ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg film-coated tablets
Orkambi 200 mg/125 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Orkambi 100 mg/125 mg film-coated tablets

Each film-coated tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 200 mg/125 mg film-coated tablets

Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Orkambi 100 mg/125 mg film-coated tablets

Pink, oval-shaped tablets (dimensions 14 × 7.6 × 4.9 mm) printed with "1V125" in black ink on one side.

Orkambi 200 mg/125 mg film-coated tablets

Pink, oval-shaped tablets (dimensions 14 × 8.4 × 6.8 mm) printed with "2V125" in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orkambi tablets are indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2, 4.4, and 5.1).

4.2 Posology and method of administration

Orkambi should only be prescribed by physicians with experience in the treatment of CF. 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.

Posology

Table 1: Dosing recommendations in patients aged 6 years and older

Age	Strength	Dose (every 12 hours)	
		Morning	Evening
6 to < 12 years	lumacaftor 100 mg/ivacaftor 125 mg	2 tablets	2 tablets
12 years and older	lumacaftor 200 mg/ivacaftor 125 mg	2 tablets	2 tablets

Patients may start treatment on any day of the week.

This medicinal product should be taken with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing (see section 5.2).

Missed dose

If less than 6 hours have passed since the missed dose, the scheduled dose 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. A double dose should not be taken to make up for the forgotten dose.

Concomitant use of CYP3A inhibitors

No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking Orkambi. However, when initiating treatment in patients taking strong CYP3A inhibitors, the dose should be reduced to one tablet daily for the first week of treatment to allow for the steady-state induction effect of lumacaftor. Following this period, the recommended daily dose should be continued (see Table 2).

Table 2: Treatment initiation in patients taking strong CYP3A inhibitors

Age	Strength	Week 1 of treatment	Week 2 onwards
6 to < 12 years	lumacaftor 100 mg/ivacaftor 125 mg	1 tablet per day	From day 8 and thereafter dosing should be at the recommended daily dose
12 years and older	lumacaftor 200 mg/ivacaftor 125 mg		

If treatment is interrupted for more than one week and then re-initiated while taking strong CYP3A inhibitors, the dose should be reduced to one tablet daily for the first week of treatment re-initiation (see Table 2). Following this period, the recommended daily dose should be continued (see section 4.5).

Special populations

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a dose reduction is recommended.

There is no experience of the use of the medicinal product 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 in patients with severe hepatic impairment, at a reduced dose (see sections 4.4, 4.8, and 5.2).

For dose adjustments for patients with moderate or severe hepatic impairment (see Table 3).

Table 3: Dose adjustment recommendations for patients with moderate or severe hepatic impairment

Age	Strength	Total Daily Dose			
		Moderate (Child-Pugh Class B)		Severe (Child-Pugh Class C)	
		Morning	Evening	Morning	Evening
6 to < 12 years	lumacaftor 100 mg/ivacaftor 125 mg	2 tablets	1 tablet	1 tablet or less frequently *	1 tablet or less frequently *
12 years and older	lumacaftor 200 mg/ivacaftor 125 mg				

* Dosing interval should be modified according to clinical response and tolerability; the frequency may be reduced for both the morning dose and the evening dose.

Paediatric population

The safety and efficacy of Orkambi in children aged less than 1 year have not yet been established. No data are available.

Method of administration

For oral use.

Patients should be instructed to swallow the tablets whole. Patients should not chew, break, or dissolve the tablets.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with CF who are heterozygous for the *F508del* mutation in the *CFTR* gene

Lumacaftor/ivacaftor is not effective in patients with CF who have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in a lack of CFTR production or that is not responsive to ivacaftor *in vitro* (see section 5.1).

Patients with CF who have a gating (Class III) mutation in the *CFTR* gene

Lumacaftor/ivacaftor has not been studied in patients with CF who have a gating (Class III) mutation in the *CFTR* gene on one allele, with or without the *F508del* mutation on the other allele. Since the exposure of ivacaftor is very significantly reduced when dosed in combination with lumacaftor, lumacaftor/ivacaftor should not be used in these patients.

Respiratory adverse reactions

Respiratory adverse reactions (e.g., chest discomfort, dyspnoea, bronchospasm, and respiration abnormal) were more common during initiation of lumacaftor/ivacaftor therapy. Serious respiratory events were seen more frequently in patients with percent predicted forced expiratory volume in 1 second ($ppFEV_1$) <40, and may lead to discontinuation of the medicinal product. Clinical experience in patients with $ppFEV_1 < 40$ is limited and additional monitoring of these patients is recommended during initiation of therapy (see section 4.8). A transient decline in FEV_1 has also been observed in some patients following initiation of lumacaftor/ivacaftor. There is no experience of initiating

treatment with lumacaftor/ivacaftor in patients having a pulmonary exacerbation and initiating treatment in patients having a pulmonary exacerbation is not advisable.

Effect on blood pressure

Increased blood pressure has been observed in some patients treated with lumacaftor/ivacaftor. Blood pressure should be monitored periodically in all patients during treatment (see section 4.8).

Patients with advanced liver disease

Abnormalities in liver function, including advanced liver disease, can be present in patients with CF. Worsening of liver function in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension receiving lumacaftor/ivacaftor. Lumacaftor/ivacaftor should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If lumacaftor/ivacaftor is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced (see sections 4.2, 4.8, and 5.2).

Hepatobiliary adverse reactions

Elevated transaminases have been commonly reported in patients with CF receiving lumacaftor/ivacaftor. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin. Transaminase elevations have been observed more frequently in paediatric patients than in adult patients (see section 4.8).

Because an association with liver injury cannot be excluded, assessments of liver function tests (ALT, AST and bilirubin) are recommended before initiating lumacaftor/ivacaftor, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered.

In the event of significant elevation of ALT or AST, with or without elevated bilirubin (either ALT or AST > 5 x the upper limit of normal [ULN], or ALT or AST > 3 x ULN with bilirubin > 2 x ULN and/or clinical jaundice), dosing with lumacaftor/ivacaftor should be discontinued and laboratory tests closely followed until the abnormalities resolve. A thorough investigation of potential causes should be conducted and patients should be followed closely for clinical progression. Following resolution of transaminase elevations, the benefits and risks of resuming dosing should be considered (see sections 4.2, 4.8, and 5.2).

Depression

Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with lumacaftor/ivacaftor, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders (see section 4.8). In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour and to seek medical advice immediately if these symptoms occur.

Interactions with medicinal products

Substrates of CYP3A

Lumacaftor is a strong inducer of CYP3A. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended (see section 4.5).

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 section 4.5).

Strong CYP3A inducers

Ivacaftor is a substrate of CYP3A4 and CYP3A5. Therefore, co-administration with strong CYP3A inducers (e.g., rifampicin, St. John's wort [*Hypericum perforatum*]) is not recommended (see section 4.5).

Renal impairment

Caution is recommended while using lumacaftor/ivacaftor in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with lumacaftor/ivacaftor 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 section 5.3). Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with lumacaftor/ivacaftor.

Patients after organ transplantation

Lumacaftor/ivacaftor has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See section 4.5 for interactions with immunosuppressants.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Lumacaftor is a strong inducer of CYP3A and ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. There is potential for other medicinal products to affect lumacaftor/ivacaftor when administered concomitantly, and also for lumacaftor/ivacaftor to affect other medicinal products.

Potential for other medicinal products to affect lumacaftor/ivacaftor

Inhibitors of CYP3A

Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor when co-administered with a CYP3A inhibitor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours, the approved dose of ivacaftor monotherapy.

No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking lumacaftor/ivacaftor. However, when initiating lumacaftor/ivacaftor in patients taking strong CYP3A inhibitors, the dose should be adjusted (see sections 4.2 and 4.4).

No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.

Inducers of CYP3A

Co-administration of lumacaftor/ivacaftor with rifampicin, a strong CYP3A inducer, had minimal effect on the exposure of lumacaftor, but decreased ivacaftor exposure (AUC) by 57%. Therefore, co-administration of lumacaftor/ivacaftor is not recommended with strong CYP3A inducers (see sections 4.2 and 4.4).

No dose adjustment is recommended when used with moderate or weak CYP3A inducers.

Potential for lumacaftor/ivacaftor to affect other medicinal products

CYP3A substrates

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. Therefore, concomitant use of lumacaftor/ivacaftor with CYP3A substrates may decrease the exposure of these substrates (see section 4.4).

P-gp substrates

In vitro studies indicated that lumacaftor has the potential to both inhibit and induce P-gp. Additionally, a clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of lumacaftor/ivacaftor with P-gp substrates (e.g., digoxin) may alter the exposure of these substrates.

CYP2B6 and CYP2C substrates

Interaction with CYP2B6 and CYP2C substrates has not been investigated *in vivo*. *In vitro* studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; however, 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 lumacaftor/ivacaftor may alter (i.e., either increase or decrease) the exposure of CYP2C8 and CYP2C9 substrates, decrease the exposure of CYP2C19 substrates, and substantially decrease the exposure of CYP2B6 substrates.

Potential for lumacaftor/ivacaftor to interact with transporters

In vitro experiments show that lumacaftor is a substrate for Breast Cancer Resistance Protein (BCRP). Co-administration of Orkambi with medicinal products that inhibit BCRP may increase plasma lumacaftor concentration. Lumacaftor inhibits the organic anion transporter (OAT) 1 and 3. Lumacaftor and ivacaftor are inhibitors of BCRP. Co-administration of Orkambi with medicinal products that are substrates for OAT1/3 and BCRP transport may increase plasma concentrations of such medicinal products. Lumacaftor and ivacaftor are not inhibitors of OATP1B1, OATP1B3, and organic cation transporter (OCT) 1 and 2. Ivacaftor is not an inhibitor of OAT1 and OAT3.

Established and other potentially significant interactions

Table 4 provides the established or predicted effect of lumacaftor/ivacaftor on other medicinal products or the effect of other medicinal products on lumacaftor/ivacaftor. The information reported in Table 4 mostly derives from *in vitro* studies. The recommendations provided under “Clinical comment” in Table 4 are based on interaction studies, clinical relevance, or predicted interactions due to elimination pathways. Interactions that have the most clinical relevance are listed first.

Table 4: Established and other potentially significant interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products

Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
Concomitant medicinal products of most clinical relevance		
Anti-allergics:		
montelukast	↔ LUM, IVA	
	↓ 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.
fexofenadine	↔ LUM, IVA	
	↑ or ↓ fexofenadine Due to potential induction or inhibition of P-gp	Dose adjustment of fexofenadine may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of fexofenadine.
Antibiotics:		
clarithromycin, telithromycin	↔ LUM ↑ IVA Due to inhibition of CYP3A by clarithromycin, telithromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin or telithromycin are initiated in patients currently taking lumacaftor/ivacaftor.
	↓ clarithromycin, telithromycin Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily for the first week of treatment when initiating lumacaftor/ ivacaftor in patients currently taking clarithromycin or telithromycin. An alternative to these antibiotics, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposures of clarithromycin and telithromycin, which may reduce their efficacy.
erythromycin	↔ LUM ↑ 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.

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
Anticonvulsants:		
carbamazepine, phenobarbital, phenytoin	↔ LUM ↓ IVA Due to induction of CYP3A by these anticonvulsants	
	↓ carbamazepine, phenobarbital, phenytoin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anticonvulsants is not recommended. The exposures of ivacaftor and the anticonvulsant may be significantly decreased, which may reduce the efficacy of both active substances.
Antifungals:		
itraconazole*, ketoconazole, posaconazole, voriconazole	↔ LUM ↑ 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.
	↓ itraconazole, ketoconazole, voriconazole Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one tablet daily for the first week of treatment when initiating lumacaftor/ ivacaftor in patients currently taking these antifungals.
	↓ posaconazole Due to induction of UGT by LUM	Concomitant use of lumacaftor/ivacaftor with these antifungals is not recommended. Patients should be monitored closely for breakthrough fungal infections if such medicinal products are necessary. Lumacaftor/ivacaftor may decrease the exposures of these antifungals, which may reduce their efficacy.
fluconazole	↔ LUM ↑ 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; fluconazole is cleared primarily by renal excretion as unchanged drug; however, modest reduction in fluconazole exposure has been observed with strong inducers	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	↔ LUM, IVA	

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
	↓ ibuprofen Due to induction of CYP3A/2C8/2C9 by LUM	A higher dose of ibuprofen may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of ibuprofen, which may reduce its efficacy.
Anti-mycobacterials:		
rifabutin, rifampicin*, rifapentine	↔ LUM ↓ IVA Due to induction of CYP3A by anti-mycobacterials	
	↓ rifabutin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anti-mycobacterials is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor. A higher dose of rifabutin may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of rifabutin, which may reduce its efficacy.
	↔ rifampicin, rifapentine	
Benzodiazepines:		
midazolam, triazolam	↔ LUM, IVA	
	↓ 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:		
ethinyl estradiol, norethindrone, and other progestogens	↓ ethinyl estradiol, norethindrone, and other progestogens Due to induction of CYP3A/UGT by LUM	Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of hormonal contraceptives, which may reduce their efficacy.
Immunosuppressants:		
ciclosporin, everolimus, sirolimus, tacrolimus	↔ LUM, IVA	

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
(used after organ transplant)	↓ ciclosporin, 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	↔ LUM, IVA	
	↓ 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.
Herbals:		
St. John's wort (*Hypericum perforatum*)	↔ LUM ↓ IVA Due to induction of CYP3A by St. John's wort	Concomitant use of lumacaftor/ivacaftor with St. John's wort is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor.
Other concomitant medicinal products of clinical relevance		
Antiarrhythmics:		
digoxin	↔ LUM, IVA	
	↑ 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:		
dabigatran	↔ LUM, IVA	
	↑ or ↓ dabigatran Due to potential induction or inhibition of P-gp	Appropriate clinical monitoring should be employed when co-administered with lumacaftor/ivacaftor. Dose adjustment of dabigatran may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of dabigatran.
warfarin	↔ LUM, IVA	
	↑ or ↓ warfarin Due to potential induction or inhibition of CYP2C9 by LUM	The international normalised ratio (INR) should be monitored when warfarin co-administration with lumacaftor/ivacaftor is required. Lumacaftor/ivacaftor may alter the exposure of warfarin.

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
Antidepressants:		
citalopram, escitalopram, sertraline	↔ LUM, IVA	
	↓ 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.
bupropion	↔ LUM, IVA	
	↓ bupropion Due to induction of CYP2B6 by LUM	A higher dose of bupropion may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of bupropion, which may reduce its efficacy.
Corticosteroids, systemic:		
methylprednisolone, prednisone	↔ LUM, IVA	
	↓ 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	↔ LUM, IVA	
	↑ 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.
Oral hypoglycemics:		
repaglinide	↔ LUM, IVA	
	↓ repaglinide Due to induction of CYP3A/2C8 by LUM	A higher dose of repaglinide may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of repaglinide, which may reduce its efficacy.

Note: ↑ = increase, ↓ = decrease, ↔ = no change; LUM = lumacaftor; IVA = ivacaftor.
* Based on clinical interaction studies. All other interactions shown are predicted.

False positive urine tests for THC

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving Orkambi. An alternative confirmatory method should be considered to verify results.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of lumacaftor/ivacaftor in pregnant women. Animal studies with lumacaftor and ivacaftor do not indicate direct or indirect harmful effects with respect to developmental and reproductive toxicity, whereas effects were noted with ivacaftor only at maternally toxic doses (see section 5.3). As a precautionary measure, it is preferable to avoid the use of lumacaftor/ivacaftor during pregnancy unless the clinical condition of the mother requires treatment with lumacaftor/ivacaftor.

Breast-feeding

Limited data show that ivacaftor and lumacaftor are excreted into human milk. There is insufficient information on the effects of lumacaftor/ivacaftor in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effects of lumacaftor and/or ivacaftor on fertility are available. Lumacaftor had no effects on fertility and reproductive performance indices in male and female rats. Ivacaftor impaired fertility and reproductive performance indices in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Ivacaftor, which is one of the active components of Orkambi, has a minor influence on the ability to drive and use machines. Ivacaftor may cause dizziness (see section 4.8). Patients experiencing dizziness while taking Orkambi should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are dyspnoea (14.0%), diarrhoea (11.0%), and nausea (10.2%). Serious adverse reactions included hepatobiliary events, e.g., transaminase elevations (0.5%), cholestatic hepatitis (0.3%) and hepatic encephalopathy (0.1%).

Tabulated list of adverse reactions

Table 5 reflects the adverse reactions reported with lumacaftor/ivacftor and ivacaftor monotherapy from clinical trials, post-authorisation safety studies and spontaneous reporting. Adverse reactions are listed by MedDRA system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/ 1,000 to < 1/100); rare (≥ 1/ 10,000 to < 1/ 1,000); very rare (< 1/ 10,000); and not known (frequency cannot be estimated using the available data).

Table 5: Adverse reactions in lumacaftor/ivacaftor-treated patients and in patients treated with ivacaftor alone

System organ class	Frequency	Adverse reactions
Infections and infestations	very common	Nasopharyngitis[*]
	common	Upper respiratory tract infection, rhinitis
Psychiatric disorders	not known	Depression
Vascular disorders	uncommon	Hypertension
Nervous system disorders	very common	Headache, dizziness[*]
	uncommon	Hepatic encephalopathy[†]
Ear and labyrinth disorders	common	Ear pain[*], ear discomfort[*], tinnitus[*], tympanic membrane hyperaemia[*], vestibular disorder[*]
	uncommon	Ear congestion[*]
Respiratory, thoracic and mediastinal disorders	very common	Nasal congestion, dyspnoea, productive cough, sputum increased
	common	Respiration abnormal, oropharyngeal pain, sinus congestion[*], rhinorrhoea, pharyngeal erythema[*], bronchospasm
Gastrointestinal disorders	very common	Abdominal pain[*], abdominal pain upper, diarrhoea, nausea
	common	Flatulence, vomiting
Hepatobiliary disorders	common	Transaminase elevations
	uncommon	Cholestatic hepatitis[‡]
Skin and subcutaneous tissue disorders	common	Rash
Reproductive system and breast disorders	common	Menstruation irregular, dysmenorrhoea, metrorrhagia, breast mass[*]
	uncommon	Menorrhagia, amenorrhoea, polymenorrhoea, breast inflammation[*], gynaecomastia[*], nipple disorder[*], nipple pain[*], oligomenorrhoea
Investigations	very common	Bacteria in sputum[*]
	common	Blood creatine phosphokinase increased
	uncommon	Blood pressure increased

[*] Adverse reactions and frequencies observed in patients in clinical studies with ivacaftor monotherapy.
[†] 1 patient out of 738
[‡] 2 patients out of 738

The safety data from a 96-week rollover study (809-105) were consistent with the safety data from the phase 3 studies (trials 809-103 and 809-104).

