ORKAMBI® (lumacaftor/ivacaftor)

DRUG-DRUG INTERACTIONS QUICK-REFERENCE GUIDE

INDICATION

ORKAMBI® (lumacaftor/ivacaftor) is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 6 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.

Please see Important Safety Information and full Prescribing Information.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

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

Drug Interactions

Substrates of CYP3A

- Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI 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

 Please see the full Prescribing Information.

Recommended Dose and Dosage Adjustments for ORKAMBI® (lumacaftor/ivacaftor) Tablets[1]

Clinical Situation	Dose	Administration Frequency	Total Daily Dose	
Recommended Doses				
For patients age 6-11 years, taken with fat-containing food	2 tablets of ORKAMBI (each containing lumacaftor 100 mg/ivacaftor 125 mg)	Every 12 hours	lumacaftor 400 mg/ivacaftor 500 mg	
For patients age 12 years and older, taken with fat-containing food	2 tablets of ORKAMBI (each containing lumacaftor 200 mg/ivacaftor 125 mg)	Every 12 hours	lumacaftor 800 mg/ivacaftor 500 mg	
Dosage Adjustments for Patients With Hepatic Impairment			**Patients 6-11 years**	**Patients 12 years and older**
Severe impairment (Child-Pugh Class C)[a]	1 tablet of ORKAMBI	Every 12 hours or less frequently	lumacaftor 200 mg/ivacaftor 250 mg	lumacaftor 400 mg/ivacaftor 250 mg
Moderate impairment (Child-Pugh Class B)	2 tablets of ORKAMBI	Morning	lumacaftor 300 mg/ivacaftor 375 mg	lumacaftor 600 mg/ivacaftor 375 mg
	1 tablet of ORKAMBI	Evening (12 hours later)		
Mild Impairment (Child-Pugh Class A)	No dose adjustment required, see Recommended Doses above			
Dosage Adjustments for CYP3A Inhibitors			**Patients 6-11 years**	**Patients 12 years and older**
Initiating ORKAMBI in patients already taking a strong CYP3A inhibitor (e.g., itraconazole)[b]	**First week:** 1 tablet of ORKAMBI	Once daily	lumacaftor 100 mg/ivacaftor 125 mg	lumacaftor 200 mg/ivacaftor 125 mg
	After first week: Continue with the full recommended daily doses as prescribed			
Initiating CYP3A inhibitors in patients already taking ORKAMBI[c]	No dose adjustment required, see Recommended Doses above			
Dose interruptions of ORKAMBI in patients taking strong CYP3A inhibitors	If ORKAMBI is interrupted for more than 1 week, and then reinitiated while taking strong CYP3A inhibitors, reduce dose to 1 tablet daily for the first week of treatment reinitiation. Following this period, continue with the full recommended daily dose as prescribed			

[a]Use with caution after weighing the risks and benefits of treatment.
[b]Additional examples include ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin.
[c]No dose adjustment is recommended when used with weak or moderate CYP3A inhibitors.

- **Prescriptions for ORKAMBI should specify the dose strength as appropriate by age**

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Please see Important Safety Information and full Prescribing Information.

Information on Drug Interactions for ORKAMBI® (lumacaftor/ivacaftor)[1]

Potential for Other Drugs to Affect lumacaftor/ivacaftor

Inhibitors of CYP3A

- Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours (the approved dose of ivacaftor monotherapy). Therefore, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI
- However, when initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce the ORKAMBI dose to 1 tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose for patients age 12 years and over; lumacaftor 100 mg/ivacaftor 125 mg total daily dose for patients age 6 through 11 years) for the first week of treatment to allow for the steady-state induction effect of lumacaftor. Following this period, continue with the recommended daily dose
- Examples of strong CYP3A inhibitors include:
  - Ketoconazole, itraconazole, posaconazole, and voriconazole
  - Telithromycin, clarithromycin
- No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors

