WHAT IS ORKAMBI® (lumacaftor/ivacaftor)?

ORKAMBI is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have two copies of the F508del mutation (F508del/F508del) in their CFTR gene.

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.

All photos are of people with CF who have 2 copies of the F508del-CFTR mutation or their caregivers. The people with CF may or may not be taking ORKAMBI.

Please see Important Safety Information and full Prescribing Information, including Patient Information.
Why start ORKAMBI® as soon as you or your child is eligible?

Everyone’s cystic fibrosis (CF) is different, but CF still works beneath the surface.

Since CF is working beneath the surface, your or your child’s treatment should be, too.

In people 2 years and older with 2 copies of the F508del-CFTR mutation, ORKAMBI treats the underlying cause of CF.

In this brochure, you will find information about ORKAMBI® (lumacaftor/ivacaftor), including Important Safety Information and details and results of ORKAMBI studies in different age groups.

**IMPORTANT SAFETY INFORMATION**

Do not take ORKAMBI if you take certain medicines or herbal supplements, such as:

- antibiotics: rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines: phenobarbital, carbamazepine (Tegretol®, Carbatro, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- sedatives and anti-anxiety medicines: triazolam (Halcion®) or midazolam (Dormicum®, Hypnovel®, and Versed®)
- immunosuppressant medicines: cyclosporine, everolimus (Zortress®), sirolimus (Rapamune®), or tacrolimus (Astagraf XL®, Envarsus XR®, Prograf®, and Protopic®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking ORKAMBI if you take any of the medicines or supplements listed above.

Please see additional Important Safety Information and full Prescribing Information, including Patient Information.
IMPORTANT SAFETY INFORMATION

Do not take ORKAMBI® if you take certain medicines or herbal supplements, such as:

- antibiotics: rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines: phenobarbital, carbamazepine (Tegretol®, Carbatrol®, and Equetro®), or phenytoin (Dilantin®, Phenytek®)
- sedatives and anti-anxiety medicines: triazolam (Halcion®) or midazolam (Dormicum®, Hypnovel®, and Versed®)
- immunosuppressant medicines: cyclosporine, everolimus (Zortress®), sirolimus (Rapamune®), or tacrolimus (Astagraf XL®, Envarsus XR®, Prograf®, and Protopic®)
- St. John’s wort (Hypericum perforatum)

Talk to your doctor before taking ORKAMBI if you take any of the medicines or supplements listed above.

Before you take ORKAMBI, tell your doctor about all of your medical conditions, including if you:

- have or have had liver problems
- have had an organ transplant
- have kidney problems
- 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. Talk to your doctor about the best birth control method you should use while taking ORKAMBI

Before taking ORKAMBI® (lumacaftor/ivacaftor), tell your doctor about all of your medical conditions, including if you (continued):

- 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

ORKAMBI may affect the way other medicines work, and other medicines may affect how ORKAMBI works.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements, because the dose of ORKAMBI may need to be adjusted when taken with certain medicines.

Especially tell your doctor if you take:

- antifungal medicines including ketoconazole (such as Nizoral®), itraconazole (such as Sporanox®), posaconazole (such as Noxafil®), or voriconazole (such as Vfend®)
- antibiotics including telithromycin (such as Ketek®), clarithromycin (such as Biaxin®), or erythromycin (such as Ery-Tab®)

Tell your doctor if you stop ORKAMBI for more than 1 week. Your doctor may need to change your dose of ORKAMBI or other medicines you take.

Please see additional Important Safety Information and full Prescribing Information, including Patient Information.
IMPORTANT SAFETY INFORMATION (continued)

What are the possible side effects of ORKAMBI®?

ORKAMBI can cause serious side effects, including:

**Worsening of liver function** in people with severe liver disease. The worsening of liver function can be serious or cause death. Talk to your doctor if you have been told you have liver disease as your doctor may need to adjust the dose of ORKAMBI.