Description of selected adverse reactions

Hepatobiliary adverse reactions

During trials 809-103 and 809-104, the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 0.8%, 2.0%, and 5.2%; and 0.5%, 1.9%, and 5.1% in lumacaftor/ivacaftor- and placebo-treated patients, respectively. The incidence of transaminase-related adverse reactions was 5.1% and 4.6% in lumacaftor/ivacaftor-treated patients and those who received placebo, respectively. Seven patients who received lumacaftor/ivacaftor had liver-related serious adverse reactions with elevated transaminases, including 3 with concurrent elevation in total bilirubin. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients (see section 4.4).

Among 7 patients with pre-existing cirrhosis and/or portal hypertension who received lumacaftor/ivacaftor in the placebo-controlled, phase 3 studies, 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 lumacaftor/ivacaftor (see section 4.4).

Post–marketing cases of liver function decompensation including liver failure leading to death have been reported in CF patients with pre-existing cirrhosis with portal hypertension who were treated with lumacaftor/ivacaftor (see section 4.4).

Respiratory adverse reactions

During trials 809-103 and 809-104, the incidence of respiratory adverse reactions (e.g., chest discomfort, dyspnoea, bronchospasm, and respiration abnormal) was 26.3% in lumacaftor/ivacaftor-treated patients compared to 17.0% in patients who received placebo. The incidence of these adverse reactions was more common in patients with lower pre-treatment FEV_1. Approximately three-quarters of the events began during the first week of treatment, and in most patients the events resolved without dosing interruption. The majority of adverse reactions were mild or moderate in severity, non-serious and did not result in treatment discontinuation (see section 4.4).

During a 24-week, open-label, phase 3b clinical study (trial 809-106) in 46 patients aged 12 years and older with advanced lung disease ($ppFEV_1 < 40$) [mean $ppFEV_1$ 29.1 at baseline (range: 18.3 to 42.0)], the incidence of respiratory adverse reactions was 65.2%. In the subgroup of 28 patients who were initiated at the full dose of lumacaftor/ivacaftor (2 tablets every 12 hours), the incidence was 71.4%, and in the 18 patients who were initiated at a reduced dose of lumacaftor/ivacaftor (1 tablet every 12 hours for up to 2 weeks, and subsequently increased to the full dose), the incidence was 55.6%. Of the patients who were initiated lumacaftor/ivacaftor at the full dose, one patient had a serious respiratory adverse reaction, three patients subsequently had their dose reduced, and three patients discontinued treatment. No serious respiratory adverse reactions, dose reductions or discontinuations were seen in patients who were initiated at the half dose (see section 4.4).

Menstrual abnormalities

During trials 809-103 and 809-104, the incidence of combined menstrual abnormalities (amenorrhoea, dysmenorrhoea, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhoea, and polymenorrhoea) was 9.9 % in lumacaftor/ivacaftor-treated female patients and 1.7% in placebo-treated females. These menstrual events occurred more frequently in the subset of female patients who were taking hormonal contraceptives (25.0%) versus patients who were not taking hormonal contraceptives (3.5%) (see section 4.5). Most of these reactions were mild or moderate in severity and non-serious. In lumacaftor/ivacaftor-treated patients, approximately two-thirds of these reactions resolved, and the median duration was 10 days.

Increased blood pressure

During trials 809-103 and 809-104, adverse reactions related to increased blood pressure (e.g., hypertension, blood pressure increased) were reported in 0.9% (7/738) of patients treated with lumacaftor/ivacaftor and in no patients who received placebo.

In patients treated with lumacaftor/ivacaftor (mean baseline 114 mmHg systolic and 69 mmHg diastolic), the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.1 mmHg and 1.8 mmHg, respectively. In patients who received placebo (mean baseline 114 mmHg systolic and 69 mmHg diastolic), the maximum increase from baseline in mean systolic and diastolic blood pressure was 0.9 mmHg and 0.9 mmHg, respectively.

The proportion of patients who experienced a systolic blood pressure value > 140 mmHg or a diastolic blood pressure > 90 mmHg on at least two occasions was 3.4% and 1.5% in patients treated with lumacaftor/ivacaftor, respectively, compared with 1.6% and 0.5% in patients who received placebo (see section 4.4).

Paediatric population

The safety data of lumacaftor/ivacaftor were evaluated in 46 patients aged 1 to less than 2 years (trial 809-122), 60 patients aged 2 to 5 years (trial 809-115), 161 patients aged 6 to less than 12 years (trials 809-011 and 809-109) and in 194 patients aged 12 to 17 years with CF who are homozygous for the *F508del* mutation and who received lumacaftor/ivacaftor in clinical studies. Patients aged 12 to 17 years were included in trials 809-103 and 809-104.

The overall safety profile in these paediatric patients is generally consistent with that in adult patients. Few selected adverse reactions are specifically reported in the paediatric population.

Long-term safety data from three 96-week extension studies in 52, 57, and 239 patients aged 1 year and older (trial 809-124), 2 years and older (trial 809-116), and 6 years and older (trial 809-110), respectively, who were homozygous for the *F508del* mutation in the *CFTR* gene, were generally consistent with the 24-week parent studies. The parent studies were conducted in patients aged 1 to less than 2 years (trial 809-122 parent of 809-124), age 2 to 5 years (trial 809-115 parent of 809-116), and age 6 to less than 12 years (trial 809-011 and 809-109 parents of 809-110).

Description of selected adverse reactions for patients aged 6 to less than 12 years

Hepatobiliary adverse reactions

During the 24-week, open-label phase 3 clinical study in 58 patients aged 6 to less than 12 years (trial 809-011), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and >3 x ULN was 5.3%, 8.8%, and 19.3%. No patients had total bilirubin levels > 2 x ULN.

Lumacaftor/ivacaftor dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except 1 patient who discontinued treatment.

During the 24-week, placebo-controlled phase 3 clinical study in 204 patients aged 6 to less than 12 years (trial 809-109), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 1.0%, 4.9%, and 12.6% in the lumacaftor/ivacaftor patients, and 2.0%, 3.0%, and 7.9% in the placebo-treated patients. No patients had total bilirubin levels > 2 x ULN. Two patients in the lumacaftor/ivacaftor group and two patients in the placebo group discontinued treatment due to transaminase elevations.

Respiratory adverse reactions

During the 24-week, open-label phase 3 clinical study (trial 809-011) in 58 patients aged 6 to less than 12 years (mean baseline $ppFEV_1$ was 91.4), the incidence of respiratory adverse reactions was 6.9% (4/58).

During the 24-week, placebo-controlled phase 3 clinical study (trial 809-109) in patients aged 6 to less than 12 years (mean baseline $ppFEV_1$ was 89.8), the incidence of respiratory adverse reactions was 18.4% in lumacaftor/ivacaftor patients and 12.9% in placebo patients. A decline in $ppFEV_1$ at initiation of therapy was observed during serial post dose spirometry assessments. The absolute change from pre-dose at 4 to 6 hours post-dose was -7.7 on day 1 and -1.3 on day 15 in lumacaftor/ivacaftor patients. The post-dose decline was resolved by week 16.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Adverse reactions that occurred at an increased incidence of ≥ 5% in the supratherapeutic dose period compared with the therapeutic dose period were headache, generalised rash, and increased transaminase.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products; ATC code: R07AX30

Mechanism of action

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation impacts the CFTR protein in multiple ways, primarily 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 has low channel-open probability (defective channel gating). Lumacaftor is a CFTR corrector that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at 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. The combined effect of lumacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. The exact mechanisms by which lumacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.

Pharmacodynamic effects

Effects on sweat chloride

Changes in sweat chloride in response to lumacaftor alone or in combination with ivacaftor were evaluated in a double-blind, placebo-controlled, phase 2 clinical trial in patients with CF aged 18 years and older. In this trial, 10 patients (homozygous for *F508del-CFTR* mutation) 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 was statistically significant at -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 was statistically significant at -11 mmol/L (95% CI: -18, -4).

In trial 809-109 (see Clinical efficacy and safety) in patients homozygous for the *F508del-CFTR* mutation aged 6 to less than 12 years, the treatment difference (LS mean) in sweat chloride for the absolute change at week 24 as compared to placebo was -24.9 mmol/L (nominal $P < 0.0001$). The treatment difference (LS mean) in sweat chloride for the average absolute change at day 15 and at week 4 as compared to placebo was -20.8 mmol/L (95% CI: -23.4, -18.2; nominal $P < 0.0001$).

Changes in FEV_1

Changes in $ppFEV_1$ in response to lumacaftor alone or in combination with ivacaftor were also evaluated in the double-blind, placebo-controlled, phase 2 trial in patients with CF aged 18 years and

older. The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean absolute change in $ppFEV_1$ was -4.6 percentage points (95% CI: -9.6, 0.4) from baseline to day 28, 4.2 percentage points (95% CI: –1.3, 9.7) from baseline to day 56, and 7.7 percentage points (95% CI: 2.6, 12.8; statistically significant) from day 28 to day 56 (following the addition of ivacaftor to lumacaftor monotherapy).

Decrease in heart rate

During the 24-week, placebo-controlled, phase 3 studies, a maximum decrease in mean heart rate of 6 beats per minute (bpm) from baseline was observed on day 1 and day 15 around 4 to 6 hours after dosing. After day 15, heart rate was not monitored in the period after dosing in these studies. From week 4, the change in mean heart rate at pre-dose ranged from 1 to 2 bpm below baseline among patients treated with lumacaftor/ivacaftor. The percentage of patients with heart rate values < 50 bpm on treatment was 11% for patients who received lumacaftor/ivacaftor, compared to 4.9% for patients who received placebo.

Cardiac electrophysiology

No meaningful changes in QTc interval or blood pressure were observed in a thorough QT clinical study evaluating lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h.

Clinical efficacy and safety

Trials in patients with CF aged 12 years and above who are homozygous for the F508del mutation in the CFTR gene

The efficacy of lumacaftor/ivacaftor in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomised, double-blind, placebo-controlled clinical trials of 1,108 clinically stable patients with CF, in which 737 patients were randomised to and dosed with lumacaftor/ivacaftor. Patients in both trials were randomised 1:1:1 to receive lumacaftor 600 mg once daily/ivacaftor 250 mg q12h, 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 a blinded extension study.

Trial 809-103 evaluated 549 patients with CF who were 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]). Trial 809-104 evaluated 559 patients 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]). Patients with a history of colonisation 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 times the ULN or total bilirubin ≥ 2 times the ULN) were excluded.

The primary efficacy endpoint in both studies was the absolute change from baseline in $ppFEV_1$ at week 24. Other efficacy variables included relative change from baseline in $ppFEV_1$, absolute change from baseline in BMI, absolute change from baseline in CFQ-R Respiratory Domain, the proportion of patients achieving ≥ 5% relative change from baseline in $ppFEV_1$ at week 24, and the number of pulmonary exacerbations (including those requiring hospitalisation or IV antibiotic therapy) through week 24.

In both trials, treatment with lumacaftor/ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ (see Table 6). Mean improvement in $ppFEV_1$ was rapid in onset (day 15) and sustained throughout the 24-week treatment period. At day 15, the treatment difference between lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo for the mean absolute change (95% CI) in $ppFEV_1$ from baseline was 2.51 percentage points in the pooled trials 809-103 and 809-104 ($P < 0.0001$). Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex and geographic

region. The phase 3 trials of lumacaftor/ivacaftor included 81 patients with $ppFEV_1 < 40$ at baseline. The treatment difference in this subgroup was comparable to that observed in patients with $ppFEV_1 \geq 40$. At week 24, the treatment difference between lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo for the mean absolute change (95% CI) in $ppFEV_1$ from baseline in the pooled trials 809-103 and 809-104 were 3.39 percentage points (P = 0.0382) for patients with $ppFEV_1 < 40$ and 2.47 percentage points (P < 0.0001) for patients with $ppFEV_1 \geq 40$.

Table 6: Summary of primary and key secondary outcomes in trial 809-103 and trial 809-104*

		Trial 809-103		**Trial 809-104**		**Pooled (trial 809-103 and trial 809-104)**	
		Placebo (n = 184)	**LUM 400 mg q12h/ IVA 250 mg q12h (n = 182)**	**Placebo (n = 187)**	**LUM 400 mg q12h/IVA 250 mg q12h (n = 187)**	**Placebo (n = 371)**	**LUM 400 mg q12h/IVA 250 mg q12h (n = 369)**
Absolute change in $ppFEV_1$ at week 24 (percentage points)	Treatment difference	–	2.41 (P = 0.0003)†	–	2.65 (P = 0.0011)†	–	2.55 (P < 0.0001)
	Within-group change	-0.73 (P = 0.2168)	1.68 (P = 0.0051)	-0.02 (P = 0.9730)	2.63 (P < 0.0001)	-0.39 (P < 0.3494)	2.16 (P < 0.0001)
Relative change in $ppFEV_1$ at week 24 (%)	Treatment difference	–	4.15 (P = 0.0028)†	–	4.69 (P = 0.0009)†	–	4.4 (P < 0.0001)
	Within-group change	-0.85 (P = 0.3934)	3.3 (P = 0.0011)	0.16 (P = 0.8793)	4.85 (P < 0.0001)	-0.34 (P = 0.6375)	4.1 (P < 0.0001)
Absolute change in BMI at week 24 (kg/m^2)	Treatment difference	–	0.13 (P = 0.1938)	–	0.36 (P < 0.0001)†	–	0.24 (P = 0.0004)
	Within-group change	0.19 (P = 0.0065)	0.32 (P < 0.0001)	0.07 (P = 0.2892)	0.43 (P < 0.0001)	0.13 (P = 0.0066)	0.37 (P < 0.0001)
Absolute change in CFQ-R Respiratory Domain Score at week 24 (points)	Treatment difference	–	1.5 (P = 0.3569)	–	2.9 (P = 0.0736)	–	2.2 (P = 0.0512)
	Within-group change	1.1 (P = 0.3423)	2.6 (P = 0.0295)	2.8 (P = 0.0152)	5.7 (P < 0.0001)	1.9 (P = 0.0213)	4.1 (P < 0.0001)
Proportion of patients with ≥5% relative change in $ppFEV_1$ at week 24	%	25%	32%	26%	41%	26%	37%
	Odds ratio	–	1.43 (P = 0.1208)	–	1.90 (P = 0.0032)	–	1.66 (P = 0.0013)
Number of pulmonary exacerbations through week 24	# of events (rate per 48 weeks)	112 (1.07)	73 (0.71)	139 (1.18)	79 (0.67)	251 (1.14)	152 (0.70)
	Rate ratio	–	0.66 (P = 0.0169)	–	0.57 (P = 0.0002)	–	0.61 (P < 0.0001)

* 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 was required for statistical significance.

† Indicates statistical significance confirmed in the hierarchical testing procedure.

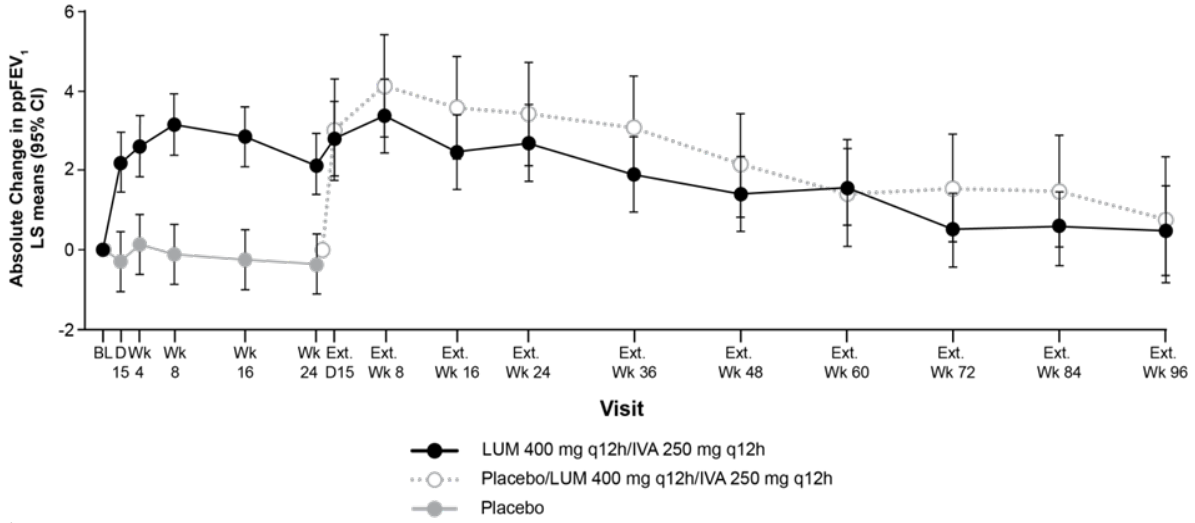
At week 24, the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with lumacaftor/ivacaftor compared with placebo. In the pooled analysis, the rate ratio of exacerbations through week 24 in subjects treated with lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h; n = 369) was 0.61 (P < 0.0001), representing a reduction of 39% relative to placebo. The event rate per year, annualised to 48 weeks, was 0.70 in the lumacaftor/ivacaftor group and 1.14 in the placebo group. Treatment with lumacaftor/ivacaftor significantly decreased the risk for exacerbations requiring hospitalisation versus placebo by 61% (rate ratio = 0.39, P < 0.0001; event rate per 48 weeks 0.17 for lumacaftor/ivacaftor and 0.45 for placebo) and reduced exacerbations requiring treatment with intravenous antibiotics by 56% (rate ratio = 0.44, P < 0.0001; event rate per 48 weeks 0.25 for lumacaftor/ivacaftor and 0.58 for placebo). These results were not considered statistically significant within the framework of the testing hierarchy for the individual studies.