Inducers of CYP3A

- Co-administration of lumacaftor/ivacaftor with rifampin, a strong CYP3A inducer, had minimal effect on the exposure of lumacaftor, but decreased ivacaftor exposure (AUC) by 57%. This may reduce the effectiveness of ORKAMBI. Therefore, co-administration of ORKAMBI with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*) is not recommended
- No dose adjustment is recommended when used with moderate or weak CYP3A inducers

Potential for lumacaftor/ivacaftor to Affect Other Drugs

CYP3A Substrates

- Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%. Administration of ORKAMBI may decrease systemic exposure of medicinal products which are substrates of CYP3A, thereby decreasing the therapeutic effect of the medicinal product
- Co-administration of ORKAMBI is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index such as:
  - **Benzodiazepines:** midazolam, triazolam (consider an alternative to these benzodiazepines)
  - **Immunosuppressants:** cyclosporine, everolimus, sirolimus, and tacrolimus (avoid the use of ORKAMBI)

CYP2B6 and CYP2C Substrates

- In vitro studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; inhibition of CYP2C8 and CYP2C9 has also been observed in vitro. Additionally, in vitro studies suggest that ivacaftor may inhibit CYP2C9. Therefore, concomitant use of ORKAMBI with CYP2B6, CYP2C8, CYP2C9, and CYP2C19 substrates may alter the exposure of these substrates

Digoxin and Other P-gp Substrates

- Based on in vitro results which showed P-gp inhibition and pregnane-X-receptor (PXR) activation, lumacaftor has the potential to both inhibit and induce P-gp. Additionally, a clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of ORKAMBI with P-gp substrates may alter the exposure of these substrates
- Monitor the serum concentration of digoxin and titrate the digoxin dose to obtain the desired clinical effect

Information on Drug Interactions for ORKAMBI® (lumacaftor/ivacaftor)[1] (cont)

***Potential for lumacaftor/ivacaftor to Affect Other Drugs* (cont)**

Anti-allergics and Systemic Corticosteroids

- ORKAMBI may decrease the exposure of montelukast, which may reduce its efficacy. No dose adjustment for montelukast is recommended. Employ appropriate clinical monitoring, as is reasonable, when co-administered with ORKAMBI
- Concomitant use of ORKAMBI may reduce the exposure and effectiveness of prednisone and methylprednisolone. A higher dose of these systemic corticosteroids may be required to obtain the desired clinical effect

Antibiotics

- Concomitant use of ORKAMBI may decrease the exposure of clarithromycin, erythromycin, and telithromycin, which may reduce the effectiveness of these antibiotics. Consider an alternative to these antibiotics, such as ciprofloxacin, azithromycin, and levofloxacin

Antifungals

- Concomitant use of ORKAMBI may reduce the exposure and effectiveness of itraconazole, ketoconazole, posaconazole, and voriconazole. Concomitant use of ORKAMBI with these antifungals is not recommended. Monitor patients closely for breakthrough fungal infections if such drugs are necessary. Consider an alternative such as fluconazole

Anti-inflammatories

- Concomitant use of ORKAMBI may reduce the exposure and effectiveness of ibuprofen. A higher dose of ibuprofen may be required to obtain the desired clinical effect

No dosage adjustment of ORKAMBI or the concomitant drug is recommended when ORKAMBI is given with the following:

- Azithromycin
- Aztreonam
- Budesonide
- Ceftazidime
- Cetirizine
- Ciprofloxacin
- Colistimethate
- Colistin
- Dornase alfa
- Fluticasone
- Ipratropium
- Levofloxacin
- Pancreatin
- Pancrelipase
- Salbutamol
- Salmeterol
- Sulfamethoxazole and trimethoprim
- Tiotropium
- Tobramycin

***Potential for lumacaftor/ivacaftor to Affect Other Drugs* (cont)**

Antidepressants

- Concomitant use of ORKAMBI may reduce the exposure and effectiveness of citalopram, escitalopram, and sertraline (SSRIs). A higher dose of these antidepressants may be required to obtain the desired clinical effect

