ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Orkambi 200 mg/125 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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)

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 is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene (see sections 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
The recommended dose is two tablets (each tablet containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours (lumacaftor 800 mg/ivacaftor 500 mg total daily dose).

Orkambi 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 of Orkambi should be taken with fat-containing food. If more than 6 hours have passed, the patient should be instructed to wait until the next scheduled dose. A double dose should not be taken to make up for the forgotten dose.

Special populations
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 to two tablets in the morning and one tablet in the evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) is recommended (see section 5.2).

There is no experience of the use of Orkambi in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, after weighing the risks and benefits of treatment, Orkambi should be used with caution at a maximum dose of lumacaftor 400 mg/ivacaftor 250 mg total daily dose, given as one tablet in the morning and one tablet in the evening, or less (see sections 4.4, 4.8, and 5.2).

Concomitant use of CYP3A inhibitors
No dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking Orkambi. However, when initiating Orkambi in patients taking strong CYP3A inhibitors, the dose should be reduced to one tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose) 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.

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

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

Paediatric population
The safety and efficacy of Orkambi in children aged less than 12 years have not yet been established. No data are available (see section 5.1).

Elderly people
The safety and efficacy of Orkambi in patients aged 65 years or older have not been evaluated.

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 events
Respiratory events (e.g., chest discomfort, dyspnoea, and respiration abnormal) were more common during initiation of lumacaftor/ivacaftor therapy. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited and additional monitoring of these patients is recommended during

initiation of therapy (see section 4.8). There is no experience of initiating treatment with lumacaftor/ivacaftor in patients having a pulmonary exacerbation and this 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 in some patients with CF 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 events
Elevated transaminases have been reported in patients with CF receiving lumacaftor/ivacaftor. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin.

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), dosing with lumacaftor/ivacaftor should be discontinued and laboratory tests closely followed until the abnormalities resolve. Following resolution of transaminase elevations, the benefits and risks of resuming dosing should be considered (see sections 4.2, 4.8, and 5.2).

Interactions with medicinal products
Substrates of CYP3A
Lumacaftor is a strong inducer of CYP3A. Administration of Orkambi may decrease systemic exposure of medicinal products which are substrates of CYP3A, thereby decreasing their therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended (see section 4.5).

Lumacaftor/ivacaftor may substantially decrease hormonal contraceptive exposure, reducing effectiveness. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi (see section 4.5).

Strong CYP3A inducers
Ivacaftor is a substrate of CYP3A4 and CYP3A5. Use of lumacaftor/ivacaftor with strong CYP3A inducers, such as rifampicin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of lumacaftor/ivacaftor. 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 reduced to one tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose) for the first week of treatment to allow for the steady state induction effect of lumacaftor. Following this period, treatment should be continued with the recommended daily dose per section 4.2. If lumacaftor/ivacaftor is interrupted for more than one week, the dose should be reduced to one tablet daily for the first week of treatment re-initiation.

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.

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.

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 drug interactions

Table 1 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 the Table mostly derives from *in vitro* studies. The recommendations provided under "Clinical comment" in Table 1 are based on drug interaction studies, clinical relevance, or predicted interactions due to elimination pathways. Drug interactions that have the most clinical relevance are listed first.

Table 1: Established and other potentially significant drug interactions - dose recommendations for use of lumacaftor/ivacaftor with other medicinal products

Concomitant drug class: **Drug 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.
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 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	
	↓ 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 or 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: 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.
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 drug-drug interaction studies. All other drug interactions shown are predicted.		

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

It is unknown whether lumacaftor and/or ivacaftor and metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of both lumacaftor and ivacaftor into the milk of lactating female rats. As such, risks to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from lumacaftor/ ivacaftor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility
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. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (see section 5.3).

4.7 Effects on ability to drive and use machines

Orkambi has no or negligible influence on the ability to drive or use machines.

Ivacaftor, which is one of the active components of Orkambi, has a minor influence on the ability to drive or 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 experienced by patients aged 12 years and older who received lumacaftor/ivacaftor in the pooled, placebo-controlled, Phase 3 studies were dyspnoea (14.0% versus 7.8% on placebo), diarrhoea (11.0% versus 8.4% on placebo), and nausea (10.2% versus 7.6% on placebo).

Serious adverse reactions occurring in at least 0.5% of patients included hepatobiliary events, e.g., transaminase elevations, cholestatic hepatitis and hepatic encephalopathy.

