Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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lumacaftor 200mg, ivacaftor 125mg film-coated tablet (Orkambi®)

SMC No. (1136/16)

Vertex Pharmaceuticals (Europe) Ltd

08 April 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan medicine process

lumacaftor, ivacaftor (Orkambi®) is not recommended for use within NHS Scotland.

Indication under review: treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

Lumacaftor-ivacaftor, compared to placebo, significantly increased percent predicted forced expiratory volume in one second ($ppFEV_1$) by less than 3% at six months and reduced the annual rate of pulmonary exacerbations in patients with CF homozygous for the F508del mutation of the CFTR gene.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician and Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.

Dosing Information

Two tablets, each containing lumacaftor 200mg and ivacaftor 125mg, taken orally every twelve hours with fat-containing food. A fat-containing meal or snack should be consumed just before or just after dosing. The tablets should be swallowed whole and not broken, dissolved or chewed.

Lumacaftor-ivacaftor tablet 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.

Product availability date

19 November 2015

Lumacaftor-ivacaftor (Orkambi®) was designated an orphan medicinal product for treatment of cystic fibrosis by the European Medicines Agency in August 2014.

Summary of evidence on comparative efficacy

Cystic fibrosis results from defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for a chloride channel (CFTR protein) on the surface membrane of epithelial cells regulating salt and water balance across the cell membrane. Patients who are homozygous for F508del mutation (i.e. deletion of genetic material that codes for phenylalanine at position 508) have a CFTR protein that does not fold correctly and is thus mostly degraded within the cell. The small amount of CFTR protein that reaches the cell membrane has reduced function there as a chloride channel, i.e. low channel opening probability. The fixed dose combination tablet, Orkambi®, contains lumacaftor and ivacaftor. Their exact mechanisms of actions are not fully characterised. It is believed that lumacaftor acts on the CFTR protein to promote proper folding and improve processing within the cell, thereby increasing the amount reaching the cell membrane. Ivacaftor is thought to potentiate opening of the CFTR chloride channel on the cell membrane, thereby increasing chloride ion transport across epithelial cells.[1-3] Lumacaftor-ivacaftor has been designated as an orphan medicinal product for the treatment of cystic fibrosis.[4]

Two identical double-blind phase III studies (TRAFFIC and TRANSPORT) recruited 549 and 559 patients, respectively, aged at least 12 years with stable cystic fibrosis who were homozygous for the F805del CFTR mutation and had a percent predicted forced expiratory volume in one second ($ppFEV_1$) of 40% to 90%. Randomisation was stratified by age (<18 or ≥18 years), sex and pulmonary function ($ppFEV_1$ <70% or ≥70%). Patients were equally assigned to 24 weeks of lumacaftor 600mg once daily (OD) plus ivacaftor 250mg twice daily (BD), lumacaftor 400mg BD plus ivacaftor 250mg BD or placebo BD. The primary outcome was absolute change from baseline to the average of week 16 and week 24 in $ppFEV_1$. This was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study medication. It was compared between groups using a mixed model repeated measures (MMRM) analysis.

Key secondary outcomes were tested in the following hierarchical order: relative change in $ppFEV_1$ to average at week 16 and 24; absolute change to week 24 in body mass index (BMI); absolute change to week 24 in cystic fibrosis questionnaire revised (CFQ-R) respiratory domain, which assesses patients' quality of life in terms of respiratory symptoms on a scale of 0 to 100 with higher scores indicating better quality of life; proportion of patients achieving at least 5% relative change in $ppFEV_1$ to average at week 16 and 24; and pulmonary exacerbation rate at week 24.[2,5] Pulmonary exacerbations were defined as a new, or change in, antibiotic therapy (oral, intravenous or inhaled) for any four or more pre-defined signs/symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue or lethargy; temperature above 38^0C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by at least 10%; or radiographic changes indicative of pulmonary infection.[2,6,7]

