Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2183

tezacaftor and ivacaftor 100mg/150mg film-coated tablets (Symkevi®)

Vertex Pharmaceuticals (Europe) Ltd

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 process

tezacaftor-ivacaftor (Symkevi®) is not recommended for use within NHSScotland.

Indication under review: In a combination regimen with ivacaftor 150mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

In phase III studies in patients ≥12 years of age with cystic fibrosis who were homozygous for the F508del CFTR mutation or heterozygous for the F508del CFTR mutation and a second allele with a CFTR mutation with residual function, tezacaftor-ivacaftor was superior to placebo for absolute change in the percent predicted forced expiratory volume in one second ($ppFEV_1$) from the baseline.

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

In a combination regimen with ivacaftor 150mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.[1]

Dosing Information

One tablet containing tezacaftor 100mg and ivacaftor 150mg taken in the morning and one ivacaftor 150mg tablet taken in the evening, approximately 12 hours apart with fat-containing food.

The dose of tezacaftor-ivacaftor and ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors. Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing. Food or drink containing grapefruit or Seville oranges should be avoided during treatment.

Tezacaftor-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 an indicated mutation using a genotyping assay.

Further information is included in the Summary of Product Characteristics (SPC).[1]

Product availability date

7 November 2018

Tezacaftor-ivacaftor meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR protein is an epithelial chloride ion channel that aids in the regulation of salt and water absorption and secretion. It is found in multiple organs, including the lungs, pancreas, intestinal tract, liver, and vas deferens. Tezacaftor is a selective CFTR corrector and ivacaftor is a CFTR potentiator that act to improve the activity of CFTR in the lungs which is required to produce normal mucus. The combination of tezacaftor and ivacaftor increases quantity and function of CFTR at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency. [1, 2]

Key evidence for this indication is from EVOLVE and EXPAND, two randomised, double-blind, placebo-controlled, phase III studies in patients ≥12 years of age with cystic fibrosis. Recruited patients in EVOLVE were homozygous for the F508del CFTR mutation and in EXPAND they were

heterozygous for the F508del CFTR mutation and a second allele with a CFTR mutation with residual function. They were required to have stable disease (investigator assessed) and a percent predicted forced expiratory volume in one second ($ppFEV_1$) of 40% to 90% at screening (values outside this range were permitted at baseline). Cystic fibrosis diagnosis had to be confirmed by a sweat chloride value ≥60mmol/L. In EXPAND, a sweat chloride concentration <60mmol/L, was allowed if there was documented evidence of chronic sino-pulmonary disease.[2-4]

A hierarchical statistical testing strategy was applied in the key studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

In EVOLVE, patients were randomised equally to receive either tezacaftor 100mg and ivacaftor 150mg in a fixed-dose combination tablet in the morning and ivacaftor 150mg tablet in the evening (n=251) or matched placebo (n=258) for 24 weeks. Randomisation was stratified according to age (<18 years versus ≥18 years), sex, and $ppFEV_1$ (<70% versus ≥70%) at screening.[2, 3]

The primary outcome, assessed in all randomised patients who had received at least one dose of study medication and were homozygous for the F508del mutation, was the absolute change in the $ppFEV_1$ from baseline through week 24, including assessments at day 15 and weeks 4, 8, 12, 16, and 24.[3] Mean baseline $ppFEV_1$ was 60% in both groups. A significantly greater absolute change from baseline in the $ppFEV_1$ was observed at week 24 for tezacaftor-ivacaftor compared with placebo.[2, 3] Pre-specified subgroup analyses were consistent with the primary outcome demonstrating superiority of tezacaftor-ivacaftor over placebo.[2, 3]

Results for two of the key secondary outcomes, the relative change in the $ppFEV_1$ from baseline through week 24 and the number of pulmonary exacerbations at week 24 significantly favoured the tezacaftor-ivacaftor group compared with the placebo group. However, no significant differences were identified between groups in the absolute change from baseline in Body Mass Index (BMI) at the week 24 visit. The absolute change in the respiratory domain score on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) from baseline through week 24 was not tested for statistical significance as the hierarchy was broken. Scores on the CFQ-R range from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status [3]

The primary and key secondary outcomes are presented in Table 1 below.