Tabulated list of adverse reactions
Adverse reactions identified from clinical studies with 24 weeks of treatment with lumacaftor/ivacaftor in patients aged 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene are presented in Table 2 and are listed by system organ class, frequency, and adverse reactions. Adverse reactions observed with ivacaftor alone are also provided in Table 2. Adverse reactions are ranked under the MedDRA frequency classification: 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 2: 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
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
	common	Respiration abnormal, oropharyngeal pain, sinus congestion*, rhinorrhoea, pharyngeal erythema*
Gastrointestinal disorders	very common	Abdominal pain*, 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*
	uncommon	Blood pressure increased

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

The safety data from patients treated with lumacaftor/ivacaftor for an additional 24 weeks in the long-term safety and efficacy rollover study (Trial 3) were similar to the 24-week, placebo-controlled studies (see section 5.1).

Description of selected adverse reactions

Hepatobiliary events

During the 24-week, placebo-controlled, Phase 3 studies, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN were 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 events 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 preexisting 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).

Respiratory events
During the 24-week, placebo-controlled, Phase 3 studies, the incidence of respiratory adverse reactions (e.g., chest discomfort, dyspnoea, and respiration abnormal) was 26.3% in lumacaftor/ivacaftor-treated patients compared to 17.0% in patients who received placebo. The incidence of these events was more common in patients with lower pre-treatment FEV_1; 29.6% and 37.7% among patients with $ppFEV_1$ <70 and <40, respectively, compared with 21.0% and 21.4% among placebo-treated patients, respectively. 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 events were mild or moderate in severity, non-serious and did not result in treatment discontinuation (see section 4.4).

Menstrual abnormalities
During the 24-week, placebo-controlled, Phase 3 studies, the incidence of combined menstrual abnormality events (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 the 24 week, placebo controlled, Phase 3 studies, 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
Safety data were collected for 194 paediatric patients with CF aged 12 to 17 years who are homozygous for the *F508del* mutation and who received lumacaftor/ivacaftor in the placebo-controlled, Phase 3 studies. The safety profile in these paediatric patients is consistent with that in adult patients.

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 Orkambi. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Adverse events 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 age 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).

Changes in FEV_1:
Changes in $ppFEV_1$ in response to lumacaftor alone or in combination with ivacaftor were also evaluated in this trial. 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.

Clinical efficacy

Trials in patients with CF 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 1108 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 1 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 2 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 $ppFEV_1$ (Table 3). 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 1 and 2 ($P<0.0001$). 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 $ppFEV_1$ ≥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 1 and 2 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 $ppFEV_1$ ≥40.

Table 3: Summary of primary and key secondary outcomes in Trial 1 and Trial 2*

		Trial 1		Trial 2		Pooled (Trial 1 and Trial 2)	
		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	Treatment difference	–	0.13 ($P=0.1938$)	–	0.36 ($P<0.0001$)†	–	0.24 ($P=0.0004$)

Week 24 (kg/m^2)	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 wks)	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.

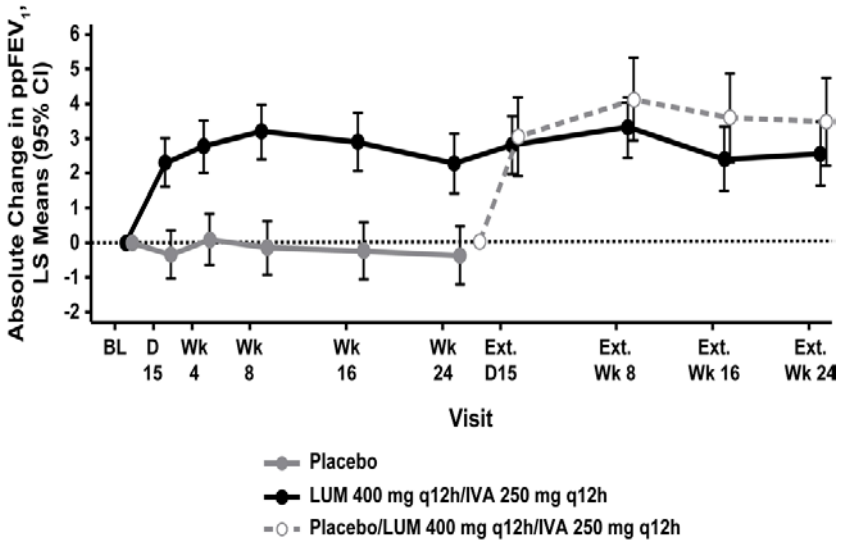
At week 24, the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with lumacaftor/ivacaftor compared with placebo. In the pooled analysis, the rate ratio of exacerbations through week 24 in subjects treated with lumacaftor/ivacaftor (lumacaftor 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 3 is a Phase 3, parallel-group, multicentre, rollover study in patients with CF that includes patients from Trial 1 and Trial 2. Of the 1108 patients who received any treatment in Trial 1 or Trial 2, 1029 (93%) enrolled and received active treatment in Trial 3. This 96-week trial is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor/ivacaftor and is ongoing.

