PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ORKAMBI®**

Lumacaftor / Ivacaftor Tablets 100 mg / 125 mg, Oral

Lumacaftor / Ivacaftor Tablets 200 mg / 125 mg, Oral

Lumacaftor / Ivacaftor Granules 75 mg / 94 mg, Oral

Lumacaftor / Ivacaftor Granules 100 mg / 125 mg, Oral

Lumacaftor / Ivacaftor Granules 150 mg / 188 mg, Oral

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Corrector and Potentiator

ATC R07AX30

Vertex Pharmaceuticals (Canada) Incorporated
20 Bay Street, Suite 1520
Toronto, Ontario
M5J 2N8

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ORKAMBI (lumacaftor/ivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients 1 year 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.

1.1 Pediatrics

Pediatrics (<1 year of age): No data in patients younger than 1 year of age are available to Health Canada; therefore, Health Canada has not authorized the use of ORKAMBI in this age group.

1.2 Geriatrics

Geriatrics (≥65 years of age): No data in patients aged 65 years and older are available to Health Canada; therefore, Health Canada has not authorized the use of ORKAMBI in this age group.

2 CONTRAINDICATIONS

ORKAMBI is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

ORKAMBI should only be administered to patients who have a mutation in the *CFTR* gene listed in 1 INDICATIONS.

ORKAMBI should only be prescribed by healthcare professional with experience in the treatment of cystic fibrosis. 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.

ORKAMBI dosing may be impacted in the following patient groups:

- Hepatic Impairment: Moderate or severe hepatic impairment
- Renal Impairment: Severe renal impairment or end-stage renal disease
- Interactions with Medicinal Products: Concomitant use of strong CYP3A inhibitors
- Elevated Liver function test (ALT, AST, and bilirubin)

4.2 Recommended Dose and Dosage Adjustment

Adults, Adolescents, and children aged 1 year and older

The recommended daily dose of ORKAMBI in adult and pediatric patients aged 1 year and

older is based on patient's age and weight as detailed in Table 1.

Table 1: Dosage of ORKAMBI by Age and Body Weight in Patients Aged 1 Year and Older				
Age	**Body Weight (kg)**	**Dose per unit (packet/tablet) every 12 hours**	**ORKAMBI Dose**	
			Morning	**Evening**
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg granules	1 packet	1 packet
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg granules		
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg granules		
2 to 5 years	< 14 kg	lumacaftor 100 mg/ivacaftor 125 mg granules	1 packet	1 packet
2 to 5 years	≥ 14 kg	lumacaftor 150 mg/ivacaftor 188 mg granules	1 packet	1 packet
6 to 11 years	-	lumacaftor 100 mg/ivacaftor 125 mg tablets	2 tablets	2 tablets
12 years and older	-	lumacaftor 200 mg/ivacaftor 125 mg tablets	2 tablets	2 tablets

Health Canada has not authorized an indication for use in pediatric patients less than 1 year of age (see 7.1 Special Populations and 10.3 Pharmacokinetics).

ORKAMBI granules and tablets should be taken with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing (see 4.4 Administration).

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction 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, after weighing the risks and benefits of treatment, Orkambi should be used with caution, at a reduced dose, in patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 8 ADVERSE REACTIONS, and 10 CLINICAL PHARMACOLOGY).

For dose adjustments for patients with hepatic impairment refer to Table 2.

Table 2: Dosage Adjustment Recommendations for Patients with Hepatic Impairment			
Hepatic Insufficiency	**Age**	**Dose Adjustment***	
		Morning Dose	**Evening Dose**
Mild hepatic impairment (Child-Pugh Class A)	1 to 5 years	No dose adjustment 1 packet	No dose adjustment 1 packet
	6 years and older	No dose adjustment 2 tablets	No dose adjustment 2 tablets
Moderate hepatic impairment (Child-Pugh	1 to 5 years	**Day 1**: 1 packet **Day 2**: 1 packet	**Day 1:** 1 packet **Day 2**: Skip evening dose

Table 2: Dosage Adjustment Recommendations for Patients with Hepatic Impairment			
Hepatic Insufficiency	**Age**	**Dose Adjustment***	
		Morning Dose	**Evening Dose**
Class B)	6 years and older	2 tablets	1 tablet
Severe hepatic impairment (Child-Pugh Class C)	1 to 5 years	1 packet of granules per day**	
	6 years and older	1 tablet	1 tablet

*See Table 1 for the appropriate dose per unit based on age and weight.
** or less frequently

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.

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 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Concomitant 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 or 1 packet of granules every other day as appropriate 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 or 1 packet of granules every other day for the first week of treatment re-initiation (see 9 DRUG INTERACTIONS). Following this period, continue with the recommended daily dose.

4.4 Administration

ORKAMBI granules and tablets should be taken with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing.

Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a typical CF diet should be given. Examples of fat-containing food: meals that contain fat that have been prepared with butter or oils, meals that have eggs, nuts, whole-dairy products (such as whole-milk, breast milk, infant formula cheese, and yogurt), or meats.