Results are presented for the licensed treatment group (lumacaftor 400mg plus ivacaftor 250mg BD) only. In both studies and in a pre-specified pooled analyses, the primary outcome measure, absolute change from baseline to average of week 16 and 24 in $ppFEV_1$, was significantly greater with lumacaftor 400mg plus ivacaftor 250mg BD, compared to placebo, as detailed in table 1. This also details key secondary outcomes presented in the hierarchical order, for which testing was stopped in the TRAFFIC study at the BMI outcome and in the TRANSPORT study at the CFQ-R respiratory domain outcome. Subsequent key secondary outcomes, including patients with at least 5% increase in relative $ppFEV_1$ and rate of pulmonary exacerbations were considered not statistically significant within the hierarchical testing procedure. P-values for comparisons of these to placebo were between 0.02 and <0.001.[2,3,5,6] The European Medicines Agency (EMA) review noted that the time-frame of the primary outcome, average of results at weeks 16 and 24, did not correspond with the recommended six-months time-point, and results at week 24 were considered to be the most reliable data.[2,8] The 24-week results were therefore presented in the summary of product characteristics (SPC)[1] and are detailed in the table below.

Table 1: Primary and secondary outcomes from TRAFFIC and TRANSPORT studies.[1-3,5-7]

	TRAFFIC		**TRANSPORT**		**POOLED**	
	PBO	**LUM400**	**PBO**	**LUM400**	**PBO**	**LUM400**
	N=184	**N=182**	**N=187**	**N=187**	**N=371**	**N=369**
Absolute change in $ppFEV_1$ from baseline to average of week 16 and week 24 (%)						
LS Mean	-0.44	2.16	-0.15	2.85	-0.32	2.49
Diff. (95% CI)	2.60 (1.18 to 4.01)*		3.00 (1.56 to 4.44)*		2.81 (1.80 to 3.82)*	
Absolute change in $ppFEV_1$ from baseline to week 24 (%)						
LS Mean	-0.73	1.68	-0.02	2.63	-0.39	2.16
Diff. (95% CI)	2.41* (0.80 to 4.02)		2.65** (1.06 to 4.24)		2.55*	
Relative change in $ppFEV_1$ from baseline to average of week 16 and week 24 (%)						
LS Mean	-0.34	3.99	0.00	5.25	-0.17	4.64
Diff. (95% CI)	4.33* (1.86 to 6.80)		5.25* (2.69 to 7.81)		4.81* (3.03 to 6.59)	
Relative change in $ppFEV_1$ from baseline to week 24 (%)						
LS Mean	-0.85	3.3	0.16	4.85	-0.34	4.1
Diff. (95% CI)	4.15**		4.69*		4.4*	
Absolute change in BMI from baseline to week 24 (kg/m^2)						
LS Mean	0.19	0.32	0.07	0.43	0.13	0.37
Diff. (95% CI)	0.13 (-0.07 to 0.32)^{NS}		0.36 (0.17 to 0.54)*		0.24 (0.11 to 0.37)*	
Absolute change in CFQ-R respiratory domain from baseline to week 24						
LS Mean	1.10	2.60	2.81	5.66	1.88	4.10
Diff.(95% CI)	1.50 (-1.69 to 4.69)^{NS}		2.85 (-0.27 to 5.98)^{NS}		2.22 (-0.01 to 4.45)^{NS}	

Relative increase of ≥5% in ppFEV$_1$ from baseline to average of week 16 and 24						
N (%)	41 (22%)	67 (37%)	42 (22%)	77 (41%)	83 (22%)	144 (39%)
OR (95% CI)	2.1 (1.3 to 3.3)**		2.4 (1.5 to 3.7)*		2.2 (1.6 to 3.1)*	
Relative increase of ≥5% in ppFEV$_1$ from baseline at week 24						
%	25%	32%	26%	41%	26%	37%
OR	1.43^{NS}		1.90**		1.66**	
Pulmonary exacerbations through to week 24						
Rate/48weeks	1.07	0.71	1.18	0.67	1.14	0.70
RR (95% CI)	0.66 (0.48 to 0.93)***		0.57 (0.42 to 0.76)*		0.61 (0.49 to 0.76)*	

ppFEV$_1$ = percent predicted forced expiratory volume in one second; LS = least squares; Diff. = LS mean difference; CI = confidence interval; OR = odds ratio: RR = rate ratio; BMI = body mass index; CFQ-R = cystic fibrosis questionnaire revised. PBO = placebo; LUM400 = lumacaftor 400mg twice daily plus ivacaftor 250mg twice daily. * p-value <0.001; ** p<0.01; *** p<0.05; NS = not significant