Table 1. Primary and key secondary outcomes from EVOLVE.[3]

	Tezacaftor-ivacaftor group (n=248)	Placebo group (n=256)	Difference (95% CI)
Absolute change from baseline to week 24 in $ppFEV_1$, percentage points.	3.4	-0.6	4.0 (3.1 to 4.8) p<0.001
Relative change from baseline to week 24 in $ppFEV_1$, percentage points.	6.3	-0.5	6.8 (5.3 to 8.3) p<0.001
Annualised estimated event rate for pulmonary exacerbations	0.64	0.99	Rate ratio: 0.65 (0.48 to 0.88) p=0.005
Absolute change from baseline to week 24 in BMI	0.18	0.12	0.06 (-0.08 to 0.19) p=0.41
Absolute change from baseline to week 24 in CFQ-R respiratory domain score	5.0	-0.1	5.1 (3.2 to 7.0)*

$ppFEV_1$: percent predicted forced expiratory volume in 1 second. BMI: body mass index. CFQ-R: Cystic Fibrosis Questionnaire-Revised. CI: confidence interval. *Not tested for significance as hierarchy broken.

Recruited patients in EXPAND were randomly assigned to one of six intervention sequences and received two of the following three treatments: tezacaftor 100mg once daily and ivacaftor 150mg every 12 hours; ivacaftor 150mg every 12 hours; or placebo. The study included two intervention periods of 8 weeks separated by a washout period of 8 weeks. Patients were stratified according to age at screening (<18 years versus ≥18 years), the $ppFEV_1$ at the screening visit (<70% versus ≥70%), and type of residual function mutation (class V non-canonical splice mutation versus class II to IV residual-function [missense] mutation).[4] In period 1, 84 patients received tezacaftor-ivacaftor, 81 received ivacaftor and 81 patients received placebo. In period 2, 78 patients received tezacaftor-ivacaftor, 76 received ivacaftor and 81 received placebo.[2]

The primary end point, assessed in all randomised patients who had the intended CFTR mutation and have received at least one dose of study medication, was the absolute change in the $ppFEV_1$ from the baseline value to the average of the week 4 and week 8 measurements in each intervention period. Mean $ppFEV_1$ at baseline was 62% to 63% across groups.[2, 4]

Treatment with tezacaftor-ivacaftor and ivacaftor monotherapy significantly improved the absolute change in the $ppFEV_1$, compared with placebo.[2, 4] A difference was observed favouring tezacaftor-ivacaftor when compared with ivacaftor monotherapy. This comparison was not part of the formal hierarchical testing strategy.[4] Pre-specified subgroup analyses were consistent with the primary outcome demonstrating superiority of tezacaftor-ivacaftor and ivacaftor alone over placebo.[2, 4]

For the key secondary end point, the absolute change in the CFQ-R respiratory domain score from the baseline score to the average of the week 4 and week 8 scores in each intervention period, superiority of tezacaftor-ivacaftor over placebo was demonstrated but not over ivacaftor monotherapy. Results of the primary, key secondary and additional secondary outcomes are included in Table 2 below.

Table 2: Primary and selected secondary outcomes from EXPAND.[2, 4]

Outcomes (results presented as	**Tezacaftor-ivacaftor group (n=161)**	**Placebo group (n=161)**	**Tezacaftor-ivacaftor versus placebo least squares mean difference [95% CI])**	
Absolute change in $ppFEV_1$, percentage points	6.5	-0.3	6.8 (5.7 to 7.8) p<0.001	
Change in CFQ-R respiratory domain score, points	10.1	-1.0	11.1 (8.7 to 13.6) p<0.001	
Relative change in $ppFEV_1$			11.4% (9.6% to 13.2%)*	
Absolute change in sweat chloride, mmol/L			-9.5 (-11.7 to -7.3)*	

$ppFEV_1$: percent predicted forced expiratory volume in 1 second. CFQ-R: Cystic Fibrosis Questionnaire-Revised.
* Statistical significance cannot be claimed for these endpoints as the gatekeeping approach was not applied.