Film-coated tablets

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

Granules

For oral use. The entire content of each packet of granules should be mixed with 5 mL (one teaspoon) of age-appropriate soft food or liquid and the mixture completely consumed. Some examples of soft foods or liquids include puréed fruits or vegetables, flavored yogurt or pudding, applesauce, water, milk, breast milk, infant formula or juice (except grapefruit). Food should be at 5 to 25ºC. Each packet is for single use only. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period and not stored for future use.

4.5 Missed Dose

If less than 6 hours have passed since the missed dose, the scheduled dose of ORKAMBI should be taken with fat containing food. If more than 6 hours have passed, the patient should be instructed to wait until the next scheduled dose. Patients should be instructed not to take a double dose to make up for the forgotten dose.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging		
Route of Administration	Dosage Form / Strength/Composition	Non-medicinal 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
Oral	Granules 75 mg lumacaftor/ 94 mg ivacaftor 100 mg lumacaftor/125 mg ivacaftor and 150 mg lumacaftor/188 mg ivacaftor	croscarmellose sodium; hypromellose acetate succinate, microcrystalline cellulose, povidone, sodium lauryl sulfate

ORKAMBI 75 mg / 94 mg, 100 mg / 125 mg and 150 mg / 188 mg granules
White to off-white granules for oral administration and enclosed in unit dose packets.

ORKAMBI 100 mg / 125 mg tablets
Pink, oval-shaped film-coated tablets for oral administration, printed with “1V125” in black ink on one side and plain on the other.

ORKAMBI 200 mg/125 mg tablets
Pink, oval-shaped film-coated tablets for oral administration, printed with “2V125” in black ink on one side and plain on the other.

Nature and contents of container

ORKAMBI tablets are packaged in a thermoform blister consisting of clear Aclar (PCTFE – polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a paper-backed aluminum foil lidding.

ORKAMBI granules are packaged in a printed, foil laminate packet. Material of construction is biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/ PE/Foil/PE). Polyethylene is the product contact layer for the packet.

Pack Sizes

Orkambi Tablets (100 mg / 125 mg):	112 tablets (supplied in a box containing 4 cartons, with each carton containing 7 blister strips with 4 tablets per strip).
Orkambi Tablets (200 mg / 125 mg):	112 tablets (supplied in a box containing 4 cartons, with each carton containing 7 blister strips, with 4 tablets per strip).
Orkambi Granules (75 mg / 94 mg)	56 packets (supplied in a box containing 4 wallets, with each wallet containing 14 packets of 75 mg/ 94 mg granules per printed foil laminate packet).

Orkambi Granules (100 mg / 125 mg):	56 packets (supplied in a box containing 4 wallets, with each wallet containing 14 packets of 100 mg / 125 mg granules per printed foil laminate packet).
Orkambi Granules (150 mg / 188 mg):	56 packets (supplied in a box containing 4 wallets, with each wallet containing 14 packets of 150 mg / 188 mg granules per printed foil laminate packet).

7 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 8 ADVERSE REACTIONS and 10 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, or other conditions that might be exacerbated by these hemodynamic 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.

Driving and Operating Machinery

Dizziness has been reported with ivacaftor, one of the active ingredients of Orkambi, which could influence the ability to drive or operate machines. It is not known if ORKAMBI can cause dizziness.

Drug Interactions

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 9 DRUG INTERACTIONS and 4 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 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION).

Exposure to ivacaftor may be reduced by the concomitant use of CYP3A inducers, potentially resulting in loss of ORKAMBI efficacy (see 9.2 Drug Interactions Overview, 9.4 Drug-Drug Interactions, and 9.6 Drug-Herb Interactions).

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 8 ADVERSE REACTIONS and 10 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 4 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 7 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.

Monitoring and Laboratory Tests

Transaminase (ALT or AST) Elevations and Monitoring

Elevated transaminases have been reported in patients with CF receiving ORKAMBI (see 8 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, and 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 8 ADVERSE REACTIONS and 10 CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics). 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 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

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 16 NON-CLINICAL 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 9 DRUG INTERACTIONS for interactions with immunosuppressants such as 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 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

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 8 ADVERSE REACTIONS and 9 DRUG INTERACTIONS).

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 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL 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 16 NON-CLINICAL 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 16 NON-CLINICAL 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 maximum recommended human dose (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 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (<1 year of age): No data in patients younger than 1 year of age, are available to Health Canada; therefore, Health Canada has not authorized the use of ORKAMBI in this age group.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): No data in patients aged 65 years and older, are available to Health Canada; therefore, Health Canada has not authorized the use of ORKAMBI in this age group.

8 ADVERSE REACTIONS

8.1 Adverse 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, transaminase elevations, cholestatic hepatitis, and hepatic encephalopathy. These occurred in 1% or less of patients.

The safety profile of ORKAMBI from a 24-week, open-label, multicentre Phase 3 trial (Trial 3) in 58 patients aged 6 through 11 years with CF who are homozygous for the *F508del-CFTR* mutation, was similar to that observed in Trials 1 and 2.

The safety profile of ORKAMBI from a 24-week, open-label, multicentre Phase 3 trial (Trial 4) in 60 patients aged 2 through 5 years with CF who were homozygous for the *F508del-CFTR* mutation was generally consistent to that observed in studies in patients aged 6 years and older.