Lumacaftor-ivacaftor, compared to placebo, significantly decreased mean duration of pulmonary exacerbations in the TRAFFIC study, 7.8 versus 13.1 days; and in the TRANSPORT study, 8.4 versus 18.2 days, respectively. There were also significant decreases, compared to placebo, in the annual rate of pulmonary exacerbations requiring hospital admission in the TRAFFIC study, 0.14 versus 0.36; and in the TRANSPORT study, 0.18 versus 0.46; and requiring intravenous antibiotics in the TRANSPORT study, 0.23 versus 0.64, respectively. For the latter outcome in the TRAFFIC study, the difference versus placebo was significant and, over the 24 weeks, there were 33 versus 62 events in the respective groups.[2,6,7]

After completing the pivotal studies, 1,030 patients entered the phase III double-blind extension study (PROGRESS) where they continued their assigned treatment, except for placebo patients who were re-randomised equally to one of the two active treatment groups as in the preceding studies. For the licensed regimen, lumacaftor 400mg plus ivacaftor 250mg BD, at the second interim analysis (December 2014 data cut) when all patients had completed at least 24 weeks treatment in the PROGRESS study, improvements at the end of the placebo-controlled studies were maintained, with LS mean absolute change from baseline to week 48 in ppFEV$_1$ of 2.6%, and annual pulmonary exacerbation rate, 0.64, while those for BMI continued to increase to 0.56kg/m^2. There were no data indicating a modifying effect on the rate of decline in ppFEV$_1$; however, results from this analysis supported a model used for extrapolation.[2,3,9,10]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The adverse event profile of ivacaftor has been characterised within its use as monotherapy for cystic fibrosis patients with other genotypes. In common with this, elevated transaminases were noted as an adverse event of special interest for lumacaftor-ivacaftor. In contrast to ivacaftor monotherapy, lumacaftor-ivacaftor is associated with an increased incidence, compared to placebo, of dyspnoea (14% versus 7.8%) and abnormal respiration, generally chest tightness, bronchospasm or wheezing (10% versus 5.9%), that were generally reported at treatment initiation, but did not require cessation of treatment. In a phase II study, lumacaftor monotherapy was associated with a dose-dependent decrease in FEV$_1$ and increased incidence of dyspnoea and abnormal respiration adverse events. However, a causal relationship was not established. A decline in FEV$_1$ at four hours post-dose was also noted in early clinical studies and, in practice, lumacaftor-ivacaftor should not be initiated during a pulmonary exacerbation as there is no experience of this.[2,5]

Across the placebo-controlled studies, the incidence of adverse events in the pooled lumacaftor-ivacaftor (both doses) group and the placebo group were similar. These were related or possibly related to treatment in more patients within the lumacaftor-ivacaftor group, 48% versus 35%, although numerous co-morbidities and concomitant medications may have confounded determination of causality. The most common adverse events across the respective groups were infective pulmonary exacerbation of cystic fibrosis, 38% versus 49%, and cough, 30% versus 40%. Serious adverse events were reported less frequently in the lumacaftor-ivacaftor group, compared to placebo: 20% versus 29%, which were considered to be related to treatment in 3.0% versus 2.2%, respectively. The most common serious adverse event was infective pulmonary exacerbation of cystic fibrosis, 13% versus 24%. Adverse events leading to treatment discontinuation were reported by more patients in the lumacaftor-ivacaftor group, compared to placebo: 4.2% versus 1.6%.[2,5,6,7]

In the pooled lumacaftor-ivacaftor group, rates of adverse events were generally lower over weeks 24 to 48 in the long-term extension study, PROGRESS, than over weeks 0 to 24 in the preceding placebo-controlled studies: 81% versus 96% for adverse events; 17% versus 46% for adverse events related or possibly related to treatment; and for the two most common adverse events, 30% versus 37% for infective pulmonary exacerbation of cystic fibrosis, 20% versus 30% for cough. For other adverse events of special interest the respective rates were 2.3% versus 5.5% for elevated transaminases; 9.0% versus 23% for respiratory symptoms; and 3.2% versus 6.3% for reactive airways. Serious adverse events rates in the respective periods were 17% versus 20%; with 1.4% versus 3.0% for those considered related to treatment; and 12% versus 14% for the most common serious adverse event, infective exacerbation of cystic fibrosis. During the EMA review, additional data on patients exposed for more than 48 weeks (up to 80 weeks) were submitted and did not give concern about new or more severe adverse events on longer-term exposure.[2]