Long-term safety and efficacy rollover trial

Trial 809-105 was a phase 3, parallel-group, multicentre, rollover extension study in patients with CF that included patients aged 12 years and older from trial 809-103 and trial 809-104. This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 1,108 patients who received any treatment in trial 809-103 or trial 809-104, 1,029 (93%) were dosed and received active treatment (lumacaftor 600 mg once daily/ivacaftor 250 mg q12h or lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in trial 809-105 for up to an additional 96 weeks (i.e., up to a total of 120 weeks). The primary efficacy analysis of this extension study included data up to week 72 of trial 809-105 with a sensitivity analysis that included data up to week 96 of trial 809-105.

Patients treated with lumacaftor/ivacaftor in trial 809-103 or trial 809-104 showed an effect that was maintained with respect to baseline after an additional 96 weeks through trial 809-105. For patients who transitioned from placebo to active treatment similar changes as those observed in patients treated with lumacaftor/ivacaftor in trial 809-103 or trial 809-104 were seen (see Table 6). Results from trial 809-105 are presented in Figure 1 and Table 7.

Figure 1. Absolute change from baseline in percent predicted FEV_1 at each visit†



† From trials 809-103, 809-104 and 809-105.

Table 7: Long-term effect of lumacaftor/ivacaftor in trial 809-105[*]

Baseline and endpoint	Placebo transitioned to lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 176)[**]			lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 369)[†]		
	Mean (SD)	**LS Means (95% CI)**	**P value**	**Mean (SD)**	**LS Means (95% CI)**	**P value**
Baseline $ppFEV_1$[‡]	60.2 (14.7)			60.5 (14.1)		
Absolute change from baseline $ppFEV_1$ (percentage points)						
Extension week 72		(n = 134) 1.5 (0.2, 2.9)	0.0254		(n = 273) 0.5 (-0.4, 1.5)	0.2806
Extension week 96		(n = 75) 0.8 (-0.8, 2.3)	0.3495		(n = 147) 0.5 (-0.7, 1.6)	0.4231
Relative change from baseline $ppFEV_1$ (%)						
Extension week 72		(n = 134) 2.6 (0.2, 5.0)	0.0332		(n = 273) 1.4 (-0.3, 3.2)	0.1074
Extension week 96		(n = 75) 1.1 (-1.7, 3.9)	0.4415		(n = 147) 1.2 (-0.8, 3.3)	0.2372
Baseline BMI (kg/m^2)[‡]	20.9 (2.8)			21.5 (3.0)		
Absolute change from baseline in BMI (kg/m^2)						
Extension week 72		(n = 145) 0.62 (0.45, 0.79)	< 0.0001		(n = 289) 0.69 (0.56, 0.81)	< 0.0001
Extension week 96		(n = 80) 0.76 (0.56, 0.97)	< 0.0001		(n = 155) 0.96 (0.81, 1.11)	< 0.0001
Baseline CFQ-R Respiratory Domain Score (points)[‡]	70.4 (18.5)			68.3 (18.0)		
Absolute change in CFQ-R Respiratory Domain Score (points)						
Extension week 72		(n = 135) 3.3 (0.7, 5.9)	0.0124		(n = 269) 5.7 (3.8, 7.5)	< 0.0001
Extension week 96		(n = 81) 0.5 (-2.7, 3.6)	0.7665		(n = 165) 3.5 (1.3, 5.8)	0.0018
Number of Pulmonary exacerbations (events)[† ***]**						
Number of events per patient- year (95% CI) (rate per 48 weeks)		0.69 (0.56, 0.85)			0.65 (0.56, 0.75)	
Number of events requiring hospitalisation per patient-year (95% CI) (rate per 48 weeks)		0.30 (0.22, 0.40)			0.24 (0.19, 0.29)	

Baseline and endpoint	Placebo transitioned to lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 176)**			lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 369)†		
	Mean (SD)	LS Means (95% CI)	P value	Mean (SD)	LS Means (95% CI)	P value
Number of events requiring intravenous antibiotics per patient-year (95% CI) (rate per 48 weeks)		0.37 (0.29, 0.49)			0.32 (0.26, 0.38)	

* A total of 82% (421 of 516 eligible patients) completed 72 weeks of this study; 42% completed 96 weeks. Majority of patients discontinued for reasons other than safety.

** For patients rolled over from trials 809-103 and 809-104 (placebo-to-lumacaftor/ivacaftor group) total exposure was up to 96 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

*** The event rate per patient-year was annualised to 48 weeks.

† For patients rolled over from trials 809-103 and 809-104 (lumacaftor/ivacaftor-to-lumacaftor/ivacaftor group) total exposure was up to 120 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

‡ Baseline for the placebo transitioned to lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the trial 809-105 baseline. Baseline for the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the trial 809-103 and 809-104 baseline.

Trial in patients with CF who are heterozygous for the F508del mutation in the CFTR gene

Trial 809-102 was a multicentre, double–blind, randomised, placebo–controlled, phase 2 trial in 125 patients with CF aged 18 years and older who had a $ppFEV_1$ of 40 to 90, inclusive, and have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in the lack of CFTR production or a CFTR that is not responsive to ivacaftor *in vitro*.

Patients received either lumacaftor/ivacaftor (n = 62) or placebo (n = 63) in addition to their prescribed CF therapies. The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline at day 56 in $ppFEV_1$. Treatment with lumacaftor/ivacaftor resulted in no significant improvement in $ppFEV_1$ relative to placebo in patients with CF heterozygous for the *F508del* mutation in the *CFTR* gene (treatment difference 0.60 [P = 0.5978]) and no meaningful improvements in BMI or weight (see section 4.4).

Paediatric population

Trials in patients with CF aged 6 to less than 12 years old who are homozygous for the F508del mutation in the CFTR gene

Trial 809-109 was a 24-week, placebo-controlled, phase 3 clinical study in 204 patients with CF aged 6 to less than 12 years old (mean age 8.8 years). Trial 809-109 evaluated subjects with lung clearance index ($LCI_{2.5}$) $\geq$ 7.5 at the initial screening visit (mean $LCI_{2.5}$ 10.28 at baseline [range: 6.55 to 16.38]) and $ppFEV_1 \geq 70$ at screening (mean $ppFEV_1$ 89.8 at baseline [range: 48.6 to 119.6]). Patients received either lumacaftor 200 mg/ivacaftor 250 mg every 12 hours (n = 103) or placebo (n = 101) in addition to their prescribed CF therapies. Patients who had 2 or more abnormal liver function tests (ALT, AST, AP, GGT $\geq$ 3 times the ULN), or ALT or AST > 5 times ULN, or total bilirubin > 2 times ULN were excluded.

The primary efficacy endpoint was absolute change in $LCI_{2.5}$ from baseline through week 24. Key secondary endpoints included average absolute change from baseline in sweat chloride at day 15 and week 4 and at week 24 (see Pharmacodynamic effects), absolute change from baseline in BMI at week 24, absolute change from baseline in CFQ-R Respiratory Domain through week 24. These results are presented in Table 8 below:

Table 8: Summary of primary and key secondary outcomes in trial 809-109

		Placebo (n = 101)	LUM 200 mg/IVA 250 mg q12h (n = 103)
Primary endpoint			
Absolute change in lung clearance index ($LCI_{2.5}$) from baseline through week 24	Treatment difference	–	-1.09 (P < 0.0001)
	Within-group change	0.08 (P = 0.5390)	-1.01 (P < 0.0001)
Key Secondary Endpoints*			
Absolute change in BMI at week 24 (kg/m^2)	Treatment difference	–	0.11 (P = 0.2522)
	Within-group change	0.27 (P = 0.0002)	0.38 (P < 0.0001)
Absolute change in CFQ-R Respiratory Domain Score through week 24 (points)	Treatment difference	–	2.5 (P = 0.0628)
	Within-group change	3.0 (P = 0.0035)	5.5 (P < 0.0001)

* Trial included key secondary and other secondary endpoints.

Percent predicted FEV_1 was also evaluated as a clinically meaningful other secondary endpoint. In the lumacaftor/ivacaftor patients, the treatment difference for absolute change in $ppFEV_1$ from baseline through week 24 was 2.4 (P = 0.0182).

Patients with CF aged 6 years and older from trial 809-011 and trial 809-109 were included in a phase 3, multicentre, rollover extension study (trial 809-110). This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 262 patients who received any treatment in trial 809-011 or trial 809-109, 239 (91%) were dosed and received active treatment (patients 6 to <12 years of age received lumacaftor 200 mg q12h/ivacaftor 250 mg q12h; patients ≥12 years of age received lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in the extension study for up to an additional 96 weeks (i.e., up to a total of 120 weeks) (see section 4.8). Secondary efficacy results and pulmonary exacerbation event rate per patient year are presented in Table 9.

Table 9: Long-term effect of lumacaftor/ivacaftor in trial 809-110

	Placebo transitioned to lumacaftor/ivacaftor (P-L/I) (n = 96)*		lumacaftor/ivacaftor – lumacaftor/ivacaftor (L/I-L/I) (n = 143)*	
Baseline and endpoint	**Mean (SD)**	**LS Mean (95% CI)**	**Mean (SD)**	**LS Mean (95% CI)**
	n = 101		n = 128	
Baseline $LCI_{2.5}$‡**	10.26 (2.24)		10.24 (2.42)	
Absolute change from baseline in $LCI_{2.5}$				
Extension week 96		(n = 69) -0.86 (-1.33, -0.38)		(n = 88) -0.85 (-1.25, -0.45)
	n = 101		n = 161	
Baseline BMI (kg/m^2)‡	16.55 (1.96)		16.56 (1.77)	
Absolute change from baseline in BMI (kg/m^2)				
Extension week 96		(n = 83) 2.04 (1.77, 2.31)		(n =130) 1.78 (1.56, 1.99)
	n = 78		n = 135	
Baseline CFQ-R‡ Respiratory Domain Score (points)	77.1 (15.5)		78.5 (14.3)	
Absolute change in CFQ-R Respiratory Domain Score (points)				
Extension week 96		(n = 65) 6.6 (3.1, 10.0)		(n = 108) 7.4 (4.8, 10.0)
Number of pulmonary exacerbations (events) (trial 809-109 FAS and ROS)†				
Number of events per patient- year (95% CI)		n = 96 0.30 (0.21, 0.43)		n = 103 0.45 (0.33, 0.61)

* Subjects treated with placebo in trial 809-109 (n=96) and transitioned onto active LUM/IVA treatment in the extension study (P-L/I). Subjects treated with LUM/IVA in either parent study [trial 809-011 (n=49) or trial 809-109 (n=94)] and continued active LUM/IVA treatment in the extension (L/I-L/I).

‡ Baseline for both groups (P-L/I and L/I-L/I) was the trial 809-011 and trial 809-109 (parent study) baseline and the corresponding n refers to the analysis set in the parent study.

** The LCI sub-study included 117 subjects in the L/I-L/I group and 96 subjects in the P-L/I group.

† FAS = Full Analysis Set (n=103) includes subjects who received L/I in trial 809-109 and in trial 809-110, assessed over the cumulative study period for L/I; ROS = Rollover Set (n=96) includes subjects who received placebo in trial 809-109 and L/I in trial 809-110, assessed over the current study period for trial 809-110.

The European Medicines Agency has deferred the obligation to submit the results of studies with Orkambi in one or more subsets of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 (see section 4.5).

After oral administration of lumacaftor 400 mg q12h/ivacaftor 250 mg q12h in a fed state, the steady-state mean (± SD) for $AUC_{0\text{-}12h}$ and C_{max} were 198 (64.8) µg·h/mL and 25.0 (7.96) µg/mL for lumacaftor, respectively, and 3.66 (2.25) µg·h/mL and 0.602 (0.304) µg/mL for ivacaftor, respectively. After oral administration of ivacaftor alone as 150 mg q12h in a fed state, the steady-state mean (± SD) for $AUC_{0\text{-}12h}$ and C_{max} were 9.08 (3.20) µg·h/mL and 1.12 (0.319) µg/mL, respectively.

Absorption

Following multiple oral doses of lumacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 50 mg to 1000 mg every 24 hours. The exposure of lumacaftor increased approximately 2.0-fold when given with fat-containing food relative to 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 dose from 150 mg every 12 hours to 250 mg every 12 hours. The exposure of ivacaftor when given in combination with lumacaftor increased approximately 3-fold when given with fat-containing food in healthy volunteers. Therefore, lumacaftor/ivacaftor should be administered with fat-containing food. The median (range) T_{max} of ivacaftor is approximately 4.0 hours (2.0; 6.0) in the fed state.

Distribution

Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin. After oral administration of 400 mg every 12 hours in patients with CF in a fed state, the typical apparent volumes of distribution for the central and peripheral compartments [coefficient of variation as a percentage (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. 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.

In vitro studies indicate that lumacaftor is a substrate of Breast Cancer Resistance Protein (BCRP).

Biotransformation

Lumacaftor is not extensively metabolised in humans, with the majority of lumacaftor excreted unchanged in the faeces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolised via oxidation and glucuronidation.

Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth 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 faeces. There was negligible urinary excretion of lumacaftor as unchanged drug. The apparent terminal half-life is approximately 26 hours. The typical apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/h (29.4%) for patients with CF.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the faeces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged

drug. In healthy subjects, the half-life of ivacaftor when given with lumacaftor is approximately 9 hours. The typical CL/F (CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/h (40.5%) for patients with CF.

Special populations

Hepatic impairment

Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had higher exposures ($AUC_{0\text{-}12h}$ by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. 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%.

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 (see sections 4.2, 4.4, and 4.8).

Renal impairment

Pharmacokinetic studies have not been performed with lumacaftor/ivacaftor in patients with renal impairment. 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). 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). A population pharmacokinetic analysis of clearance versus creatinine clearance shows no trend for subjects with mild and moderate renal impairment (see section 4.2).

Elderly

The safety and efficacy of lumacaftor/ivacaftor in patients aged 65 years or older have not been evaluated.

Gender

The effect of gender on lumacaftor pharmacokinetics 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 or ivacaftor between males and females. No dose adjustments are necessary based on gender.

Paediatric population

The exposures are similar between adults and the paediatric population based on population (PK) analyses as presented in Table 10:

Table 10: Mean (SD) lumacaftor and ivacaftor exposure by age group

Age group	Dose	Mean lumacaftor (SD) AUCss (µg·h/mL)	Mean ivacaftor (SD) AUCss (µg·h/mL)
Patients aged 6 to <12 years	lumacaftor 200 mg/ivacaftor 250 mg every 12 hours	203 (57.4)	5.26 (3.08)
Patients aged 12 to <18 years	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	241 (61.4)	3.90 (1.56)
Patients aged 18 years and older	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	198 (64.8)	3.66 (2.25)

5.3 Preclinical safety data

Lumacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Specific studies to evaluate the phototoxic potential of lumacaftor were not conducted; however, evaluation of the available non-clinical and clinical data suggests no phototoxic liability.

Ivacaftor

Effects in repeated dose studies were observed only at exposures considered sufficiently in excess (> 25-, > 45-, and > 35-fold for mice, rats, and dogs, respectively) of the maximum human exposure of ivacaftor when administered as Orkambi, indicating little relevance to clinical use. Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Safety pharmacology

Ivacaftor produced concentration-dependent inhibitory effect on hERG (human ether-à-go-go related gene) tail currents, with an IC_{15} of 5.5 µM, compared to the C_{max} (1.5 µM) for ivacaftor at the therapeutic dose for lumacaftor/ivacaftor. However, no ivacaftor-induced 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 of up to 1 year duration at the 60 mg/kg/day dose level in dogs (C_{max} after 365 days = 36.2 to 47.6 µM). Ivacaftor produced a dose-related but transient increase in the blood pressure parameters in dogs at single oral doses up to 60 mg/kg (see section 5.1).

Pregnancy and fertility

Ivacaftor was not teratogenic when dosed orally to pregnant rats and rabbits during the organogenesis stage of foetal development at doses approximately 7 times (ivacaftor and metabolite exposure) and 46 times the ivacaftor exposure in humans at the therapeutic lumacaftor/ivacaftor dose, respectively. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight; an increase in the incidence of variations in cervical ribs, hypoplastic ribs, and wavy ribs; and sternal irregularities, including fusions. The significance of these findings for humans is unknown.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (yielding exposures approximately 11 and 7 times, respectively, those obtained with the maximum recommended human dose 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 and gestation day 17 exposures in the pilot embryofoetal development study in this species) 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 (yielding exposures approximately 8 and 5 times, respectively, those obtained with the maximum recommended human dose 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 and gestation day 17 exposures in the embryofoetal development study in this species). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

Peri- and post-natal development

Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day (yielding exposures that were approximately 4 times those obtained with the maximum recommended human dose of the ivacaftor component of Orkambi based on summed AUCs of ivacaftor and its metabolites). Doses above 100 mg/kg/day resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights.

Juvenile animals

Findings of cataracts were observed in juvenile rats dosed with ivacaftor at 0.32 times the maximum recommended human dose based on systemic exposure of ivacaftor and its metabolites when co-administered with lumacaftor as Orkambi. Cataracts were not observed in foetuses derived from rat dams treated during the organogenesis stage of foetal development, in rat pups exposed to a certain extent through milk ingestion prior to weaning, or in repeated dose toxicity studies with ivacaftor. The potential relevance of these findings in humans is unknown.