An *ad hoc* efficacy analysis was performed after all patients who had received lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h) in Trial 1 or Trial 2 had completed the Week 24 Visit in Trial 3 (up to 48 weeks of treatment). The improvements in ppFEV$_1$ observed in patients treated with lumacaftor/ivacaftor in Trial 1 or Trial 2 were sustained in Trial 3 (Figure 1). At Week 24 in Trial 3, improvements in ppFEV$_1$ were 2.6 percentage points absolute and 4.7% relative change compared to baseline in Trial 1 or Trial 2. Patients treated with lumacaftor/ivacaftor for 24 weeks in Trial 1 or Trial 2 continued to show improvements in BMI after an additional 24 weeks. The mean absolute change in BMI from baseline in Trial 1 or Trial 2 at week 24 in Trial 3 was 0.56 kg/m^2 (*P*<0.0001).

In addition, for patients treated with placebo for 24 weeks in Trial 1 or Trial 2, the magnitude of improvement in ppFEV$_1$ at Day 15 of lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h) treatment in Trial 3 (Figure 1), 3.0 percentage points absolute and 4.8% relative change from Trial 3 baseline, was similar to the improvement observed in the active treatment groups in Trial 1 and Trial 2. The mean absolute change in BMI from baseline in Trial 1 or Trial 2 at week 24 in Trial 3 for patients initially treated with placebo then followed by lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h) was 0.34 kg/m^2 (*P*<0.0001).

Figure 1. Absolute change from baseline in percent predicted FEV_1 at each visit in Trial 3



Long-term data also show that earlier initiation of lumacaftor/ivacaftor (lumacaftor 400 mg/ivacaftor 250 mg q12h) reduces the rate of pulmonary exacerbations. For patients treated for up to 48 weeks with lumacaftor/ivacaftor, the event rate per year of pulmonary exacerbations (0.64; 95% CI: 0.55, 0.76) was lower than that in patients who received 24 weeks of placebo in Trial 1 or Trial 2 followed by up to 24 weeks of lumacaftor/ivacaftor in Trial 3 (0.96; 95% CI: 0.79, 1.17).

Trial in patients with CF who are heterozygous for the F508del *mutation in the* CFTR *gene*
Trial 4 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 - 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
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·hr/mL and 25.0 (7.96) μg/mL for

lumacaftor, respectively, and 3.66 (2.25) μg·hr/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_{0-12h} and C_{max} were 9.08 (3.20) μg·hr/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 (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/hr (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/hr (40.5%) for patients with CF.

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_{0-12hr} by approximately 50% and C_{max} by approximately 30%) compared with healthy subjects matched for demographics. Therefore, the Orkambi dose should be reduced to two tablets in the morning and one tablet in the

evening (lumacaftor 600 mg/ivacaftor 375 mg total daily dose) for patients with moderate hepatic impairment (Child-Pugh Class B). The impact of mild hepatic impairment (Child-Pugh Class A, score 5 to 6) on pharmacokinetics of lumacaftor given in combination with ivacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C, score 10 to 15), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, lumacaftor/ivacaftor should be used with caution at a maximum dose of one tablet in the morning and one tablet in the evening (lumacaftor 400 mg/ivacaftor 250 mg total daily dose), or less, in patients with severe hepatic impairment after weighing the risks and benefits of treatment (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. Therefore, no dose adjustment for lumacaftor/ivacaftor are recommended for mild or moderate renal impairment. However, caution is recommended when administering lumacaftor/ivacaftor to patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease.

Elderly people
The safety and efficacy of lumacaftor/ivacaftor in patients age 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 of Orkambi are necessary based on gender.

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. No meaningful changes in QTc interval or blood pressure were observed in a thorough QT clinical study evaluating either lumacaftor 600 mg once daily/ivacaftor 250 mg q12h or lumacaftor 1000 mg once daily/ivacaftor 450 mg q12h, demonstrating a lack of translation of these non-clinical findings to the clinic.

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 10 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 14 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 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 times 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 in this species).

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. Doses above 100 mg/kg/day produced 92% and 98% reduction of survival and lactation indices, 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 aluminum lake (E133)
Indigo carmine aluminum lake (E132)

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminium foil lidding.

Orkambi is available in the following pack sizes:
Pack size of 112 tablets (4 packs of 28 tablets each).
Pack size of 56 tablets (2 packs of 28 tablets each).
Pack size of 28 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001
EU/1/15/1059/002
EU/1/15/1059/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
County Armagh
BT63 5UA
United Kingdom

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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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 following measure:

Description	Due Date
The applicant should conduct a 5-year long-term observational study with lumacaftor/ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations) according to an approved protocol. The Applicant should submit yearly analyses from December 2017 to 2020 and the final CSR by December 2021.	Final CSR December 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

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

112 film-coated tablets (4 packs of 28 tablets).
56 film-coated tablets (2 packs of 28 tablets).
28 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Instructions for use

Morning
Evening

Take 2 tablets whole every 12 hours (morning and evening) with fat-containing food (unless told otherwise by your doctor).

