PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**ORKAMBI**®

Lumacaftor/Ivacaftor tablets

100 mg/125 mg tablets and 200 mg/125 mg tablets

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

ATC R07AX30

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^{Pr}ORKAMBI®

Lumacaftor/Ivacaftor tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 100 mg lumacaftor/ 125 mg ivacaftor and 200 mg lumacaftor/ 125 mg ivacaftor	Cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate. The tablet film coat contains carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac

INDICATIONS AND CLINICAL USE

ORKAMBI (lumacaftor/ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who are homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator* (*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.

Geriatrics (≥65 years of age):
The safety and efficacy of ORKAMBI in patients age 65 years and older have not been evaluated.

Pediatrics (<6 years of age):
The safety and efficacy of ORKAMBI in patients younger than 6 years of age have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to the active substances within this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Cardiovascular

***Effect on Blood Pressure and Heart Rate*:**

Increased blood pressure and decreased heart rate have been observed during treatment with ORKAMBI (see **ADVERSE REACTIONS**, **ACTION AND CLINICAL PHARMACOLOGY**). Blood pressure should be monitored periodically in all patients during treatment. Caution should be observed in patients with pre-existing hypertension, a low heart rate at baseline (<60 beats per minute), or other conditions that might be exacerbated by these haemodynamic effects. Concomitant medications that result in an increase in blood pressure and/or a decrease in heart rate should be avoided to the extent possible during treatment with ORKAMBI.

Hepatic/Biliary/Pancreatic

***Hepatic Impairment*:**

Abnormalities in liver function, including advanced liver disease, can be present in patients with CF. Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported in some patients with CF while receiving ORKAMBI. Liver function decompensation, including liver failure leading to death, has been reported in patients with CF who have pre-existing cirrhosis with portal hypertension receiving ORKAMBI.

Use ORKAMBI with caution, monitoring closely after the initiation of treatment, in patients with advanced liver disease (e.g., cirrhosis and/or portal hypertension) and only if the benefits are expected to outweigh the risks (see **ADVERSE REACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

If ORKAMBI is used in patients with moderate to severe hepatic impairment, they should be closely monitored after the initiation of treatment and the dose should be reduced as recommended (see **DOSAGE AND ADMINISTRATION**).

***Effect on Liver Function Tests*:**

Serious adverse reactions related to elevated transaminases (alanine transaminase [ALT] or aspartate transaminase [AST]) have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Dosing should be interrupted and laboratory tests closely followed 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 and laboratory tests closely followed 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.

***Concomitant Use with CYP3A substrates*:**
Lumacaftor is a strong inducer of CYP3A. Co-administration of ORKAMBI with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.

ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing 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 (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**).

***Concomitant Use with CYP3A Inhibitors or Inducers*:**
Ivacaftor is a substrate of CYP3A. Medicinal products that inhibit or induce CYP3A activity, may impact the pharmacokinetics of ivacaftor.

The dose of ORKAMBI may need to be adjusted when concomitantly used with strong or moderate CYP3A inhibitors (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**).

Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in loss of ORKAMBI efficacy (see **DRUG INTERACTIONS**, **Drug-Drug Interactions**, and **Drug-Herb Interactions**).

Ophthalmologic
***Cataracts*:**
Cases of non-congenital lens opacities without impact on vision have been reported in pediatric patients treated with ORKAMBI and ivacaftor monotherapy. 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 (see **TOXICOLOGY**). Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ORKAMBI treatment.

Peri-Operative Considerations
***Patients after Organ Transplantation*:**
ORKAMBI has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See **DRUG INTERACTIONS** for interactions with cyclosporine or tacrolimus.

Renal
Caution is recommended while using ORKAMBI in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Respiratory
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 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 (see **ADVERSE REACTIONS**).

Special Populations

Pregnant Women:

No adequate and well-controlled studies of ORKAMBI have been conducted in pregnant women. The extent of exposure to ORKAMBI in pregnant women during clinical trials was very limited.

Animal reproduction studies were performed with the individual components of ORKAMBI, lumacaftor and ivacaftor (see **TOXICOLOGY**). Because animal reproduction studies are not always predictive of human response, ORKAMBI should be used during pregnancy only if the expected benefit to the patient clearly outweighs the potential risk to the fetus.

Lumacaftor

Lumacaftor was not teratogenic in rats and rabbits (see **TOXICOLOGY** for details). Placental transfer of lumacaftor was observed in pregnant rats and rabbits.

Ivacaftor

Ivacaftor was not teratogenic in rats and rabbits; placental transfer of ivacaftor was observed in pregnant rats and rabbits (see **TOXICOLOGY** for details).

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 11 and 7 times, respectively, the MRHD of the ivacaftor component of ORKAMBI) when dams were dosed prior to and during early pregnancy. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 8 and 4.5 times the MRHD of the ivacaftor component of ORKAMBI) (see **TOXICOLOGY**).

Nursing Women:

Both lumacaftor and ivacaftor are excreted into the milk of lactating female rats. Excretion of lumacaftor or ivacaftor into human milk is probable. There are no human trials that have investigated the effects of lumacaftor and/or ivacaftor on breastfed infants. ORKAMBI should only be used during breastfeeding if the potential benefit to the patient outweighs the potential risk to the breastfed infant.

Menstrual abnormalities

Women taking ORKAMBI, particularly those on hormonal contraceptives, may have an increased incidence of combined menstrual abnormality events, such as amenorrhea, dysmenorrhea, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhea, and polymenorrhea (see **ADVERSE REACTIONS** and **DRUG INTERACTIONS**).

Pediatrics (<6 years of age):

The efficacy and safety of ORKAMBI in patients younger than 6 years of age have not been established.

Geriatrics (≥65 years of age):
The safety and efficacy of ORKAMBI in patients age 65 years and older have not been evaluated.

Monitoring and Laboratory Tests
Transaminase (ALT or AST) Elevations and Monitoring
Elevated transaminases have been reported in patients with CF receiving ORKAMBI (see **ADVERSE REACTIONS**). Because an association with liver injury cannot be excluded, assessments of liver function tests (ALT, AST, and bilirubin) are recommended before initiating ORKAMBI, every three months during the first year of treatment, and annually thereafter. For patients with a history of transaminase or bilirubin elevations, more frequent monitoring of liver function tests should be considered.

Patients who develop increased transaminase or bilirubin levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 x upper limit of normal (ULN). 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 ORKAMBI dosing.

Patients should be advised to contact their doctor immediately if they develop symptoms suggestive of increased transaminases (e.g., abdominal pain, anorexia, jaundice, dark urine, pale stools, pruritus).

Patients with advanced liver disease should be closely monitored while using ORKAMBI.

Blood Pressure Monitoring
ORKAMBI is associated with increases in blood pressure (see **ADVERSE REACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**, **Cardiac Electrophysiology and Haemodynamics**). Blood pressure should be monitored periodically during treatment.

Respiratory
Clinical experience in patients with ppFEV$_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety profile of ORKAMBI is based on the pooled data from 1108 patients with CF 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who received at least 1 dose of study drug in 2 double-blind, placebo-controlled, Phase 3 clinical studies, each with 24 weeks of treatment (Trials 1 and 2). A total of 738 patients received lumacaftor/ivacaftor [369 patients received ORKAMBI (lumacaftor 400 mg q12h in combination with ivacaftor 250 mg q12h) and 369 patients received lumacaftor 600 mg qd in combination

with ivacaftor 250 mg q12h] and 370 patients received placebo. Of the 1108 patients, 49% were female and 99% were Caucasian.

The proportion of patients who prematurely discontinued study drug due to adverse events was 5% for ORKAMBI-treated patients and 2% for placebo-treated patients.

The most common adverse reactions experienced by patients who received ORKAMBI in the pooled, placebo-controlled, Phase 3 studies were dyspnea (13%), nasopharyngitis (13%), nausea (13%), diarrhea (12%), and upper respiratory tract infection (10%).

Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred 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 safety profile of ORKAMBI from a 24-week, open-label, multicentre Phase 3 study in 58 patients aged 6 through 11 years with CF who are homozygous for the *F508del-CFTR* mutation (Trial 3), was similar to that observed in Trials 1 and 2.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials of a drug cannot be compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Patients with CF Over 12 years of Age Who Are Homozygous for the* F508del *Mutation (Trials 1 and 2)

The incidence of adverse reactions below is based upon the pooled analyses of Trials 1 and 2.