Lumacaftor and ivacaftor

Repeat-dose toxicity studies involving the co-administration of lumacaftor and ivacaftor revealed no special hazard for humans in terms of potential for additive and/or synergistic toxicities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Croscarmellose sodium
Hypromellose acetate succinate
Povidone (K30)
Sodium laurilsulfate
Magnesium stearate

Coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol (3350)
Talc
Carmine (E120)
Brilliant blue FCF aluminium lake (E133)
Indigo carmine aluminium lake (E132)

Printing ink

Shellac
Iron oxide black (E172)

Propylene glycol
Ammonia solution, concentrated

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Orkambi 100 mg/125 mg film-coated tablets

3 years

Orkambi 200 mg/125 mg film-coated tablets

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister consisting of PolyChloroTriFluoroEthylene (PCTFE)/PolyVinyl Chloride (PVC) with a paper-backed aluminium foil lidding.

Orkambi 100 mg/125 mg film-coated tablets

Pack containing 112 (4 packs of 28) film-coated tablets.

Orkambi 200 mg/125 mg film-coated tablets

Multipacks containing 112 (4 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001

EU/1/15/1059/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015
Date of latest renewal: 17 September 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 75 mg/94 mg granules in sachet
Orkambi 100 mg/125 mg granules in sachet
Orkambi 150 mg/188 mg granules in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Orkambi 75 mg/94 mg granules in sachet

Each sachet contains 75 mg of lumacaftor and 94 mg of ivacaftor.

Orkambi 100 mg/125 mg granules in sachet

Each sachet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 150 mg/188 mg granules in sachet

Each sachet contains 150 mg of lumacaftor and 188 mg of ivacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules

White to off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orkambi granules are indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2, 4.4, and 5.1).

4.2 Posology and method of administration

Orkambi should only be prescribed by physicians with experience in the treatment of CF. 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.

Posology

Table 1: Dosing recommendations in patients aged 1 year and older

Age	Weight	Strength	Dose (every 12 hours)	
			Morning	Evening
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg	1 sachet	1 sachet
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg	1 sachet	1 sachet
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg	1 sachet	1 sachet
2 to 5 years	<14 kg	lumacaftor 100 mg/ivacaftor 125 mg	1 sachet	1 sachet
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg	1 sachet	1 sachet
6 years and older	See Orkambi tablets SmPC for further details			

Patients may start treatment on any day of the week.

This medicinal product should be taken with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing (see section 5.2).

Missed dose

If less than 6 hours have passed since the missed dose, the scheduled dose 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. A double dose should not be taken to make up for the forgotten dose.

Concomitant use of CYP3A inhibitors

No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking Orkambi. However, when initiating treatment in patients taking strong CYP3A inhibitors, the dose should be reduced to one sachet every other day for the first week of treatment to allow for the steady state induction effect of lumacaftor. Following this period, the recommended daily dose should be continued (see Table 2).

Table 2: Treatment initiation in patients taking strong CYP3A inhibitors:

Age	Weight	Strength	Week 1 of treatment	Week 2 onwards
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ivacaftor 94 mg	1 sachet every other day, i.e. Day 1,3,5,7.	From day 8 and thereafter dosing should be at the recommended daily dose
	9 kg to <14 kg	lumacaftor 100 mg/ivacaftor 125 mg		
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg		
2 to 5 years	<14 kg	lumacaftor 100 mg/ivacaftor 125 mg		
	≥14 kg	lumacaftor 150 mg/ivacaftor 188 mg		
6 years and older	See Orkambi tablets SmPC for further details			

If treatment is interrupted for more than one week and then re-initiated while taking strong CYP3A inhibitors, the dose should be reduced to one sachet every other day for the first week of treatment

re-initiation (see Table 2). Following this period, the recommended daily dose should be continued (see section 4.5).

Special populations

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). For patients with moderate hepatic impairment (Child-Pugh Class B), a dose reduction is recommended.

There is no experience of the use of the medicinal product 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 in patients with severe hepatic impairment at a reduced dose (see sections 4.4, 4.8, and 5.2).

For dose adjustments for patients with moderate or severe hepatic impairment (see Table 3).

Table 3: Dose adjustment recommendations for patients with moderate or severe hepatic impairment

<table>
<tr><th rowspan="2">Age</th><th rowspan="2">Weight</th><th rowspan="2">Strength</th><th colspan="2">Moderate (Child-Pugh Class B)</th><th colspan="2">Severe (Child-Pugh Class C)</th></tr>
<tr><th>Morning</th><th>Evening</th><th>Morning</th><th>Evening</th></tr>
<tr><td rowspan="3">1 to <2 years</td><td>7 kg to <9 kg</td><td>lumacaftor 75 mg/ivacaftor 94 mg</td><td rowspan="5">1 sachet of oral granules per day</td><td rowspan="5">1 sachet of oral granules every other day</td><td rowspan="5">1 sachet of oral granules per day or less frequently*</td><td rowspan="5">No dose</td></tr>
<tr><td>9 kg to <14 kg</td><td>lumacaftor 100 mg/ivacaftor 125 mg</td></tr>
<tr><td>≥14 kg</td><td>lumacaftor 150 mg/ivacaftor 188 mg</td></tr>
<tr><td rowspan="2">2 to 5 years</td><td><14 kg</td><td>lumacaftor 100 mg/ivacaftor 125 mg</td></tr>
<tr><td>≥14 kg</td><td>lumacaftor 150 mg/ivacaftor 188 mg</td></tr>
</table>

* Dosing interval should be modified according to clinical response and tolerability.

Paediatric population

The safety and efficacy of Orkambi in children aged less than 1 year have not yet been established. No data are available.

Method of administration

For oral use.

Each sachet is for single use only.

The entire content of each sachet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Some examples of soft foods or liquids include puréed fruits or vegetables, flavoured yogurt, applesauce, water, milk, breast milk, infant formula or juice. Food or liquid should be at room temperature or below. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with CF who are heterozygous for the *F508del* mutation in the *CFTR* gene

Lumacaftor/ivacaftor is not effective in patients with CF who have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in a lack of CFTR production or that is not responsive to ivacaftor *in vitro* (see section 5.1).

Patients with CF who have a gating (Class III) mutation in the *CFTR* gene

Lumacaftor/ivacaftor has not been studied in patients with CF who have a gating (Class III) mutation in the *CFTR* gene on one allele, with or without the *F508del* mutation on the other allele. Since the exposure of ivacaftor is very significantly reduced when dosed in combination with lumacaftor, lumacaftor/ivacaftor should not be used in these patients.

Respiratory adverse reactions

Respiratory adverse reactions (e.g., chest discomfort, dyspnoea, bronchospasm, and respiration abnormal) were more common during initiation of lumacaftor/ivacaftor therapy. Serious respiratory events were seen more frequently in patients with percent predicted forced expiratory volume in 1 second ($ppFEV_1$) <40, and may lead to discontinuation of the medicinal product. Clinical experience in patients with $ppFEV_1$ <40 is limited and additional monitoring of these patients is recommended during initiation of therapy (see section 4.8). A transient decline in FEV_1 has also been observed in some patients following initiation of lumacaftor/ivacaftor. There is no experience of initiating treatment with lumacaftor/ivacaftor in patients having a pulmonary exacerbation and initiating treatment in patients having a pulmonary exacerbation is not advisable.

Effect on blood pressure

Increased blood pressure has been observed in some patients treated with lumacaftor/ivacaftor. Blood pressure should be monitored periodically in all patients during treatment (see section 4.8).

Patients with advanced liver disease

Abnormalities in liver function, including advanced liver disease, can be present in patients with CF. Worsening of liver function in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension receiving lumacaftor/ivacaftor. Lumacaftor/ivacaftor should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If lumacaftor/ivacaftor is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced (see sections 4.2, 4.8, and 5.2).

Hepatobiliary adverse reactions

Elevated transaminases have been commonly reported in patients with CF receiving lumacaftor/ivacaftor. In some instances, these elevations have been associated with concomitant

elevations in total serum bilirubin. Transaminase elevations have been observed more frequently in paediatric patients than in adult patients. Among different age paediatric cohorts, in the 2 to 5 years old patients, transaminase elevations have been observed more frequently than in the 6 to less than 12 years old (see section 4.8).

Because an association with liver injury cannot be excluded, assessments of liver function tests (ALT, AST and bilirubin) are recommended before initiating lumacaftor/ivacaftor, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered.

In the event of significant elevation of ALT or AST, with or without elevated bilirubin (either ALT or AST > 5 x the upper limit of normal [ULN], or ALT or AST > 3 x ULN with bilirubin > 2 x ULN and/or clinical jaundice), dosing with lumacaftor/ivacaftor should be discontinued and laboratory tests closely followed until the abnormalities resolve. A thorough investigation of potential causes should be conducted and patients should be followed closely for clinical progression. Following resolution of transaminase elevations, the benefits and risks of resuming dosing should be considered (see sections 4.2, 4.8, and 5.2).

Depression

Depression (including suicidal ideation and suicide attempt) has been reported in patients treated with lumacaftor/ivacaftor, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders (see section 4.8). In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour and to seek medical advice immediately if these symptoms occur.

Interactions with medicinal products

Substrates of CYP3A

Lumacaftor is a strong inducer of CYP3A. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended (see section 4.5). 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 section 4.5).

Strong CYP3A inducers

Ivacaftor is a substrate of CYP3A4 and CYP3A5. Therefore, co-administration with strong CYP3A inducers (e.g., rifampicin, St. John's wort [*Hypericum perforatum*]) is not recommended (see section 4.5).

Renal impairment

Caution is recommended while using lumacaftor/ivacaftor in patients with severe renal impairment or end-stage renal disease (see sections 4.2 and 5.2).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with lumacaftor/ivacaftor 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 section 5.3). Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with lumacaftor/ivacaftor.

Patients after organ transplantation

Lumacaftor/ivacaftor has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. See section 4.5 for interactions with immunosuppressants.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Lumacaftor is a strong inducer of CYP3A and ivacaftor is a weak inhibitor of CYP3A when given as monotherapy. There is potential for other medicinal products to affect lumacaftor/ivacaftor when administered concomitantly, and also for lumacaftor/ivacaftor to affect other medicinal products.

Potential for other medicinal products to affect lumacaftor/ivacaftor

Inhibitors of CYP3A

Co-administration of lumacaftor/ivacaftor with itraconazole, a strong CYP3A inhibitor, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. Due to the induction effect of lumacaftor on CYP3A, at steady-state, the net exposure of ivacaftor when co-administered with a CYP3A inhibitor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours, the approved dose of ivacaftor monotherapy.

No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking lumacaftor/ivacaftor. However, when initiating lumacaftor/ivacaftor in patients taking strong CYP3A inhibitors, the dose should be adjusted (see sections 4.2 and 4.4).

No dose adjustment is recommended when used with moderate or weak CYP3A inhibitors.

Inducers of CYP3A

Co-administration of lumacaftor/ivacaftor with rifampicin, a strong CYP3A inducer, had minimal effect on the exposure of lumacaftor, but decreased ivacaftor exposure (AUC) by 57%. Therefore, co-administration of lumacaftor/ivacaftor is not recommended with strong CYP3A inducers (see sections 4.2 and 4.4).

No dose adjustment is recommended when used with moderate or weak CYP3A inducers.

Potential for lumacaftor/ivacaftor to affect other medicinal products

CYP3A substrates

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. Therefore, concomitant use of lumacaftor/ivacaftor with CYP3A substrates may decrease the exposure of these substrates (see section 4.4).

P-gp substrates

In vitro studies indicated that lumacaftor has the potential to both inhibit and induce P-gp. Additionally, a clinical study with ivacaftor monotherapy showed that ivacaftor is a weak inhibitor of P-gp. Therefore, concomitant use of lumacaftor/ivacaftor with P-gp substrates (e.g., digoxin) may alter the exposure of these substrates.

CYP2B6 and CYP2C substrates

Interaction with CYP2B6 and CYP2C substrates has not been investigated *in vivo*. *In vitro* studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; however, 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 lumacaftor/ivacaftor may alter (i.e., either increase or decrease) the exposure of CYP2C8 and CYP2C9 substrates, decrease the exposure of CYP2C19 substrates, and substantially decrease the exposure of CYP2B6 substrates.

Potential for lumacaftor/ivacaftor to interact with transporters

In vitro experiments show that lumacaftor is a substrate for Breast Cancer Resistance Protein (BCRP). Co-administration of Orkambi with medicinal products that inhibit BCRP may increase plasma lumacaftor concentration. Lumacaftor inhibits the organic anion transporter (OAT) 1 and 3. Lumacaftor and ivacaftor are inhibitors of BCRP. Co-administration of Orkambi with medicinal products that are substrates for OAT1/3 and BCRP transport may increase plasma concentrations of such medicinal products. Lumacaftor and ivacaftor are not inhibitors of OATP1B1, OATP1B3, and organic cation transporter (OCT) 1 and 2. Ivacaftor is not an inhibitor of OAT1 and OAT3.

Established and other potentially significant interactions

Table 4 provides the established or predicted effect of lumacaftor/ivacaftor on other medicinal products or the effect of other medicinal products on lumacaftor/ivacaftor. The information reported in Table 4 mostly derives from *in vitro* studies. The recommendations provided under "Clinical comment" in Table 4 are based on interaction studies, clinical relevance, or predicted interactions due to elimination pathways. Interactions that have the most clinical relevance are listed first.

Table 4: Established and other potentially significant interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products

Concomitant medicinal product class: Active substance name	**Effect**	**Clinical comment**
Concomitant medicinal products of most clinical relevance		
Anti-allergics:		
montelukast	↔ LUM, IVA	
	↓ 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.
fexofenadine	↔ LUM, IVA	

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
	↑ or ↓ fexofenadine Due to potential induction or inhibition of P-gp	Dose adjustment of fexofenadine may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of fexofenadine.
Antibiotics:		
clarithromycin, telithromycin	↔ LUM ↑ IVA Due to inhibition of CYP3A by clarithromycin, telithromycin	No dose adjustment of lumacaftor/ivacaftor is recommended when clarithromycin or telithromycin are initiated in patients currently taking lumacaftor/ivacaftor.
	↓ clarithromycin, telithromycin Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one sachet every other day for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking clarithromycin or telithromycin. An alternative to these antibiotics, such as azithromycin, should be considered. Lumacaftor/ivacaftor may decrease the exposures of clarithromycin and telithromycin, which may reduce their efficacy.
erythromycin	↔ LUM ↑ 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	↔ LUM ↓ IVA Due to induction of CYP3A by these anticonvulsants	
	↓ carbamazepine, phenobarbital, phenytoin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anticonvulsants is not recommended. The exposures of ivacaftor and the anticonvulsant may be significantly decreased, which may reduce the efficacy of both active substances.
Antifungals:		
itraconazole*, ketoconazole, posaconazole, voriconazole	↔ LUM ↑ 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.

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
	↓ itraconazole, ketoconazole, voriconazole Due to induction of CYP3A by LUM	The dose of lumacaftor/ivacaftor should be reduced to one sachet every other day for the first week of treatment when initiating lumacaftor/ivacaftor in patients currently taking these antifungals.
	↓ posaconazole Due to induction of UGT by LUM	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	↔ LUM ↑ 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; fluconazole is cleared primarily by renal excretion as unchanged drug; however, modest reduction in fluconazole exposure has been observed with strong inducers	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	↔ LUM, IVA	
	↓ ibuprofen Due to induction of CYP3A/2C8/2C9 by LUM	A higher dose of ibuprofen may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of ibuprofen, which may reduce its efficacy.
Anti-mycobacterials:		
rifabutin, rifampicin*, rifapentine	↔ LUM ↓ IVA Due to induction of CYP3A by anti-mycobacterials	

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
	↓ rifabutin Due to induction of CYP3A by LUM	Concomitant use of lumacaftor/ivacaftor with these anti-mycobacterials is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor. A higher dose of rifabutin may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of rifabutin, which may reduce its efficacy.
	↔ rifampicin, rifapentine	
Benzodiazepines:		
midazolam, triazolam	↔ LUM, IVA	
	↓ 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:		
ethinyl estradiol, norethindrone, and other progestogens	↓ ethinyl estradiol, norethindrone, and other progestogens Due to induction of CYP3A/UGT by LUM	Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with lumacaftor/ivacaftor. Lumacaftor/ivacaftor may decrease the exposure of hormonal contraceptives, which may reduce their efficacy.
Immunosuppressants:		
ciclosporin, everolimus, sirolimus, tacrolimus (used after organ transplant)	↔ LUM, IVA	
	↓ ciclosporin, 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:		
	↔ LUM, IVA	

Concomitant medicinal product class: **Active substance name**	**Effect**	**Clinical comment**
esomeprazole, lansoprazole, omeprazole	↓ 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.
Herbals:		
St. John's wort (*Hypericum perforatum*)	↔ LUM ↓ IVA Due to induction of CYP3A by St. John's wort	Concomitant use of lumacaftor/ivacaftor with St. John's wort is not recommended. The exposure of ivacaftor will be decreased, which may reduce the efficacy of lumacaftor/ivacaftor.
Other concomitant medicinal products of clinical relevance		
Antiarrhythmics:		
digoxin	↔ LUM, IVA	
	↑ 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:		
dabigatran	↔ LUM, IVA	
	↑ or ↓ dabigatran Due to potential induction or inhibition of P-gp	Appropriate clinical monitoring should be employed when co-administered with lumacaftor/ivacaftor. Dose adjustment of dabigatran may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may alter the exposure of dabigatran.
warfarin	↔ LUM, IVA	
	↑ or ↓ warfarin Due to potential induction or inhibition of CYP2C9 by LUM	The international normalised ratio (INR) should be monitored when warfarin co-administration with lumacaftor/ivacaftor is required. Lumacaftor/ivacaftor may alter the exposure of warfarin.
Antidepressants:		
citalopram, escitalopram, sertraline	↔ LUM, IVA	
	↓ 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.
bupropion	↔ LUM, IVA	

Concomitant medicinal product class: Active substance name	Effect	Clinical comment
	↓ bupropion Due to induction of CYP2B6 by LUM	A higher dose of bupropion may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of bupropion, which may reduce its efficacy.
Corticosteroids, systemic:		
methylprednisolone, prednisone	↔ LUM, IVA	
	↓ 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	↔ LUM, IVA	
	↑ 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.
Oral hypoglycemics:		
repaglinide	↔ LUM, IVA	
	↓ repaglinide Due to induction of CYP3A/2C8 by LUM	A higher dose of repaglinide may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposure of repaglinide, which may reduce its efficacy.