Hormonal Contraceptives

- ORKAMBI may decrease hormonal contraceptive exposure, reducing the effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI
- Concomitant use of ORKAMBI with hormonal contraceptives increased the menstrual abnormality events. Avoid concomitant use unless the benefit outweighs the risks

Oral Hypoglycemics

- Concomitant use of ORKAMBI may reduce the exposure and effectiveness of repaglinide, and may alter the exposure of sulfonylurea. A dose adjustment may be required to obtain the desired clinical effect. No dose adjustment is recommended for metformin

Proton Pump Inhibitors, H2 Blockers, Antacids

- ORKAMBI may reduce the exposure and effectiveness of proton pump inhibitors such as omeprazole, esomeprazole, and lansoprazole, and may alter the exposure of ranitidine. A dose adjustment may be required to obtain the desired clinical effect. No dose adjustment is recommended for calcium carbonate antacid

Warfarin

- ORKAMBI may alter the exposure of warfarin. Monitor the international normalized ratio (INR) when warfarin co-administration with ORKAMBI is required

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

The Drug-Drug Interaction table provides the established or predicted effect of ORKAMBI® (lumacaftor/ivacaftor) on other medicinal products or effect of other medicinal products on ORKAMBI. These are listed in alphabetical order by class

- The clinical comments are based on drug interaction studies, clinical relevance, or predicted interactions due to elimination pathways
  - Drug names in **bold** indicate those that are listed in the full Prescribing Information for ORKAMBI
- Drugs shown within a therapeutic class do not represent all possible drugs within the class. Drugs within a therapeutic class may have different metabolic profiles and therefore, clinical recommendations apply only to the indicated drugs and not the class. The table does not represent all possible drugs or drug classes that a patient could be receiving

Drug Class	Generic (Common Brand Names)	Potential Effect on Exposure on Concomitant Drug	Clinical Comment
Anti-allergics	**Montelukast (Singulair®)**[1]	Decreased ↓	• No dose adjustment recommended • Appropriate clinical monitoring, as is reasonable
Anti-arrhythmics	**Digoxin (Lanoxin®)**[1]	Increased ↑ or decreased ↓	• Monitor the serum concentration and titrate the dose to obtain desired clinical effect
Antibiotics, macrolides	**Clarithromycin (Biaxin®)**[1]	Decreased ↓	• Consider an alternative, such as ciprofloxacin, azithromycin, and levofloxacin • No dose adjustment recommended for ORKAMBI when these antibiotics are initiated in patients currently taking ORKAMBI • When initiating ORKAMBI in patients taking these antibiotics, reduce ORKAMBI dose to 1 tablet daily for first week, then 2 tablets every 12 hours
	Telithromycin (Ketek®)[1]		
	Erythromycin (Eryc®, Ery-Tab®, PCE®)[1]		
Anticoagulants	**Warfarin (Coumadin®, Jantoven®)**[1]	Increased ↑ or decreased ↓	• Monitor international normalized ratio when co-administration of ORKAMBI is required
Anticonvulsants	**Carbamazepine (Tegretol®, Equetro®, Carbatrol®)**[1]		• Concomitant use not recommended • Decreased ivacaftor exposure; may reduce the effectiveness of ORKAMBI
	Phenobarbital (Luminal®)[1]		
	Phenytoin (Dilantin®)[1]		
Antifungals	**Itraconazole[a,b] (Sporanox®)**[1]	Decreased ↓	• Concomitant use not recommended • Monitor closely for breakthrough fungal infections if use is necessary • Consider an alternative such as fluconazole • No dose adjustment recommended for ORKAMBI when these antifungals are initiated in patients currently taking ORKAMBI • When initiating ORKAMBI in patients taking these antifungals, reduce dose to 1 tablet daily for first week, then 2 tablets every 12 hours
	Ketoconazole (Nizoral®)[1]		
	Posaconazole (Noxafil®)[1]		
	Voriconazole (Vfend®)[1]		
Anti-inflammatories	**Ibuprofen (Advil®, Motrin®)**[1]	Decreased ↓	• A higher dose of ibuprofen may be required to obtain desired clinical effect

[a]Co-administration of lumacaftor/ivacaftor with itraconazole did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold.

