Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2182

lumacaftor and ivacaftor 200mg/125mg, 100mg/125mg film-coated tablets and 100mg/125mg,150mg/188mg granules in sachets (Orkambi®)

Vertex Pharmaceuticals (Europe) Limited

5 July 2019

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 NHSScotland. The advice is summarised as follows:

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

lumacaftor - ivacaftor (Orkambi®) is not recommended for use within NHSScotland.

Indication under review: the treatment of cystic fibrosis in patients aged 6 years and older (tablets) and aged 2 to 5 years (granules) who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

lumacaftor-ivacaftor, compared with placebo, improved measures of lung function in patients with cystic fibrosis who were homozygous for the F508del mutation in 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 Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Lumacaftor-ivacaftor tablets are indicated for the treatment of cystic fibrosis in patients aged 6 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Lumacaftor-ivacaftor granules are indicated for the treatment of cystic fibrosis in children aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene.[1]

Dosing Information

Lumacaftor 200mg, ivacaftor 125mg: two tablets twice daily in patients aged 12 years or more.
Lumacaftor 100mg, ivacaftor 125mg: two tablets twice daily in patients aged 6 to 11 years.
Lumacaftor 150mg, ivacaftor 188mg granules: one sachet twice daily in patients aged 2 to 5 years who weigh 14kg or more.
Lumacaftor 100mg, ivacaftor 125mg granules: one sachet twice daily in patients aged 2 to 5 years who weigh less than 14kg.
Lumacaftor-ivacaftor should be taken 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. The entire contents of a granule sachet should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed within one hour.
Lumacaftor-ivacaftor should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the F508del mutation on both alleles of the CFTR gene.[1]

Product availability date

December 2015 (tablets), March 2019 (granules)
Lumacaftor-ivacaftor in this indication meets SMC orphan equivalent criteria.

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 have CFTR protein that does not fold correctly and is mostly degraded in the cell. The small amount of CFTR protein that reaches the cell membrane has reduced function as a chloride channel, with low channel opening probability. Lumacaftor and ivacaftor's exact mechanisms of actions are not fully characterised. It is believed that lumacaftor acts on CFTR protein to promote proper folding and improve processing in the cell, thereby increasing the amount reaching the 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]

Evidence in patients aged 12 years and older

Two double-blind phase III studies (TRAFFIC and TRANSPORT) recruited 559 and 563 patients with stable cystic fibrosis who were homozygous for F508del CFTR mutation and aged at least 12 years with 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 plus ivacaftor 250mg twice daily; lumacaftor 400mg plus ivacaftor 250mg twice daily; or placebo twice daily. The primary outcome was absolute change from baseline to the average of week 16 and week 24 in $ppFEV_1$ assessed in all randomised patients who received at least one dose of study medication.[3,4]

Results of TRAFFIC and TRANSPORT are presented for the licensed dose group (lumacaftor 400mg plus ivacaftor 250mg twice daily) only. Absolute change from baseline to average of week 16 and 24 in $ppFEV_1$ was significantly greater with lumacaftor-ivacaftor, compared with placebo, in both TRAFFIC, 2.16% versus -0.44%, and in TRANSPORT, 2.85% versus -0.15%, with differences (95% confidence interval [CI]) of 2.60% (1.18 to 4.01) and 3.0% (1.56 to 4.44) in the respective studies.[3,4] The European Medicines Agency (EMA) noted that the time-frame of the primary outcome did not correspond with the recommended six months.[4] The results at week 24 were considered most reliable and were presented in the summary of product characteristics (SPC)[1] and are detailed in table 1. Secondary outcomes were tested in a hierarchical order, starting with relative change in $ppFEV_1$ to average at week 16 and 24. Statistical testing was stopped at the next outcome (change to week 24 in body mass index [BMI]) in TRAFFIC and at the third outcome (change to week 24 in Cystic Fibrosis Questionnaire Revised [CFQ-R] respiratory domain) in TRANSPORT.[3,4]