Note: ↑ = increase, ↓ = decrease, ↔ = no change; LUM = lumacaftor; IVA = ivacaftor.
* Based on clinical interaction studies. All other interactions shown are predicted.

False positive urine tests for THC

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving Orkambi. An alternative confirmatory method should be considered to verify results.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of lumacaftor/ivacaftor in pregnant women. Animal studies with lumacaftor and ivacaftor do not indicate direct or indirect harmful effects with respect to developmental and reproductive toxicity, whereas effects were noted with ivacaftor only at maternally toxic doses (see section 5.3). As a precautionary

measure, it is preferable to avoid the use of lumacaftor/ivacaftor during pregnancy unless the clinical condition of the mother requires treatment with lumacaftor/ivacaftor.

Breast-feeding

Limited data show that ivacaftor and lumacaftor are excreted into human milk. There is insufficient information on the effects of lumacaftor/ivacaftor in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effects of lumacaftor and/or ivacaftor on fertility are available. Lumacaftor had no effects on fertility and reproductive performance indices in male and female rats. Ivacaftor impaired fertility and reproductive performance indices in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Ivacaftor, which is one of the active components of Orkambi, has a minor influence on the ability to drive and use machines. Ivacaftor may cause dizziness (see section 4.8). Patients experiencing dizziness while taking Orkambi should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are dyspnoea (14.0%), diarrhoea (11.0%), and nausea (10.2%).

Serious adverse reactions included hepatobiliary events, e.g., transaminase elevations (0.5%), cholestatic hepatitis (0.3%) and hepatic encephalopathy (0.1%).

Tabulated list of adverse reactions

Table 5 reflects the adverse reactions reported with lumacaftor/ivacaftor and ivacaftor monotherapy from clinical trials, post-authorisation safety studies and spontaneous reporting. Adverse reactions are listed by MedDRA system organ class and frequency: very common (≥ 1/ 10); common (≥ 1/ 100 to < 1/ 10); uncommon (≥ 1/ 1,000 to < 1/ 100); rare (≥ 1/ 10,000 to < 1/ 1,000); very rare (< 1/ 10,000); and not known (frequency cannot be estimated from the available data).

Table 5: Adverse reactions in lumacaftor/ivacaftor-treated patients and in patients treated with ivacaftor alone

System organ class	Frequency	Adverse reactions
Infections and infestations	very common	Nasopharyngitis*
	common	Upper respiratory tract infection, rhinitis
Psychiatric disorders	not known	Depression
Vascular disorders	uncommon	Hypertension
Nervous system disorders	very common	Headache, dizziness*
	uncommon	Hepatic encephalopathy†
Ear and labyrinth disorders	common	Ear pain*, ear discomfort*, tinnitus*, tympanic membrane hyperaemia*, vestibular disorder*
	uncommon	Ear congestion*
Respiratory, thoracic and mediastinal disorders	very common	Nasal congestion, dyspnoea, productive cough, sputum increased
	common	Respiration abnormal, oropharyngeal pain, sinus congestion*, rhinorrhoea, pharyngeal erythema*, bronchospasm

System organ class	Frequency	Adverse reactions
Gastrointestinal disorders	very common	Abdominal pain*, abdominal pain upper, diarrhoea, nausea
	common	Flatulence, vomiting
Hepatobiliary disorders	common	Transaminase elevations
	uncommon	Cholestatic hepatitis‡
Skin and subcutaneous tissue disorders	common	Rash
Reproductive system and breast disorders	common	Menstruation irregular, dysmenorrhoea, metrorrhagia, breast mass*
	uncommon	Menorrhagia, amenorrhoea, polymenorrhoea, breast inflammation*, gynaecomastia*, nipple disorder*, nipple pain*, oligomenorrhoea
Investigations	very common	Bacteria in sputum*
	common	Blood creatine phosphokinase increased
	uncommon	Blood pressure increased

* Adverse reactions and frequencies observed in patients in clinical studies with ivacaftor monotherapy.
† 1 patient out of 738
‡ 2 patients out of 738

The safety data from a 96-week rollover study (809-105) were consistent with the safety data from the phase 3 studies (trials 809-103 and 809-104).

Description of selected adverse reactions

Hepatobiliary adverse reactions

During trials 809-103 and 809-104, the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 0.8%, 2.0%, and 5.2%, and 0.5%, 1.9%, and 5.1% in lumacaftor/ivacaftor- and placebo-treated patients, respectively. The incidence of transaminase-related adverse reactions was 5.1% and 4.6% in lumacaftor/ivacaftor-treated patients and those who received placebo, respectively. Seven patients who received lumacaftor/ivacaftor had liver-related serious adverse reactions with elevated transaminases, including 3 with concurrent elevation in total bilirubin. Following discontinuation of lumacaftor/ivacaftor, liver function tests returned to baseline or improved substantially in all patients (see section 4.4).

Among 7 patients with pre-existing cirrhosis and/or portal hypertension who received lumacaftor/ivacaftor in the placebo-controlled, phase 3 studies, 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 lumacaftor/ivacaftor (see section 4.4).

Post–marketing cases of liver function decompensation including liver failure leading to death have been reported in CF patients with pre-existing cirrhosis with portal hypertension who were treated with lumacaftor/ivacaftor (see section 4.4).

Respiratory adverse reactions

During trials 809-103 and 809-104, the incidence of respiratory adverse reactions (e.g., chest discomfort, dyspnoea, bronchospasm, and respiration abnormal) was 26.3% in lumacaftor/ivacaftor-treated patients compared to 17.0% in patients who received placebo. The incidence of these adverse reactions was more common in patients with lower pre-treatment FEV_1. Approximately three-quarters of the adverse reactions began during the first week of treatment, and in most patients the events resolved without dosing interruption. The majority of events were mild or moderate in severity, non-serious and did not result in treatment discontinuation (see section 4.4).

During a 24-week, open-label, phase 3b clinical study (trial 809-106]) in 46 patients aged 12 years and older with advanced lung disease ($ppFEV_1 < 40$) [mean $ppFEV_1$ 29.1 at baseline (range: 18.3 to 42.0)], the incidence of respiratory adverse reactions was 65.2%. In the subgroup of 28 patients who were initiated at the full dose of lumacaftor/ivacaftor (2 tablets every 12 hours), the incidence was 71.4%, and in the 18 patients who were initiated at a reduced dose of lumacaftor/ivacaftor (1 tablet every 12 hours for up to 2 weeks, and subsequently increased to the full dose), the incidence was 55.6%. Of the patients who were initiated lumacaftor/ivacaftor at the full dose, one patient had a serious respiratory adverse reaction, three patients subsequently had their dose reduced, and three patients discontinued treatment. No serious respiratory adverse reactions, dose reductions or discontinuations were seen in patients who were initiated at the half dose (see section 4.4).

Menstrual abnormalities

During trials 809-103 and 809-104, the incidence of combined menstrual abnormalities (amenorrhoea, dysmenorrhoea, menorrhagia, menstruation irregular, metrorrhagia, oligomenorrhoea, and polymenorrhoea) was 9.9% in lumacaftor/ivacaftor-treated female patients and 1.7% in placebo-treated females. These menstrual events occurred more frequently in the subset of female patients who were taking hormonal contraceptives (25.0%) versus patients who were not taking hormonal contraceptives (3.5%) (see section 4.5). Most of these reactions were mild or moderate in severity and non-serious. In lumacaftor/ivacaftor-treated patients, approximately two-thirds of these reactions resolved, and the median duration was 10 days.

Increased blood pressure

During trials 809-103 and 809-104, adverse reactions related to increased blood pressure (e.g., hypertension, blood pressure increased) were reported in 0.9% (7/738) of patients treated with lumacaftor/ivacaftor and in no patients who received placebo.

In patients treated with lumacaftor/ivacaftor (mean baseline 114 mmHg systolic and 69 mmHg diastolic), the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.1 mmHg and 1.8 mmHg, respectively. In patients who received placebo (mean baseline 114 mmHg systolic and 69 mmHg diastolic), the maximum increase from baseline in mean systolic and diastolic blood pressure was 0.9 mmHg and 0.9 mmHg, respectively.

The proportion of patients who experienced a systolic blood pressure value > 140 mmHg or a diastolic blood pressure > 90 mmHg on at least two occasions was 3.4% and 1.5% in patients treated with lumacaftor/ivacaftor, respectively, compared with 1.6% and 0.5% in patients who received placebo (see section 4.4).

Paediatric population

The safety data of lumacaftor/ivacaftor were evaluated in 46 patients aged 1 to less than 2 years (trial 809-122), 60 patients aged 2 to 5 years (trial 809-115), 161 patients aged 6 to less than 12 years (trials 809-011 and 809-109) and in 194 patients aged 12 to 17 years with CF who are homozygous for the *F508del* mutation and who received lumacaftor/ivacaftor in clinical studies. Patients aged 12 to 17 years were included in trials 809-103 and 809-104.

The overall safety profile in these paediatric patients is generally consistent with that in adult patients. Few selected adverse reactions are specifically reported in the paediatric population.

Long-term safety data from three 96-week extension studies in 52, 57, and 239 patients aged 1 year and older (trial 809-124), 2 years and older (trial 809-116), and 6 years and older (trial 809-110), respectively, who were homozygous for the *F508del* mutation in the *CFTR* gene, were generally consistent with the 24-week parent studies. The parent studies were conducted in patients aged 1 to less than 2 years (trial 809-122 parent of 809-124), age 2 to 5 years (trial 809-115 parent of 809-116), and age 6 to less than 12 years (trial 809-011 and 809-109 parents of 809-110).

Description of selected adverse reactions for paediatric patients aged 1 to less than 12 years

Hepatobiliary adverse reactions

During the 24-week, open-label phase 3 clinical study in 58 patients aged 6 to less than 12 years (trial 809-011), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 5.3%, 8.8%, and 19.3%. No patients had total bilirubin levels > 2 x ULN. Lumacaftor/ivacaftor dosing was maintained or successfully resumed after interruption in all patients with transaminase elevations, except 1 patient who discontinued treatment.

During the 24-week, placebo-controlled phase 3 clinical study in 204 patients aged 6 to less than 12 years (trial 809-109), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 1.0%, 4.9%, and 12.6% in the lumacaftor/ivacaftor patients, and 2.0%, 3.0%, and 7.9% in the placebo-treated patients. No patients had total bilirubin levels > 2 x ULN. Two patients in the lumacaftor/ivacaftor group and two patients in the placebo group discontinued treatment due to transaminase elevations.

During the 24-week, open-label phase 3 clinical study in 60 patients aged 2 through 5 years (trial 809-115), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 8.3% (5/60), 11.7% (7/60), and 15.0% (9/60). No patients had total bilirubin levels > 2 x ULN. Three patients discontinued lumacaftor/ivacaftor treatment due to transaminase elevations.

During the 24-week, open-label phase 3 clinical study in 46 patients aged 1 to less than 2 years (trial 809-122), the incidence of maximum transaminase (ALT or AST) levels > 8, > 5, and > 3 x ULN was 2.2% (1/46), 4.3% (2/46), and 10.9% (5/46). No patients had total bilirubin levels > 2 x ULN. One patient discontinued lumacaftor/ivacaftor treatment due to transaminase elevations.

Respiratory adverse reactions

During the 24-week, open-label phase 3 clinical study (trial 809-011) in 58 patients aged 6 to less than 12 years (mean baseline $ppFEV_1$ was 91.4), the incidence of respiratory adverse reactions was 6.9% (4/58).

During the 24-week, placebo-controlled phase 3 clinical study (trial 809-109) in patients aged 6 to less than 12 years (mean baseline $ppFEV_1$ was 89.8), the incidence of respiratory adverse reactions was 18.4% in lumacaftor/ivacaftor patients and 12.9% in placebo patients. A decline in $ppFEV_1$ at initiation of therapy was observed during serial post dose spirometry assessments. The absolute change from pre-dose at 4 to 6 hours post-dose was -7.7 on day 1 and -1.3 on day 15 in lumacaftor/ivacaftor patients. The post-dose decline was resolved by week 16.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Adverse reactions that occurred at an increased incidence of ≥ 5% in the supratherapeutic dose period compared with the therapeutic dose period were headache, generalised rash, and increased transaminase.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products; ATC code: R07AX30

Mechanism of action

The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. The *F508del* mutation impacts the CFTR protein in multiple ways, primarily 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 has low channel-open probability (defective channel gating). Lumacaftor is a CFTR corrector that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at 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. The combined effect of lumacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. The exact mechanisms by which lumacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.

Pharmacodynamic effects

Effects on sweat chloride

Changes in sweat chloride in response to lumacaftor alone or in combination with ivacaftor were evaluated in a double-blind, placebo-controlled, phase 2 clinical trial in patients with CF aged 18 years and older. In this trial, 10 patients (homozygous for *F508del-CFTR* mutation) 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 was statistically significant at -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 was statistically significant at -11 mmol/L (95% CI: -18, -4).

In trial 809-109 in patients homozygous for the *F508del-CFTR* mutation aged 6 to less than 12 years, the treatment difference (LS mean) in sweat chloride for the absolute change at week 24 as compared to placebo was -24.9 mmol/L (nominal $P < 0.0001$). The treatment difference (LS mean) in sweat chloride for the average absolute change at day 15 and at week 4 as compared to placebo was -20.8 mmol/L (95% CI: -23.4, -18.2; nominal $P < 0.0001$).

In trial 809-115 in patients homozygous for *F508del-CFTR* mutation aged 2 to 5 years, the mean absolute within-group change in sweat chloride from baseline at week 24 was -31.7 mmol/L (95% CI: -35.7, -27.6). In addition, the mean absolute change in sweat chloride from week 24 at week 26 following the 2-week washout period (to evaluate off-drug response) was an increase of 33.0 mmol/L (95% CI: 28.9, 37.1; nominal $P < 0.0001$), representing a return to baseline after treatment washout. At week 24, 16% of children had a reduction in sweat chloride below 60 mmol/L, and none below 30 mmol/L.

In trial 809-122 in patients homozygous for *F508del-CFTR* mutation aged 1 to less than 2 years, treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at week 4 which was sustained through week 24. The mean 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, 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.

Changes in FEV_1

Changes in $ppFEV_1$ in response to lumacaftor alone or in combination with ivacaftor were also evaluated in the double-blind, placebo-controlled, phase 2 trial in patients with CF aged 18 years and older. The treatment difference between lumacaftor 400 mg q12h alone and placebo evaluated as mean absolute change in $ppFEV_1$ was -4.6 percentage points (95% CI: -9.6, 0.4) from baseline to day 28, 4.2 percentage points (95% CI: –1.3, 9.7) from baseline to day 56, and 7.7 percentage points (95% CI: 2.6, 12.8; statistically significant) from day 28 to day 56 (following the addition of ivacaftor to lumacaftor monotherapy).

Decrease in heart rate

During the 24-week, placebo-controlled, phase 3 studies, a maximum decrease in mean heart rate of 6 beats per minute (bpm) from baseline was observed on day 1 and day 15 around 4 to 6 hours after dosing. After day 15, heart rate was not monitored in the period after dosing in these studies. From week 4, the change in mean heart rate at pre-dose ranged from 1 to 2 bpm below baseline among patients treated with lumacaftor/ivacaftor. The percentage of patients with heart rate values < 50 bpm on treatment was 11% for patients who received lumacaftor/ivacaftor, compared to 4.9% for patients who received placebo.

Cardiac electrophysiology

No meaningful changes in QTc interval or blood pressure were observed in a thorough QT clinical study evaluating lumacaftor 600 mg once daily/ivacaftor 250 mg q12h and lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h.

Clinical efficacy and safety

Trials in patients with CF aged 12 years and above who are homozygous for the F508del mutation in the CFTR gene

The efficacy of lumacaftor/ivacaftor in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene was evaluated in two randomised, double-blind, placebo-controlled clinical trials of 1,108 clinically stable patients with CF, in which 737 patients were randomised to and dosed with lumacaftor/ivacaftor. Patients in both trials were randomised 1:1:1 to receive lumacaftor 600 mg once daily/ivacaftor 250 mg q12h, 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 a blinded extension study.

Trial 809-103 evaluated 549 patients with CF who were 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]). Trial 809-104 evaluated 559 patients 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]). Patients with a history of colonisation 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 times the ULN or total bilirubin ≥ 2 times the ULN) were excluded.

The primary efficacy endpoint in both studies was the absolute change from baseline in $ppFEV_1$ at week 24. Other efficacy variables included relative change from baseline in $ppFEV_1$, absolute change from baseline in BMI, absolute change from baseline in CFQ-R Respiratory Domain, the proportion of patients achieving ≥ 5% relative change from baseline in $ppFEV_1$ at week 24, and the number of pulmonary exacerbations (including those requiring hospitalisation or IV antibiotic therapy) through week 24.

In both trials, treatment with lumacaftor/ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ (see Table 6). Mean improvement in $ppFEV_1$ was rapid in onset (day 15) and sustained throughout the 24-week treatment period. At day 15, the treatment difference between lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo for the mean absolute change (95% CI) in $ppFEV_1$ from baseline was 2.51 percentage points in the pooled trials 809-103 and 809-104 ($P < 0.0001$). Improvements in $ppFEV_1$ were observed regardless of age, disease severity, sex and geographic region. The phase 3 trials of lumacaftor/ivacaftor included 81 patients with $ppFEV_1 < 40$ at baseline. The treatment difference in this subgroup was comparable to that observed in patients with $ppFEV_1 \geq 40$. At week 24, the treatment difference between lumacaftor 400 mg/ivacaftor 250 mg q12h and placebo for the mean absolute change (95% CI) in $ppFEV_1$ from baseline in the pooled trials 809-103 and 809-104 were 3.39 percentage points ($P = 0.0382$) for patients with $ppFEV_1 < 40$ and 2.47 percentage points ($P < 0.0001$) for patients with $ppFEV_1 \geq 40$.