**High liver enzymes in the blood**, which can be a sign of liver injury in people receiving ORKAMBI. Your doctor will do blood tests to check your liver:

- before you start ORKAMBI
- every 3 months during your first year of taking ORKAMBI
- every year while you are taking ORKAMBI

Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of the skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine
- confusion

**Breathing problems** such as shortness of breath or chest tightness 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** in some people receiving ORKAMBI. Your doctor should monitor your blood pressure during treatment with ORKAMBI.

Abnormality of the eye lens (cataract) in some children and adolescents receiving ORKAMBI® (lumacaftor/ivacaftor). If you are a child or adolescent, your doctor should perform eye examinations before and during treatment with ORKAMBI to look for cataracts.

The most common side effects of ORKAMBI include:

- breathing problems such as shortness of breath and chest tightness
- nausea
- diarrhea
- fatigue
- increase in a certain blood enzyme called creatine phosphokinase
- rash
- gas
- common cold, including sore throat, stuffy or runny nose
- flu or flu-like symptoms
- irregular, missed, or abnormal periods (menses) and increase in the amount of menstrual bleeding

Side effects seen in children are similar to those seen in adults and adolescents. Additional common side effects seen in children include:

- cough with sputum
- stuffy nose
- headache
- stomach pain
- increase in sputum

These are not all the possible side effects of ORKAMBI. Call your doctor for medical advice about side effects. You are encouraged to report side effects to FDA at 1-800-FDA-1088.

Please see additional Important Safety Information and full Prescribing Information, including Patient Information.
“We try to find ways to prioritize Sydney’s treatment routine while still doing what we love as a family.”
— Kristi, Sydney’s mom

In this section, you will find study details and results for a study that evaluated the safety of ORKAMBI® (lumacaftor/ivacaftor) in children age 2 through 5 years with 2 copies of the F508del mutation in their CFTR gene.

Please see Important Safety Information and full Prescribing Information, including Patient Information.
ORKAMBI® was studied in children age 2 through 5 years

Safety study

The primary purpose of the 24-week study of 60 children age 2 through 5 years with 2 copies of the F508del-CFTR mutation was to determine the safety of ORKAMBI.

This study also evaluated sweat chloride levels, which are a measure of the amount of salt in a child’s sweat (mmol/L). Sweat chloride level measurement is used to help diagnose cystic fibrosis (CF). High sweat chloride levels are a hallmark of CF. After 24 weeks, there was a 2-week period when the children stopped taking ORKAMBI in order to observe any changes in sweat chloride.

How ORKAMBI was given

- Children who weighed less than ~31 pounds (less than 14 kg) received ORKAMBI oral granules (lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours.
- Children who weighed ~31 pounds or more (14 kg or more) received ORKAMBI oral granules (lumacaftor 150 mg/ivacaftor 188 mg) every 12 hours.

All children took 1 packet of ORKAMBI oral granules mixed with 1 teaspoon of soft food or liquid every 12 hours. All children also ate fat-containing food just before or just after taking the oral granules dose. No children in the study took placebo. All children continued to take their other prescribed cystic fibrosis (CF) treatments throughout the full study, including the 2-week period when they stopped taking ORKAMBI.

Study results

The safety in this study was similar to what was observed in studies of ORKAMBI® (lumacaftor/ivacaftor) in people age 6 years and older.

Please see pages 4-7 for full important Safety Information, including side effects.

- After taking ORKAMBI for 24 weeks: Decreased 31.7 mmol/L on average (average mmol/L at beginning of study was 105.8)
- After ORKAMBI was stopped for 2 weeks: Increased 33.0 mmol/L on average

Study considerations

- Because no one took placebo, it is not known if changes in sweat chloride levels were due to ORKAMBI
- Changes in sweat chloride levels are not related to changes in lung function

Watch Taking ORKAMBI Oral Granules With Cammy & Sam

For more information about how to take ORKAMBI, visit ORKAMBI.com and watch this fun and informative video.