EXTEND is an open-label, phase III, 96-week study to evaluate the safety and efficacy of long-term treatment with tezacaftor-ivacaftor.[1] In the EVOLVE study, 91% of patients who received at least one dose of study medication enrolled in the treatment cohort of the extension study[3] and in the EXPAND study, 92% of patients enrolled in the treatment cohort.[2] Results are available from a second interim analysis where patients from EVOLVE had completed at least 24 weeks of treatment in the extension study and those from EXPAND had completed 16 weeks. Efficacy was assessed as a secondary outcome.[2, 5]

In patients who were homozygous for the F508del CFTR mutation (recruited from EVOLVE), the least-squares mean absolute change from baseline in $ppFEV_1$ was 4.2 percentage points in those who were initially treated with placebo then tezacaftor-ivacaftor and -0.2 percentage points for those who continued on tezacaftor-ivacaftor. The estimated event rate of pulmonary exacerbations was 0.65 (95% CI: 0.52 to 0.80) and 0.72 (95% CI: 0.60 to 0.87), the change in CFQ-R was 3.3 points and 0.4 points and the change in BMI was 0.23kg/m^2 and zero in the respective groups.[2]

In patients who were heterozygous for the F508del *CFTR* mutation and a second allele with a *CFTR* mutation with residual function (recruited from EXPAND) the least-squares mean absolute change from baseline in ppFEV1 for patients in the placebo to tezacaftor-ivacaftor group was 4.9 percentage points, for patients in the ivacaftor to tezacaftor-ivacaftor group 2.4 percentage points and for patients who continued on tezacaftor-ivacaftor it was zero. The event rate per year of pulmonary exacerbations was 0.38 (95% CI 0.24 to 0.61), 0.26 (95% CI 0.15 to 0.44) and 0.22 (95% CI 0.13 to 0.37), the change in CFQ-R was 8.1 points, 3.9 points and 4.4 points, the change in BMI was 0.35kg/m^2, 0.15 kg/m^2 and 0.54 kg/m^2 in the respective groups.[2]

Summary of evidence on comparative safety

It was concluded by the European Medicines Agency (EMA) that no significant new or additional safety concerns were identified with the addition of tezacaftor to ivacaftor. The safety profile appeared similar across studies. There were no additional long term risks or safety concerns identified in the extension study. Tezacaftor-ivacaftor appeared to be well tolerated and discontinuation rates due to adverse events were low.[2] The safety profile is generally consistent among adolescents and adult patients.[1]

EVOLVE: patients homozygous for the F508del CFTR mutation

At least one adverse event was reported by 90% of the tezacaftor-ivacaftor group and 95% of the placebo group. Grade 3 or 4 events were reported in 8.8% and 11% and serious adverse events in 12% and 18% of the tezacaftor-ivacaftor and placebo groups respectively. The most commonly reported adverse events were infective pulmonary exacerbation (30% and 37%), cough (26% and 33%), headache (18% and 14%), nasopharyngitis (17% and 15%), increased sputum production (14% and 16%), pyrexia (11% and 12%), haemoptysis (10% and 14%), oropharyngeal pain (8.8% and 11%), and fatigue (6.4% and 12%).[3] Adverse events occurring more frequently in the tezacaftor-ivacaftor group than in the placebo group were headache, nausea, and nasopharyngitis.[3]

EXPAND: heterozygous for the F508del CFTR mutation and a second allele with a residual-function CFTR mutation

At least one adverse event was reported by 72% of patients initially assigned to the tezacaftor-ivacaftor group, 73% of the ivacaftor group and 78% of the placebo group. Grade 3 or 4 adverse events occurred in 2%, 5% and 6% and serious adverse events in 5%, 6% and 9% of the tezacaftor/ivacaftor, ivacaftor and placebo groups respectively. The most commonly reported adverse events were infective pulmonary exacerbation of cystic fibrosis (13%, 13% and 19%), cough (14%, 11% and 19%), haemoptysis (7%, 11% and 9%), headache (12%, 7% and 8%), and fatigue (7%, 4% and 10%).[4] Adverse events occurring more frequently in the tezacaftor-ivacaftor group than in the placebo group were increase in sputum production, nasopharyngitis, diarrhoea, and headache.[4]

EXTEND: Open-label extension study

Data are available for patients who completed at least 48 weeks of treatment with tezacaftor-ivacaftor in the open-label extension study. No additional safety concerns were identified.[2, 5]

Study 114

Study 114 was a randomised, double-blind, placebo-controlled Phase IIIb study in patients ≥12 years with cystic fibrosis homozygous for the F508del CFTR mutation who previously discontinued lumacaftor-ivacaftor due to respiratory adverse events. Patients were randomised equally to tezacaftor 100mg/ivacaftor 150mg in the morning and ivacaftor 150mg in the evening (n=50) or placebo (n=47) for 56 days. The primary outcome was the incidence of respiratory adverse event of special interest through the treatment-emergent period. The overall safety profile was generally similar to other studies. [6]