The safety profile of ORKAMBI from a 24-week, open-label, multicenter Phase 3 trial (Trial 5 Part B) in 46 patients aged 1 to less than 2 years with CF who are homozygous for the *F508del-CFTR* mutation was generally consistent with the established safety profile of lumacaftor/ivacaftor observed in patients 2 years and older.

8.2 Clinical Trial Adverse 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 12 Years of Age and Older 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 **4** shows Adverse Reactions occurring in ≥5% of ORKAMBI-treated patients and at a frequency higher than placebo.

Table 4: Incidence of Adverse Drug Reactions in ≥5% of ORKAMBI-Treated Patients who are Homozygous for the *F508del* Mutation in the *CFTR* Gene in -Two Placebo-Controlled Phase 3 Clinical Trials of 24 Weeks Duration in Patients 12 Years and Older		
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)

Respiratory Adverse Reactions

During 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 7 WARNINGS AND PRECAUTIONS).

During 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).

During Trial 4, in 60 patients aged 2 through 5 years, the incidence of respiratory symptom-related adverse reactions was 5% (3/60 patients).

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 7 WARNINGS AND PRECAUTIONS and 9 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 patients 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 patients 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Monitoring and Laboratory Tests, 9 DRUG INTERACTIONS, and 10.2 Pharmacodynamics, Cardiac Electrophysiology and Hemodynamics).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety profile is generally consistent among pediatric and adult patients. Pediatric patients younger than 1 year of age have not been studied.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Transaminase Elevations

The incidence of maximum transaminase (ALT or AST) in patients 12 years and older (Trials 1 and 2) are presented in Table 5. 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 7 WARNINGS AND PRECAUTIONS).

Among six 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 7 WARNINGS AND PRECAUTIONS).

Table 5: Threshold Analysis of Transaminase Elevations in Patients 12 Years and Older Treated with ORKAMBI (Trials 1 and 2)		
Threshold Analysis Criteria ALT or AST	**ORKAMBI N = 369**	**Placebo N = 370**
>3 × ULN	4.3%	5.1%
>5 × ULN	1.4%	1.9%
>8 × ULN	0.8%	0.5%
ALT: alanine aminotransferase; AST: aspartate aminotransferase		

The incidence of maximum transaminase (ALT or AST) in patients 1 year and older (Trial 3, 4 and 5 respectively) are presented in Table 6. In Trial 3, ORKAMBI dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except one patient who discontinued treatment. In Trial 4, three patients discontinued lumacaftor/ivacaftor treatment permanently due to transaminase elevations. In Trial 5, one patient discontinued lumacaftor/ivacaftor treatment due to transaminase elevations. No patients in either trial had total bilirubin levels >2 x ULN.

Table 6: Threshold Analysis of Transaminase Elevations in Patients 1 to Less than 12 Years of Age Treated with ORKAMBI (Trials 3, 4 and 5)			
Threshold Analysis Criteria ALT or AST	**Trial 3 6 to 11 years N=58**	**Trial 4 2 to 5 years N=60**	**Trial 5 1 to <2 years N=46**
>3 × ULN	19.3%	15.0%	10.9%
>5 × ULN	8.8%	11.7%	4.3%
>8 × ULN	5.3%	8.3%	2.2%
ALT: alanine aminotransferase; AST: aspartate aminotransferase			

8.5 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 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 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.

9.4 Drug-Drug Interactions

Based on exposure and indicated doses, the drug interaction profile is considered to be the same for all dosage strengths and forms.

The drugs listed in Table 7 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 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products

Concomitant drug class: Drug name	Source of Evidence	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	T	↑ IVA Due to inhibition of CYP3A by clarithromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin is initiated in patients currently taking lumacaftor/ivacaftor.
		↓ clarithromycin Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily or one packet of granules every other day for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking clarithromycin. An alternative to clarithromycin, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposures of clarithromycin, which may reduce it's efficacy.

Table 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products			
Concomitant drug class: Drug name	**Source of Evidence**	**Effect**	**Clinical comment**
erythromycin	T	↑ IVA Due to inhibition of CYP3A by erythromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when co-administered with erythromycin.
		↓ 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	↓ IVA Due to induction of CYP3A by these anticonvulsants	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.
		↓ carbamazepine, phenobarbital, phenytoin Due to induction of CYP3A by LUM	

Table 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products

Concomitant drug class: Drug name	Source of Evidence	Effect	Clinical comment
Antifungals : itraconazole, ketoconazole, posaconazole, voriconazole	CT (itraconazole),	↑ IVA Due to inhibition of CYP3A by these antifungals	No dose adjustment of lumacaftor/ivacaftor is recommended when these antifungals are initiated in patients currently taking lumacaftor/ivacaftor.
	T	↓ itraconazole, ketoconazole, voriconazole Due to induction of CYP3A by LUM ↓ posaconazole Due to induction of UGT by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily or one packet of granules every other day 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	↑ IVA Due to inhibition of CYP3A by fluconazole	No dose adjustment of lumacaftor/ivacaftor is recommended when co-administered with fluconazole
		↓ 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.

Table 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products			
Concomitant drug class: Drug name	**Source of Evidence**	**Effect**	**Clinical comment**
Anti-mycobacterials:			
rifabutin, rifampicin,	CT (rifampicin)	↓ IVA Due to induction of CYP3A by anti-mycobacterials	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.
	T	↓ rifabutin Due to induction of CYP3A by LUM	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 and 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.