Please see Important Safety Information and full Prescribing Information, including Patient Information.
Nolan takes an active role in his treatments and at the doctor’s office when he asks about test results. He puts in a lot of effort.”
— Heather, Nolan’s mom

In this section, you will find study details and results for a study that evaluated the safety of ORKAMBI® (lumacaftor/ivacaftor) in children age 6 through 11 years with 2 copies of the F508del mutation in their CFTR gene.

Please see Important Safety Information and full Prescribing Information, including Patient Information.
The study also evaluated changes in lung function and sweat chloride levels. Lung function is determined with an FEV1 test, which measures how much air a person can exhale in a forced breath. Lung function was part of the safety assessment in this trial.

Sweat chloride is a measure of the amount of salt in a child’s sweat (mmol/L). Sweat chloride level measurement is used to help diagnose cystic fibrosis (CF). High sweat chloride levels are a hallmark of CF.

After 24 weeks, there was a 2-week period when ORKAMBI was stopped in order to observe any changes in results. For the last 2 weeks of the study children only took their other prescribed CF therapies and did not take ORKAMBI.

How ORKAMBI was given

All children in the study took 2 tablets of ORKAMBI (lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours with fat-containing food. No children in the study took placebo. All children continued to take their other prescribed cystic fibrosis (CF) treatments throughout the full study, including the 2-week period when they stopped taking ORKAMBI.

Safety Study

The primary purpose of the 24-week Safety Study of 58 children age 6 through 11 years with 2 copies of the F508del-CFTR mutation was to determine the safety of ORKAMBI.

Study considerations

• Because no one took placebo in the Safety Study, it is not known if changes in lung function and sweat chloride levels were due to ORKAMBI
• Changes in sweat chloride levels observed in the Safety Study are not related to changes in lung function

Please see Important Safety Information and full Prescribing Information, including Patient Information.
The primary purpose of the 24-week Efficacy and Safety Study of 204 children with 2 copies of the F508del-CFTR mutation was to determine the efficacy of ORKAMBI on lung function based on lung clearance index (LCI). LCI is a measure of lung function that determines how well the lungs are working. This study also evaluated the safety of ORKAMBI.

ORKAMBI® was studied in children age 6 through 11 years

Efficacy and Safety Study

In this study, 103 children took 2 tablets of ORKAMBI (lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours with fat-containing food. The remaining 101 children took placebo every 12 hours with fat-containing food. All children continued to take their other prescribed cystic fibrosis (CF) therapies.

Efficacy and Safety Study results

After taking ORKAMBI for 24 weeks:
Lung function was improved versus placebo, based on LCI

The safety of ORKAMBI® (lumacaftor/ivacaftor), observed in the Efficacy and Safety Study, was similar to what was observed in people age 12 years and older, with the addition of these side effects: cough with sputum, stuffy nose, headache, stomach pain, and increase in sputum.

Please see pages 4–7 for full Important Safety Information, including side effects.

Study considerations

- The efficacy results from the Efficacy and Safety Study are not included in the full Prescribing Information. Also, the FDA did not consider the results of this study when approving ORKAMBI
"I’m all about sticking with ORKAMBI because it’s working for me."

— Brad, F508del/F508del

In this section, you will find study details and results for ORKAMBI® (lumacaftor/ivacaftor) in people age 12 years and older with 2 copies of the F508del mutation in their CFTR gene. These results are from:

- 2 Short-Term Studies that lasted 24 weeks
- 1 Long-Term Study that lasted 96 weeks

Please see Important Safety Information and full Prescribing Information, including Patient Information.
Measuring the results with ORKAMBI®

The possible benefits and risks of treatment with ORKAMBI were studied for up to 2 years in people with cystic fibrosis (CF) age 12 years and older with 2 copies of the F508del mutation in their CFTR gene.