In paediatric patients receiving ivacaftor monotherapy there have been reports of non-congenital lens opacities without impact on vision. Some patients had risk factors (such as corticosteroids and radiation) but a possible risk attributable to ivacaftor cannot be excluded. The phase III studies of lumacaftor-ivacaftor included an ophthalmology examination at baseline to exclude pre-existing abnormalities; however, follow-up examinations were not performed and detection of cataracts was reliant upon adverse event reporting. In response to a request from the EMA, the company has agreed to follow up patients in the study with an ophthalmology examination.[2]

Summary of clinical effectiveness issues

Patients who are homozygous for the F508del mutation have a severe form of cystic fibrosis. Clinical symptoms usually derive from abnormal functioning of cells in the lungs, and glands in the gut and pancreas, that secrete mucus and digestive juices. The fluids become thick and viscous, blocking airways and the flow of digestive juices. This leads to problems with digestion and absorption of food, resulting in poor growth. It also contributes to chronic pulmonary infection and inflammation, leading to a loss of lung function. The majority of patients die from respiratory failure.[2,3] In 2014, the UK median age at death of patients with cystic fibrosis was 28 years and the median predicted survival for all patients included in the UK Cystic Fibrosis registry was 40 years.[11] Cystic fibrosis is currently managed with mainly symptomatic treatment in best supportive care, including inhaled and systemic antibiotics (e.g. cephalosporins, aminoglycosides, fluoroquinolones and colistimethate sodium); inhaled mucolytics (e.g. hypertonic saline, dornase alfa and mannitol), inhaled bronchodilators and anti-inflammatory therapy; pancreatic enzyme replacement; vitamin supplements (especially fat-soluble vitamins); electrolyte and nutritional supplements and a high-calorie diet.[2,3,5]

The fixed-dose combination tablet, Orkambi®, containing lumacaftor and ivacaftor, is the first combination preparation containing lumacaftor to be marketed in the UK, and the first medicine to be

licensed for treatment of cystic fibrosis in patients homozygous for the F508del mutation.[1] Ivacaftor is available in the UK for treatment of cystic fibrosis in patients aged six years and older and weighing 25kg or more who have one of the following gating (class III) CFTR gene mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.[12] Ivacaftor granules have recently been licensed for treatment of children with cystic fibrosis who have one of these gating mutations, are aged at least two years and weigh less than 25kg.

Approximately 50% of patients with cystic fibrosis are homozygous for the F508del mutation[11] and it is estimated that there may be around 300 patients in Scotland eligible for treatment with lumacaftor-ivacaftor within its licensed indication.

In the pivotal phase III studies, the primary outcome, $ppFEV_1$, a measure of pulmonary function, was significantly increased with lumacaftor-ivacaftor relative to placebo. The effect of the licensed dose of lumacaftor-ivacaftor corrected for placebo in absolute change in $ppFEV_1$ at 24 weeks was 2.6% and considered to be small by the EMA. Only 37% to 41% (compared with 22% in the placebo groups) achieved at least a 5% improvement in relative change in $ppFEV_1$. The EMA also concluded that effects on CFQ-R and BMI were not indicative of a clinically relevant benefit. The decrease in annual rate of pulmonary exacerbations with lumacaftor-ivacaftor, compared to placebo, to 0.7 (versus 1.1 with placebo), may be the most perceptible benefit for patients. There was also a reduction in duration and severity of pulmonary exacerbations with lumacaftor-ivacaftor. In the long-term extension study, effects on FEV_1, and pulmonary exacerbations were maintained and those on BMI increased. However, there is currently no demonstrated benefit on rate of decline in FEV_1 or other organ function, to support the disease-modifying expectations based on pharmacology. The EMA noted the clinical relevance of lumacaftor-ivacaftor effects overall, but considered them to be similar to symptomatic treatments licensed for cystic fibrosis.[2]