Table 1 shows adverse reactions occurring in ≥5% of ORKAMBI-treated patients and at a frequency higher than placebo.

Table 1: Incidence of Adverse Drug Reactions in ≥5% of ORKAMBI-Treated Patients Who are Homozygous for the *F508del* Mutation in the *CFTR* Gene in 2 Placebo-Controlled Phase 3 Clinical Trials of 24 Weeks Duration

Adverse Reaction (Preferred Term)	ORKAMBI N=369 (%)	Placebo N=370 (%)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	48 (13)	29 (8)
Respiration abnormal	32 (9)	22 (6)
Rhinorrhea	21 (6)	15 (4)
Infections and infestations		
Nasopharyngitis	48 (13)	40 (11)
Upper respiratory tract infection	37 (10)	20 (5)
Influenza	19 (5)	8 (2)
Gastrointestinal disorders		
Nausea	46 (13)	28 (8)
Diarrhea	45 (12)	31 (8)
Flatulence	24 (7)	11 (3)
General disorders and administration site conditions		
Fatigue	34 (9)	29 (8)
Investigations		
Blood creatine phosphokinase increased	27 (7)	20 (5)
Skin and subcutaneous tissue disorders		
Rash	25 (7)	7 (2)

Description of Selected Adverse Reactions

Liver-related Adverse Reactions

In Trials 1 and 2, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN elevations was 0.8%, 1.4%, and 4.3% in patients receiving ORKAMBI, and 0.5%, 1.9%, and 5.1% in placebo-treated patients. Three patients who received ORKAMBI had liver-related serious adverse reactions, including 2 reported as transaminase elevations and 1 as hepatic encephalopathy, compared to none in the placebo group. Of these three, one had elevated transaminases (>3 x ULN) associated with bilirubin elevation >2 x ULN. Following discontinuation or interruption of ORKAMBI, transaminases decreased to <3 x ULN (see **WARNINGS AND PRECAUTIONS**).

Among 6 patients with pre-existing cirrhosis and/or portal hypertension who received ORKAMBI, worsening liver function with increased ALT, AST, bilirubin, and hepatic encephalopathy was observed in one patient. The event occurred within 5 days of the start of

dosing and resolved following discontinuation of ORKAMBI (see **WARNINGS AND PRECAUTIONS**).

In Trial 3, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 5.3%, 8.8%, and 19.3%. No patients had total bilirubin levels >2 x ULN. ORKAMBI dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except 1 patient who discontinued treatment permanently.

Respiratory Adverse Reactions
In Trials 1 and 2, the incidence of respiratory symptom-related adverse reactions (e.g., chest discomfort, dyspnea, and respiration abnormal) was more common in patients treated with ORKAMBI (22%) compared to patients who received placebo (14%). The incidence of these adverse reactions was more common in patients treated with ORKAMBI with lower pre-treatment FEV_1. In patients treated with ORKAMBI, approximately three-quarters of the events began during the first week of treatment (see **WARNINGS AND PRECAUTIONS**).

In Trial 3, in 58 patients aged 6 through 11 years (mean baseline $ppFEV_1$ was 91.4), the incidence of respiratory symptom-related adverse reactions was 3% (2/58).

Menstrual abnormalities
In Trials 1 and 2, the incidence of combined menstrual abnormality events (amenorrhea, dysmenorrhea, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhea, and polymenorrhea) was more common in female patients treated with ORKAMBI (10.4%) compared to placebo (1.7%). These events occurred more frequently in the subset of female patients who were taking hormonal contraceptives (26.8%) compared to patients who were not taking hormonal contraceptives (3.2%) (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Increased Blood Pressure
In Trial 1 and Trial 2, the 24-week, placebo-controlled, Phase 3 studies, adverse reactions related to increased blood pressure (e.g., hypertension, blood pressure increased) were reported in 1.1% (4/369) of patients treated with ORKAMBI and in no patients who received placebo (0/370).

A placebo-adjusted mean increase from baseline in trough systolic blood pressure of 3.1 mmHg was observed at Week 24 in patients receiving ORKAMBI. The proportion of subjects with at least one treatment-emergent systolic blood pressure value >140 mmHg was higher in patients receiving ORKAMBI (10.9%) than in the placebo group (5.4%).

A placebo-adjusted mean increase from baseline in trough diastolic blood pressure of 1.7 mmHg was observed at Week 24 in patients receiving ORKAMBI. The proportion of subjects with at least one treatment-emergent diastolic blood pressure value >90 mmHg was higher in patients receiving ORKAMBI (4.9%) than in the placebo group (1.9%).

Decreased Heart Rate
In Trial 1 and Trial 2, serial ECG recordings were performed on Days 1 and 15. In patients treated with ORKAMBI, maximum placebo-adjusted decrease in mean heart rate of 6 and

5 beats per minute (bpm) from baseline were observed on Day 1 and Day 15, respectively. The percentage of patients with heart rate values <50 bpm on treatment was 10.0% for patients who received ORKAMBI compared to 4.9% for patients who received placebo (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **Monitoring and Laboratory Tests**, **DRUG INTERACTIONS**, **ACTION AND CLINICAL PHARMACOLOGY**, **Cardiac Electrophysiology and Haemodynamics**).

Post-Market Adverse Reactions

The following additional adverse reactions were observed in a placebo-controlled clinical trial in patients aged 6 through 11 years receiving ORKAMBI: pulmonary exacerbation, productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, headache, sputum increased, and rhinitis. A transient post-dose ppFEV$_1$ decline was also observed. Increased incidence of transaminase elevations were also observed compared to previous clinical trials in patients aged 12 years and older.

Post-marketing cases of liver function decompensation including liver failure leading to death have been reported in patients with CF who have pre-existing cirrhosis with portal hypertension who were treated with ORKAMBI (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

Lumacaftor is a strong inducer of CYP3A. Ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. The net effect of lumacaftor/ivacaftor therapy is expected to be strong CYP3A induction. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by approximately 80%.

Lumacaftor is not extensively metabolized in humans with the majority of lumacaftor excreted unchanged in the feces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolized via oxidation and glucuronidation. Ivacaftor is extensively metabolized in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolized by CYP3A.

Drug interaction studies were performed in adults with lumacaftor/ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies.

Drug-Drug Interactions

The drug interaction profile for lumacaftor 200 mg/ivacaftor 250 mg q12h is considered to be the same as that for lumacaftor 400 mg q12h/ivacaftor 250 mg q12h, based on exposure at the indicated dose.

The drugs listed in Table 2 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products			
Concomitant drug class: **Drug name**	**Ref**	**Effect**	**Clinical comment**
Concomitant medicinal products of most clinical relevance			
Anti-allergics: montelukast	T	↓ montelukast Due to the induction of CYP3A/2C8/2C9 by LUM	No dose adjustment for montelukast is recommended. Appropriate clinical monitoring should be employed, as is reasonable, when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of montelukast, which may reduce its efficacy.
Antibiotics: clarithromycin, telithromycin	T	↑ IVA Due to inhibition of CYP3A by clarithromycin, telithromycin ↓ clarithromycin, telithromycin Due to induction of CYP3A by LUM	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin or telithromycin are initiated in patients currently taking lumacaftor/ivacaftor. The dose of lumacaftor/ivacaftor should be reduced to one tablet daily for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking clarithromycin or telithromycin. An alternative to these antibiotics, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposures of clarithromycin and telithromycin, which may reduce their efficacy.
erythromycin	T	↓ erythromycin Due to induction of CYP3A by LUM	An alternative to erythromycin, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposure of erythromycin, which may reduce its efficacy.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	T	↓ carbamazepine, phenobarbital, phenytoin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anticonvulsants is not recommended. The exposures of ivacaftor and the anticonvulsant may be significantly decreased, which may reduce the efficacy of both active substances.

Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole	CT (itraconazole), T	↑ IVA Due to inhibition of CYP3A by these antifungals ↓ itraconazole, ketoconazole, voriconazole Due to induction of CYP3A by LUM ↓ posaconazole Due to induction of UGT by LUM	No dose adjustment of lumacaftor/ivacaftor is recommended when these antifungals are initiated in patients currently taking lumacaftor/ivacaftor. The dose of lumacaftor/ivacaftor should be reduced to one tablet daily for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking these antifungals. Concomitant use of lumacaftor/ivacaftor with these antifungals is not recommended. Patients should be monitored closely for breakthrough fungal infections if such drugs are necessary. Lumacaftor/ivacaftor may decrease the exposures of these antifungals, which may reduce their efficacy.
fluconazole	T	↓ fluconazole Due to induction by LUM	A higher dose of fluconazole may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of fluconazole, which may reduce its efficacy.
Anti-inflammatories: ibuprofen	T	↓ ibuprofen Due to induction of CYP3A/2C8/2C9 by LUM	A higher dose of ibuprofen may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of ibuprofen, which may reduce its efficacy.
Anti-mycobacterials: rifabutin, rifampicin,	CT (rifampicin) T	↓ IVA Due to induction of CYP3A by anti-mycobacterials ↓ rifabutin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anti-mycobacterials is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor. A higher dose of rifabutin may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of rifabutin, which may reduce its efficacy.
Benzodiazepines: midazolam, triazolam	T	↓ midazolam, triazolam Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these benzodiazepines is not recommended. Lumacaftor/ivacaftor will decrease the exposures of midazolam or triazolam, which will reduce their efficacy.

Hormonal contraceptives: ethinylestradiol, norethindrone, and other progestogens	T	↓ ethinyl estradiol, norethindrone, and other progestogens Due to induction of CYP3A/UGT by LUM	Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of hormonal contraceptives, which may reduce their efficacy.
Immunosuppressants: cyclosporine, everolimus, sirolimus, tacrolimus (used after organ transplant)	T	↓ cyclosporine, everolimus, sirolimus, tacrolimus Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these immunosuppressants is not recommended. Lumacaftor/ivacaftor will decrease the exposure of these immunosuppressants, which may reduce the efficacy of these immunosuppressants. The use of lumacaftor/ivacaftor in organ transplant patients has not been studied.
Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole	T	↓ esomeprazole, lansoprazole, omeprazole Due to induction of CYP3A/2C19 by LUM	A higher dose of these proton pump inhibitors may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of these proton pump inhibitors, which may reduce their efficacy.
Other concomitant medicinal products of clinical relevance			
Antiarrhythmics: digoxin	T	↑ or ↓ digoxin Due to potential induction or inhibition of P-gp	The serum concentration of digoxin should be monitored and the dose should be titrated to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of digoxin.
Anticoagulants: warfarin	T	↑ or ↓ warfarin Due to potential induction or inhibition of CYP2C9 by LUM	The international normalized ratio (INR) should be monitored when warfarin co-administration with lumacaftor/ivacaftor is required. Lumacaftor/ivacaftor may alter the exposure of warfarin.
Antidepressants: citalopram, escitalopram, sertraline	T	↓ citalopram, escitalopram, sertraline Due to induction of CYP3A/2C19 by LUM	A higher dose of these antidepressants may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of these antidepressants, which may reduce their efficacy.
Corticosteroids, systemic: methylprednisolone, prednisone	T	↓ methylprednisolone, prednisone Due to induction of CYP3A by LUM	A higher dose of these systemic corticosteroids may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of methylprednisolone and prednisone, which may reduce their efficacy.

H2 blockers:			
ranitidine	T	↑ or ↓ ranitidine Due to potential induction or inhibition of P-gp	Dose adjustment of ranitidine may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of ranitidine.
Note: ↑ = increase, ↓ = decrease, LUM = lumacaftor; IVA = ivacaftor. Legend: CT = Clinical Trial; T = Theoretical			

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.

Drug-Food Interaction
Increased exposure to lumacaftor and ivacaftor was observed following administration with food compared to fasting conditions. ORKAMBI should be taken with fat-containing food (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Drug-Herb Interactions
Co-administration of ORKAMBI with herbal products that strongly induce CYP3A (e.g., St. John's wort) may decrease efficacy and is not recommended.

Drug-Lifestyle Interactions
Effects on Ability to Drive and Use Machines
ORKAMBI is not expected to have an impact on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations
ORKAMBI should only be administered to patients who have a mutation in the *CFTR* gene listed in **INDICATIONS AND CLINICAL USE**. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the *F508del* mutation on both alleles of the *CFTR* gene.

Recommended Dose and Dosage Adjustment
Patients Aged 6 Through 11 Years
The recommended dose is two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 400 mg/ivacaftor 500 mg total daily dose) with fat-containing food.

Patients Aged 12 Years and Older
The recommended dose is two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose) with fat-containing food.

Table 3: Dosage of ORKAMBI in Patients Age 6 Years and Older		
Age	ORKAMBI Dose	Total Daily Dose
6 through 11 years	Two lumacaftor 100 mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food	400 mg lumacaftor + 500 mg ivacaftor
12 years and older	Two lumacaftor 200 mg/ivacaftor 125 mg tablets every 12 hours with fat-containing food	800 mg lumacaftor + 500 mg ivacaftor

Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. Examples of meals that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats.

Dosage Adjustment for Patients with Hepatic Impairment
No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction to 2 tablets in the morning and 1 tablet in the evening is recommended for patients with moderate hepatic impairment (Child-Pugh Class B).Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution after weighing the risks and benefits of treatment and reduce the dose to 1 tablet in the morning and 1 tablet in the evening, or less (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**, **ADVERSE REACTIONS**, and **ACTION AND CLINICAL PHARMACOLOGY**).

Dosage Adjustment for Patients with Hepatic Impairment

Hepatic Insufficiency	**Dose adjustment**	**Total Daily Dose**
Mild hepatic impairment (Child-Pugh Class A)	No dose adjustment 2 tablets in the morning + 2 tablets in the evening (standard dose)	*For patients aged 6 through 11 years* 400 mg lumacaftor + 500 mg ivacaftor *For patients aged 12 years and older* 800 mg lumacaftor + 500 mg ivacaftor
Moderate hepatic impairment (Child-Pugh Class B)	2 tablets in the morning + 1 tablet in the evening	*For patients aged 6 through 11 years* 300 mg lumacaftor + 375 mg ivacaftor *For patients aged 12 years and older* 600 mg lumacaftor + 375 mg ivacaftor
Severe hepatic impairment (Child-Pugh Class C)	1 tablet in the morning + 1 tablet in the evening	*For patients aged 6 through 11 years* 200 mg lumacaftor + 250 mg ivacaftor (or a lower dose) *For patients aged 12 years and older* 400 mg lumacaftor + 250 mg ivacaftor

Patients with Elevated Liver Function Tests
Dosing should be interrupted and laboratory tests closely followed 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 and laboratory tests closely followed in patients with ALT or AST elevations greater than 3 x ULN when associated with bilirubin elevations greater than 2 x ULN.

Dosage Adjustment for Patients with Renal Impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using ORKAMBI in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Dosage Adjustment for Patients Taking CYP3A Inhibitors
No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking ORKAMBI. However, when initiating ORKAMBI in patients currently taking strong CYP3A inhibitors (e.g., itraconazole), reduce ORKAMBI dose to 1 tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose for patients aged 12 years and older; lumacaftor 100 mg/ivacaftor 125 mg total daily dose for patients aged 6 through 11 years) for the first week of treatment. Following this period, continue with the recommended daily dose.

If ORKAMBI is interrupted for more than 1 week and then re-initiated while taking strong CYP3A inhibitors, reduce ORKAMBI dose to 1 tablet daily for the first week of treatment re-initiation (see **DRUG INTERACTIONS**). Following this period, continue with the recommended daily dose.

Missed Dose
If a patient misses a dose and remembers the missed dose within 6 hours, the patient should take the dose as soon as possible with fat-containing food. If more than 6 hours have elapsed since the dose should have been taken, this dose should be skipped and the usual dosing schedule resumed. Patients should not take a double dose to make up for the forgotten dose.

Method of administration
For oral use. Patients should be instructed to swallow the tablets whole (e.g., patients should not chew, break, or dissolve the tablets).

OVERDOSAGE

The highest repeated dose was lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h administered to 49 healthy subjects for 7 days in a trial evaluating the effect of ORKAMBI on electrocardiograms (ECGs). Adverse events reported at an increased incidence of ≥5% compared to the lumacaftor 600 mg/ivacaftor 250 mg dosing period and placebo included: headache (29%), transaminase increased (18%), and generalized rash (10%).

No specific antidote is available for overdose with ORKAMBI. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation results in protein misfolding by causing a defect in cellular processing and trafficking that reduces the quantity of CFTR at the cell surface. The small amount of F508del-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective channel gating) compared to wild-type CFTR protein.