Table 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products			
Concomitant drug class: Drug name	**Source of Evidence**	**Effect**	**Clinical comment**
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 co-administration of warfarin 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.

Table 7: Established and Other Potentially Significant Drug Interactions - Dose Recommendations for Use of Lumacaftor/Ivacaftor with Other Medicinal Products			
Concomitant drug class: Drug name	**Source of Evidence**	**Effect**	**Clinical comment**
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.

9.5 Drug-Food Interactions

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 10 CLINICAL PHARMACOLOGY, and 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

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 *F508delCFTR* 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.

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.

Cardiac Electrophysiology and Hemodynamics

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 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS, Increased 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 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.

Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24 week, open-label Phase 3 clinical trial (Trial 4) in 60 patients with CF, aged 2 through 5 years (homozygous for *F508del*) who received either lumacaftor 100 mg/ivacaftor 125 mg every 12 hours (patients <14 kg in weight) or lumacaftor 150 mg/ivacaftor 188 mg every 12 hours (patients ≥14 kg in weight) for 24 weeks. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 through Week 24. The mean absolute change from baseline in sweat chloride was –31.7 mmol/L (95% CI: –35.7, -27.6) at Week 24. In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off drug response. The mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was an increase of 33.0 mmol/L (95% CI: 28.9, 37.1). This change represents a return to baseline after treatment washout.

Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open-label Phase 3 clinical trial (Trial 5 Part B) in 46 patients with CF, aged 1 to less than 2 years (homozygous for *F508del*) who received lumacaftor 75 mg/ivacaftor 94 mg (1 patient weighing 7 kg to <9 kg at screening), lumacaftor 100 mg/ivacaftor 125 mg (44 patients weighing 9 kg to <14 kg at screening), lumacaftor 150 mg/ivacaftor 188 mg (1 patient weighing ≥14 kg at screening), every 12 hours for 24 weeks. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 which was sustained through Week 24. The mean (SD) absolute change from baseline in sweat chloride at Week 24 was -29.1(13.5) mmol/L (95% CI: -34.8, -23.4). In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean (SD) absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 27.3 (11.1) mmol/L (95% CI:22.3, 32.3). This change represents a return towards baseline after treatment washout.

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

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.

10.3 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.

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. Key pharmacokinetic parameters for lumacaftor / ivacaftor at steady state are shown in Table 8.

Table 8: Summary of Lumacaftor and Ivacaftor Pharmacokinetic Parameters† at Steady State in Patients with CF 18 Years of Age and Older							
	Drug	**C_{max} (mcg/mL)**	**T_{max} (h)**	**$t_{½}$ (h) ‡**	**AUC_{0-12h} (mcg*h/mL)**	**Typical Apparent Clearance CL/F (L/h)**	**Apparent Volume of Distribution Vz/F (L) ‡**
Lumacaftor 400 mg q12h/ Ivacaftor 250 mg q12h	Lumacaftor	25.0 (7.96)	2.15 (0.00, 12.00)	25.2 (9.94)	198 (64.8)	2.38 (29.4%)	50.1 (17.4)
	Ivacaftor	0.602 (0.304)	2.10 (0.00, 11.10)	9.34 (3.81)	3.66 (2.25)	25.1 (40.5%)	1000 (550)
† Based on tablet formulation ‡ Based on lumacaftor 200 mg q12h/ivacaftor 250 mg q12h studied in healthy subjects T_{max} is the median (minimum, maximum); C_{max}, $t_{1/2}$, AUC_{0-12h} = mean (SD); CL/F and Vz/F = mean (CV)							

Absorption: *Tablet Formulation:* 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 $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ and C_{max} of ivacaftor increased by 2.5-fold and 3.7-fold, respectively 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.

Granule Formulation: Following administration of a single 100 mg/125 mg dose of ORKAMBI with a high-fat, high-calorie meal to healthy adult volunteers, the $AUC_{0-\infty}$ and C_{max} of lumacaftor increased by 1.2-fold and 1.5-fold, respectively when compared to administration under fasted conditions. The median (range) T_{max} of lumacaftor is approximately 6.0 hours (2.0; 12.0) in the fed state.

Following administration of a single 100 mg/125 mg dose of ORKAMBI with a high-fat, high-calorie meal to healthy adult volunteers, the $AUC_{0-\infty}$ and C_{max} of ivacaftor increased by 1.8-fold and 1.9-fold, respectively when compared to administration under fasted conditions. The median (range) t_{max} of ivacaftor is approximately 6.0 hours (3.0; 12.0) 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.

Elimination: 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 9.