After completing TRAFFIC and TRANSPORT 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. Efficacy analysis were conducted at week 72 of PROGRESS, with week 96 data considered a sensitivity analysis because there was a large drop out of patients after week 72, mainly due to the introduction of commercially available lumacaftor-ivacaftor. Improvements in efficacy outcomes were generally maintained as detailed in table 1.[5]

The rate of decline in $ppFEV_1$ within 455 patients treated with the licensed dose of lumacaftor-ivacaftor in PROGRESS was compared with that in a matched cohort of 1,588 patients in the United States Cystic Fibrosis Foundation Patient Registry (CFFPR). Patients were matched using propensity scores from logistic regression models using the following variables: age, sex, race, diabetes, bacteriology, concomitant medicines, height- and weight-for-age z-score, BMI and spirometry. This estimated an annualised rate of decline in $ppFEV_1$ of -1.3% (95% CI: -1.8% to -0.8%) in patients given the licensed dose of lumacaftor-ivacaftor in PROGRESS and -2.3% (95% CI: -2.6% to -2.0%) in the matched control patients.[5]

Table 1: Secondary outcomes from TRAFFIC and TRANSPORT studies.[1-7]

	TRAFFIC		TRANSPORT		PROGRESS			
	Week 24		Week 24		Week 72		Week 96	
	Placebo	LUM4	Placebo	LUM4	P/LUM	LUM4	P/LUM	LUM4
Absolute change in $ppFEV_1$ from baseline (%)								
LS Mean	-0.73	1.68	-0.02	2.63	1.5	0.5	0.8	0.5
Diff. (95% CI)	2.41*		2.65#					
Absolute change in body mass index (BMI) from baseline (kg/m^2)								
LS Mean	0.19	0.32	0.07	0.43	0.62	0.69	0.76	0.96
Diff. (95% CI)	0.13 (-0.07 to 0.32)		0.36 (0.17 to 0.54)*					
Absolute change in CFQ-R respiratory domain from baseline								
LS Mean	1.10	2.60	2.81	5.66	3.3	5.7	0.5	3.5
Diff.(95% CI)	1.50 (-1.69 to 4.69)		2.85 (-0.27 to 5.98)					
Pulmonary exacerbations (events per patient-year)								
All	1.07	0.71	1.18	0.67			0.69	0.65
RR (95% CI)	0.66 (0.48 to 0.93)		0.57 (0.42 to 0.76)					
Hospitalisation							0.30	0.24
IV Antibiotics							0.37	0.32

$ppFEV_1$ = percent predicted forced expiratory volume in one second; LS = least squares; Diff. = LS mean difference; CI = confidence interval; RR = rate ratio; CFQ-R = cystic fibrosis questionnaire revised - respiratory domain rates respiratory symptoms on a scale of 0 to 100 with higher scores indicating better quality of life. Pulmonary exacerbations were defined as new or change in antibiotic therapy for any four or more pre-defined signs/symptoms. LUM4 = lumacaftor 400mg twice daily plus ivacaftor 250mg twice daily. P/LUM = transferred from placebo to lumacaftor 400mg twice daily plus ivacaftor 250mg twice daily at PROGRESS baseline. * $p<0.001$; # $p<0.01$.

An open-label phase III study (study 106) recruited patients to similar criteria as in the TRAFFIC and TRANSPORT studies, except for $ppFEV_1$, which was less than 40% and considered indicative of advanced disease. These patients received lumacaftor 400mg plus ivacaftor 250mg twice daily orally for 24 weeks, with an option of seven days at half strength dose or initiating treatment at this reduced dose at the physician's discretion. The study was primarily designed to assess safety and not powered for efficacy analyses. There was an initial decline from baseline in mean $ppFEV_1$ at day 15 (-1.7%), which returned to baseline by week 4 and remained near baseline through week 24, -0.4% (95% CI: -1.9 to 1.1). The change from baseline to week 24 was -20.2mmol/L (95% CI: -24.3 to -16.1) for sweat chloride, 2.5 (95% CI: -1.0 to 5.9) for CFQ-R respiratory domain, and 0.29kg/m^2 for BMI. The annualised rate of pulmonary exacerbations during the six-month study was lower than in the six-month pre-study period: 1.1 versus 2.8.[8]