As the pivotal studies did not include monotherapy treatment groups for the constituent drugs, it was not possible to estimate treatment effects of these individually. In the DISCOVER study, which recruited patients homozygous for the F508del mutation, ivacaftor 150mg BD monotherapy improved relative to placebo $ppFEV_1$ by 1.7% at 16 weeks. The study was not powered to investigate efficacy and this result was not statistically significant.[13] In the phase II study VX12-809-102, in patients homozygous for the F508del mutation, lumacaftor monotherapy was associated with a dose-dependent decrease in FEV_1, which was reversed upon addition of ivacaftor.[14] In this study and two phase I studies, a decrease in FEV_1 four hours post-dose for lumacaftor regimens was observed. Concerns with respect to contributions of the component drugs are compounded by reports of dyspnoea and abnormal respiration (i.e. chest tightness and bronchospam) with lumacaftor monotherapy and with lumacaftor-ivacaftor.[2]

Patients were excluded from the pivotal studies if they had $ppFEV_1$ less than 40% or greater than 90% at screening. This may limit application of results to patients with a marked reduction of pulmonary function (FEV_1 <40%) and to those whose disease has had little effect on FEV_1 (FEV_1 >90%).[2,5] However, in 81 patients within the pivotal phase III studies who had ppFEV1 <40% at baseline, improvements in $ppFEV_1$ ranged from 3.3% to 3.7%, which were comparable to those in patients with $ppFEV_1$ greater than 40%. There were also reductions in pulmonary exacerbation rate and increase in BMI with active treatment compared to placebo.[2] Patients were also excluded if they had unstable disease or colonisation with organisms associated with a more rapid decline in pulmonary status, and this may limit application of results to patients in these circumstances.[2,5] In practice, this may not be an issue because the SPC recommends that lumacaftor-ivacaftor should not be initiated in patients experiencing a pulmonary exacerbation.[1]

Lumacaftor is a strong inducer of CYP3A enzymes and increases the excretion of ivacaftor, which is primarily metabolised by CYP3A enzymes. When dosed with lumacaftor 400mg BD as in Orkambi®, ivacaftor exposure is reduced by more than 80% and is lower than the exposure of ivacaftor (150mg

BD) as monotherapy. However, the adequacy of this dose in the combination was supported by *in vitro* data indicating that F508del-CFTR cells are ten times more sensitive than G551D-CFTR cells.[1-3]

Lumacaftor-ivacaftor may have benefits for patients in terms of respiratory function, with effects on pulmonary exacerbations likely to be the most perceptible to patients. However, longer-term efficacy and safety are undefined.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely for medicines that specifically target the F508del mutation, as existing pharmacological therapies are symptomatic. Clinical experts consulted by SMC consider that lumacaftor-ivacaftor is a therapeutic advancement due to its mechanism of action on the defective CFTR protein produced by F508del mutated gene, although they noted that treatment effects were modest. Clinical experts consulted by SMC consider that the place in therapy for lumacaftor-ivacaftor is for patients homozygous for the F508del mutation in addition to existing therapies.

Summary of Patient and Clinician Engagement (PACE)

A Patient and Clinician Engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of lumacaftor-ivacaftor, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Cystic fibrosis (CF) is a progressive, life limiting disease that results in a decline in lung function and death due to respiratory failure at a median age of 26 years old in Scotland.
- Patients who are homozygous for the F508del mutation are currently managed solely with supportive treatment.
- Lumacaftor/ivacaftor is the first medicine licensed to treat the underlying cause of the condition that could potentially mitigate the disease mechanism in patients with this mutation.
- Trial data show the treatment reduced exacerbations and would be expected to cause a slowing of disease progression alongside an associated increase in life expectancy, thus reducing mental anguish for patients and carers.
- Of key importance is that any reduction in lung exacerbation rate requiring IV antibiotics may allow patients and their carers to remain in employment or study, thus reducing the burden of care on families and the wider society.
- Lumacaftor-ivacaftor is available in other countries so there is an equity issue that is distressing for patients and their families.

Additional Patient and Carer Involvement

We received patient group submissions from Cystic Fibrosis Trust, which is a registered charity, and the Ivacaftor Patient Interest Group (iPIG), which is an unincorporated organisation. Cystic Fibrosis Trust has received <3% pharmaceutical company funding in the past two years, including from the submitting company; iPIG has not received any pharmaceutical company funding in the last two years. Representatives from both patient groups participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing costs and outcomes of lumacaftor-ivacaftor plus standard care against standard care alone when used to treat patients aged 12 years or older with cystic fibrosis, who are homozygous for the F508del mutation in the CFTR gene.