Table 9: Mean (SD) Lumacaftor and Ivacaftor Exposure by Age Group

Age Group	Weight	Dose	Mean lumacaftor (SD) AUC_{ss} (mcg*h/mL)	Mean ivacaftor (SD) AUC_{ss} (mcg*h/mL)
Patients 1 to <2 years	7 kg to <9 kg	lumacaftor75 mg/ivacaftor 94 mg packet every 12 hours	234[a]	7.98[a]
	9 kg to < 14kg	lumacaftor100 mg/ivacaftor 125 mg packet every 12 hours	191 (40.6)	5.35 (1.61)
	≥14 kg	lumacaftor150 mg/ivacaftor 188 mg packet every 12 hours	116[a]	5.82[a]
Patients 2 to 5 years	<14 kg	lumacaftor 100 mg/ivacaftor 125 mg packet every 12 hours	180 (45.5)	5.92 (4.61)
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg packet every 12 hours	217 (48.6)	5.90 (1.93)
Patients 6 to 11 years		lumacaftor 200 mg/ivacaftor 250 mg every 12 hours	203 (57.4)	5.26 (3.08)
Patients 12 to <18 years		lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	241 (61.4)	3.90 (1.56)
Patients 18 years and older		lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	198 (64.8)	3.66 (2.25)

[a] Values based on data from a single patient; standard deviation not reported.

Geriatrics The safety and efficacy of ORKAMBI in patients aged 65 years and older have not been evaluated.

Sex: 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, patients 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 patients matched for demographics. Therefore, a dose reduction is recommended for these patients (see 4 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 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS). A dose reduction is recommended for these patients (see 4 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 10.3 Pharmacokinetics, Elimination). 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 7 WARNINGS AND PRECAUTIONS).

11 STORAGE, STABILITY AND DISPOSAL

Store at or below 30°C.

Keep out of the sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

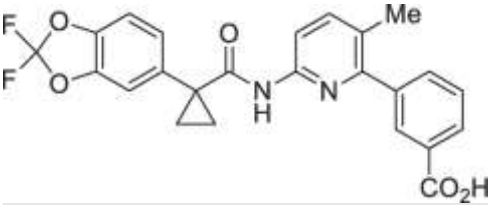
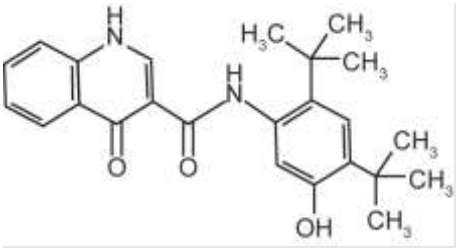
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Use established “collection systems” if available.

PART II: SCIENTIFIC INFORMATION

13 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 mcg/mL)

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The efficacy of ORKAMBI (lumacaftor/ivacaftor) in patients with CF was demonstrated in four Phase 3, clinical trials. Trials 1 and 2 were randomized, double-blind, placebo-controlled trials and Trials 3, 4 and 5 were open-label trials. These studies enrolled CF patients homozygous for the *F508del* mutation in the *CFTR* gene.

Patients with CF aged 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene

Table 10: Summary of Patient Demographics for Clinical Trials (Trials 1 and 2) in CF Patients with a *F508del* mutation in *CFTR* gene

Study #	Trial design	Dosage; route of administration; and duration	Study patients*	Mean age (Range)	Sex
Trial 1 (patients 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 (patients 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 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.

Trials 1 and 2:

Efficacy

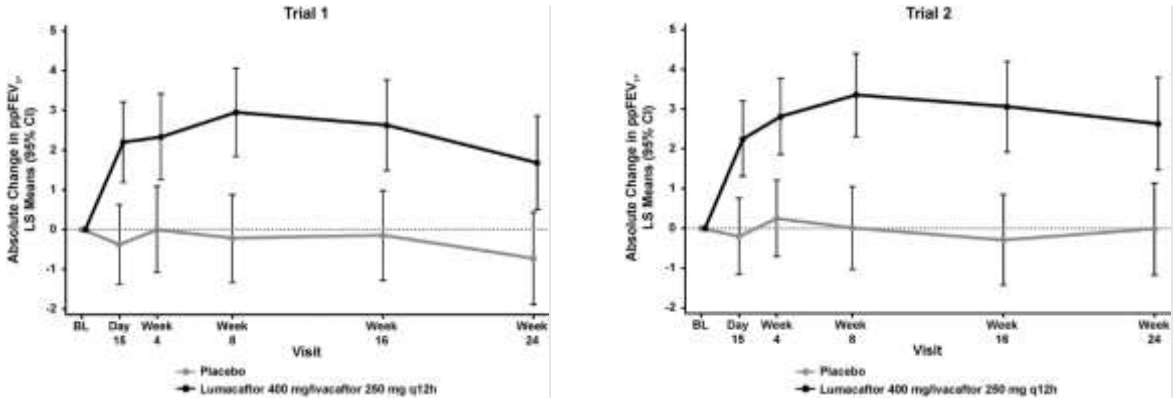
The efficacy of ORKAMBI in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomized, double-blind, placebo-controlled Phase 3 clinical trials in which 1108 clinically stable patients with CF were randomized and received at least 1 dose of study 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 24 was 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) (see Table 11).