Evidence in patients aged 2 to 11 years

A double-blind phase III study (study 109) recruited children aged 6 to 11 years with stable cystic fibrosis who were homozygous for the F508del CFTR mutation, weighed at least 15kg, had $ppFEV_1$ of at least 70% and lung clearance $index_{2.5}$ ($LCI_{2.5}$) of at least 7.5. Randomisation was stratified by weight (<25kg or ≥25kg) and $ppFEV_1$ (<90% or ≥90%) and patients were equally assigned to lumacaftor 200mg plus ivacaftor 250mg twice daily orally or placebo for 24 weeks. The primary outcome was mean absolute change in $LCI_{2.5}$ from baseline at all study visits up to and including

week 24 and was assessed in all randomised patients who received at least one dose of study treatment.[9,10]

Two open-label phase III safety studies (Study 115 and 011) recruited children with stable cystic fibrosis who were homozygous for the F508del CFTR mutation. Study 115 included 60 children aged 2 to 5 years who weighed at least 8kg and had sweat chloride concentration ≥60mmol/L.[11,12] Study 011 included 58 children aged 6 to 11 who weighed at least 15kg and had $ppFEV_1$ at least 40%.[10,13] In study 115, children received oral granules of lumacaftor 100mg plus ivacaftor 125mg twice daily if weight was less than 14kg (n=19) and lumacaftor 150mg plus ivacaftor 188mg twice daily (n=41) if weight was 14kg or greater. In study 011, children received lumacaftor 200mg plus ivacaftor 250mg twice daily. The studies were primarily designed to assess safety and not powered for efficacy analyses. Efficacy outcomes are detailed in table 2.

Table 2: Efficacy outcomes in studies 109, 115 and 011.[10-13]

	Study 109			**Study 115**	**Study 011**
	Change at week 24			**Change (95% CI) at week 24**	
	Placebo	**LUM-IVA**	**Difference (95% CI)**	**LUM-IVA**	**LUM-IVA**
$LCI_{2.5}$	0.1	-1.0	-1.1 (-1.4, -0.8)	-0.58 (-1.17, 0.02)	-0.88 (-1.40, -0.37)[A]
Sweat chloride*	0.8	-20	-21 (-23, -18)	-32 (-36, -28)	-25 (-29, -20)
$ppFEV_1$ (%)	-1.3	1.1	2.4 (0.4, 4.4)	0.5 (-6.9, 7.9)[B]	2.5 (-0.2, 5.2)
BMI (kg/m^2)	0.3	0.4	0.1 (-0.1 to 0.3)	0.27 (0.07, 0.47)	0.64 (0.46, 0.83)
BMI-z-score	0.1	0.1	0.0 (-0.1 to 0.1)	0.29 (0.14, 0.45)	0.15 (0.08, 0.22)
CFQ-R RD	3.0	5.5	2.5 (-0.1, 5.1)	-	5.4 (1.4, 9.4)

A = based on subgroup data, n=30. B = based on a subgroup data, n=12. $ppFEV_1$ = percent predicted forced expiratory volume in one second. CFQ-R = cystic fibrosis questionnaire revised. * mmol/L, results for study 109 are mean of day 15 and week 4. LUM-IVA lumacaftor-ivacaftor.

There were 240 patients who completed study 109 or 011 and entered study 110, a 96-week open-label extension study where patients received lumacaftor-ivacaftor. $LCI_{2.5}$, sweat chloride, BMI, and CFQ-R respiratory domain score improved in patients who transferred from placebo and in those who remained on lumacaftor-ivacaftor improvements in these outcomes in the preceding studies were maintained at week 24 of the extension study.[14 15]