The SPC notes that elevated transaminases are common in patients with cystic fibrosis, and have been seen in some patients treated with tezacaftor/ivacaftor, as well as with ivacaftor monotherapy. Co-administration with strong CYP3A inducers is not recommended due to potentially reduced efficacy of tezacaftor/ivacaftor. Dose adjustments are recommended when used in combination with strong or moderate CYP3A inhibitors.[1]

Summary of clinical effectiveness issues

Cystic fibrosis is a long-term debilitating condition with a high premature mortality and there is currently no cure. It is caused by mutations in the CFTR gene and results in lung disease and may also affect pancreatic function and male reproductive function. F508del is the most common mutation and patients who are homozygous for this have a severe form of cystic fibrosis. Patients with a mutation with residual function are likely to have slower disease progression but will still experience the severe symptoms of cystic fibrosis and premature mortality.[2]

Current treatment of cystic fibrosis is based on supportive care targeting the symptoms of the disease and may include antibiotics, mucolytics, bronchodilators, corticosteroids, enzyme and nutritional supplements. CFTR modulators target the underlying defect in the CFTR protein.[2] Ivacaftor monotherapy is licensed for the treatment of cystic fibrosis in patients aged two years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R and patients aged 18 years and older who have an R117H mutation in the CFTR gene. Lumacaftor-ivacaftor was the first medicine to be licensed for treatment of cystic fibrosis in patients aged six years and older and homozygous for the F508del mutation but it is not recommended for use in NHSScotland. Tezacaftor-ivacaftor is the only CFTR modulator currently licensed for use in patients heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.[1]

Clinical experts consulted by SMC considered that tezacaftor-ivacaftor fills an unmet need in this therapeutic area, namely because it targets the CFTR defect. Tezacaftor-ivacaftor meets SMC orphan criteria.

In the key studies, EVOLVE and EXPAND, a significantly greater absolute change from baseline in the ppFEV$_1$ was observed for patients who received tezacaftor-ivacaftor compared with placebo. These results were modest but may be considered clinically relevant.[2] In EVOLVE, the annualised estimated pulmonary exacerbation event rate, a key secondary outcome, was significantly lower in the tezacaftor-ivacaftor group compared with the placebo group. In EXPAND, the key secondary outcome, change in CFQ-R respiratory domain, significantly favoured tezacaftor-ivacaftor over placebo.[2-4] The EMA Report of the workshop on endpoints for cystic fibrosis clinical trials noted that FEV$_1$, despite its major limitations, remains an important outcome measure for clinical

efficacy evaluations of medicines for cystic fibrosis.[7] FEV_1 is a surrogate outcome, however rate of decline in FEV_1 has been demonstrated to correlate with survival and to be the strongest clinical predictor of mortality. The EMA note that preservation of lung function and reducing pulmonary exacerbation rate are the main goals of treatment of cystic fibrosis.[2, 8]

Adolescents aged 12 years and older were included together with adults in the key studies. Subgroups analysed by age supported the primary outcomes results in EVOLVE and EXPAND of superiority of tezacaftor-ivacaftor over placebo. Patients were excluded from EVOLVE and EXPAND if they had ppFEV1 <40% at screening which is likely to have excluded those with severe lung disease. Patients were also excluded if they had acute upper/lower respiratory infection, pulmonary exacerbation, or changes in therapy for lung disease within 28 days before the first day of the study which could affect the generalisability to some patients.

The placebo controlled phase of EXPAND was 8 weeks per treatment which was short and may not have captured a difference for all outcomes. The EMA recommend a treatment duration of 6 months for studies investigating medications for cystic fibrosis. An additional 16 weeks of data are available from the open-label extension study and the results generally support the results of the EXPAND study. In the population included in EXPAND, there are limited data for some mutations as patient numbers were low. As they can be rare it may be difficult to obtain more robust clinical data and the EMA concluded that the available results were promising and allowed inclusion in the licensed indication. Further long-term results are awaited from the open-label extension study.