Table 11: 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 weeks)	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*≤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

Patients with CF aged 1 to 11 years old who are homozygous for the *F508del* mutation in the CFTR gene

Table 12: Summary of Patient Demographics for Clinical Trials (Trials 3, 4, and 5) in CF Patients with a *F508del* mutation in *CFTR* gene					
Study #	**Trial design**	**Dosage; route of administration; and duration**	**Study patients***	**Mean age (Range)**	**Sex**
Trial 3 (patients homozygous for *F508del* mutation in *CFTR* gene)	Open-label, multiple-dose, multicentre, safety trial	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%

Trial 4 (patients homozygous for *F508del* mutation in *CFTR* gene)	Open-label, multiple-dose, multicentre, safety trial	lumacaftor 100 mg q12h/ ivacaftor 125 mg q12h <14 kg; granules oral; with food; 24 weeks or lumacaftor 150 mg q12h/ivacaftor 188 mg q12h ≥14 kg; granules oral; with food; 24 weeks	60	3.7 years (2 through 5 years)	Male 52.6% Female: 47.4% Male: 51.2% Female: 48.8%
Trial 5 (patients homozygous for *F508del* mutation in *CFTR* gene)	Open-label, multiple-dose, multi-centre, safety trial	lumacaftor 75 mg q12h/ ivacaftor 94 mg q12h 7 to <9 kg; granules oral; with food; 24 weeks lumacaftor 100 mg q12h/ivacaftor 125 mg q12h 9 to <14 kg; granules oral; with food; 24 weeks lumacaftor 150 mg q12/ivacaftor 188 mg q12h ≥14 kg; granules oral; with food; 24 weeks	46	18.1 months (1 to <2 years)	Male: 47.8% Female: 52.2%
* n=Number of patients randomized and dosed † n=Number of patients dosed					

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 aged 6 through 11 years (see Table 9).

Additional safety data were obtained from a 24-week, open-label, Phase 3 clinical trial in 58 patients with CF aged 6 through 11 years (mean age 9.1 years) with $ppFEV_1$ at screening ≥40 and weight ≥15 kg (Trial 3). Patients 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.

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.

Trial 4: Safety and tolerability study in pediatric patients with CF aged 2 through 5 years homozygous for the *F508del* mutation in the *CFTR* gene

The efficacy of ORKAMBI in children ages 2 through 5 years is extrapolated from efficacy in patients ages 6 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 6 years and older administered ORKAMBI tablets and in children ages 2 through 5 years (see Table 9) administered ORKAMBI oral granules.

Trial 4 was a 24-week open-label, safety trial that evaluated 60 patients with CF aged 2 through 5 years at screening (mean age at baseline 3.7 years) homozygous for *F508del* mutation. According to their weight at screening, patients were administered granules mixed with food every 12 hours, at a dose of lumacaftor 100 mg/ ivacaftor 125 mg granules for patients weighing less than 14 kg or lumacaftor 150 mg/ivacaftor 188 mg for patients weighing 14 kg or greater, for 24 weeks in addition to their prescribed CF therapies. All patients had a weight of greater than 8 kg. Patients who had an abnormal liver function test (ALT, AST or total bilirubin >2x ULN) were excluded. In order to evaluate off drug effects, patients had a safety follow-up visit following a 2-week washout period.

Spirometry (ppFEV$_1$) was assessed in patients more than 3 years of age, however, data were available for only 13 patients at baseline and at Week 24 with all but 1 patients receiving the higher dose (lumacaftor 150 mg/ivacaftor 188 mg). The mean absolute change from baseline in ppFEV$_1$ was 0.5 percentage points at Week 24 in the lumacaftor 150 mg /ivacaftor 188 mg group.

Clinical trial outcomes included BMI and BMI-for-age z-score as other secondary endpoints. The absolute change from baseline in BMI and in BMI-for-age z-score were 0.27 kg/m^2 and 0.29, respectively at Week 24.

Trial 5: Safety and Pharmacokinetics study in patients with CF aged 1 to less than 2 years homozygous for *F508del* mutation in the *CFTR* gene

The efficacy of ORKAMBI in children ages 1 to less than 2 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 2 years and older administered ORKAMBI.

Trial 5 Part B was a 24-week, open-label, safety trial that evaluated 46 patients with CF aged 1 to less than 2 years (mean age at baseline 18.1 months) homozygous for *F508del* mutation. According to their weight at screening, patients were administered granules mixed with food every 12 hours, at a dose of lumacaftor 75 mg/ivacaftor 94 mg for patients weighing 7 kg to less than 9 kg (1 patient) or lumacaftor 100 mg/ivacaftor 125 mg for patients weighing 9 kg to less than 14 kg (44 patients) or lumacaftor 150 mg/ivacaftor 188 mg for patients weighing 14 kg or greater (1 patient), for 24 weeks in addition to their prescribed CF therapies. Patients who had an abnormal liver function test (ALT, AST or total bilirubin >2x ULN) were excluded. In order to evaluate off drug effects, patients had a safety follow-up visit following a 2-week washout period.

In Trial 5 Part B, the primary endpoint of safety and tolerability was evaluated across 24 weeks. Secondary endpoints evaluated were pharmacokinetics and absolute change from baseline in sweat chloride at Week 24 (see section 10.2 Pharmacodynamics). Additional

pharmacodynamic endpoints included BMI and BMI-for-age z-score. The absolute change from baseline in BMI and in BMI for age z-score were -0.2 kg/m^2 and 0.04 kg/m^2, respectively, at Week 24.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 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 (³600 mg/kg/day in a 3-month study) and rats (³200 mg/kg/day in the 3-month study and ³100 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 were 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.

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.

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.