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

Summary of evidence on comparative safety

The EMA review of safety for the initial licence of lumacaftor-ivacaftor (in patients aged at least 12 years) noted that the adverse event profile of ivacaftor had been characterised within its use as monotherapy for cystic fibrosis patients with other genotypes. Consistent with this, elevated transaminases were noted as an adverse event of special interest for lumacaftor-ivacaftor. In contrast to ivacaftor monotherapy, lumacaftor-ivacaftor was associated with an increased incidence compared with placebo, of dyspnoea and abnormal respiration (chest tightness, bronchospasm or wheezing) that were generally reported at treatment initiation, but did not require cessation of treatment. There was also a potential concern about development of lens opacities. The EMA reviews of safety for the licence extension to children aged 6 to 11 years and the subsequent extension to those aged 2 to 5 years both concluded that the safety outcomes were generally consistent with those in established profile of lumacaftor-ivacaftor. At the review of patients aged 6 to 11 years, additional information was added to the SPC confirming the temporary decline in FEV_1 at the start of treatment with lumacaftor-ivacaftor. At the subsequent review of patients aged 2 to 5 years additional information was added to the SPC to indicate that elevated transaminases occurred at a higher frequency in children aged 2 to 5 years compared with those aged 6 to 12 years. This review also noted that data in children aged 2 to 5 years were limited to six-months and additional long-term safety data were requested.[4,10,12]

Across the placebo-controlled and uncontrolled studies the most common adverse events were respiratory, mainly symptoms of cystic fibrosis, and gastro-intestinal. Rates of particular adverse events in the extension studies were generally similar or lower than in the preceding studies.[4,5,10,12]

Summary of clinical effectiveness issues

Cystic fibrosis results from defects in the CFTR gene that codes for a chloride channel (CFTR protein) on the surface of epithelial cells, which regulates salt and water balance across the cell membrane. Patients who are homozygous for 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 the 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.[4,16]

Current treatment is based on best supportive care, including inhaled and systemic antibiotics (cephalosporins, aminoglycosides, fluoroquinolones and the polymyxin, colistimethate sodium); inhaled mucolytics (hypertonic saline, dornase alfa, mannitol), inhaled bronchodilators and anti-inflammatory therapy; pancreatic enzyme replacement therapies; vitamin supplements (especially fat-soluble vitamins); electrolyte and nutritional supplements and a high-calorie diet.[2,4]

Clinical experts consulted by SMC noted an unmet clinical need for treatments that target the defective CFTR protein in patients with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. Lumacaftor-ivacaftor meets SMC orphan equivalent criteria.

The fixed-dose combination tablet, Orkambi®, is the first 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. SMC has issued advice (number 1136/16) that Orkambi® 200mg/125mg tablets are not recommended for use within NHSScotland in its initial indication: treatment of cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Subsequent to this a new strength, 100mg/125mg, tablet has been licensed and the indication of both tablet formulations extended to include patients aged 6 to 11 years. Following on from this two new formulations, Orkambi® 150mg/188mg and 100mg/125mg granules, have been licensed for treatment of cystic fibrosis in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.[1,10,12] In October 2018 an EU licence for treatment of cystic fibrosis in patients aged at least 12 years who are homozygous for the F508del mutation was issued for the second fixed-dose medicine (Symkevi®) containing ivacaftor and a CFTR corrector, tezacaftor.[17] It was not licensed within the timeframe to be a relevant comparator in this submission.

The primary outcomes of the TRAFFIC and TRANSPORT studies indicated that in patients aged at least 12 years lumacaftor-ivacaftor produced a placebo-corrected increase in $ppFEV_1$ over 24 weeks of 2.6%, which was considered small by the EMA. It was noted that only 37% to 41% of patients (versus 22% in the placebo group) achieved at least a 5% improvement in $ppFEV_1$.[4]

In adults with more advanced disease, $ppFEV_1$ <40%, lumacaftor-ivacaftor was associated with an initial decline in $ppFEV_1$ at week 2, which resolved by week 16 and remained around baseline through to week 24.[8]

The studies in children aged 6 to 11 years found small changes in $ppFEV_1$ (increase at week 24 of 2.5% in study 011 and of 1.1% [versus decline of 1.3% with placebo] in study 109).[9,13] It was not possible to obtain robust ppFEV1 data from patients aged 2 to 5 years in study 115.[11]