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

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 WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.

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 (Europe) Limited
2 Kingdom Street
London
W2 6BD
United Kingdom
Tel: +44 (0) 1923 437672

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001
EU/1/15/1059/002
EU/1/15/1059/003

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi

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 (Europe) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

Morning

Evening

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

INTERMEDIATE CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

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

5. METHOD AND ROUTE OF ADMINISTRATION

Instructions for use

Morning

Evening

Take 2 tablets whole every 12 hours (morning and evening) with fat-containing food (unless told otherwise by your doctor).

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

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 WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC.

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 (Europe) Limited
2 Kingdom Street
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1059/001-003

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orkambi

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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
2. What you need to know before you take Orkambi
3. How to take Orkambi
4. Possible side effects
5. How to store Orkambi
6. Contents of the pack and other information

1. What Orkambi is and what it is used for

Orkambi is a medicine used for long-term treatment of cystic fibrosis (CF) in patients aged 12 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.

Orkambi contains two active substances, lumacaftor and ivacaftor that 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.

While taking Orkambi, you may notice that your breathing is easier, that you don’t get ill as often, and/or 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 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 seen in some people receiving Orkambi. Tell your doctor right away if you have any of these symptoms, which may be a sign of liver problems:

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

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

Respiratory events such as shortness of breath or chest tightness were seen in patients when starting Orkambi. 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 ivacaftor, a component of Orkambi.

Your doctor may perform some eye examinations prior to and during treatment with Orkambi.

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

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

Children
It is not known if Orkambi is safe and effective in children under 12 years of age. Therefore, Orkambi should not be used in children under the age of 12 years.

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 hypoglycemics (used for the management of type 2 diabetes): repaglinide

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.

It is unknown if lumacaftor or ivacaftor are found in human milk. 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
Orkambi has no or negligible influence on the ability to drive or use 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.

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.

Dose
The recommended dose for patients aged 12 years and over is two tablets twice a day (12 hours apart, a total of four tablets [800 mg of lumacaftor/500 mg of ivacaftor] per day).

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 functions.

- Moderate liver problems: the dose may be reduced to two tablets in the morning and one tablet in the evening (a total of lumacaftor 600 mg/ivacaftor 375 mg per day)
- Severe liver problems: the dose may be reduced to one tablet (200 mg of lumacaftor/125 mg of ivacaftor) every 12 hours

Method of administration
Orkambi is to be taken by mouth.
Swallow the tablets whole. Do not chew, break, or dissolve the tablets.

A fat-containing meal or snack should be consumed just before or just after taking Orkambi.

Taking Orkambi with fat-containing food is important to get the right levels of medicine in your 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, 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 the forgotten tablets.

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 confusion related to poor liver function. These serious side effects are uncommon. Tell your doctor right away if you have significant symptoms like 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 and dark urine.

Side effects for Orkambi and for ivacaftor alone (marked with an asterisk):

Very common may affect more than 1 in 10 people:
- headache*
- abdominal pain (stomach ache) *
- nasal congestion*
- common cold*
- shortness of breath
- changes in the type of bacteria in mucus*
- dizziness*
- nausea
- diarrhoea

Common may affect up to 1 in 10 people:
- chest tightness
- sinus congestion*
- upper respiratory tract infection
- sore throat
- stuffy or runny nose
- passing gas
- rash
- vomiting
- throat redness*
- irregular periods (menses) or pain with menses
- ear pain, ear discomfort*
- ringing in the ears*
- redness inside the ear*
- 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*
- nipple changes or pain*

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 that is stated on the carton/blister after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

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 to protect the environment.

6. Contents of the pack and other information

What Orkambi contains
The active substances are lumacaftor and ivacaftor. Each film-coated tablet contains 200 mg of lumacaftor and 125 mg of ivacaftor.

The other ingredients are:

- Tablet core: cellulose, microcrystalline; croscarmellose sodium; hypromellose acetate succinate; povidone K30; sodium laurilsulfate; magnesium stearate
- Tablet coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, carmine (E120), brilliant blue FCF aluminum lake (E133), indigo carmine aluminum lake (E132)
- Printing ink: shellac, iron oxide black (E172), propylene glycol, ammonium hydroxide

What Orkambi looks like and contents of the pack
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 is available in the following pack sizes:
Pack size of 112 tablets (4 packs of 28 tablets each).
Pack size of 56 tablets (2 packs of 28 tablets each).
Pack size of 28 tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Vertex Pharmaceuticals (Europe) Limited
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London
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This leaflet was last revised in

Other sources of information

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