# Dosing and Administration Guide

## For indicated patients taking ORKAMBI® (lumacaftor/ivacaftor)

### INDICATIONS AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

Limitations of Use

The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation.

**Click here for Important Safety Information and full Prescribing Information.**

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets
100/125 mg • 150/188 mg oral granules

# Important Safety Information

## USE IN PATIENTS WITH ADVANCED LIVER DISEASE

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI® (lumacaftor/ivacaftor)
- Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

## LIVER-RELATED EVENTS

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve
- Dosing should be interrupted in patients with ALT or AST greater than 5 x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

## RESPIRATORY EVENTS

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted $FEV_1$ ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

## EFFECT ON BLOOD PRESSURE

- Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

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# Important Safety Information (cont)

## DRUG INTERACTIONS

Substrates of CYP3A

- Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI® (lumacaftor/ivacaftor) may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended
- ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

Strong CYP3A Inducers

- Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

## CATARACTS

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI

## ADVERSE REACTIONS

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients
- The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- The safety profile in patients age 6 through 11 years from an open-label Phase 3 trial (Trial 3; N=58) and a placebo-controlled Phase 3 trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased. The safety profile in patients age 2 through 5 years from an open-label Phase 3 trial (Trial 6; N=60) was similar to that in patients aged 6 years and older

**Click here for additional Important Safety Information and full Prescribing Information.**

# Recommended dose for ORKAMBI® (lumacaftor/ivacaftor)

| Dosage Forms[1] | Recommended Dose[1] |
|---|---|
|  **Oral Granules** Not actual size. | **For patients age 2 to <6 years, the recommended dose is weight based**<br>▪ **<14 kg:** One packet containing lumacaftor 100 mg/ivacaftor 125 mg every 12 hours[a]<br>▪ **≥14 kg:** One packet containing lumacaftor 150 mg/ivacaftor 188 mg every 12 hours[a] |
|  **Tablets** Not actual size. | **For patients age 6 years and older**<br>▪ Age 6-11 years: 2 tablets (each containing **lumacaftor 100 mg/ivacaftor 125 mg**) every 12 hours<br>▪ Age 12+ years: 2 tablets (each containing **lumacaftor 200 mg/ivacaftor 125 mg**) every 12 hours |

**ORKAMBI oral granules and tablets should be taken with fat-containing food[1]**

[a]14 kg ≈ 31 lbs.

- A safe and efficacious dose of ORKAMBI for pediatric patients less than 2 years of age has not been established. The use of ORKAMBI (oral granules) in children under the age of 2 years is not recommended[1]
- See page 6 for additional information on administering oral granules

**Patients should continue taking all of their prescribed CF therapies with ORKAMBI[1]**

# Dosage adjustments for ORKAMBI® (lumacaftor/ivacaftor)

<table>
<tr><th></th><th colspan="2">Tablets Dose[1]</th><th colspan="2">Oral Granules Dose[1]</th></tr>
<tr><td colspan="5">Hepatic Impairment</td></tr>
<tr><td>Severe impairment (Child-Pugh Class C)[a]</td><td colspan="2">1 tablet in the morning and 1 tablet in the evening, or less frequently</td><td colspan="2">1 packet in the morning or less frequently<br>No dose in the evening</td></tr>
<tr><td>Moderate impairment (Child-Pugh Class B)</td><td colspan="2">2 tablets in the morning and 1 tablet in the evening</td><td colspan="2">1 packet in the morning every day and 1 packet in the evening every other day</td></tr>
<tr><td>Mild impairment (Child-Pugh Class A)</td><td colspan="4">No dose adjustment required</td></tr>
<tr><td colspan="5">CYP3A Inhibitors</td></tr>
<tr><td rowspan="2">Initiating ORKAMBI in patients already taking a strong CYP3A inhibitor (e.g., itraconazole)[b]</td><td>First Week</td><td>After First Week</td><td>First Week</td><td>After First Week</td></tr>
<tr><td>1 tablet daily</td><td>Continue with the full recommended daily dose as prescribed</td><td>1 packet every other day</td><td>Continue with the full recommended daily dose as prescribed</td></tr>
<tr><td>Initiating CYP3A inhibitors in patients already taking ORKAMBI[c]</td><td colspan="4">No dose adjustment required</td></tr>
<tr><td>Dose interruptions of ORKAMBI while taking strong CYP3A inhibitors</td><td colspan="4">If ORKAMBI is interrupted for more than 1 week and then reinitiated while taking strong CYP3A inhibitors, reduce dose to 1 tablet daily or 1 packet every other day for the first week of treatment reinitiation. Following this period, continue with the full recommended daily dose as prescribed.</td></tr>
</table>

[a]Use with caution after weighing the risks and benefits of treatment.[1]

[b]Additional examples include **ketoconazole, posaconazole, voriconazole, telithromycin,** and **clarithromycin**.[1]

[c]No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.[1]

## Missed dose of oral granules or tablets[1]

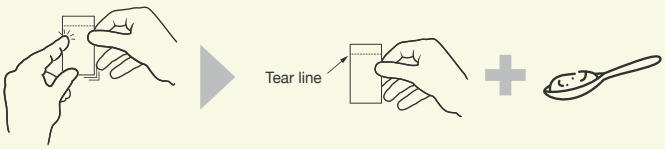
- If **≤6 hours** have passed: Advise patient to take the dose with fat-containing food
- If **>6 hours** have passed: Advise patient to **skip that dose** and resume the normal schedule for the following dose. A double dose should **not** be taken to make up for the forgotten dose

**Click here for Important Safety Information and full Prescribing Information.**

# How to administer ORKAMBI® (lumacaftor/ivacaftor) oral granules

## 1 PREPARATION[1]

- Caregiver should hold the packet with the perforation on top, shake the packet gently to settle the granules, and tear or cut the packet open along the perforation
- Caregiver should mix all granules into 1 teaspoon (5 mL) of soft food or liquid
- Food or liquid should be at or below room temperature




**Examples of soft foods or liquids include:**

Pureed fruits or applesauce | Flavored yogurt or pudding | Milk or juice

## 2 ADMINISTRATION[1]

- After mixing, caregiver should give within 1 hour
- Caregiver should make sure the child finishes the dose completely

## 3 GIVE WITH FAT-CONTAINING FOOD[1]

- Food that contains fat must be taken just before or after the oral granules dose

**Examples of fat-containing foods include:**

- Eggs
- Avocado
- Nuts
- Butter
- Peanut butter
- Cheese pizza
- Whole-milk dairy products (e.g., whole milk, cheese, and yogurt)

**It is important that patients consume the entire oral granules mixture with each dose**

## PALATABILITY OF ORKAMBI ORAL GRANULES

- Children may find the taste of the oral granules to be bitter
- Mixing the oral granules with soft foods or liquids that are sweet or rich, such as pudding or chocolate sauce, may help with the taste[2,3]

**Refer your patients to ORKAMBI.com for more information on administering ORKAMBI oral granules.**

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# Distinctive packaging for each dosage strength

## ORKAMBI® (lumacaftor/ivacaftor) TABLETS


Not actual size.

## ORKAMBI ORAL GRANULES

Not actual size.

**Click here for Important Safety Information and full Prescribing Information.**

**References: 1.** ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018. **2.** UC Davis Children's Hospital. How to help your child take medicine. http://www.ucdmc.ucdavis.edu/children/patients_family_resources/Patient_and_Family_Education_A_to_Z/PDFs/HowToHelpTakeMedicine.pdf. Accessed June 7, 2018. **3.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. VXR-HQ-88-00201; 2018.

VERTEX



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