Reproductive and Developmental Toxicology

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.

Special Toxicology

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.

Juvenile Toxicity

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrORKAMBI®

Lumacaftor / Ivacaftor Tablets, and Lumacaftor / Ivacaftor Granules

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

What is ORKAMBI used for?

ORKAMBI is used to treat cystic fibrosis (CF) in children and adults (1 year of age and older) who have two copies of the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene (*F508del/F508del*).

How does ORKAMBI work?

ORKAMBI belongs to a group of medicines known as "*CFTR* modulators", and is a combination of two medicinal ingredients, lumacaftor and ivacaftor. It works to treat CF by affecting the *CFTR* protein in the body. This protein helps move chloride ions in and out of the cells in many organs of the body. In patients with CF, the *CFTR* protein is in lower amounts and/or the *CFTR* protein does not work properly causing mucus build-up in the lungs and many organs. Each ingredient in ORKAMBI works as follows:

- **Lumacaftor** (a *CFTR* corrector): Increases the amount of the *CFTR* protein on the surface of the cell.
- **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:

- **Tablets:** ammonium hydroxide, carmine, croscarmellose sodium, FD&C Blue #1, FD&C Blue #2, hypromellose acetate succinate, iron oxide black, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, propylene glycol, shellac, sodium lauryl sulfate, talc, and titanium dioxide.
- **Granules:** croscarmellose sodium, hypromellose acetate succinate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

ORKAMBI comes in the following dosage forms:

- **Tablets:** 100 mg/125 mg, and 200 mg/125 mg of lumacaftor/ivacaftor.
- **Granules:** 75 mg/94 mg, 100 mg/125 mg, and 150 mg/188 mg of lumacaftor/ivacaftor.

Do not use ORKAMBI if:

- You are allergic to lumacaftor, ivacaftor, or any of the other ingredients in ORKAMBI.

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 problems. Taking ORKAMBI when you already have severe liver disease can cause serious life-threatening problems. Your healthcare professional 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 problems.
- have kidney problems.
- are using birth control (e.g., hormonal contraceptives including oral, injectable, transdermal, or implantable types). 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 healthcare professional should decide if you will take ORKAMBI while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ORKAMBI passes into your breast milk. You and your healthcare professional should decide if you will take ORKAMBI while you are breastfeeding.

Other warnings you should know about:

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.

Testing and check-ups: Your healthcare professional will regularly monitor your health throughout your treatment. They may do this by performing certain tests before and during your treatment. These may be used to monitor your health including your:

- **Blood pressure and heart rate:** An increase in blood pressure and/or a decrease in heart rate has been reported in patients taking ORKAMBI. Your healthcare professional may monitor your blood pressure and heart rate during your treatment.
- **Eyes (e.g., for cataracts):** Cataracts (cloudiness of the eye lens) has been reported in children and adolescents taking ORKAMBI. Your healthcare professional may do an eye exam before you start taking ORKAMBI and during your treatment.
- **Lungs:** When you first start taking ORKAMBI, you may have shortness of breath or tightness in your chest. This is more likely to occur if you already have poor lung function. Your healthcare professional may monitor your lung function throughout your treatment.
- **Liver:** ORKAMBI can cause an increase in liver enzymes leading to serious liver problems, especially if you already have a liver problem. Your healthcare professional will order blood tests to check your liver function:
  - before you take ORKAMBI,
  - every 3 months of the first year while you are taking ORKAMBI, and
  - every year while you are taking ORKAMBI.

  Additional blood tests may be required if you have had abnormal blood tests of the liver in the past.

Liver problems: ORKAMBI can cause serious liver problems. Tell your healthcare professional 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

Driving and using machines: It is not known if ORKAMBI can cause 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, and fluconazole.
- Antibiotic medicines (used for the treatment of bacterial infections) such as clarithromycin, rifabutin, rifampicin, levofloxacin, and erythromycin.
- Anticonvulsant medicines (used for the treatment of epileptic seizures) such as phenobarbital, carbamazepine, and phenytoin.
- Ranitidine (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 and triazolam.
- Antidepressants (used for the treatment of depression) such as citalopram, escitalopram, and sertraline.
- Anti-allergics (used for the treatment of allergy symptoms) such as montelukast.
- Anti-inflammatories (used to reduce pain, inflammation, and fever) such as ibuprofen.
- Immunosuppressants (used after an organ transplantation) such as cyclosporine, everolimus, sirolimus, and 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) including oral, injectable, skin patches (transdermal), and implantable products such as ethinylestradiol, norethindrone, and other progestogens. 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, and prednisone.
- Proton pump inhibitors (used to treat acid reflux disease and ulcers) such as omeprazole, esomeprazole, and lansoprazole.
- Antimycobacterial medicines (used to treat a certain type of bacterial infection caused by *Mycobacterium*).

Know the medicines you take. Keep a list of them to show your healthcare professional when you get a new medicine.

How to take ORKAMBI:

- Take ORKAMBI exactly as your healthcare professional tells you to, even if you feel well. Check with your healthcare professional if you are not sure. Do not change the dose or stop taking ORKAMBI without first talking to your healthcare professional.
- **Always take ORKAMBI with a fat-containing food.** This helps to ensure that you get the right amount of medicine in your body. Meals and snacks recommended in CF guidelines contain acceptable amounts of fat. This includes meals that have been prepared with butter or oils, meals that have eggs, nuts, whole milk dairy products (such as whole milk, breastmilk, infant formula, cheese, and yogurt), or meats.