Table 6: Summary of primary and key secondary outcomes in trial 809-103 and trial 809-104*

		Trial 809-103		**Trial 809-104**		**Pooled (trial 809-103 and trial 809-104)**	
		Placebo (n = 184)	**LUM 400 mg q12h/ IVA 250 mg q12h (n = 182)**	**Placebo (n = 187)**	**LUM 400 mg q12h/IVA 250 mg q12h (n = 187)**	**Placebo (n = 371)**	**LUM 400 mg q12h/IVA 250 mg q12h (n = 369)**
Absolute change in $ppFEV_1$ at week 24 (percentage points)	Treatment difference	–	2.41 (P = 0.0003)†	–	2.65 (P = 0.0011)†	–	2.55 (P < 0.0001)
	Within-group change	-0.73 (P = 0.2168)	1.68 (P = 0.0051)	-0.02 (P = 0.9730)	2.63 (P < 0.0001)	-0.39 (P < 0.3494)	2.16 (P < 0.0001)
Relative change in $ppFEV_1$ at week 24 (%)	Treatment difference	–	4.15 (P = 0.0028)†	–	4.69 (P = 0.0009)†	–	4.4 (P < 0.0001)
	Within-group change	-0.85 (P = 0.3934)	3.3 (P = 0.0011)	0.16 (P = 0.8793)	4.85 (P < 0.0001)	-0.34 (P = 0.6375)	4.1 (P < 0.0001)
Absolute change in BMI at week 24 (kg/m^2)	Treatment difference	–	0.13 (P = 0.1938)	–	0.36 (P < 0.0001)†	–	0.24 (P = 0.0004)
	Within-group change	0.19 (P = 0.0065)	0.32 (P < 0.0001)	0.07 (P = 0.2892)	0.43 (P < 0.0001)	0.13 (P = 0.0066)	0.37 (P < 0.0001)
Absolute change in CFQ-R Respiratory Domain Score at week 24 (points)	Treatment difference	–	1.5 (P = 0.3569)	–	2.9 (P = 0.0736)	–	2.2 (P = 0.0512)
	Within-group change	1.1 (P = 0.3423)	2.6 (P = 0.0295)	2.8 (P = 0.0152)	5.7 (P < 0.0001)	1.9 (P = 0.0213)	4.1 (P < 0.0001)
Proportion of patients with ≥5% relative change in $ppFEV_1$ at week 24	%	25%	32%	26%	41%	26%	37%
	Odds ratio	–	1.43 (P = 0.1208)	–	1.90 (P = 0.0032)	–	1.66 (P = 0.0013)

		Trial 809-103		Trial 809-104		Pooled (trial 809-103 and trial 809-104)	
		Placebo (n = 184)	LUM 400 mg q12h/ IVA 250 mg q12h (n = 182)	Placebo (n = 187)	LUM 400 mg q12h/IVA 250 mg q12h (n = 187)	Placebo (n = 371)	LUM 400 mg q12h/IVA 250 mg q12h (n = 369)
Number of pulmonary exacerbations through week 24	# of events (rate per 48 weeks)	112 (1.07)	73 (0.71)	139 (1.18)	79 (0.67)	251 (1.14)	152 (0.70)
	Rate ratio	–	0.66 (P = 0.0169)	–	0.57 (P = 0.0002)	–	0.61 (P < 0.0001)

[*] In each study, a hierarchical testing procedure was performed within each active treatment arm for primary and secondary endpoints vs. placebo; at each step, $P \leq 0.0250$ and all previous tests also meeting this level of significance was required for statistical significance.

[†] Indicates statistical significance confirmed in the hierarchical testing procedure.

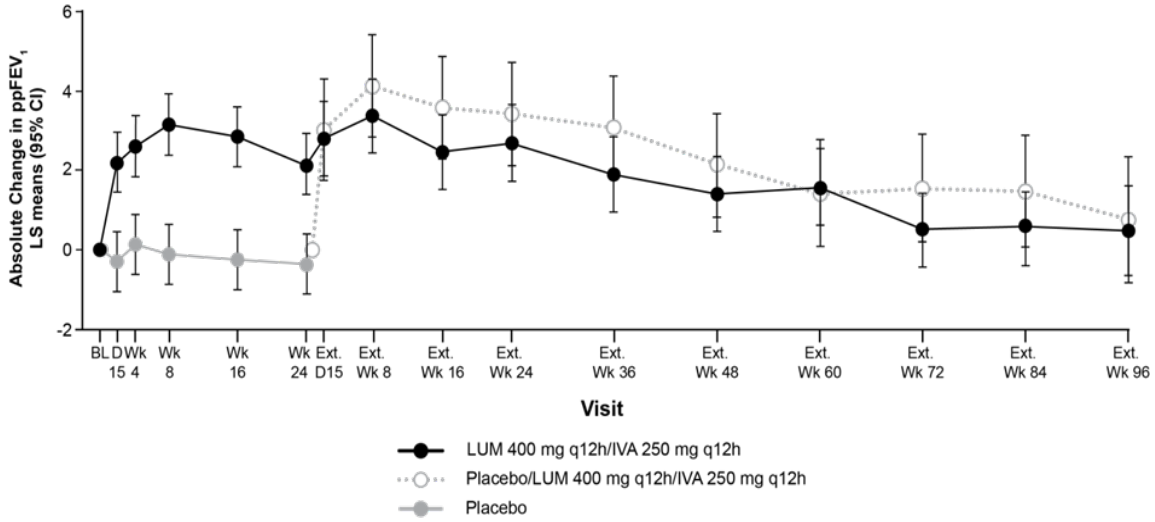
At week 24, the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with lumacaftor/ivacaftor compared with placebo. In the pooled analysis, the rate ratio of exacerbations through week 24 in subjects treated with lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h; n = 369) was 0.61 (P < 0.0001), representing a reduction of 39% relative to placebo. The event rate per year, annualised to 48 weeks, was 0.70 in the lumacaftor/ivacaftor group and 1.14 in the placebo group. Treatment with lumacaftor/ivacaftor significantly decreased the risk for exacerbations requiring hospitalisation versus placebo by 61% (rate ratio = 0.39, P < 0.0001; event rate per 48 weeks 0.17 for lumacaftor/ivacaftor and 0.45 for placebo) and reduced exacerbations requiring treatment with intravenous antibiotics by 56% (rate ratio = 0.44, P < 0.0001; event rate per 48 weeks 0.25 for lumacaftor/ivacaftor and 0.58 for placebo). These results were not considered statistically significant within the framework of the testing hierarchy for the individual studies.

Long-term safety and efficacy rollover trial

Trial 809-105 was a phase 3, parallel-group, multicentre, rollover extension study in patients with CF that included patients aged 12 years and older from trial 809-103 and trial 809-104. This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 1,108 patients who received any treatment in trial 809-103 or trial 809-104, 1,029 (93%) were dosed and received active treatment (lumacaftor 600 mg once daily/ivacaftor 250 mg q12h or lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in trial 809-105 for up to an additional 96 weeks (i.e., up to a total of 120 weeks). The primary efficacy analysis of this extension study included data up to week 72 of trial 809-105 with a sensitivity analysis that included data up to week 96 of trial 809-105.

Patients treated with lumacaftor/ivacaftor in trial 809-103 or trial 809-104 showed an effect that was maintained with respect to baseline after an additional 96 weeks through trial 809-105. For patients who transitioned from placebo to active treatment similar changes as those observed in patients treated with lumacaftor/ivacaftor in trial 809-103 or trial 809-104 were seen (see Table 6). Results from trial 809-105 are presented in Figure 1 and Table 7.

Figure 1. Absolute change from baseline in percent predicted FEV_1 at each visit†



† From trials 809-103, 809-104 and 809-105.

Table 7: Long-term effect of lumacaftor/ivacaftor in trial 809-105*

Baseline and endpoint	Placebo transitioned to lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 176)**			lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 369)†		
	Mean (SD)	**LS Means (95% CI)**	**P value**	**Mean (SD)**	**LS Means (95% CI)**	**P value**
Baseline $ppFEV_1$‡	60.2 (14.7)			60.5 (14.1)		
Absolute change from baseline $ppFEV_1$ (percentage points)						
Extension week 72		(n = 134) 1.5 (0.2, 2.9)	0.0254		(n = 273) 0.5 (-0.4, 1.5)	0.2806
Extension week 96		(n = 75) 0.8 (-0.8, 2.3)	0.3495		(n = 147) 0.5 (-0.7, 1.6)	0.4231
Relative change from baseline $ppFEV_1$ (%)						
Extension week 72		(n = 134) 2.6 (0.2, 5.0)	0.0332		(n = 273) 1.4 (-0.3, 3.2)	0.1074
Extension week 96		(n = 75) 1.1 (-1.7, 3.9)	0.4415		(n = 147) 1.2 (-0.8, 3.3)	0.2372
Baseline BMI (kg/m^2)‡	20.9 (2.8)			21.5 (3.0)		
Absolute change from baseline in BMI (kg/m^2)						
Extension week 72		(n = 145) 0.62 (0.45, 0.79)	< 0.0001		(n = 289) 0.69 (0.56, 0.81)	< 0.0001
Extension week 96		(n = 80) 0.76 (0.56, 0.97)	< 0.0001		(n = 155) 0.96 (0.81, 1.11)	< 0.0001

Baseline and endpoint	Placebo transitioned to lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 176)** Mean (SD)	LS Means (95% CI)	P value	lumacaftor 400 mg q12h/ ivacaftor 250 mg q12h (n = 369)† Mean (SD)	LS Means (95% CI)	P value
Baseline CFQ-R Respiratory Domain Score (points)‡	70.4 (18.5)			68.3 (18.0)		
Absolute change in CFQ-R Respiratory Domain Score (points)						
Extension week 72		(n = 135) 3.3 (0.7, 5.9)	0.0124		(n = 269) 5.7 (3.8, 7.5)	< 0.0001
Extension week 96		(n = 81) 0.5 (-2.7, 3.6)	0.7665		(n = 165) 3.5 (1.3, 5.8)	0.0018
Number of Pulmonary exacerbations (events)** † ***						
Number of events per patient- year (95% CI) (rate per 48 weeks)		0.69 (0.56, 0.85)			0.65 (0.56, 0.75)	
Number of events requiring hospitalisation per patient-year (95% CI) (rate per 48 weeks)		0.30 (0.22, 0.40)			0.24 (0.19, 0.29)	
Number of events requiring intravenous antibiotics per patient-year (95% CI) (rate per 48 weeks)		0.37 (0.29, 0.49)			0.32 (0.26, 0.38)	

* A total of 82% (421 of 516 eligible patients) completed 72 weeks of this study; 42% completed 96 weeks. Majority of patients discontinued for reasons other than safety.

** For patients rolled over from trials 809-103 and 809-104 (placebo-to-lumacaftor/ivacaftor group) total exposure was up to 96 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

*** The event rate per patient-year was annualised to 48 weeks.

† For patients rolled over from trials 809-103 and 809-104 (lumacaftor/ivacaftor-to-lumacaftor/ivacaftor group) total exposure was up to 120 weeks. Presentation of the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h dose group is consistent with recommended posology.

‡ Baseline for the placebo transitioned to lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the trial 809-105 baseline. Baseline for the lumacaftor 400 mg q12h/ivacaftor 250 mg q12h group was the trial 809-103 and 809-104 baseline.

Trial in patients with CF who are heterozygous for the F508del mutation in the CFTR gene

Trial 809-102 was a multicentre, double–blind, randomised, placebo–controlled, phase 2 trial in 125 patients with CF aged 18 years and older who had a $ppFEV_1$ of 40 to 90, inclusive, and have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in the lack of CFTR production or a CFTR that is not responsive to ivacaftor *in vitro*.

Patients received either lumacaftor/ivacaftor (n = 62) or placebo (n = 63) in addition to their prescribed CF therapies. The primary endpoint was improvement in lung function as determined by the mean absolute change from baseline at day 56 in $ppFEV_1$. Treatment with lumacaftor/ivacaftor resulted in no significant improvement in $ppFEV_1$ relative to placebo in patients with CF heterozygous for the *F508del* mutation in the *CFTR* gene (treatment difference 0.60 [P = 0.5978]) and no meaningful improvements in BMI or weight (see section 4.4).

Paediatric population

Trials in patients with CF aged 6 to less than 12 years old who are homozygous for the F508del mutation in the CFTR gene

Trial 809-109 was a 24-week, placebo-controlled, phase 3 clinical study in 204 patients with CF aged 6 to less than 12 years old (mean age 8.8 years). Trial 809-109 evaluated subjects with lung clearance index ($LCI_{2.5}$) ≥ 7.5 at the initial screening visit (mean $LCI_{2.5}$ 10.28 at baseline [range: 6.55 to 16.38]) and $ppFEV_1$ ≥ 70 at screening (mean $ppFEV_1$ 89.8 at baseline [range: 48.6 to 119.6]). Patients received either lumacaftor 200 mg/ivacaftor 250 mg every 12 hours (n = 103) or placebo (n = 101) in addition to their prescribed CF therapies. Patients who had 2 or more abnormal liver function tests (ALT, AST, AP, GGT ≥ 3 times the ULN), or ALT or AST > 5 times ULN, or total bilirubin > 2 times ULN were excluded.

The primary efficacy endpoint was absolute change in $LCI_{2.5}$ from baseline through week 24. Key secondary endpoints included average absolute change from baseline in sweat chloride at day 15 and week 4 and at week 24 (see Pharmacodynamic effects), absolute change from baseline in BMI at week 24, absolute change from baseline in CFQ-R Respiratory Domain through week 24. These results are presented in Table 8 below:

Table 8: Summary of primary and key secondary outcomes in trial 809-109

		Placebo (n = 101)	**LUM 200 mg/IVA 250 mg q12h (n = 103)**
Primary Endpoint			
Absolute change in lung clearance index ($LCI_{2.5}$) from baseline through week 24	Treatment difference	–	-1.09 (P < 0.0001)
	Within-group change	0.08 (P = 0.5390)	-1.01 (P < 0.0001)
Key Secondary Endpoints*			
Absolute change in BMI at week 24 (kg/m^2)	Treatment difference	–	0.11 (P = 0.2522)
	Within-group change	0.27 (P = 0.0002)	0.38 (P < 0.0001)
Absolute change in CFQ-R Respiratory Domain Score through week 24 (points)	Treatment difference	–	2.5 (P = 0.0628)
	Within-group change	3.0 (P = 0.0035)	5.5 (P < 0.0001)

* Trial included key secondary and other secondary endpoints.

Percent predicted FEV_1 was also evaluated as a clinically meaningful other secondary endpoint. In the lumacaftor/ivacaftor patients, the treatment difference for absolute change in $ppFEV_1$ from baseline through week 24 was 2.4 (P = 0.0182).

Patients with CF aged 6 years and older from trial 809-011 and trial 809-109 were included in a phase 3, multicentre, rollover extension study (trial -809-110). This extension trial was designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor. Of the 262 patients who received any treatment in trial 809-011 or trial 809-109, 239 (91%) were dosed and received active treatment (patients 6 to less than 12 years of age received lumacaftor 200 mg q12h/ivacaftor 250 mg q12h; patients ≥12 years of age received lumacaftor 400 mg q12h/ivacaftor 250 mg q12h) in the extension study for up to an additional 96 weeks (i.e., up to a total of 120 weeks) (see section 4.8). Secondary efficacy results and pulmonary exacerbation event rate per patient year are presented in Table 9.

Table 9: Long-term effect of lumacaftor/ivacaftor in trial 809-110

	Placebo transitioned to lumacaftor/ivacaftor (P-L/I) (n = 96)*		lumacaftor/ivacaftor – lumacaftor/ivacaftor (L/I-L/I) (n = 143)*	
Baseline and endpoint	**Mean (SD)**	**LS Mean (95% CI)**	**Mean (SD)**	**LS Mean (95% CI)**
	n = 101		n = 128	
Baseline $LCI_{2.5}$‡**	10.26 (2.24)		10.24 (2.42)	
Absolute change from baseline in $LCI_{2.5}$				
Extension week 96		(n = 69) -0.86 (-1.33, -0.38)		(n = 88) -0.85 (-1.25, -0.45)
	n = 101		n = 161	
Baseline BMI (kg/m^2)‡	16.55 (1.96)		16.56 (1.77)	
Absolute change from baseline in BMI (kg/m^2)				
Extension week 96		(n = 83) 2.04 (1.77, 2.31)		(n =130) 1.78 (1.56, 1.99)
	n = 78		n = 135	
Baseline CFQ-R‡ Respiratory Domain Score (points)	77.1 (15.5)		78.5 (14.3)	
Absolute change in CFQ-R Respiratory Domain Score (points)				
Extension week 96		(n = 65) 6.6 (3.1, 10.0)		(n = 108) 7.4 (4.8, 10.0)
Number of pulmonary exacerbations (events) (trial 809-109 FAS and ROS)†				
Number of events per patient- year (95% CI)		n = 96 0.30 (0.21, 0.43)		n = 103 0.45 (0.33, 0.61)

* Subjects treated with placebo in trial 809-109 (n=96) and transitioned onto active LUM/IVA treatment in the extension study (P-L/I). Subjects treated with LUM/IVA in either parent study [trial 809-011 (n=49) or trial 809-109 (n=94)] and continued active LUM/IVA treatment in the extension (L/I-L/I).

‡ Baseline for both groups (P-L/I and L/I-L/I) was the trial 809-011 and trial 809-109 (parent study) baseline and the corresponding n refers to the analysis set in the parent study.

** The LCI sub-study included 117 subjects in the L/I-L/I group and 96 subjects in the P-L/I group.

† FAS = Full Analysis Set (n=103) includes subjects who received L/I in trial 809-109 and in trial 809-110, assessed over the cumulative study period for L/I; ROS = Rollover Set (n=96) includes subjects who received placebo in trial 809-109 and L/I in trial 809-110, assessed over the current study period for trial 809-110.