Lumacaftor is a CFTR corrector that is believed to improve the conformational stability of F508del-CFTR protein, resulting in increased processing and trafficking of mature F508del-CFTR protein to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. *In vitro* studies have demonstrated that both lumacaftor and ivacaftor act directly on the CFTR protein in primary human bronchial epithelial cultures and other cell lines harbouring the *F508del-CFTR* mutation to increase the quantity, stability, and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. *In vitro* responses do not necessarily correspond to *in vivo* pharmacodynamic response or clinical benefit.

Pharmacodynamics

Cardiac Electrophysiology and Haemodynamics

The effect of multiple doses of lumacaftor 600 mg once daily/ivacaftor 250 mg q12h for 7 days, followed by lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h for an additional 7 days was evaluated in a randomized, placebo- and active-controlled parallel group, ascending dose thorough ECG study in 168 healthy subjects. No meaningful changes in the QTc interval, the QRS duration, or the PR interval were observed with either lumacaftor 600 mg once daily/ivacaftor 250 mg q12h or lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h.

A decrease in heart rate was observed in subjects who received lumacaftor/ivacaftor. On Day 7, during treatment with lumacaftor 600 mg once daily/ivacaftor 250 mg q12h, statistically significant negative mean differences from placebo were observed at 9 of 10 time points, with a maximum mean difference from placebo of -7.86 bpm (90% CI -10.23, -5.49) at 3 hours post-dosing. On Day 14, during treatment with lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h, statistically significant negative mean differences from placebo were observed at 4 of 10 time points, with a maximum mean difference from placebo of -4.09 bpm (90% CI -6.87, -1.31) at 6 hours.

Blood pressure assessments were performed prior to dosing on every treatment day. Placebo-adjusted mean increases from baseline in trough systolic blood pressure of 2 to 4 mmHg from Day 2 to Day 15 were observed in subjects who received lumacaftor/ivacaftor.

Placebo-adjusted mean increases from baseline in trough diastolic blood pressure of 2 to 6 mmHg from Day 2 to Day 15 were observed in subjects who received lumacaftor/ivacaftor (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **Monitoring and Laboratory Tests**; **ADVERSE REACTIONS**, **Blood Pressure**).

Sweat Chloride Evaluation:
Changes in sweat chloride in response to relevant doses of lumacaftor alone or in combination with ivacaftor were evaluated in a double-blind, placebo-controlled, Phase 2 clinical trial in patients with CF 18 years of age and older either homozygous or heterozygous for the *F508del* mutation. In that trial, 10 patients (homozygous for *F508del*) completed dosing with lumacaftor alone 400 mg q12h for 28 days followed by the addition of ivacaftor 250 mg q12h for an additional 28 days and 25 patients (homozygous or heterozygous for *F508del*) completed dosing with placebo. The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean change in sweat chloride from baseline to Day 28 compared to placebo was -8.2 mmol/L (95% CI -14, -2). The treatment difference between the combination of lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo evaluated as mean change in sweat chloride from baseline to Day 56 compared to placebo was -11 mmol/L (95% CI -18, -4).

Changes in sweat chloride in response to lumacaftor/ivacaftor were also evaluated in a 24-week, open-label Phase 3 clinical trial (Trial 3) in 58 patients with CF, aged 6 through 11 years (homozygous for *F508del*) who received lumacaftor 200 mg/ivacaftor 250 mg q12h for 24 weeks. Patients treated with lumacaftor/ivacaftor had a reduction in sweat chloride at Day 15 that was sustained through Week 24. The within-group LS mean absolute change from baseline in sweat chloride was -20.4 mmol/L at Day 15 and -24.8 mmol/L at Week 24. In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The within-group LS mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 21.3 mmol/L.

There was no direct correlation between decrease in sweat chloride levels and improvement in lung function ($ppFEV_1$).

Pharmacokinetics

Table 4: Mean (SD) Pharmacokinetic Parameters of Lumacaftor and Ivacaftor at Steady State in Subjects with CF

	Drug	C_{max} (mcg/mL)	$t_{½}$* (h)	$AUC_{0\text{-}12h}$ (mcg·h/mL)
Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Lumacaftor	25.0 (7.96)	25.2 (9.94)	198 (64.8)
	Ivacaftor	0.602 (0.304)	9.34 (3.81)	3.66 (2.25)

* Based on lumacaftor 200 mg q12h/ivacaftor 250 mg q12h studied in healthy subjects

The exposure (AUC) of lumacaftor is approximately 2-fold higher in healthy adult volunteers compared to exposure in patients with CF. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF. After twice-daily dosing, steady-state plasma concentrations of lumacaftor and ivacaftor in healthy subjects were generally reached after approximately 7 days of treatment, with an accumulation ratio of approximately 1.9 for lumacaftor. The steady-state exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor. The apparent terminal half-life of lumacaftor is approximately 26 hours. The typical apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/hr (29.4%) for patients with CF. In healthy subjects, the half-life of ivacaftor when given with lumacaftor is approximately 9 hours. The typical CL/F (CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/hr (40.5%) for patients with CF.

Absorption:
Following multiple oral doses of lumacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 50 mg to 1000 mg every 24 hours. Following administration of a single 400 mg/250 mg dose of ORKAMBI with a high-fat, high-calorie meal, the AUC_T and C_{max} of lumacaftor increased by 1.6-fold and 2.2-fold, respectively when compared to administration under fasted conditions. The median (range) t_{max} of lumacaftor is approximately 4.0 hours (2.0; 9.0) in the fed state.

Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with doses of 150 mg every 12 hours to 250 mg every 12 hours. Following administration of a single 400 mg/250 mg dose of ORKAMBI with a high-fat, high-calorie meal, the AUC_T and C_{max} of ivacaftor increased by 2.6-fold and 3.7-fold, respective when compared to administration under fasted conditions. The median (range) t_{max} of ivacaftor is approximately 4.0 hours (2.0; 6.0) in the fed state.

Distribution:
Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin. After oral administration of 400 mg every 12 hours in CF patients in a fed state, the typical apparent volumes of distribution for the central and peripheral compartments (CV) were estimated to be 23.5 L (48.7%) and 33.3 L (30.5%), respectively.

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

After oral administration of ivacaftor 250 mg every 12 hours in combination with lumacaftor, the typical apparent volumes of distribution for the central and peripheral compartments (CV) were estimated to be 95.0 L (53.9%) and 201 L (26.6%), respectively.

Metabolism:
Lumacaftor is not extensively metabolized in humans with the majority of lumacaftor excreted unchanged in the feces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolized via oxidation and glucuronidation.

Ivacaftor is extensively metabolized in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately 1/6th the potency of ivacaftor and is considered pharmacologically active. M6 has less than 1/50th the potency of ivacaftor and is not considered pharmacologically active.

Excretion:
Following oral administration of lumacaftor, the majority of lumacaftor (51%) is excreted unchanged in the feces. In a human pharmacokinetic study with lumacaftor alone, there was minimal elimination of lumacaftor and its metabolites in urine (only 8.6% of total radioactivity was recovered in the urine with 0.18% as unchanged parent).

Following oral administration of ivacaftor alone, the majority of ivacaftor (88%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. In a human pharmacokinetic study with ivacaftor alone, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine). There was negligible urinary excretion of ivacaftor as unchanged parent.

Special Populations and Conditions
Pediatrics:
The following exposures are comparable between adults and the pediatric population based on population pharmacokinetics (PK) analyses as presented in Table 5.

Table 5: Mean (SD) Lumacaftor and Ivacaftor Exposure by Age Group

Age Group	Dose	Mean lumacaftor (SD) AUC_{ss} (mcg/mL*h)	Mean ivacaftor (SD) AUC_{ss} (mcg/mL*h)
Patients aged 6 through 11 years	lumacaftor 200 mg/ivacaftor 250 mg every 12 hours	203 (57.4)	5.26 (3.08)
Patients aged 12 to less than 18 years	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	241 (61.4)	3.90 (1.56)
Patients 18 years of age and older	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	198 (64.8)	3.66 (2.25)

Gender:
The effect of gender was evaluated using a population pharmacokinetics analysis of data from clinical studies of lumacaftor given in combination with ivacaftor. Results indicate no clinically relevant difference in pharmacokinetic parameters for lumacaftor and ivacaftor between males and females. No dose adjustments of ORKAMBI are necessary based on gender.

Hepatic Insufficiency:
The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on pharmacokinetics of lumacaftor given in combination with ivacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Therefore, no dose adjustment is recommended for patients with mild hepatic impairment.

Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired

hepatic function (Child-Pugh Class B, score 7 to 9) had higher exposures ($AUC_{0\text{-}12hr}$ by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. Therefore, a dose reduction is recommended for these patients (see **DOSAGE AND ADMINISTRATION**).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, ORKAMBI should be used with caution in patients with severe hepatic impairment after weighing the risks and benefits of treatment (see **WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS)**. A dose reduction is recommended for these patients (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency:
Pharmacokinetic studies have not been performed with ORKAMBI in patients with renal impairment. However, in human pharmacokinetic studies with lumacaftor or ivacaftor alone, there was negligible urinary excretion of lumacaftor or ivacaftor as unchanged parent (see Excretion). Therefore, no dose adjustments for ORKAMBI are recommended for mild to moderate renal impairment. However, caution is recommended when administering ORKAMBI to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see **WARNINGS AND PRECATIONS**).

STORAGE AND STABILITY

Store below 30°C.

Keep out of the sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

Disposal of unused/expired medicines:

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems" if available.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form:

200 mg/125 mg film-coated tablets
ORKAMBI (lumacaftor/ivacaftor) is supplied as pink, oval-shaped tablets for oral administration, printed with "2V125" in black ink on one side and plain on the other.

100 mg/125 mg film-coated tablets
ORKAMBI (lumacaftor/ivacaftor) is supplied as pink, oval-shaped tablets for oral administration, printed with "1V125" in black ink on one side and plain on the other.

Composition:

200 mg/125 mg tablets and 100 mg/125 mg tablets
Each tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor and the following non-medicinal ingredients: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate. The tablet film coat contains carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

Packaging:

The following pack sizes are available:

200 mg/125 mg tablets
112–count tablet box containing a 4-week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip).

100 mg/125 mg tablets
112–count tablet box containing a 4-week supply (4 weekly cartons of 7 daily blister strips with 4 tablets per strip).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: lumacaftor/ivacaftor (INN)

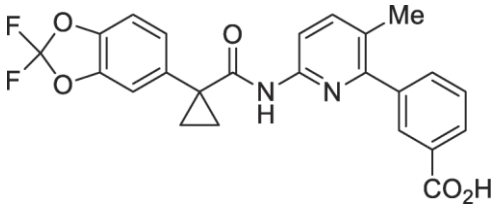
Chemical name:

lumacaftor: 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid
ivacaftor: N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

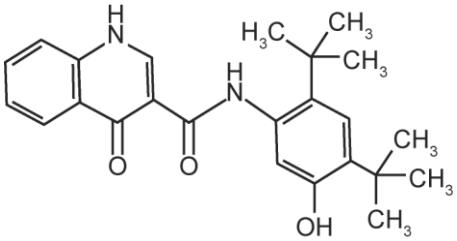
Molecular formula and molecular mass:

lumacaftor: $C_{24}H_{18}F_2N_2O_5$; 452.41
ivacaftor: $C_{24}H_{28}N_2O_3$; 392.49

Structural formula:



lumacaftor



ivacaftor

Physicochemical properties: Lumacaftor is a white to off-white powder that is practically insoluble in water (0.02 mg/mL). Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 microgram/mL).

CLINICAL TRIALS

Study demographics and trial design

The trial design and patient demographics for the ORKAMBI clinical trials are summarized in Table 6 below.

Table 6: Summary of patient demographics for Trials 1, 2, and 3

Study #	Trial design	Dosage; route of administration; and duration	Number of Subjects*	Mean age (Range)	Gender
Trial 1 (subjects homozygous for *F508del* mutation in *CFTR* gene)	Randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, multicentre	lumacaftor 600 mg once daily/ivacaftor 250 mg q12h, lumacaftor 400 mg q12h/ivacaftor 250 mg q12h, or placebo; oral; with food; 24 weeks	549	25.1 years (12 to 64 years)	Male: 53.7% Female: 46.3%
Trial 2 (subjects homozygous for *F508del* mutation in *CFTR* gene)	Randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, multicentre	lumacaftor 600 mg once daily/ivacaftor 250 mg q12h, lumacaftor 400 mg q12h/ivacaftor 250 mg q12h, or placebo; oral; with food; 24 weeks	559	25.0 years (12 to 55 years)	Male: 47.9% Female: 52.1%
Trial 3 (subjects homozygous for *F508del* mutation in *CFTR* gene)	Open-label, multiple-dose, multicentre	lumacaftor 200 mg q12h/ivacaftor 250 mg q12h; oral; with food; 24 weeks	58**	9.1 years (6 through 11 years)	Male: 46.6% Female: 53.4%

* n=Number of patients randomized and dosed
**n=Number of patients dosed

***Trial 1*:**

Trial 1 evaluated 549 patients with CF aged 12 years and older (mean age 25.1 years) with percent predicted FEV_1 ($ppFEV_1$) at screening between 40-90 [mean $ppFEV_1$ 60.7 at baseline (range: 31.1 to 94.0)]. All patients were tested for the CF genotype at screening; eligible patients had the *F508del* mutation on both alleles. Patients with a history of colonization with organisms such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x the ULN or total bilirubin ≥2 x the ULN) were excluded.

***Trial 2*:**

Trial 2 evaluated 559 patients with CF aged 12 years and older (mean age 25.0 years) with $ppFEV_1$ at screening between 40-90 [mean $ppFEV_1$ 60.5 at baseline (range: 31.3 to 99.8)]. All patients were tested for the CF genotype at screening; eligible patients had the *F508del* mutation on both alleles. Patients with a history of colonization with organisms such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x the ULN or total bilirubin ≥2 x the ULN) were excluded.

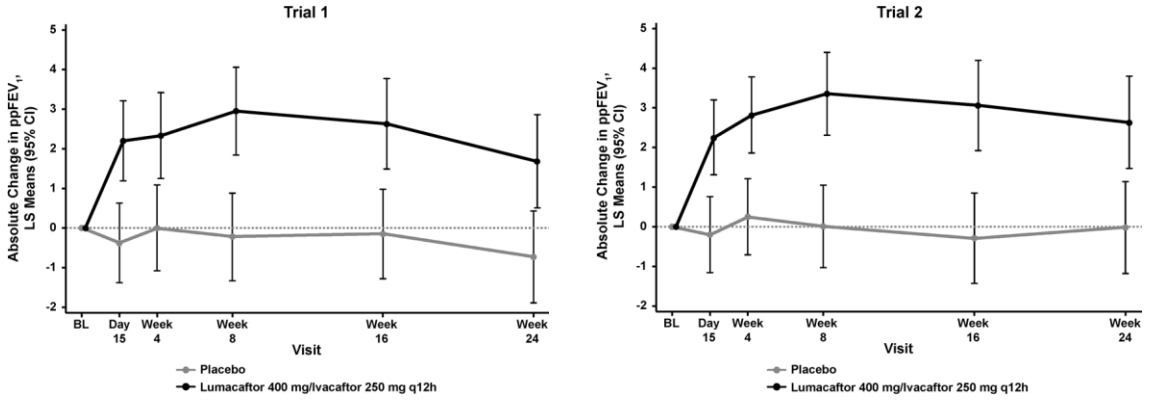
***Trial 3*:**
Trial 3 evaluated 58 patients with CF aged 6 through 11 years with $ppFEV_1$ at screening ≥40 and weight ≥15 kg. Subjects had a mean baseline $ppFEV_1$ of 91.4 (range: 55 to 122.7). All patients were tested for the CF genotype at screening; eligible patients had the *F508del* mutation on both alleles. Patients who had 3 or more abnormal liver function tests (ALT, AST, AP, GGT ≥3 x the ULN), or ALT or AST >5 x ULN, or total bilirubin >2 x the ULN were excluded.

Study results
Efficacy
Trials 1 and 2 in Patients with CF who are Homozygous for the F508del *Mutation in the* CFTR *Gene*
The efficacy of ORKAMBI in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled Phase 3 clinical trials in which 1108 clinically stable patients with CF were randomized and received at least 1 dose of study drug; 369 of these patients were randomized to the ORKAMBI (lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) dose. Patients in both trials were randomized 1:1:1 to receive lumacaftor 600 mg once daily/ivacaftor 250 mg q12h; or ORKAMBI (lumacaftor 400 mg q12h/ivacaftor 250 mg q12h); or placebo. Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline). Patients from these trials were eligible to roll over into an uncontrolled extension study.

The primary efficacy endpoint in both studies was improvement in lung function as determined by the absolute change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24.