ORKAMBI tablets:

Each ORKAMBI box contains 4 cartons (i.e., a 4 week supply). Each carton contains 7 blister strips, one for each day. Each blister strip contains 4 tablets (i.e., 2 morning doses and 2 evening doses).

1. To separate your prescribed dose from the blister strip, you may cut along the dotted line.
2. Unpeel the paper backing from the blister strip. Do **NOT** push the tablet through the paper backing because the tablet could break.
3. Remove your dose and swallow the tablet(s) whole with food that contains fat. Do **NOT** break, crush, or chew the tablet(s).
4. Take your evening dose 12 hours after your morning dose.

ORKAMBI granules:

Each ORKAMBI box contains 4 individual wallets (i.e., a 4 week supply). Each wallet contains 14 packets of granules (i.e., 7 morning doses and 7 evening doses for a total of 7 days). Finish the entire wallet (i.e., all 7 days' doses) before starting a new wallet. Each packet is for single use only.

1. Remove 1 packet from the wallet.
2. Hold the packet with cut line on top.
3. Shake the packet gently to settle the granules to the bottom of the packet.
4. Tear or cut packet completely open along cut line.
5. Pour all the granules of the packet into 5 mL (1 teaspoon) of soft food or liquid that is between 5°C to 25°C and mix until granules are dissolved. Some examples of soft foods or liquids include puréed fruits or vegetables, flavoured yogurt or pudding, applesauce, milk, or juice (except grapefruit).
6. **After mixing, give within 1 hour and do NOT store for future use. Make sure all medicine is taken. This is very important for it to work properly and be effective.**
7. In addition to the granule mixture, fat-containing food must be ingested just **before** or just **after** the granules dose. This helps the body better absorb the medicine.
8. Take your evening dose 12 hours after your morning dose.

Refilling your prescription: Remember to get a new prescription from your healthcare professional, or a refill from your pharmacy before all your tablets or granules are taken.

Usual dose:

Your healthcare professional will determine the right dose of ORKAMBI tablets or ORKAMBI granules for you. This may depend on your health condition, other medicines you are taking, your weight, your age, and how you respond to ORKAMBI.

The usual dose for ORKAMBI is as follows:

- **ORKAMBI Tablets**
  - **6 to 11 years of age:** Two tablets (ORKAMBI 100 mg/125 mg) every 12 hours in the morning and in the evening.
  - **12 years of age and older:** Two tablets (ORKAMBI 200 mg/125 mg) every 12 hours in the morning and in the evening.
- **ORKAMBI Granules (1 to 5 years of age):** Based on weight and age, as seen in the table below.

Age	Weight	Product	Dose	
			Morning	Evening
1 to <2 years	7 kg to <9 kg	ORKAMBI 75 mg/94 mg granules per packet	1 packet	1 packet
	9 kg to <14 kg	ORKAMBI 100 mg/125 mg granules per packet		
	≥14 kg	ORKAMBI 150 mg/188 mg granules per packet		
2 to 5 years	<14 kg	ORKAMBI 100 mg/125 mg granules per packet		
	≥14 kg	ORKAMBI 150 mg/188 mg granules per packet		

Overdose:

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

Missed Dose:

If you miss a dose of ORKAMBI and:

- **it is within 6 hours** of when you usually take it, take your dose of ORKAMBI as prescribed as soon as possible with fat-containing food.
- **it is more than 6 hours** after the time you usually take it, skip the missed dose and take the next dose at your regularly scheduled time. Do **NOT** double your dose to make up for the missed dose.

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

Side effects may include:

- 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
- nausea
- diarrhea
- passing gas
- rash
- fatigue
- flu or flu like symptoms
- irregular, abnormal, or painful periods (menses) and increase in the amount of menstrual bleeding

Additional side effects in children may include:

- headache
- upper abdominal pain
- increased cough and/or mucus in the lungs or airways

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			
Liver problems: pain or discomfort in the upper right stomach (abdominal) area, yellowing of the skin or eyes (jaundice), loss of appetite, nausea, vomiting, dark urine, confusion, unusual tiredness, itchy skin, anorexia or pale stools.		√	
Liver disease (worsening of liver function): confusion, coma, death.			√
Increased creatine phosphokinase levels in the blood: muscle pain, or dark urine.		√	
Pulmonary exacerbations: new or increased cough or sputum production, change in sputum appearance, fever, fatigue, increased shortness of breath.		√	
Pneumonia (infection in the lungs): chest pain when you breath or cough, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, or shortness of breath.		√	
Hemoptysis: coughing up blood.	√		
Coughing	√		
UNKNOWN FREQUENCY			
Allergic reaction: rash; hives; swelling of the face, lips, tongue, or throat; difficult swallowing; drop in blood pressure; or difficult 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, tell your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

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

Store at or below 30°C.

Keep out of reach and sight of children.

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

If you want more information about ORKAMBI:

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

This leaflet was prepared by Vertex Pharmaceuticals (Canada) Incorporated.

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