An EMA Report of the workshop on endpoints for cystic fibrosis clinical trials noted that as FEV_1 may not be sufficiently sensitive to detect a treatment effect in younger patients with respiratory function as determined by spirometry that has not begun to decline, it recommended that a more sensitive endpoint such as LCI should be evaluated in these patients.[18]

The primary outcome in study 109 indicated that in patients aged 6 to 11 years lumacaftor-ivacaftor produced a placebo-corrected improvement of 1.1 in $LCI_{2.5}$. This was considered small by the EMA, although it was noted that there are limited data from studies using $LCI_{2.5}$ as an outcome and a minimum clinically relevant difference has not been defined.[10]

The most perceptible benefit for patients may be effects on rate of pulmonary exacerbations of cystic fibrosis. In the TRAFFIC and TRANSPORT studies there was a decrease in annual event rate of pulmonary exacerbation with lumacaftor-ivacaftor, compared to placebo, to about 0.7 (versus 1.1 with placebo) and this reduced rate was maintained with lumacaftor-ivacaftor during the 96-week PROGRESS extension study.[3-5] The differences in exacerbation rates could not be statistically tested

due to the hierarchical plan. In study 106, which recruited adults with advanced disease, the annualised rate during the six-month study was lower than in the six-month pre-study period (1.1 versus 2.8).[8] Studies in children aged 6 to 11 and 2 to 5 years provided no evidence of an effect on pulmonary exacerbation rate.[9-13]

The EMA review of the TRAFFIC and TRANSPORT studies noted that effects on BMI and CFQ-R respiratory domain were not indicative of a clinically relevant benefit of treatment.[4] The EMA review of data supporting the licence extension to children aged 6 to 11 years noted that it was difficult to determine whether the BMI results reflected an improvement in nutritional status and that the limited effect on CFQ-R respiratory domain may to be related to some extent to a lack of sensitivity in patients at an early stage of their disease.[10] As the only study in patients aged 2 to 5 years was uncontrolled it is not possible to determine whether changes from baseline in BMI were due to lumacaftor-ivacaftor or to the expected growth in this age group.[12]

The TRAFFIC and TRANSPORT studies were larger than required and therefore a small difference in the primary endpoint (<3%) was statistically significant.[4] The open-label design of studies 115, 011 and 106 and the long-term extension studies, PROGRESS and 110, may affect subjective outcomes such as CFQ-R respiratory domain and adverse events. None of the phase III studies included monotherapy treatment groups for the constituent drugs. It is therefore not possible to estimate treatment effects of the constituent drugs.

The lack of a control group in studies 115 (patients aged 2 to 5 years), 011 (patients aged 6 to 11 years) and 106 (adults with advanced disease) raised some issues with interpretation of efficacy data. In studies 115 and 011 it is not clear whether the increase in BMI, weight and stature were due to improved pancreatic function and subsequent improved nutritional status or due to the expected growth that would occur in children aged 2 to 11 years. Similarly, it is difficult to differentiate the effect on pulmonary exacerbations, hospitalisations and $ppFEV_1$ of lumacaftor-ivacaftor from that of concomitant therapies, such as dornase alfa, which may affect these.[10,12]

Placebo-controlled data are limited to six months duration. There are no longer term placebo-controlled data, which would be required to provide robust evidence of disease modifying effects on rate of decline in respiratory function as measured by ppFEV1 versus standard of care (placebo). The EMA guideline for the clinical development of medicinal products for cystic fibrosis notes that that rate of decline in FEV1 has been shown to correlate with survival and to be the strongest clinical predictor of mortality, with a more marked effect in patients with pancreatic-insufficient disease. This prognostic value increases as patients grow older, with a plateau at age 15.[19] The rate of decline in ppFEV1 with the licensed dose of lumacaftor-ivacaftor in the PROGRESS study was compared with a matched historical control to provide support for an improvement in this with lumacaftor-ivacaftor.[5] However, this was limited by weaknesses characteristic of this type of analysis, including possible differences in baseline demographic or disease characteristics, failure to adjust for unknown effect modifiers or potential biases, such as those related to analysis inclusion criteria.

