1 teaspoon) of soft food or liquid which should be at or below room temperature (5 to 25°C) and mix until granules are dissolved.
- Some examples of soft foods or liquids include puréed fruits or vegetables, flavoured yogurt or pudding, applesauce, milk, or juice (except grapefruit).
- **After mixing, give within 1 hour. Make sure all medicine is taken. This is very important for it to work properly and be effective.**
- If mixed with food, ORKAMBI granules must not be stored for future use.
- **Evening dose:** This dose should be taken 12 hours after your **Morning dose**. Follow the same steps listed above under **Morning dose**.

Usual dose:

Patients ages 2 through 5 years and less than 14 kg: give 1 packet of 100 mg lumacaftor/125 mg ivacaftor granules (morning and evening) every 12 hours with fat-containing food.

Patients Aged 2 through 5 Years and greater than or equal to 14 kg: give 1 packet of 150 mg lumacaftor/188 mg ivacaftor granules (morning and evening) every 12 hours with fat-containing food.

Patients aged 6 through 11 years: give 2 tablets of the 100 mg lumacaftor/125 mg ivacaftor tablets every 12 hours (morning and evening) just before or just after eating fat-containing food.

Patients aged 12 years and over: give 2 tablets of the 200 mg lumacaftor/125 mg ivacaftor tablets every 12 hours (morning and evening) just before or just after eating fat-containing food.

Refilling your prescription:

Remember to get a new prescription from your doctor or a refill from your pharmacy before all your tablets are taken.

Overdose:

If you think you have taken too much ORKAMBI, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. If possible, have your medicine and this leaflet with you.

Missed Dose:

If you miss a dose of ORKAMBI and:

- **it is within 6 hours** of when you usually take it, take your dose of ORKAMBI as prescribed as soon as possible with fat-containing food.
- **it is more than 6 hours** after the time you usually take it, **do not** take the missed dose. Wait until it is time for your next dose and take it at the usual time.
- **Do not** take 2 doses at the same time to make up for your missed dose.

What are possible side effects from using ORKAMBI?

These are not all the possible side effects you may feel when taking ORKAMBI. If you experience any side effects not listed here, contact your healthcare professional.

Please also see Warnings and Precautions.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

- shortness of breath and/or chest tightness
- increase in blood pressure
- decrease in heart rate
- upper respiratory tract infection (common cold), including sore throat, stuffy or runny nose
- gastrointestinal symptoms, including nausea, diarrhea, and gas
- rash
- fatigue
- flu or flu-like symptoms
- increase in muscle enzyme levels
- irregular, abnormal, or painful periods (menses) and increase in the amount of menstrual bleeding

Additional side effects in children

Side effects seen in children are similar to those seen in adults and adolescents. Additional

common side effects seen in children include:

- stuffy or runny nose
- headache
- stomach pain
- increased cough and/or sputum
- sore throat
- pulmonary exacerbations

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 if you have been told you have liver disease, as your doctor may need to adjust the dose of ORKAMBI.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Abnormal blood tests of the liver: pain or discomfort in the upper right stomach (abdominal) area, yellowing of the skin or eyes, loss of appetite, nausea or vomiting, dark urine, confusion, pale stools		√	
Worsening of liver function in patients with severe liver disease: confusion, coma, death			√
Increased blood creatine phosphokinase: muscle pain, dark urine		√	
Pneumonia (lung infection)		√	
Hemoptysis (cough up blood)	√		
Cough	√		
UNKNOWN Allergic reaction: rash; hives; swelling of the face, lips, tongue, or throat; difficult swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or

Calling Toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Store at or below 30°C.

Keep out of reach and sight of children.

You may need to read this leaflet again. Please do not throw this away.

If you want more information about ORKAMBI:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada.html>); the manufacturer's website (<http://www.vrtx.com/canada>); or by calling 1-877-634- 8789.

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