In both trials, treatment with ORKAMBI resulted in a statistically significant improvement in $ppFEV_1$. The treatment difference between ORKAMBI and placebo for the mean absolute change in $ppFEV_1$ from baseline at Week 24 (assessed as the average of the treatment effects at Week 16 and at Week 24) was 2.6 percentage points in Trial 1 (P=0.0003) and 3.0 percentage points in Trial 2 (P<0.0001) (Figure 1). These changes persisted throughout the 24-week treatment period (Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex, and geographic region.

Figure 1. Absolute Change From Baseline at Each Visit in Percent Predicted FEV_1 in Trial 1 and Trial 2



LS, least squares; q12h, every 12 hours.

Other Clinical Endpoints

Other efficacy variables included relative change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in CFQ-R Respiratory Domain at Week 24 (the CFQ-R is a disease-specific, patient-reported, health-related quality-of-life measure for cystic fibrosis consisting of generic and CF-specific scales). The respiratory domain of the CFQ-R was used as an assessment tool for clinically relevant respiratory symptoms such as cough, wheeze, congestion, sputum production, and difficulty breathing. The proportion of patients achieving ≥5% relative change from baseline in $ppFEV_1$ using the average of Week 16 and Week 24was also assessed in both trials along with the number of pulmonary exacerbations through Week 24. For the purposes of these trials, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. Patients treated with ORKAMBI demonstrated statistically significant improvements in relative change in $ppFEV_1$ and absolute change in BMI (in Trial 2 only) (Table 7).

Table 7: Summary of Key Secondary Outcomes in Trial 1 and Trial 2*

		Trial 1		Trial 2	
		Placebo (n=184)	**LUM 400 mg/IVA 250 mg q12h (n=182)**	**Placebo (n=187)**	**LUM 400 mg/IVA 250 mg q12h (n=187)**
Relative change in $ppFEV_1$ at Week 24† (%)	Treatment difference[a]	–	4.3 (P=0.0006)‡	–	5.3 (P<0.0001)‡
Absolute change in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI)	–	0.1 (-0.1, 0.3)	–	0.4 (P=0.0001)‡
Absolute change in CFQ-R Respiratory Domain Score at Week 24 (points)	Treatment difference (95% CI)	–	1.5 (-1.7, 4.7)	–	2.9 (-0.3, 6.0)
Proportion of patients with ≥5% relative change in $ppFEV_1$ using the average of Week 16 and Week 24	%	22%	37%	23%	41%
	Odds ratio[b] (95% CI)	–	2.1 (1.3, 3.3)	–	2.4 (1.5, 3.7)
Number of pulmonary exacerbations through Week 24	# of events (rate per 48 wks)	112 (1.1)	73 (0.7)	139 (1.2)	79 (0.7)
	Rate ratio[c] (95% CI)	–	0.7 (0.5, 0.9)	–	0.6 (0.4, 0.8)

* In each study, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.0250$ and all previous tests also meeting this level of significance were required for statistical significance.
† As assessed as the average of the treatment effects at Week 16 and Week 24.
‡ Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures are not considered statistically significant.
CI: confidence interval
[a] Treatment difference = effect of ORKAMBI – effect of placebo
[b] Odds ratio (LUM/IVA vs. placebo): odds of the event of LUM/IVA divided by odds of the event of placebo
[c] Rate ratio (LUM/IVA vs. placebo): event rate of LUM/IVA divided by event rate of placebo

Trial 3

Safety and tolerability study in pediatric patients with CF aged 6 through 11 years homozygous for the F508del *mutation in the* CFTR *gene*

The efficacy of ORKAMBI in children ages 6 through 11 years is extrapolated from efficacy in patients ages 12 years and older homozygous for the *F508del* mutation in the *CFTR* gene with support from population pharmacokinetic analyses showing similar drug exposure levels in patients ages 12 years and older and in children ages 6 through 11 years (see Table 5).

Additional safety data were obtained from a 24-week, open-label, Phase 3 clinical trial in 58 patients aged 6 through 11 years, mean age 9 years (Trial 3).

In Trial 3, spirometry ($ppFEV_1$) was assessed as a planned safety endpoint. The within-group LS mean absolute change from baseline in $ppFEV_1$ at Week 24 was 2.5 percentage points. At the Week 26 safety follow-up visit (following a planned discontinuation) $ppFEV_1$ was also assessed. The within-group LS mean absolute change in $ppFEV_1$ from Week 24 at Week 26 was -3.2 percentage points.

BMI and BMI-for-age z-score were assessed as secondary endpoints. The within-group LS mean absolute change in BMI was 0.64 kg/m^2 at Week 24 and BMI-for-age z-score was 0.15 at Week 24.

DETAILED PHARMACOLOGY

Lumacaftor, a CFTR corrector, improved the cellular processing and trafficking of F508del-CFTR to enhance chloride transport in primary cultures of human bronchial epithelial (HBE) cells derived from people with CF homozygous for *F508del*. Ivacaftor, a CFTR potentiator, potentiated the channel-gating activity (open probability) of the F508del-CFTR channels delivered to the cell surface by lumacaftor to further enhance chloride transport. The magnitude of chloride transport observed with the combination of lumacaftor and ivacaftor treatment was greater than that observed with either agent alone.

Secondary Pharmacodynamics

Lumacaftor

Lumacaftor did not correct the processing or trafficking of 38 other proteins examined, including other misfolded proteins, ABC-transporters, ion channels, kinases, and G-protein coupled receptors at concentrations up to 10 μM, suggesting that lumacaftor is not a general corrector of misfolded or normally folded proteins and therefore has a specific effect on CFTR. Lumacaftor was evaluated *in vitro* for off-target effects on a wide variety of receptors and enzymes in radioligand binding assays, as well as for interactions with a variety of ion channels. Binding activity was limited to the human thromboxane A2 (TXA2) receptor with a K_i=2.97 μM and lumacaftor was subsequently demonstrated to be a functional antagonist of TXA2 activity using rat aortic ring preparations. Overall, these results indicate a low potential for lumacaftor-mediated off-target or secondary pharmacodynamic effects.

Although limited by solubility in the test system, lumacaftor was not considered a potent hERG channel blocker (non-statistically significant 0.2% inhibition at maximum soluble concentration of 4.6 μM). The IC_{50} for the inhibitory effect could not be determined due to lack of significant inhibition at the limit of solubility and these results were corroborated *in vivo* by the lack of any cardiovascular, particularly ECG, findings in telemetered Beagle dogs at single oral doses of 200 mg/kg.

Ivacaftor

Ivacaftor was evaluated *in vitro* for off-target effects on a wide variety of receptors and enzymes in radioligand binding assays, as well as for interactions with a variety of ion channels. Ivacaftor did not potently bind to or alter the function of these targets, indicating a low potential for off-target effects. In electrophysiological studies, ivacaftor inhibited only $Ca_V1.2$ (IC_{50}=1.3 μM) and $K_V1.5$ (IC_{50}=3.4 μM) with moderate potency and had little or no measurable activity (IC_{50}>10 μM) on the other sodium, calcium, and potassium channels tested.

Ivacaftor produced concentration-dependent inhibition of hERG (human ether-à-go-go related gene) tail currents, with an IC_{15} of 5.5 μM, which is higher than the C_{max} (1.5 μM) for ivacaftor

at the therapeutic dose. However, no ivacaftor-related QT prolongation was observed in a dog telemetry study at single doses up to 60 mg/kg, or in ECG measurements from repeat-dose studies in dogs up to 1 year at 60 mg/kg/day. Ivacaftor produced dose-related but transient increase in the blood pressure parameters in dogs at single oral doses up to 60 mg/kg.

Safety Pharmacology

Lumacaftor

Oral administration of lumacaftor did not cause adverse effects on CNS, respiratory systems, or gastrointestinal motility in rats at single oral doses of up to 1000 mg/kg.

Ivacaftor

Oral administration of ivacaftor did not cause adverse effects on CNS, or respiratory systems in rats at single oral doses of up to 1000 mg/kg. Ivacaftor did not cause adverse effects on the cardiovascular system in telemetry studies at single oral doses up to 100 mg/kg in rats and 60 mg/kg in dogs. Ivacaftor produced an inhibition of gastric emptying and gastrointestinal transit in rats at single oral doses of 500 and 1000 mg/kg.