There were no placebo-controlled data in patients aged 2 to 5 years and evidence of efficacy in this age group was provided from secondary outcomes in study 115, which was primarily designed to assess safety. These indicated improvements from baseline in pharmacodynamic outcomes, $LCI_{2.5}$, sweat chloride and faecal elastase-1.[11] The EMA review noted that efficacy in the 2 to 5 year age

group was extrapolated from placebo-controlled studies in patients aged 6 to 11 years (study 109) and in patients aged at least 12 years (TRAFFIC and TRANSPORT studies) as the same underlying pathophysiology of cystic fibrosis applies across the age groups.[12]

Clinical experts consulted by SMC noted that lumacaftor-ivacaftor in the treatment of patients with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene is a therapeutic advance as it targets the defective CFTR protein. They note that in practice lumacaftor-ivacaftor would be added to current standard of care. If the use of lumacaftor-ivacaftor led to less pulmonary exacerbations then SMC clinical experts suggest a reduction in the use of antibiotics may be expected.

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 NHSScotland.

The key points expressed by the group were:

- Cystic fibrosis is a devastating, chronic, genetic condition with severe symptoms and no cure that results in death at a young age. It affects the lungs causing inflammation, recurring lung infections, scarring and declining lung function leading to respiratory failure and early death. Other complications include pancreatic failure, gastrointestinal effects, diabetes, low body weight, arthropathy and liver disease.

- Current therapy only treats the complications of cystic fibrosis. Treatment is time consuming to administer, invasive and associated with toxicity. Patients require frequent courses of intravenous antibiotics and have prolonged hospital admissions.

- Lumacaftor-ivacaftor is a transformational treatment as it targets the underlying disease. It is expected to slow or reverse the decline in patients with cystic fibrosis homozygous for the F508del mutation. It is the only medication licensed for this indication for patients aged 2 and above.

- Reducing exacerbations, hospital admissions and the overall burden of care would benefit both the patients and their families. Attendance at school or work could be improved, patients could participate in family activities, could socialise more and have an improved quality of life. This could have a positive psychological impact and reduce anxiety/depression for the patient and their family.

- Patients face the unpredictability of exacerbations and acute episodes with the uncertainty of potential deterioration at any time. Lumacaftor-ivacaftor offers the potential for patients to plan their lives further ahead with the associated psychological benefits.

- There would be service implications associated with the introduction of lumacaftor-ivacaftor including the need for medical, nursing and pharmacy support to undertake patient

counselling, reviews for drug interactions, assessment of response and monitoring for potential adverse effects.

Additional Patient and Carer Involvement

We received patient group submissions from the Cystic Fibrosis Trust and Quest for a CF Cure. The Cystic Fibrosis Trust is a registered charity and Quest for a CF Cure is an unincorporated organisation. The Cystic Fibrosis Trust has received 14% pharmaceutical company funding in the past two years, including from the submitting company. Quest for a CF Cure has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

A cost-utility analysis was presented comparing lumacaftor-ivacaftor plus standard of care (SoC) compared to SoC alone in patients with cystic fibrosis aged 2 years and older who are homozygous for the F508del mutation.

An individual patient state-transition microsimulation model was presented, which tracks cystic fibrosis disease progression and treatment impact over time. The analysis adopted a health and social care perspective and a lifetime horizon, which is reasonable considering the nature of the disease.

The model simulated two cohorts with identical baseline characteristics, informed by individual patient-level baseline data collected in the clinical studies of lumacaftor-ivacaftor. Survival predictions were based on a Cox proportional hazards model that links survival to nine characteristics of patients with cystic fibrosis: age, gender, $ppFEV_1$, annual number of pulmonary exacerbations, respiratory infections, CF-related diabetes (CFRD), weight-for-age z-score, and pancreatic sufficiency status. Values for these nine characteristics were assigned to each patient at baseline and updated with every cycle to give individualised predictions of death.