[b]Based on clinical drug-drug interaction studies.

[c]Co-administration of lumacaftor/ivacaftor with rifampin had minimal effect on the exposure of lumacaftor but decreased ivacaftor exposure (AUC) by 57%.

Drug Class	Generic (Common Brand Names)	Potential Effect on Exposure on Concomitant Drug	Clinical Comment
Anti-mycobacterials	**Rifabutin (Mycobutin®)**[1]		• Concomitant use not recommended • Decreased ivacaftor exposure; may reduce the effectiveness of ORKAMBI
	Rifampin[b,c] (Rifadin®)[1]		
Antipsychotics	Aripiprazole (Abilify®)[1,2]	Decreased ↓	• A higher dose of aripiprazole may be required to obtain the desired clinical effect
	Clozapine (Clozaril®)[1,3]	Decreased ↓	• A higher dose of clozapine may be required to obtain the desired clinical effect
	Quetiapine (Seroquel®)[1,4]	Decreased ↓	• A higher dose of quetiapine may be required to obtain the desired clinical effect
Benzodiazepines	Alprazolam (Xanax®)[1,5]	Decreased ↓	• A higher dose of alprazolam may be required to obtain the desired clinical effect
	Clonazepam (Klonopin®)[1,6]	Decreased ↓	• A higher dose of these benzodiazepines may be required to obtain the desired clinical effect
	Diazepam (Valium®)[1,7]		
	Midazolam (Versed®)[1,4]	Decreased ↓	• Concomitant use not recommended • Consider an alternative to these benzodiazepines
	Triazolam (Halcion®)[1,4]		
Corticosteroids (systemic)	**Methylprednisolone (Solu-Medrol®)**[1]	Decreased ↓	• A higher dose of these systemic corticosteroids may be required to obtain desired clinical effect
	Prednisone (Prednisone Intensol®, Rayos®)[1]		
Herbals	**St. John's wort (*Hypericum perforatum*)**[1]		• Concomitant use not recommended • Decreased ivacaftor exposure; may reduce the effectiveness of ORKAMBI
Hormonal Contraceptives	**Estrogen, progestins**[1,8]	Decreased ↓	• Do not rely on hormonal contraceptives, including oral, injectable, transdermal, and implantable, as an effective method of contraception • Concomitant use of ORKAMBI with hormonal contraceptives increased menstrual abnormality events • Avoid concomitant use unless the benefits outweigh the risks

Drug Class	Generic (Common Brand Names)	Potential Effect on Exposure on Concomitant Drug	Clinical Comment
H2 Blockers	**Ranitidine (Zantac®)**[1]	Increased ↑ or decreased ↓	• A dose adjustment may be required to obtain desired clinical effect
Immuno-suppressants	**Cyclosporine (Sandimmune®)**[1]	Decreased ↓	• Concomitant use not recommended • Avoid the use of ORKAMBI
	Everolimus (Zortress®, Afinitor®)[1]		
	Sirolimus (Rapamune®)[1]		
	Tacrolimus (Prograf®)[1]		
Oral Hypoglycemics	**Repaglinide (Prandin®)**[1]	Decreased ↓	• A dose adjustment for these agents may be required to obtain desired clinical effect • No dose adjustment is recommended for metformin
	Sulfonylureas[1]	Increased ↑ or decreased ↓	
Proton Pump Inhibitors	**Esomeprazole (Nexium®)**[1]	Decreased ↓	• A dose adjustment may be required to obtain desired clinical effect • No dose adjustment is recommended for calcium carbonate antacid
	Lansoprazole (Prevacid®)[1]		
	Omeprazole (Prilosec®)[1]		
SNRIs	Duloxetine (Cymbalta®)[1,9,10]	No effect predicted	
SSRIs	**Citalopram (Celexa®)**[1]	Decreased ↓	• A higher dose of these antidepressants may be required to obtain the desired clinical effect
	Escitalopram (Lexapro®)[1]		
	Fluoxetine (Prozac®)[1,4,9]	No effect predicted	
	Paroxetine (Paxil®)[1,11]	Decreased ↓	• A higher dose of these antidepressants may be required to obtain the desired clinical effect
	Sertraline (Zoloft®)[1]		
Tetracyclic Antidepressants	Mirtazapine (Remeron®)[1,12]	Decreased ↓	• A higher dose of these antidepressants may be required to obtain the desired clinical effect
	Trazodone (Desyrel®)[1,13]		