Trial 809-115: Safety and tolerability study in paediatric patients with CF aged 2 to 5 years homozygous for the F508del mutation in the CFTR gene

Trial 809-115 evaluated 60 patients aged 2 to 5 years at screening (mean age at baseline 3.7 years). 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 than14 kg (n = 19) or lumacaftor 150 mg/ivacaftor 188 mg for patients weighing 14 kg or greater (n = 41), for 24 weeks in addition to their prescribed CF therapies. In order to evaluate off drug effects, patients had a safety follow-up visit following a 2-week washout period.

Secondary endpoints included absolute change from baseline in sweat chloride at week 24 and absolute change in sweat chloride from week 24 at week 26 (see Pharmacodynamic effects) as well as

the endpoints listed in Table 10. The clinical relevance of the magnitude of these changes in children aged 2 to 5 years with cystic fibrosis has not been clearly ascertained in longer-term treatment.

Table 10: Summary of secondary outcomes in Trial 809-115

Secondary endpoints*	**LUM/IVA**
Absolute change from baseline in body mass index (BMI)	n = 57 0.27 95% CI: 0.07, 0.47; P = 0.0091
Absolute change from baseline in BMI-for-age-z-score	n = 57 0.29 95% CI: 0.14, 0.45; P = 0.0003
Absolute change from baseline in weight (kg)	n = 57 1.4 95% CI: 1.2, 1.7; P < 0.0001
Absolute change from baseline in weight-for-age z-score	n = 57 0.26 95% CI: 0.15, 0.38; P < 0.0001
Absolute change from baseline in stature (cm)	n = 57 3.6 95% CI: 3.3, 3.9; P < 0.0001
Absolute change from baseline in stature-for-age z-score	n = 57 0.09 95% CI: 0.02, 0.15; P = 0.0104
Absolute change from baseline in faecal elastase-1 (FE-1) levels (µg/g)**	n = 35 52.6 95% CI: 22.5, 82.7; P = 0.0012
$LCI_{2.5}$	n = 17 -0.58 95% CI: -1.17, 0.02; P = 0.0559

Note: P values in the table are nominal.

* For the endpoints listed, absolute change from baseline is the mean absolute change from baseline at week 24.

** All patients had pancreatic insufficiency at baseline. Three of the 48 patients who had faecal elastase-1 values < 100 µg/g at baseline achieved a level of ≥ 200 µg/g at week 24.

Trial 809-122: Safety and tolerability study in paediatric patients with CF aged 1 to less than 2 years homozygous for the F508del mutation in the CFTR gene

In Trial 809-122 Part B the primary endpoint of safety and tolerability was evaluated in 46 patients across 24 weeks (mean age at baseline 18.1 months). Secondary endpoints evaluated were pharmacokinetics and absolute change from baseline in sweat chloride at week 24 (see Pharmacodynamic effects). According to their weight at screening, patients were administered granules mixed with food every 12 hours for 24 weeks, at a dose of lumacaftor 75 mg/ivacaftor 94 mg granules (patients weighing 7 kg to <9 kg) or lumacaftor 100 mg/ivacaftor 125 mg granules (patients weighing 9 kg to <14 kg) or lumacaftor 150 mg/ivacaftor 188 mg granules (patients weighing ≥14 kg), in addition to their prescribed CF therapies. In order to evaluate off-drug effects, patients had a safety follow-up visit following a 2-week washout period.

The European Medicines Agency has deferred the obligation to submit the results of studies with Orkambi in one or more subsets of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 (see section 4.5).

After oral administration of lumacaftor 400 mg q12h/ivacaftor 250 mg q12h in a fed state, the steady-state mean (± SD) for $AUC_{0\text{-}12h}$ and C_{max} were 198 (64.8) µg·h/mL and 25.0 (7.96) µg/mL for lumacaftor, respectively, and 3.66 (2.25) µg·h/mL and 0.602 (0.304) µg/mL for ivacaftor, respectively. After oral administration of ivacaftor alone as 150 mg q12h in a fed state, the steady-state mean (± SD) for $AUC_{0\text{-}12h}$ and C_{max} were 9.08 (3.20) µg·h/mL and 1.12 (0.319) µg/mL, respectively.

Absorption

Following multiple oral doses of lumacaftor, the exposure of lumacaftor generally increased proportional to dose over the range of 50 mg to 1000 mg every 24 hours. The exposure of lumacaftor increased approximately 2.0-fold when given with fat-containing food relative to 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 dose from 150 mg every 12 hours to 250 mg every 12 hours. The exposure of ivacaftor when given in combination with lumacaftor increased approximately 3-fold when given with fat-containing food in healthy volunteers. Therefore, lumacaftor/ivacaftor should be administered with fat-containing food. The median (range) T_{max} of ivacaftor is approximately 4.0 hours (2.0; 6.0) in the fed state.

Distribution

Lumacaftor is approximately 99% bound to plasma proteins, primarily to albumin. After oral administration of 400 mg every 12 hours in patients with CF in a fed state, the typical apparent volumes of distribution for the central and peripheral compartments [coefficient of variation as a percentage (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. 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.

In vitro studies indicate that lumacaftor is a substrate of Breast Cancer Resistance Protein (BCRP).

Biotransformation

Lumacaftor is not extensively metabolised in humans, with the majority of lumacaftor excreted unchanged in the faeces. *In vitro* and *in vivo* data indicate that lumacaftor is mainly metabolised via oxidation and glucuronidation.

Ivacaftor is extensively metabolised in humans. *In vitro* and *in vivo* data indicate that ivacaftor is primarily metabolised by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth 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 faeces. There was negligible urinary excretion of lumacaftor as unchanged drug. The apparent terminal half-life is approximately 26 hours. The typical apparent clearance, CL/F (CV), of lumacaftor was estimated to be 2.38 L/h (29.4%) for patients with CF.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the faeces after metabolic conversion. There was negligible urinary excretion of ivacaftor as unchanged drug. In healthy subjects, the half-life of ivacaftor when given with lumacaftor is approximately 9 hours. The typical CL/F (CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/h (40.5%) for patients with CF.

Special populations

Hepatic impairment

Following multiple doses of lumacaftor/ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had higher exposures ($AUC_{0\text{-}12h}$ by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. 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%.

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 (see sections 4.2, 4.4, and 4.8).

Renal impairment

Pharmacokinetic studies have not been performed with lumacaftor/ivacaftor in patients with renal impairment. 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). 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). A population pharmacokinetic analysis of clearance versus creatinine clearance shows no trend for subjects with mild and moderate renal impairment (see section 4.2).

Elderly

The safety and efficacy of lumacaftor/ivacaftor in patients aged 65 years or older have not been evaluated.

Gender

The effect of gender on lumacaftor pharmacokinetics 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 or ivacaftor between males and females. No dose adjustments are necessary based on gender.

Paediatric population

The exposures are similar between adults and the paediatric populations based on population PK analysis as presented in Table 11.

Table 11: Mean (SD) lumacaftor and ivacaftor exposure by age group

Age group	Weight	Dose	Mean lumacaftor (SD) AUCss (µg·h/mL)	Mean ivacaftor (SD) AUCss (µg·h/mL)
Patients aged 1 to <2 years	7 kg to <9 kg N=1	lumacaftor 75 mg/ivacaftor 94 mg sachet every 12 hours	234	7.98
	9 kg to <14 kg N=44	lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours	191 (40.6)	5.35 (1.61)
	≥14 kg N=1	lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	116	5.82
Patients aged 2 to 5 years	<14 kg N=20	lumacaftor 100 mg/ivacaftor 125 mg sachet every 12 hours	180 (45.5)	5.92 (4.61)
	≥14 kg N=42	lumacaftor 150 mg/ivacaftor 188 mg sachet every 12 hours	217 (48.6)	5.90 (1.93)
Patients aged 6 to <12 years	- N=62	lumacaftor 200 mg/ivacaftor 250 mg every 12 hours	203 (57.4)	5.26 (3.08)
Patients aged 12 to <18 years	- N=98	lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	241 (61.4)	3.90 (1.56)
Patients aged 18 years and older	- N=55	Lumacaftor 400 mg/ivacaftor 250 mg every 12 hours	198 (64.8)	3.66(2.25)

Notes: Exposures for patients < 18 years of age are from population PK analyses. Exposures for adult patients are from noncompartmental analyses.

5.3 Preclinical safety data

Lumacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. Specific studies to evaluate the phototoxic potential of lumacaftor were not conducted; however, evaluation of the available non-clinical and clinical data suggests no phototoxic liability.

Ivacaftor

Effects in repeated dose studies were observed only at exposures considered sufficiently in excess (> 25-, > 45-, and > 35-fold for mice, rats, and dogs, respectively) of the maximum human exposure of ivacaftor when administered as Orkambi, indicating little relevance to clinical use. Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Safety pharmacology

Ivacaftor produced concentration-dependent inhibitory effect on hERG (human ether-à-go-go related gene) tail currents, with an IC_{15} of 5.5 µM, compared to the C_{max} (1.5 µM) for ivacaftor at the therapeutic dose for lumacaftor/ivacaftor. However, no ivacaftor-induced 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 of up to 1 year duration at the 60 mg/kg/day dose level in dogs (C_{max} after 365 days = 36.2 to 47.6 μM). Ivacaftor produced a dose-related but transient increase in the blood pressure parameters in dogs at single oral doses up to 60 mg/kg (see section 5.1).

Pregnancy and fertility

Ivacaftor was not teratogenic when dosed orally to pregnant rats and rabbits during the organogenesis stage of foetal development at doses approximately 7 times (ivacaftor and metabolite exposure) and 46 times the ivacaftor exposure in humans at the therapeutic lumacaftor/ivacaftor dose, respectively. At maternally toxic doses in rats, ivacaftor produced reductions in foetal body weight; an increase in the incidence of variations in cervical ribs, hypoplastic ribs, and wavy ribs; and sternal irregularities, including fusions. The significance of these findings for humans is unknown.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (yielding exposures approximately 11 and 7 times, respectively, those obtained with the maximum recommended human dose 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 and gestation day 17 exposures in the pilot embryofoetal development study in this species) 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 (yielding exposures approximately 8 and 5 times, respectively, those obtained with the maximum recommended human dose 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 and gestation day 17 exposures in the embryofoetal development study in this species). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

Peri- and post-natal development

Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day (yielding exposures that were approximately 4 times those obtained with the maximum recommended human dose of the ivacaftor component of Orkambi based on summed AUCs of ivacaftor and its metabolites). Doses above 100 mg/kg/day resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights.

Juvenile animals

Findings of cataracts were observed in juvenile rats dosed with ivacaftor at 0.32 times the maximum recommended human dose based on systemic exposure of ivacaftor and its metabolites when co-administered with lumacaftor as Orkambi. Cataracts were not observed in foetuses derived from rat dams treated during the organogenesis stage of foetal development, in rat pups exposed to a certain extent through milk ingestion prior to weaning, or in repeated dose toxicity studies with ivacaftor. The potential relevance of these findings in humans is unknown.

Lumacaftor and ivacaftor

Repeat-dose toxicity studies involving the co-administration of lumacaftor and ivacaftor revealed no special hazard for humans in terms of potential for additive and/or synergistic toxicities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Croscarmellose sodium

Hypromellose acetate succinate
Povidone (K30)
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

Once mixed, the mixture has been shown to be stable for one hour.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Orkambi granules are packaged in a foil laminate [biaxially-oriented polyethylene terephthalate/polyethylene/foil/polyethylene (BOPET/PE/Foil/PE)] sachet.

Pack size of 56 (4 wallets with 14 sachets per wallet) sachets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/006

EU/1/15/1059/007

EU/1/15/1059/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015

Date of latest renewal: 17 September 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures:**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-Authorisation Efficacy Study (PAES) Based on an agreed protocol, the Applicant should conduct a long-term effectiveness study to compare disease progression among children with CF homozygous for *F508del-CFTR* and are aged 1 through 5 years at the time of Orkambi treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Orkambi treatment, in addition to a longitudinal historical cohort.	Interim Analysis: December 2022 Final Report: December 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

112 film-coated tablets (4 packs of 28 tablets).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi 100 mg/125 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg tablets
lumacaftor/ivacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Morning

Evening

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON - MULTIPACK - WITH BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 200 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 112 (4 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001 112 film-coated tablets (4 packs of 28 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi 200 mg/125 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON FOR MULTIPACK

NO BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 200 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001 112 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 200 mg/125 mg tablets
lumacaftor/ivacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Morning

Evening

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 100 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

56 sachets

4 individual wallets with 14 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Lift here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi 100 mg/125 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 100 mg/125 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 100 mg of lumacaftor and 125 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Instructions for Use
Mix entire content of sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Consume it completely. Use within one hour after mixing, just before or after a fat-containing meal or snack.

Read the package leaflet before use.

Oral use

Morning

Evening

Use all 7 days' doses before starting a new wallet.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/006

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Orkambi 100 mg/125 mg granules
lumacaftor/ivacaftor

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 150 mg/188 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 150 mg of lumacaftor and 188 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

56 sachets

4 individual wallets with 14 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Lift here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi 150 mg/188 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 150 mg/188 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 150 mg of lumacaftor and 188 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Instructions for Use
Mix entire content of sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Consume it completely. Use within one hour after mixing, just before or after a fat-containing meal or snack.

Read the package leaflet before use.

Oral use

Morning

Evening

Use all 7 days' doses before starting a new wallet.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Orkambi 150 mg/188 mg granules
lumacaftor/ivacaftor

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 75 mg/94 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 75 mg of lumacaftor and 94 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

56 sachets

4 individual wallets with 14 sachets per wallet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Lift here to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi 75 mg/94 mg granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET FOR SACHET

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 75 mg/94 mg granules in sachet
lumacaftor/ivacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of granules contains 75 mg of lumacaftor and 94 mg of ivacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

granules

14 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Instructions for Use
Mix entire content of sachet with 5 mL of age-appropriate soft food or liquid that is at or below room temperature. Consume it completely. Use within one hour after mixing, just before or after a fat-containing meal or snack.

Read the package leaflet before use.

Oral use

Morning

Evening

Use all 7 days' doses before starting a new wallet.

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHETS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Orkambi 75 mg/94 mg granules
lumacaftor/ivacaftor

Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Orkambi 100 mg/125 mg film-coated tablets
Orkambi 200 mg/125 mg film-coated tablets
lumacaftor/ivacaftor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orkambi is and what it is used for

Orkambi contains two active substances, lumacaftor and ivacaftor. It is a medicine used for long-term treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a specific change (called *F508del* mutation) affecting the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR), which plays an important role in regulating the flow of mucus in the lungs. People with the mutation will produce an abnormal CFTR protein. Cells contain two copies of the *CFTR* gene; Orkambi is used in patients in whom both copies are affected by the *F508del* mutation (homozygotes).

Lumacaftor and ivacaftor work together to improve the function of the abnormal CFTR protein. Lumacaftor increases the amount of CFTR available and ivacaftor helps the abnormal protein to work more normally.

Orkambi may help your breathing by improving your lung function. You may also notice that it is easier to gain weight.

2. What you need to know before you take Orkambi

Do not take Orkambi

- if you are allergic to lumacaftor, ivacaftor, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Orkambi.

Orkambi should not be used in patients other than those **who have two copies of the *F508del* mutation** in their *CFTR* gene.

Talk to your doctor before taking Orkambi if you have been told you have **liver or kidney** disease as your doctor may need to adjust the dose of Orkambi.

Abnormal blood tests of the liver have been commonly seen in some people receiving Orkambi. Tell your doctor straight 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

Your doctor should do some blood tests to check your liver before and while you are taking Orkambi, particularly during the first year.

Depression (including suicidal thoughts and behaviours) has been reported in patients while taking Orkambi, usually starting within the first three months of treatment. Talk to a doctor straightaway if you (or someone taking this medicine) experience any of the following symptoms: sad or altered mood, anxiety, feelings of emotional discomfort or thoughts of harming or killing yourself, which may be signs of depression.

Respiratory events such as **shortness of breath or chest tightness or narrowing of the airways** were seen in patients when starting Orkambi, especially in patients who have poor lung function. If you have poor lung function your doctor may monitor you more closely when you start Orkambi.

An **increase in blood pressure** has been seen in some patients treated with Orkambi. Your doctor may monitor your blood pressure during treatment with Orkambi.

Abnormality of the lens of the eye (cataract) without any effect on vision has been noted in some children and adolescents treated with Orkambi and ivacaftor alone (one of the components of Orkambi). Your doctor may perform some eye examinations prior to and during treatment with Orkambi.

Orkambi is not recommended in patients who have undergone **an organ transplant.**

Children under 6 years old

Orkambi tablets should not be used in children under the age of 6 years. Other forms of this medicine (granules in a sachet) are more suitable for children under 6 years of age, ask your doctor or pharmacist.

Other medicines and Orkambi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially tell your doctor if you take any of the following medicines:
- Antibiotic medicines (used for the treatment of bacterial infections) for example: telithromycin, clarithromycin, rifampicin, rifabutin, rifapentine, erythromycin
- Anticonvulsant medicines (used for the treatment of fits [epileptic seizures]) for example: phenobarbital, carbamazepine, phenytoin
- Benzodiazepines (used for the treatment of anxiety or sleeplessness [insomnia], agitation, etc.) for example: midazolam, triazolam

- Antifungal medicines (used for the treatment of fungal infections) for example:
  fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
- Immunosuppressants (used after an organ transplantation) for example:
  ciclosporin, everolimus, sirolimus, tacrolimus
- Herbal medicines, for example:
  St. John's wort (*Hypericum perforatum*)
- Anti-allergic medicines (used for the treatment of allergies and/or asthma) for example:
  montelukast, fexofenadine
- Antidepressant medicines (used for the treatment of depression) for example:
  citalopram, escitalopram, sertraline, bupropion
- Anti-inflammatory medicines (used for the treatment of inflammation) for example:
  ibuprofen
- H2 Antagonist medicines (used to reduce stomach acid) for example:
  ranitidine
- Cardiac glycosides (used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation) for example:
  digoxin
- Anticoagulants (used to prevent blood clots from forming or growing larger in blood and blood vessels) for example:
  warfarin, dabigatran
- Contraceptive medicines (used for the prevention of pregnancy):
  oral, injectable, and implantable contraceptives as well as contraceptive skin patches; that may include ethinyl estradiol, norethindrone, and other progestogens. These should not be relied upon as an effective method of birth control when given with Orkambi
- Corticosteroid medicines (used to treat inflammation):
  methylprednisolone, prednisone
- Proton pump inhibitor medicines (used to treat acid reflux disease and ulcers):
  omeprazole, esomeprazole, lansoprazole
- Oral hypoglycaemics (used for the management of type 2 diabetes):
  repaglinide

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC - an active component in cannabis) in patients receiving Orkambi. Your doctor may request another test to verify results.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine. It may be better to avoid using Orkambi during pregnancy, if possible, and your doctor will help you decide what is best for you and your child.