Survival differences amongst patients between treatment cohorts were driven by the impact of lumacaftor-ivacaftor on $ppFEV_1$, annual pulmonary exacerbations, and weight for age z-score. Gender, respiratory infection status and pancreatic sufficiency status did not change from baseline over time, but age and CFRD status were updated at each cycle.

The primary source of data for patients aged 12 years and over were from a pooled analysis of the TRAFFIC and TRANSPORT studies.[3] For patients aged 6 to 11 years, clinical evidence was obtained from study 109 and study 011B.[9,13] For patients aged 2 to 5 years, there was no placebo-controlled evidence available. Open-label extension studies and observational registry studies were also employed as sources for some model parameters.[5, 11]

Both acute and long term changes in lung function were tracked in the model. For long term impact, compared to patients on SoC alone, the model assumed a 58% reduction in annual $ppFEV_1$ decline from age 6 and above for patients initiating lumacaftor-ivacaftor at ages 2-5 years and a 50%

reduction if treatment was initiated during ages 6-11. Annual $ppFEV_1$ decline for patients aged 12+ was 42% lower than decline in patients on SoC alone.

Although EQ5D data were collected as part of the studies, the resulting utility values were judged by the submitting company to be abnormally high due to the response shift phenomenon arising from patients adapting to long-term illness. The model therefore used utility values stratified by $ppFEV_1$ derived from a cross-sectional observational study undertaken in the UK in which 401 adult patients with CF completed the CFQ-R, the EQ-5D and a demographic/clinical background form. Additionally, the model applied a 0.05 treatment utility increment for the patients on lumacaftor-ivacaftor to account for improvements in quality of life due to factors other than improved respiratory function.

The annual cost of lumacaftor-ivacaftor per patient at list price is £104,286. A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. SMC is unable to present the with-PAS cost-effectiveness estimates that informed the decision due to commercial confidentiality. As such, only the without-PAS figures can be presented. The base case analysis presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of £214,772 per quality-adjusted life-year (QALY) based on the list price. This results from an estimated QALY gain of 4.33 and an estimated difference in costs of £930K.

Scenario analysis showed that the ICER decreased if the use of lumacaftor-ivacaftor was restricted to patients aged 2 to 11 years due to the better outcomes assumed as a result of early intervention. The ICER was approximately £173K if lumacaftor-ivacaftor was initiated only in patients aged 2 years and £185K if initiated only in patients aged 2 to 11 years.

A range of optimistic scenario analyses were provided which included: applying substantial discounts on treatment costs past 12 years to reflect generic entrants to the market, doubling and tripling the 0.05 treatment-related utility increase, and excluding disease management costs during the life extension period.

One-way sensitivity analysis showed results were most sensitive to discount rates for cost and benefits. Results were also sensitive to the treatment utility increment, treatment compliance rates and utility values stratified by $ppFEV_1$.

Table 3: Sensitivity analysis at list price

Scenario	ICER (£/QALY)
Base Case	**£214,772**
Treatment utility increment 0.10 (base case 0.05)	£183,037
Exclusion of disease management costs during life extension period	£194,819
Utilising UK CF registry data to derive the reference survival curve in the model	£217,715
Excluding treatment effects on weight-for-age score	£218,104
Continuous treatment discontinuation after 96 weeks	£227,928
Omission of age-dependent treatment effects in $ppFEV_1$ decline in young patients (assume 42% reduction in rate of decline for all patients)	£236,034

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life-year, $ppFEV_1$ = percent predicted forced expiratory volume in one second

The main weaknesses with the economic analysis are:

- Evidence to support the claimed long-term disease modifying effect of lumacaftor-ivacaftor is lacking. Evidence for sustained treatment effect for patients aged 12 and older was primarily based on a historical cohort matched analysis and there were no placebo-controlled studies for younger patients aged 2 to 11 years.
- Long-term impact on lung function: The reduction in long-term $ppFEV_1$ decline in the treatment arm relative to the control arm may have been overestimated because the propensity-matched analysis from which it was derived included patients participating in the parent phase III studies as well as patients from the open-label extension studies that were treated with placebo in the parent studies. Despite clarification that the analyses excluded the $ppFEV_1$ data in the initial period of 21 days in the homozygous population there is still potential for overlapping and overestimating the long-term reduction in $ppFEV_1$ decline. Additionally, the uncertainty in this estimated reduction in long-term $ppFEV_1$ decline is further propagated by the propensity-score matching methods utilised.
- No alternative analysis was presented that would conservatively remove the treatment impact on long-term $ppFEV_1$ decline to address the uncertainties associated with this aspect of the model. The model also assumed that patients initiated between ages 2-5 would experience a 100% reduction in $ppFEV_1$ decline up to age 6. Sensitivity analysis which removed the age-dependent treatment effects in ppFEV1 decline in young patients by applying a 42% reduction in the rate of decline for all patients increased the ICER to £236k.
- Pulmonary exacerbations: The rate of pulmonary exacerbations is extrapolated based on an exponential equation driven by age and $ppFEV_1$ estimated from 2004 US CFFPR data which covers multiple genotypes and may not be representative of the trial-based model populations.
- Treatment compliance rate*:* An 80% treatment compliance rate was assumed based on a retrospective cohort-study assessing the impact of ivacaftor monotherapy on resource

utilisation from the analysis of US claims data. This is assumed to translate into 20% fewer lumacaftor-ivacaftor prescriptions issued to Scottish patients compared to the full treatment dose recommended. This is an important and uncertain assumption which essentially applies a 20% discount on the treatment cost in the treatment arm of the model, while assuming no change in the health benefits derived, and hence has important implications for the results. Clinical experts contacted by SMC suggested compliance is very high in these patients and applying the higher rates observed in the clinical studies may have been more appropriate. Sensitivity analysis showed an increased ICER of approximately £250K when a 100% compliance rate was assumed for patients aged 12+.

- Baseline utilities: The face-validity of the utilities used in the model from a UK observational study may seem more plausible despite also being subject to response shift. However, uncertainty remains given the differences in clinical characteristics and genotype mix between the population from which they were derived and the trial-based model population.
- Treatment utility increment**:** The treatment-specific utility increment is subject to uncertainty. This utility increment is likely to make a significant contribution to the undiscounted incremental QALY gain in the treatment arm of the model over a patient's lifetime. A decrease or removal of the utility increment was not tested as part of the sensitivity analysis.

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 equivalent 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 NHSScotland.

Additional information: guidelines and protocols

In October 2017 the National Institute for Health and Care Excellence (NICE) published clinical guideline number 78: Cystic fibrosis: diagnosis and management. With regards to the management of cystic fibrosis, there is no single standard of care. Treatment is determined according to particular patient's needs considering that current options are aimed to manage the symptoms and complications associated with this condition rather than its cause. This guideline also list a series of recommendations on treating the most common infections in people with cystic fibrosis.[20]

Additional information: comparators

Supportive care.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Lumacaftor 200mg, ivacaftor 125mg	**two tablets twice daily**	**104,000**
Lumacaftor 100mg, ivacaftor 125mg	**two tablets twice daily**	**104,000**
Lumacaftor 150mg, ivacaftor 188mg	**one sachet twice daily**	**104,000**
Lumacaftor 100mg, ivacaftor 125mg	**one sachet twice daily**	**104,000**

Costs from BNF online on 16 April 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated 390 patients to be eligible for lumacaftor-ivacaftor in year 1 rising to 422 patients in year 5. These estimates were based on incidence rates reported in the 2017 CF Trust UK Registry report. A treatment uptake of 100% and a discontinuation rate of 18% was assumed. An estimated 90 patients are expected to be aged between 2 – 11 years in year 1 rising to 98 in year 5.

SMC is unable to publish the budget impact estimates due to the company's requirement for commercial confidentiality.

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

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This assessment is based on data submitted by the applicant company up to and including 16 May 2019

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

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.