SNRIs, serotonin-norepinephrine reuptake inhibitors;
SSRIs, selective serotonin reuptake inhibitors.

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

Please see Important Safety Information and full Prescribing Information.

Overview of ORKAMBI® (lumacaftor/ivacaftor) Drug Interactions

	Effect of ORKAMBI on other drugs							Effect of other drugs on ORKAMBI	
	CYP3A Substrates[1,a]	CYP2B6 Substrates[1]	CYP2C19 Substrates[1]	CYP2C9 Substrates[1]	CYP2D6 Substrates[9]	CYP2C8 Substrates[1]	P-gp Substrates[1]	CYP3A Inhibitors[1,c]	CYP3A Inducers[1,d]
Potential Effect	Strong induction	Potential to induce[b]	Potential to induce[b]	May induce or inhibit[b]	No potential to inhibit[b]	May induce or inhibit[b]	May induce or inhibit[b]	Increased ivacaftor exposure 4.3-fold[c]	Decreased ivacaftor exposure 57%[d]

[a]Co-administration of ORKAMBI is not recommended with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index.

[b]In vitro studies only.[1]

[c]Due to the induction effect of lumacaftor on CYP3A, at steady state, the net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours. Therefore, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI; however, when initiating ORKAMBI in patients taking strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, telithromycin, clarithromycin), reduce the ORKAMBI dose to one tablet daily for the first week of treatment to allow for the steady state induction effect of lumacaftor. Following this period, continue with the recommended daily dose.[1]

[d]Co-administration of ORKAMBI with strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort [*Hypericum perforatum*]) is not recommended.[1]

ORKAMBI®
(lumacaftor/ivacaftor)
200/125 mg • 100/125 mg tablets

ORKAMBI®

(lumacaftor/ivacaftor)

200/125 mg • 100/125 mg tablets

For more information, visit www.ORKAMBIhcp.com

Please see Important Safety Information and full Prescribing Information.

References: 1. ORKAMBI [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2018. **2.** Abilify [prescribing information]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; February 2017. **3.** Clozaril [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2017. **4.** Drug development and drug interactions: table of substrates, inhibitors, and inducers. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Updated September 26, 2016. Accessed January 26, 2018. **5.** Xanax [prescribing information]. New York, NY: Pfizer; January 2017. **6.** Klonopin [prescribing information]. South San Francisco, CA: Genentech, Inc.; December 2016. **7.** Valium [prescribing information]. South San Francisco, CA: Genentech, Inc.; April 2017. **8.** US Food and Drug Administration. US Department of Health and Human Services. For consumers. http://www.fda.gov/ForConsumers/ByAudience/ForWomen/FreePublications/ucm313215.htm. Updated January 19, 2018. Accessed January 26, 2018. **9.** Data on file. Boston, MA. Vertex Pharmaceuticals Incorporated; VXR-HQ-88-00004(1); 2018. **10.** Cymbalta [prescribing information]. Indianapolis, IN: Eli Lilly and Company; December 2017. **11.** Paxil [prescribing information]. Research Triangle Park, NC: GlaxoSmith-Kline; June 2008. **12.** Remeron [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; November 2016. **13.** Trazodone [prescribing information]. Weston, FL: Apotex Inc.; July 2017.

VERTEX®