Pharmacokinetics

The findings from the *in vivo* studies demonstrated that the absorption of lumacaftor and ivacaftor in mice, rats, rabbits, and dogs is rapid and bioavailability (%F) ranged from 30% to 100%. When co-administered in combination studies in rats and dogs, systemic exposures to lumacaftor and ivacaftor were similar to exposures achieved when these compounds were administered individually. The apparent permeability of lumacaftor and ivacaftor in Caco-2 cell monolayer was high, which may have contributed to a high oral bioavailability. Neither lumacaftor nor ivacaftor is a substrate for efflux transporter P-gp.

A dose-proportional increase in exposure was observed when lumacaftor and ivacaftor were dosed at lower PK doses; whereas, exposure was generally less than dose proportional at higher doses explored in toxicity studies. No significant sex differences in exposure were observed for either lumacaftor or ivacaftor. Following repeated administration in mice, rats, rabbits, and dogs, there was no evidence of accumulation of lumacaftor; whereas, ivacaftor exposures were higher at steady state compared to single dose exposures and accumulation was evident over time in longer duration repeat-dose toxicity studies. In addition, systemic exposure to ivacaftor's major metabolites (data not shown) was higher for M1 than for M6 for all 3 species measured (mice, rats, and dogs); however, M1 and M6 exposures were less than ivacaftor in these species.

In vitro protein binding of lumacaftor, M28-lumacaftor, ivacaftor, M1-ivacaftor, and M6-ivacaftor, was high (>98%) in mouse, rat, dog, and human plasma. Results from studies with isolated human plasma protein components indicate that these compounds are primarily bound to human serum albumin (HSA). *In vivo*, neither lumacaftor nor ivacaftor bind to melanin-containing tissues (skin and/or eyes). Placental transfer of ^{14}C-labelled lumacaftor and ^{14}C-labelled ivacaftor after a single oral dose to pregnant rats and rabbits occurred, but the exposures to ivacaftor in fetuses were low and variable.

Lumacaftor and ivacaftor are both substrates of CYP3A4; however, sensitivity to CYP3A4 metabolism was much greater for ivacaftor than lumacaftor. Neither lumacaftor nor ivacaftor is a substrate for OATP1B1 or OATP1B3 liver uptake transporters.

Based on studies in cultured human hepatocytes, lumacaftor has the potential to induce CYP3A4, CYP2B6, and the CYP2C family of enzymes; whereas ivacaftor, M1-ivacaftor, and M6-ivacaftor are not inducers of CYPs.

In *in vitro* inhibition studies, lumacaftor was a moderate inhibitor of CYP2C8 and ivacaftor has potential to inhibit CYP2C8 and CYP2C9, suggesting drug-drug interaction potential through inhibition of CYP2C8 and CYP2C9. Based on *in vitro* studies, lumacaftor and ivacaftor have potential to inhibit P-gp, but are not expected to inhibit OATP1B1 or OATP1B3.

Lumacaftor and ivacaftor were excreted predominately in the feces of all species evaluated. Lumacaftor was excreted primarily as the unchanged parent; whereas, ivacaftor was eliminated as polar oxidative metabolites. Lumacaftor and ivacaftor were also excreted in the milk of lactating rats.

TOXICOLOGY

The toxicities of lumacaftor and ivacaftor were evaluated in acute, repeat-dose, genetic, carcinogenicity, developmental and reproductive, local tolerance, and other toxicity studies.

Acute Toxicity

Lumacaftor

Lumacaftor demonstrated a low potential for acute toxicity from high single doses in both rats and mice (maximum tolerated dose [MTD] ≥2000 mg/kg for both species). The established MTDs represent 10- to 20-times the maximum recommended human dose (MRHD) on a mg/kg basis (assuming a 50-kg human).

Ivacaftor

Ivacaftor demonstrated a low potential for acute toxicity from high single doses in both mice, (MTD=2000 mg/kg) and rats (MTD=500 mg/kg). No ivacaftor-related adverse effects were seen at levels that represent 8- to 16-times the MRHD on a mg/kg basis (assuming a 50-kg human).

Repeat-dose Toxicity

Lumacaftor

Repeat-dose toxicity studies in mice up to 3 months, rats up to 6 months, and dogs up to 12 months in duration failed to identify any target organs of lumacaftor-related toxicity at dose levels up to and exceeding the MTDs established in these species in the 3-month studies. Noteworthy findings observed in both rats and dogs following repeated administration were limited to dose-related body weight decrements and dose-related minimal-to-moderate decreases in erythrocytic parameters which were regenerative in rats and non-regenerative in dogs. Noteworthy findings observed only in rats following repeated administration included the regenerative response to decreases in erythrocytic parameters (comprising an increase in circulating reticulocytes and, at high doses, extramedullary hematopoiesis in the spleen); and

microscopic findings of minimal centrilobular hypertrophy in male livers at high doses considered an adaptive or compensatory response to the observed cytochrome P450 (CYP) induction in rats. Noteworthy findings observed only in dogs following repeated administration included mortality (3 animals requiring euthanasia due to deteriorating body condition, severely decreased food consumption, and/or associated clinical signs) occurring at a dose level clearly exceeding the MTD in this species as evidenced by additional clinical signs of toxicity (irregular gait, trembling, jerky movements, and/or muscle rigidity) observed sporadically in individual animals combined with significant body weight decrements (23%) noted in both sexes. With exception of those adverse effects noted at dose levels exceeding the MTD in dogs, these noteworthy findings were considered non-adverse, did not progress in severity over time, and were reversible or partially-reversible following recovery assessments built into the respective study designs.

In the chronic toxicity studies, lumacaftor exposures at the no observed adverse effect level (NOAEL) in rats (1000 mg/kg/day) and dogs (500 mg/kg/day), were at least 1.1- to 8-fold higher than established steady-state $AUC_{0\text{-}24hr}$ (396 mcg·hr/mL) at the recommended human therapeutic dose administered in combination with ivacaftor as ORKAMBI.

Ivacaftor

Ivacaftor was tested in repeat-dose studies of up to 3 months in duration in mice, 6 months in duration in rats, and 12 months in duration in dogs. The only target organ of toxicity identified for ivacaftor was the liver of mice and rats. Clinical chemistry and/or morphological evidence of hepatotoxicity were observed at high dosages in mice (≥600 mg/kg/day in a 3-month study) and rats (≥200 mg/kg/day in the 3-month study and ≥100 mg/kg/day in the 6-month study). In mice, the main clinical pathology changes at the end of 3 months of dosing were elevated alanine aminotransferase (ALT), alkaline phosphatase (ALP), and serum electrolytes relative to the control group, and lower cholesterol and glucose, which was accompanied by minimal foci of hepatocellular necrosis in only a few of the animals. The main ivacaftor-related clinical pathology changes in rats (relative to the control group) included prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT); increases in ALT, gamma-glutamyltransferase (GGT), total protein, and blood urea nitrogen (BUN); serum electrolyte changes; and lower bicarbonate. Dose-related elevations in liver weights were accompanied by histopathological findings of centrilobular hepatocellular necrosis with acute/subacute inflammation in a few rats and mixed inflammatory cells occasionally seen in the liver. The hepatic enzyme elevations were typically less than 3-fold greater than normal.

Occasional instances of atrio-ventricular (AV) block occurred in dogs in repeat-dose studies. AV block is a well-documented background finding in this species. In addition, a slight increase in the incidence of supraventricular premature complex (SVPC) runs was observed in the chronic (12-month) study. The SVPC runs, which occurred in only 3 out of 40 dogs in this study, consisted of multiple events within a single electrocardiogram (ECG) recording at dosages ≥30 mg/kg/day and were reversible following a 28-day recovery period. All other ECG parameters were normal in all groups and the SVPC runs were not accompanied by morphological changes in the heart or changes in health status of these dogs.

In the chronic toxicity studies, summed exposures to ivacaftor and its metabolites at the NOAEL in rats (50 mg/kg/day) and dogs (60 mg/kg/day), were at least 3.6- to 6.4-fold higher than the established steady-state summed $AUC_{0\text{-}24hr}$ (81.12 mcg·hr/mL) at the recommended human therapeutic dosage administered in combination with lumacaftor as ORKAMBI.