- In the Short-Term Studies, ORKAMBI and placebo were compared. In the Long-Term Study, all participants took ORKAMBI.
- Every 12 hours, participants took 2 tablets of ORKAMBI (lumacaftor 200 mg/ivacaftor 125 mg) or placebo, with fat-containing food. People continued to take their other prescribed CF therapies.

On the following pages, you’ll see the results from these studies for ORKAMBI, including:

- Lung function (FEV1)
- Body mass index (BMI)
- CF respiratory symptoms
  - Includes cough, difficulty breathing, amount of mucus coughed up
  - Based on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) survey
- Pulmonary exacerbations
- Safety

All of the results shown for each study are an average of all people studied.

Please see Important Safety Information and full Prescribing Information, including Patient Information.

Study considerations

- The Long-Term Study did not have any participants who took placebo. All patients knew they were taking ORKAMBI® (lumacaftor/ivacaftor), which may have influenced the results.
- The FDA did not consider the Long-Term Study when approving ORKAMBI, and it is not included in the full Prescribing Information. The Long-Term Study may not meet the FDA's definition of an acceptable study because there was no placebo group included for comparison.
- At around Week 72, almost half the participants stopped taking part in the Long-Term Study because ORKAMBI was approved by the FDA at that time. Participants could start getting ORKAMBI from their own doctor.
2 years of study suggest that ORKAMBI® could have a long-term impact

**Results from 2 Short-Term Studies**

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<tr>
<td><strong>Lung function</strong></td>
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<td>3.0</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td><strong>CF Respiratory Symptoms</strong></td>
<td>1.5</td>
<td>2.9</td>
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<tr>
<td><strong>Pulmonary Exacerbations</strong></td>
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<td>40%</td>
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**Results from a Long-Term Study**

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<td><strong>Lung function</strong></td>
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<td><strong>Safety</strong></td>
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Please see Important Safety Information and full Prescribing Information, including Patient Information.
ORKAMBI® (lumacaftor/ivacaftor) was evaluated in studies involving different age groups

For age 2 through 5 years
The safety of ORKAMBI was evaluated in a 24-week study. See pages 10-11.

For age 6 through 11 years
The safety of ORKAMBI was evaluated in a 24-week study. The efficacy and safety of ORKAMBI were evaluated in a separate 24-week study. See pages 14-17.

For age 12 years and older
The efficacy and safety of ORKAMBI were evaluated in 2 Short-Term (24-week) Studies and 1 Long-Term (96-week) Study. See pages 20-23.

Review how ORKAMBI® may help you or your child

ORKAMBI targets the underlying cause
Watch a video that explains how ORKAMBI works in people age 2 years and older who have 2 copies of the F508del mutation in their CFTR gene. Visit ORKAMBI.com/how-orkambi-works.

Review the Important Safety Information for ORKAMBI
ORKAMBI can cause serious side effects. Be sure to review pages 4-7.

Learn more about taking ORKAMBI
Visit ORKAMBI.com for information on:
- Taking ORKAMBI tablets
- Taking ORKAMBI oral granules
- Taking ORKAMBI with fat-containing foods

Work with your healthcare provider
Your experience with ORKAMBI may be different from others. Always speak with your healthcare provider if you have any questions about your treatment.

Check out ORKAMBI at Facebook.com/ORKAMBI
Explore how Vertex GPS™: Guidance & Patient Support can help

Vertex GPS: Guidance & Patient Support provides eligible patients with reimbursement support, information about financial resources, refill reminders, and ongoing educational materials.

If you are currently enrolled and want to learn more about how GPS can provide you with product support, you can speak to your Case Manager at 1-877-752-5933 (press 2), Monday through Friday from 8:30 AM to 7:00 PM ET. If you or your child has been prescribed ORKAMBI® (lumacaftor/ivacaftor) and you are not enrolled, please speak with your healthcare provider.

To find out more about GPS and the support resources available to you, including Delicious Dishes and Navigating Life With CF, visit VertexGPS.com.

Please see full Prescribing Information, including Patient Information.