A patient-level survival model with time varying risk factors was adopted. This estimated the survival, clinical and health outcomes, and associated costs for a given patient based on their baseline data. Baseline data for age, gender, weight-for-age z-score and $ppFEV_1$ for each of 1,000 patients were modelled. The characteristics were informed from patients in the two randomised controlled studies. Parameters were estimated using a 4-week cycle for the first two years and annually thereafter. Only $ppFEV_1$, weight-for-age z-score and exacerbations were assumed responsive to lumacaftor-ivacaftor. Other events modelled were death, lung transplant, discontinuation and adverse events.

The survival gain was modelled by applying the values from a risk equation which identified the key clinical features of cystic fibrosis and the relationship of each with survival. Results from the clinical studies were used to model changes in $ppFEV_1$ at week 24 for the lumacaftor-ivacaftor arm only; the value for patients in the standard care arm was assumed to remain at baseline values to week 24. The annual rate of pulmonary exacerbations for the standard care arm came from published studies, and the rate reduction observed in the clinical studies was applied to obtain the lumicaftor-ivacaftor rate. The weight-for-age z-scores for the standard care arm were assumed to remain at baseline for the entire time horizon and the values reported in the studies were not used.

The clinical studies reported utility values ranging from 0.88 for patients with $ppFEV_1$ <40% to 0.95 for those with $ppFEV_1$ ≥90%, and were used to inform an equation that used $ppFEV_1$ and pulmonary exacerbation as predictors of EQ-5D utility score.

Health state costs came from a 2 year chart review study of 200 patients with cystic fibrosis from 8 centres across the UK. The list price of lumacaftor-ivacaftor was used.

The model adopted a lifetime horizon and discounted costs and benefits at 3.5%. Costs, life-years and quality adjusted life years (QALYs) were assigned for each time period. These were summed over each patient's lifetime for each treatment group, with results expressed as an incremental cost effectiveness ratio (ICER) in the form of cost/QALY.

The base case reported an ICER of £310,879.The base case results showed lumacaftor-ivacaftor plus standard care improved QALYs by 39% (12.4 versus 8.9). Costs increased by 384% (£1,449k versus £378k).

An analysis of clinical outcomes found that patients on lumacaftor-ivacaftor lost 13.5% $ppFEV_1$ compared to 21.9% for patients on standard care. The annual exacerbation rate was reduced from 1.2 to 0.5, whilst lung transplants were predicted to decline from 6.8% of the population receiving one to 1.8%. The modelled median survival benefit when lumacaftor-ivacaftor was added to standard care was estimated at 7.7 years (projected survival with standard care 36.1 years compared to 43.8 years with lumacaftor-ivacaftor added).

Sensitivity analysis using EQ-5D values for mild, moderate and severe $ppFEV_1$ of 0.741, 0.695 and 0.553 respectively, a 3.5% discount rate, other parameters as per existing base case, and using different time horizons resulted in the following ICERs:

- Lifetime horizon, reported an ICER of £403,469.
- 10 years horizon, reported an ICER of £1,017,638.

- 20 years horizon, reported an ICER of £618,853.
- 40 years horizon, reported an ICER of £435,640.

Adopting EQ-5D values for mild, moderate and severe ppFEV$_1$ of 0.86, 0.81 and 0.64 respectively and a 3.5% discount rate produced an ICER of £343,162. A sensitivity analysis using the same parameters but the patient characteristics of those enrolled in the UK Cystic Fibrosis Registry population (all genotypes) rather than from the pivotal studies increased the ICER to £349,377.

The results were also sensitive to:

- Annual rate of decline in ppFEV1 with ICERs ranging from under £200k with annual increase of 0.16%, rising to about £550k with an annual decline of 1.5%.
- Adopting discount rate of 0% with ICERs ranging from £100k per QALY with no discounting of health benefits £600k with no discounting of costs.