Lumacaftor and Ivacaftor Combination
A combination repeat-dose toxicity study involving the co-administration of lumacaftor and ivacaftor up to 3 months in duration in rats and 28 days in duration in dogs failed to produce any unexpected toxicities or interactions. Noteworthy findings in dogs were limited to a higher incidence of non-adverse cardiovascular findings (PR prolongation and AV block at doses ≥600/15 mg/kg/day lumacaftor/ivacaftor, and SVPC runs at doses of 600/60 mg/kg/day lumacaftor/ivacaftor) than previously noted in studies conducted with ivacaftor alone. Noteworthy findings in rats were limited to non-adverse microscopic findings of occasional small foci of erosion and necrosis in the glandular mucosa of the stomach, indicating that the combination was irritating to the gastrointestinal tract of rats (observed at doses ≥500/10 mg/kg/day lumacaftor/ivacaftor). These findings were not observed in dogs and were attributed to a local irritant effect of lumacaftor and ivacaftor at high concentrations that are likely not relevant to humans administered lumacaftor in combination with ivacaftor.

Genotoxicity
Lumacaftor
Lumacaftor was shown to be non-mutagenic and non-clastogenic in the following standard *in vitro* and *in vivo* genotoxicity tests: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Ivacaftor
Ivacaftor was shown to be non-mutagenic and non-clastogenic in the following standard *in vitro* and *in vivo* genotoxicity tests: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Carcinogenicity
Lumacaftor
A two-year study conducted in rats and a 26-week study conducted in transgenic Tg.rasH2 mice to assess carcinogenic potential of lumacaftor demonstrated that lumacaftor was not carcinogenic. Plasma exposures in male and female rats at the non-carcinogenic dosage (1000 mg/kg/day, the highest dosage tested) were 5.4- to 12.7-fold higher than the plasma levels for the lumacaftor component of ORKAMBI measured in humans following combination therapy. Plasma exposures to lumacaftor in mice at the non-carcinogenic dosage (2000 and 1500 mg/kg/day, the highest dose tested for each sex) were approximately 3.5- to 5.3-fold higher than the plasma levels for the lumacaftor component of ORKAMBI measured in humans following combination therapy.

Ivacaftor
Two-year studies in mice and rats to assess carcinogenic potential of ivacaftor demonstrated that ivacaftor was not carcinogenic in either species. Summed plasma exposures to ivacaftor and

metabolites in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 1.7- to 3.4-fold higher than the summed plasma levels for the ivacaftor and metabolites components of ORKAMBI measured in humans following combination therapy. Summed plasma exposures to ivacaftor and its metabolites in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 8.9- to 13-fold higher than the summed plasma levels for the ivacaftor and its metabolites components of ORKAMBI measured in humans following combination therapy.

Developmental and Reproductive Toxicity

Lumacaftor

Lumacaftor had no effects on fertility and reproductive performance indices in male and female rats at 1000 mg/kg/day (approximately 3 and 8 times, respectively, the MRHD for the lumacaftor component of ORKAMBI on a lumacaftor AUC basis extrapolated from lumacaftor exposures in the 6-month repeat-dose toxicity study in this species). Lumacaftor was not teratogenic in rats at approximately 8 times the MRHD of the lumacaftor component of ORKAMBI (on a lumacaftor AUC basis at a maternal dose of 2000 mg/kg/day). Lumacaftor was not teratogenic in rabbits at approximately 5 times the MRHD of the lumacaftor component of ORKAMBI (on a lumacaftor AUC basis at a maternal dose of 200 mg/kg/day). Placental transfer of lumacaftor was observed in pregnant rats and rabbits. Lumacaftor did not cause developmental defects (learning and memory, reproductive capacity) in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning.

Ivacaftor

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 11 and 7 times, respectively, the MRHD of the ivacaftor component of ORKAMBI based on summed AUCs of ivacaftor and its metabolites extrapolated from Day 90 exposures at 150 mg/kg/day in the 6-month repeat-dose toxicity study in males and Day 17 of the pilot embryofetal developmental study in this species). Decreased weight of seminal vesicles in males and increases in prolonged diestrus in females were observed at 200 mg/kg/day. Ivacaftor decreased the fertility index in female rats and the number of corpora lutea, implantations, and viable embryos at 200 mg/kg/day when dams were dosed prior to and during early pregnancy. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 8 and 4.5 times the MRHD based on summed AUCs of the ivacaftor component of ORKAMBI based on summed AUCs of ivacaftor and its metabolites extrapolated from Day 90 exposures at 100 mg/kg/day in the 6-month repeat-dose toxicity study in this species). Ivacaftor was not teratogenic in rats at approximately 7 times the MRHD of the ivacaftor component of ORKAMBI (based on summed AUCs for ivacaftor and its metabolites at a maternal dose of 200 mg/kg/day extrapolated from ivacaftor female exposures in the pilot embryofetal development study and female metabolite-to-parent ratios in the 6-month toxicity study in this species). Ivacaftor was not teratogenic in rabbits at approximately 46 times the MRHD of the ivacaftor component of ORKAMBI (on an ivacaftor AUC basis at a maternal dose of 100 mg/kg/day). Placental transfer of ivacaftor was observed in pregnant rats and rabbits. Ivacaftor did not cause developmental defects (learning and memory, reproductive capacity) in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning. M1 and M6 were not directly quantitated in the developmental and reproductive toxicity studies.

Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal day 7 to 35 at dose levels of 10 mg/kg/day and higher (approximately 0.32 times the MRHD for the ivacaftor component of ORKAMBI based on summed AUCs of ivacaftor and metabolites). This finding was not observed in older animals.

Other Toxicity

Lumacaftor

Lumacaftor was determined to be non-irritating to skin based on results in the *in vitro* EPISKIN™ skin irritation test. Lumacaftor was classified as a non-irritant to eyes when tested *in vitro* on isolated bovine corneas (bovine corneal opacity and permeability assay). In a murine local lymph node assay, lumacaftor had no effects on the proliferative response of lymph node cells from the draining auricular lymph nodes, demonstrating that lumacaftor does not show the potential to induce skin sensitization.

Ivacaftor

Ivacaftor was not irritating to skin after topical administration to rabbits. Ivacaftor was classified as a non-irritant to eyes when tested *in vitro* on isolated bovine corneas (bovine corneal opacity and permeability assay). In a murine local lymph node assay, ivacaftor had no effects on the proliferative response of lymph node cells from the draining auricular lymph nodes, demonstrating that ivacaftor does not show the potential to induce skin sensitization.

REFERENCES

None.

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

[Pr]ORKAMBI®
Lumacaftor/Ivacaftor tablets

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 6 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 6 years of age.

How does ORKAMBI work?

- The CFTR protein helps bring chloride ions out of the cells in many organs.
- People who have two copies of the *F508del* mutation in the *CFTR* gene have a lower amount of working CFTR protein at the surface of their cells.
- ORKAMBI is a type of medicine called a "*cystic fibrosis transmembrane conductance regulator corrector and potentiator*."
- The two ingredients in ORKAMBI help bring more chloride ions out of the cells in many organs:
    - 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: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; magnesium stearate; povidone; and sodium lauryl sulfate. The tablet film coat contains carmine, FD&C Blue #1, FD&C Blue #2, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

ORKAMBI comes in the following dosage forms:
Tablet: 100 mg lumacaftor /125 mg ivacaftor
Tablet: 200 mg lumacaftor/125 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
A problem with the lens of the eye (cataract) has been seen in some children and adolescents while taking ORKAMBI. If you are a child or adolescent, your doctor may perform eye examinations 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 6 years. It is not known if ORKAMBI is safe and effective in children under 6 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 telithromycin, 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:

- **Do not** break, crush, or chew the tablet. Swallow the tablet **whole**.
- Take it 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 should always be taken with a fat-containing food:

- Taking ORKAMBI with fat-containing food is important to get the right amount of medicine in your body.
- Each dose should be taken just before or just after eating fat-containing food.
- Meals and snacks recommended in CF guidelines contain acceptable amounts of fat.
- Examples of meals that contain fat are:
  - 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.
- Each box contains a 4-week supply of ORKAMBI.
- Each carton contains 7 daily blister strips (1 strip per day).
- Each blister strip contains 4 tablets: 2 for the morning dose and 2 for the evening dose.
- You may cut along the dotted line to separate your doses from the blister strip.
- Peel back the paper backing from a blister strip to remove the tablets. **Do not** push tablet through paper backing.

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

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

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 with fat-containing food as soon as possible.
- If you miss a dose of ORKAMBI and it is **more than 6 hours** after the time you usually take it, **skip** that dose only and take the next dose when you usually take it.
- Do **not** take 2 doses at the same time to make up for your missed dose.

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

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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:
Store 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; the manufacturer's website http://www.vrtx.ca, or by calling 1-877-634-VRTX (8789).

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