Ivacaftor and lumacaftor pass into breastmilk. If you plan to breast-feed, ask your doctor for advice before taking Orkambi. Your doctor will decide whether to recommend that you stop breast-feeding or for you to stop lumacaftor/ivacaftor therapy. Your doctor will take into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines

Dizziness has been reported in patients receiving ivacaftor, a component of Orkambi, which could influence the ability to drive or use machines. If you experience dizziness, you should not drive or use machines until these symptoms disappear.

If a child experiences dizziness while taking Orkambi, it is advised that the child does not ride a bike or do anything else that needs their full attention, until their symptoms disappear.

Orkambi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take Orkambi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Recommended dose

The recommended dose for patients aged 6 years and over is two tablets in the morning, and two tablets in the evening (12 hours apart). That is a total of four tablets per day, to be taken with food containing fat.

There are different strengths of Orkambi tablet for different age groups. Check you have been given the right tablet (below).

Age	Tablets	Dose	
		Morning	Evening
6 to <12 years	Orkambi 100 mg/125 mg	2 tablets	2 tablets
12 years and older	Orkambi 200 mg/125 mg	2 tablets	2 tablets

You may start taking Orkambi on any day of the week.

If you have moderate or severe problems with liver function, your doctor may need to reduce the dose of Orkambi as your liver will not clear Orkambi as fast as in people who have normal liver function.

- **Moderate liver problems:** the dose may be reduced to two tablets in the morning and one tablet in the evening.
- **Severe liver problems:** the dose may be reduced to one tablet in the morning and one tablet in the evening. Your doctor may decide to reduce the frequency of administration based on clinical response and tolerability.

Method of administration

Orkambi is for oral use. Swallow the tablets whole. Do not chew, break, or dissolve the tablets.

Taking Orkambi with fat-containing food is important to get the right levels of medicine in your body. A fat-containing meal or snack should be consumed just before or just after taking Orkambi. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs. Examples of other fat-containing foods are:

- Cheese, whole milk, whole-milk dairy products
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nutritional bars or drinks

If you take more Orkambi than you should

Contact your doctor or pharmacist for advice. If possible, have your medicine and this leaflet with you. You may experience side effects, including those mentioned in section 4 below.

If you forget to take Orkambi

Take the missed dose with fat-containing food if less than 6 hours have passed since the time you missed the dose. Otherwise, wait until your next scheduled dose as you normally would. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Orkambi

You should keep taking the medicine as your doctor directs even if you feel well.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects reported with Orkambi and ivacaftor alone (one of the active substances of Orkambi) are listed below and may occur with the use of Orkambi.

Serious side effects for Orkambi include raised levels of liver enzymes in the blood, liver injury, and worsening of pre-existing severe liver disease. The worsening of liver function can be fatal. These serious side effects are uncommon (may affect up to 1 in 100 people).

Tell your doctor straight away if you have any of the following symptoms:
- 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
- Confusion
- Dark urine

Depression

Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort.

Tell your doctor straight away if you have any of these symptoms.

Other side effects

Very common (may affect more than 1 in 10 people)
- Cough with sputum
- Nasal congestion
- Shortness of breath
- Headache
- Abdominal pain (stomach ache)
- Diarrhoea
- Increase in sputum
- Nausea
- Common cold*
- Dizziness*
- Changes in the type of bacteria in mucus*

Common (may affect up to 1 in 10 people)
- Chest tightness
- Narrowing of the airways
- Sinus congestion*
- Stuffy or runny nose
- Upper respiratory tract infection
- Sore throat
- Redness in the throat*
- Rash
- Passing gas
- Vomiting
- Increase of an enzyme in your blood (blood creatine phosphokinase)
- High levels of liver enzymes, shown by blood test
- Irregular periods (menses) or pain with menses
- Ear pain, ear discomfort*
- Ringing in the ears*
- Redness inside the ear*
- Inner ear disorder (feeling dizzy or spinning)*
- Breast mass*

Uncommon (may affect up to 1 in 100 people)
- Abnormal periods, including the absence or infrequent menses, or more frequent or heavier menstrual bleeding
- Increase in blood pressure
- Ear congestion*
- Breast inflammation*
- Enlargement of the breast in males*
- Nipple changes or pain*

*Side effects seen for ivacaftor alone.

Additional side effects in children

Side effects seen in children are similar to those seen in adults and adolescents. However, increased liver enzymes in the blood have been seen more frequently in younger children than in adults.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orkambi

Keep this medicine out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Orkambi contains

The active substances are lumacaftor and ivacaftor.

Orkambi 100 mg/125 mg film-coated tablets:

Each film-coated tablet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 200 mg/125 mg film-coated tablets:

Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 100 mg/125 mg film-coated tablets and Orkambi 200 mg/125 mg film-coated tablets:

The other ingredients are:
- Tablet core: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone (K30); sodium laurilsulfate; and magnesium stearate (see section 2 "Orkambi contains sodium").
- Tablet coating: polyvinyl alcohol; titanium dioxide (E171); macrogol 3350; talc; carmine (E120); brilliant blue FCF aluminium lake (E133); and indigo carmine aluminium lake (E132).
- Printing ink: shellac; iron oxide black (E172); propylene glycol; and ammonium hydroxide.

What Orkambi looks like and contents of the pack

Orkambi 100 mg/125 mg film-coated tablets

Orkambi 100 mg/125 mg film-coated tablets (tablets) are pink, oval-shaped tablets (dimensions 14 × 7.6 × 4.9 mm) printed with "1V125" in black ink on one side.

Orkambi 100 mg/125 mg is available in packs containing 112 film-coated tablets (4 packs of 28 film-coated tablets).

Orkambi 200 mg/125 mg film-coated tablets

Orkambi 200 mg/125 mg film-coated tablets (tablets) are pink, oval-shaped tablets (dimensions 14 × 8.4 × 6.8 mm) printed with "2V125" in black ink on one side.

Orkambi 200 mg/125 mg is available in multipacks containing 112 film-coated tablets (4 packs of 28 film-coated tablets).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland
Tel: +353 (0)1 761 7299

Manufacturer
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth

A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the patient

Orkambi 75 mg/94 mg granules in sachet
Orkambi 100 mg/125 mg granules in sachet
Orkambi 150 mg/188 mg granules in sachet
lumacaftor/ivacaftor

Read all of this leaflet carefully before your child starts taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your child's doctor or pharmacist.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them even if their signs of illness are the same as your child's.
- If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Orkambi is and what it is used for

Orkambi contains two active substances, lumacaftor and ivacaftor. It is a medicine used for long-term treatment of cystic fibrosis (CF) in patients aged 1 year and older who have a specific change (called *F508del* mutation) affecting the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR), which plays an important role in regulating the flow of mucus in the lungs. People with the mutation will produce an abnormal CFTR protein. Cells contain two copies of the *CFTR* gene; Orkambi is used in patients in whom both copies are affected by the *F508del* mutation (homozygotes).

Lumacaftor and ivacaftor work together to improve the function of the abnormal CFTR protein. Lumacaftor increases the amount of CFTR available and ivacaftor helps the abnormal protein to work more normally.

2. What you need to know before your child takes Orkambi

Do not use Orkambi

- if your child is allergic to lumacaftor, ivacaftor, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your child's doctor or pharmacist before taking Orkambi.

Orkambi should not be used in patients other than those **who have two copies of the *F508del* mutation** in their *CFTR* gene.

Talk to your child's doctor before taking Orkambi if you have been told your child has **liver or kidney** disease as the doctor may need to adjust the dose of Orkambi.

Abnormal blood tests of the liver have been commonly seen in some people receiving Orkambi. Tell your child's doctor straight away if your child has any of these symptoms, which may be a sign of liver problems:

- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine
- Confusion

Your child's doctor should do some blood tests to check your child's liver before and while she/he is taking Orkambi, particularly during the first year.

Depression (including suicidal thoughts and behaviours) has been reported in patients while taking Orkambi, usually starting within the first three months of treatment. Talk to a doctor straightaway if you (or someone taking this medicine) experience any of the following symptoms: sad or altered mood, anxiety, feelings of emotional discomfort or thoughts of harming or killing yourself, which may be signs of depression.

Respiratory events such as **shortness of breath or chest tightness or narrowing of the airways** were seen in patients when starting Orkambi, especially in patients who have poor lung function. If your child has poor lung function your child's doctor may monitor your child more closely when she/he starts Orkambi.

An **increase in blood pressure** has been seen in some patients treated with Orkambi. Your child's doctor may monitor your child's blood pressure during treatment with Orkambi.

Abnormality of the lens of the eye (cataract) without any effect on vision has been noted in some children and adolescents treated with Orkambi and ivacaftor alone (one of the components of Orkambi). Your child's doctor may perform some eye examinations prior to and during treatment with Orkambi.

Orkambi is not recommended in patients who have undergone **an organ transplant.**

Children under 1 year old

It is not known if Orkambi is safe and effective in children under 1 year of age. Therefore, Orkambi should not be used in children under the age of 1 year.

Other medicines and Orkambi

Tell your child's doctor or pharmacist if your child is taking, has recently taken or might take any other medicines.

Especially tell the doctor if your child takes any of the following medicines:
- Antibiotic medicines (used for the treatment of bacterial infections) for example: telithromycin, clarithromycin, rifampicin, rifabutin, rifapentine, erythromycin
- Anticonvulsant medicines (used for the treatment of fits [epileptic seizures]) for example: phenobarbital, carbamazepine, phenytoin
- Benzodiazepines (used for the treatment of anxiety or sleeplessness [insomnia], agitation, etc.) for example:
  midazolam, triazolam

- Antifungal medicines (used for the treatment of fungal infections) for example:
  fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole
- Immunosuppressants (used after an organ transplantation) for example:
  ciclosporin, everolimus, sirolimus, tacrolimus
- Herbal medicines, for example:
  St. John's wort (*Hypericum perforatum*)
- Anti-allergic medicines (used for the treatment of allergies and/or asthma) for example:
  montelukast, fexofenadine
- Antidepressant medicines (used for the treatment of depression) for example:
  citalopram, escitalopram, sertraline, bupropion
- Anti-inflammatory medicines (used for the treatment of inflammation) for example:
  ibuprofen
- H2 Antagonist medicines (used to reduce stomach acid) for example:
  ranitidine
- Cardiac glycosides (used for the treatment of mild to moderate congestive heart failure and an abnormal heart rhythm called atrial fibrillation) for example:
  digoxin
- Anticoagulants (used to prevent blood clots from forming or growing larger in blood and blood vessels) for example:
  warfarin, dabigatran
- Contraceptive medicines (used for the prevention of pregnancy):
  oral, injectable, and implantable contraceptives as well as contraceptive skin patches; that may include ethinyl estradiol, norethindrone, and other progestogens. These should not be relied upon as an effective method of birth control when given with Orkambi
- Corticosteroid medicines (used to treat inflammation):
  methylprednisolone, prednisone
- Proton pump inhibitor medicines (used to treat acid reflux disease and ulcers):
  omeprazole, esomeprazole, lansoprazole
- Oral hypoglycaemics (used for the management of type 2 diabetes):
  repaglinide

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC - an active component in cannabis) in patients receiving Orkambi. Your child's doctor may request another test to verify results.

Driving and using machines

Dizziness has been reported in patients receiving ivacaftor, a component of Orkambi, which could influence the ability to drive or use machines.

If a child experiences dizziness while taking Orkambi, it is advised that the child does not ride a bike or do anything else that needs their full attention, until their symptoms disappear.

Orkambi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take Orkambi

Always give your child this medicine exactly as your child's doctor has told you. Check with the doctor if you are not sure.

Your child's doctor will determine the correct dose for your child. Your child must keep using all other medicines, unless your child's doctor tells you to stop using any.

Recommended dose

The recommended dose for patients aged 1 year and over is indicated in the table below. Orkambi has to be taken in the morning and in the evening (12 hours apart) with food containing fat.

There are different strengths of Orkambi according to a child's age and weight. Check your child has been given the right dose (below).

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

If your child has moderate or severe problems with liver function, your child's doctor may need to reduce the dose of Orkambi as your child's liver will not clear Orkambi as fast as in children who have normal liver function.

- **Moderate liver problems:** the dose may be reduced to one sachet per day in the morning and one sachet every other day in the evening.
- **Severe liver problems:** the dose may be reduced to one sachet per day or less frequently in the morning. No dose should be administered in the evening.

Method of administration

Orkambi is for oral use.

Each sachet is for single use only.

You may start giving your child Orkambi on any day of the week.

Giving Orkambi granules to your child:

- Hold sachet of granules with cut line on top.
- Shake sachet gently to settle contents.
- Tear or cut sachet open along the line.
- Mix the entire contents of a sachet with one teaspoon (5 mL) of age-appropriate soft food or liquid. Food or liquid should be at room temperature or below. Some examples of age-appropriate soft foods and liquids include puréed fruits or vegetables, flavoured yogurt, applesauce, water, milk, breast milk, infant formulae or juice.
- Once mixed, give the product to your child immediately. If this is not possible, give it within the hour after mixing. Make sure that the mixture is consumed immediately and completely.
- Food containing fat should be given to your child just before or just after dosing (some examples are provided below).

Taking Orkambi with fat-containing food is important to get the right levels of medicine in the body. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional

guidelines contain adequate amounts of fat. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs. Examples of other fat-containing foods are:

- Cheese, breast milk, infant formula, whole milk, whole-milk dairy products
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nutritional bars or drinks

If your child takes more Orkambi than he/she should

Contact your child's doctor or pharmacist for advice. If possible, have your child's medicine and this leaflet with you. Your child may experience side effects, including those mentioned in section 4 below.

If you forget to give your child Orkambi

Give the missed dose with fat-containing food if less than 6 hours have passed since the time your child missed the dose. Otherwise, wait until your child's next scheduled dose as you normally would. Do not give your child a double dose to make up for a forgotten dose.

If you stop giving your child Orkambi

Give Orkambi to your child for as long as your child's doctor recommends. Do not stop unless your child's doctor advises you to. You should keep giving the medicine as the doctor directs even if the child feels well.

If you have any further questions on the use of this medicine, ask your child's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects reported with Orkambi and ivacaftor alone (one of the active substances of Orkambi) are listed below and may occur with the use of Orkambi.

Serious side effects for Orkambi include raised levels of liver enzymes in the blood, liver injury and worsening of pre-existing severe liver disease. The worsening of liver function can be fatal. These serious side effects are uncommon (may affect up to 1 in 100 people).

Tell your child's doctor straight away if he/she gets any of these:

- Pain or discomfort in the upper right stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Confusion
- Dark urine

Depression

Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort.

Tell your doctor straight away if you have any of these symptoms.

Other side effects

Very common (may affect more than 1 in 10 people)
- Cough with sputum
- Nasal congestion
- Shortness of breath
- Headache
- Abdominal pain (stomach ache)
- Diarrhoea
- Increase in sputum
- Nausea
- Common cold*
- Dizziness*
- Changes in the type of bacteria in mucus*

Common (may affect up to 1 in 10 people)

- Chest tightness
- Narrowing of the airways
- Sinus congestion*
- Stuffy or runny nose
- Upper respiratory tract infection
- Sore throat
- Redness in the throat*
- Rash
- Passing gas
- Vomiting
- Increase of an enzyme in the blood (blood creatine phosphokinase)
- High levels of liver enzymes, shown by blood test
- Irregular periods (menses) or pain with menses
- Ear pain, ear discomfort*
- Ringing in the ears*
- Redness inside the ear*
- Inner ear disorder (feeling dizzy or spinning)*
- Breast mass*

Uncommon (may affect up to 1 in 100 people)

- Abnormal periods, including the absence or infrequent menses, or more frequent or heavier menstrual bleeding
- Increase in blood pressure
- Ear congestion*
- Breast inflammation*
- Enlargement of the breast in males*
- Nipple changes or pain*

*Side effects seen for ivacaftor alone.

Additional side effects in children

Side effects seen in children are similar to those seen in adults and adolescents. However, increased liver enzymes in the blood have been seen more frequently in younger children than in adults.

Reporting of side effects

If your child gets any side effects, talk to your child's doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Orkambi

Keep this medicine out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your child's pharmacist how to throw away medicines your child no longer uses. These measures will help protect the environment.

6. Contents of the pack and other information

What Orkambi contains

The active substances are lumacaftor and ivacaftor.

Orkambi 75 mg/94 mg granules in sachet:

Each sachet contains 75 mg of lumacaftor and 94 mg of ivacaftor.

Orkambi 100 mg/125 mg granules in sachet:

Each sachet contains 100 mg of lumacaftor and 125 mg of ivacaftor.

Orkambi 150 mg/188 mg granules in sachet:

Each sachet contains 150 mg of lumacaftor and 188 mg of ivacaftor.

The other ingredients are: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone (K30); and sodium laurilsulfate (see section 2 "Orkambi contains sodium").

What Orkambi looks like and contents of the pack

Orkambi granules are white to off-white.

The granules are supplied in sachets.

Pack size of 56 sachets (contains 4 individual wallets with 14 sachets per wallet).

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.