Subgroup analyses reported that ICERs were sensitive to:

- Age, with ICER for those <18 years of £322,529 vs. £351,265 for those ≥18 years.
- Patients with initial ppFEV$_1$ <70% had ICER of £325,408 vs. £366,567 for those with ppFEV$_1$ ≥70%.

The result was not sensitive to gender, the utility equation or age component of the risk equation.

The main strengths of the economic evaluation were design of the study and use of data from valid sources including the clinical studies, the UK Cystic Fibrosis Registry and 2 year chart review.

The main weaknesses are:

- Absence of long-term efficacy data on the benefit of lumacaftor-ivacaftor in maintaining ppFEV$_1$ and reducing exacerbations, and the impact of these factors on survival rates.
- Selective approach to use of data from clinical studies; for example, the approach used to model pulmonary exacerbations overstates absolute rates and relative benefit of lumacaftor-ivacaftor at week 24 compared to data from the clinical studies.
- Concern that the modelled survival for standard care (36.15 years) is low compared with projected median survival of 40.1 years reported in the UK Cystic Fibrosis Trust Registry (although those modeled were over 12 years old and had lower ppFEV$_1$, so some difference may be expected).
- Concern that rate of decline of ppFEV$_1$ is modelled to vary with age only, yet evidence suggests the rate of decline reduces at lower levels of ppFEV$_1$.
- Utility values in base case appeared to lack face validity. The submitting company noted their methodology yielded high scores even for very sick patients; this was explained to arise because patients born with the disease perceive their quality of life to be equivalent to people without CF. Using more conservative utility values increased the ICER by over £90k.
- No disaggregation of resources and unit costs, and other data suggest that the cost of care adopted, particularly the cost of hospitalisation, may be on the high side. Sensitivity analysis showed that using a 35% lower cost for standard care increased the ICER by about £50k.
- The patient group in the clinical studies had lower ppFEV$_1$ than those with the indication in Scotland (60.6% in clinical studies versus 75% average in Cystic Fibrosis Registry). Note that only slightly over half of the patients in the Registry have this genotype and, as noted above, the modeled group was over 12 years old, so some difference may be expected.
- No sensitivity analyses on efficacy of lumacaftor-ivacaftor in respect of baseline rate of exacerbations or weight-for-age scores.

The Committee also considered the benefits of lumacaftor-ivacaftor in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the

criterion for the absence of other treatments of proven benefit was satisfied. In addition, as lumacaftor-ivacaftor is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept lumacaftor-ivacaftor for use in NHS Scotland.

Additional information: guidelines and protocols

There are no published guidelines relevant to the indication under review.

Additional information: comparators

Lumacaftor-ivacaftor is likely to be used in addition to the current standard of care and would be associated with an additional cost.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
lumacaftor 200mg, ivacaftor 125mg (Orkambi®)	**2 tablets twice daily**	**104,000**

Costs from new product assessment form.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 300 in year 1 rising to 347 in year 5, with an estimated uptake of 100% in all years. An annual discontinuation rate of 14% was applied to give estimates of 258 treated patients in year 1 and 298 in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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2. European Medicines Agency. European public assessment report, Committee for Medicinal Products for Human Use (CHMP) assessment report for Orkambi®, EMA/667775/2015, 24 September 2015.

3. US Food and Drug Administration. FDA briefing document on Orkambi® for FDA advisory committee meeting. www.fda.gov

4. European Medicines Agency. Public summary of opinion on orphan designation lumacaftor ivacaftor for the treatment of cystic fibrosis, EMA/COMP/440253/2014, 23 September 2014.

5. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med 2015; 373 (3): 220-31.

6. *Commercial In Confidence*

7. *Commercial In Confidence*

8. European Medicines Agency. Guideline for the clinical development of medicinal products for the treatment of cystic fibrosis, EMEA/CHMP/EWP/9147/2008-corr*, 22 October 2009.

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10. Clinicaltrials.gov. Record for NCT01931839.

11. UK Cystic Fibrosis Registry. Annual data report 2014, July 2015.

12. Vertex. Summary of product characteristics for Kalydeco, last updated 21 September 2015.

13. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest 2012 Sep; 142(3): 718-24.

14. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. Lancet Respir Med 2014; 2(7): 527-38.

This assessment is based on data submitted by the applicant company up to and including 12 February 2016.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed

Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.