In EVOLVE the hierarchical testing procedure for the secondary outcomes was broken by the results of change in BMI (p=0.41). The reduction in sweat chloride in homozygous F508del patients was modest, given that these patients have baseline sweat chloride of around 100mmol/L. Results for homozygous F508del patients at the second interim analysis of the extension study identified a loss in $ppFEV_1$ however this was lower than the expected annual loss in this group of patients.

Currently patients with cystic fibrosis are treated with medications to control symptoms of their disease. The introduction of tezacaftor-ivacaftor could provide a treatment that improves lung function. Clinical experts consulted by SMC considered that tezacaftor-ivacaftor is a therapeutic advancement as it is a CFTR modulator. If the use of tezacaftor-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 tezacaftor-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 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.

- Tezacaftor-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 or heterozygous with one of the specified mutations.

- 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. Tezacaftor-ivacaftor offers the potential for patients to plan their lives ahead a little further with the associated psychological benefits.

- There would be service implications associated with the introduction of tezacaftor-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

The company submitted a cost-utility analysis of tezacaftor-ivacaftor in combination with standard of care (SoC) compared to SoC alone within its licensed indication for the treatment of cystic fibrosis (CF) in patients 12 years and older who are homozygous for the F508del CFTR mutation, or heterozygous and have a second allele with a CFTR mutation with residual function. The two populations have been investigated in different clinical studies and therefore the corresponding cost-utility results are presented separately for each population but are estimated using the same model framework.

The perspective adopted in the analysis was that of health and social care and the analysis was conducted over a lifetime horizon, which is reasonable considering the nature of the disease.

The model used in the analysis was structured as an individual patient state-transition micro-simulation model which tracks CF disease progression and treatment impact over time. Two cohorts with identical baseline characteristics, informed by patient-level data collected at baseline in the clinical studies, were simulated and assigned treatment with tezacaftor-ivacaftor in combination with SoC or SoC alone. Survival predictions were based on a Cox proportional hazards (CPH) model that links survival to nine characteristics of patients with CF: age, gender, $ppFEV_1$, annual number of pulmonary exacerbations, respiratory infections, CF-related diabetes (CFRD), weight-for-age z-score, and pancreatic sufficiency status.

Survival differences between treatment cohorts were driven by differences in $ppFEV_1$ and annual number of pulmonary exacerbations in both populations, and additionally by weight-for-age z-score in the heterozygous population, as tezacaftor-ivacaftor is assumed to impact these characteristics, whereas the other characteristics were not impacted by treatment and were assumed to remain unchanged (gender, pancreatic sufficiency, respiratory infection status) or updated at the beginning of each cycle (age, CFRD). Additionally, occurrence of relevant events such as adverse events (AEs), treatment discontinuation, and lung transplantation was recorded in each cycle. Four-week cycles were used for the first two years to capture shorter-term outcomes observed in the relevant tezacaftor-ivacaftor clinical trials followed by one-year cycles over the remaining time horizon.

Data on all nine characteristics driving the survival model were derived from a range of clinical studies and extension studies covering tezacaftor-ivacaftor and other CFTR modulators, as well as a range of observational registry studies and other published sources. Pulmonary function measured through the $ppFEV_1$ level seems to be the key clinical outcome which drives survival in the model. The acute treatment impact on $ppFEV_1$ was informed by the rates of change observed in the phase III trials. The long-term decline in $ppFEV_1$ in the SoC arm was based on data in patients with the homozygous mutation from the US Cystic Fibrosis Foundation Patient Registry (CFFPR). In the treatment arm, a proxy percentage reduction in long-term decline was assumed based on data from other CFTR modulators. In the homozygous population, this proxy (42%) was derived by comparing data on $ppFEV_1$ decline from the phase III and open-label extension studies of lumacaftor-ivacaftor with data in patients with the homozygous mutation from the US CFFPR. In the heterozygous population, a different proxy measure was used (47%) which was derived by comparing data on $ppFEV_1$ decline from the phase III and open-label extension studies of ivacaftor monotherapy with data in patients with the homozygous mutation from the US CFFPR.

SF-6D utility scores were collected in the phase III studies but were not utilised in the economic analysis due to the submitting company stating that there was an issue with potential response shift, i.e. patients with CF have adapted to life with a chronic condition and accordingly rate their quality of life higher, resulting in utility scores with face-values higher than expected. Instead, the analysis incorporated utility scores stratified by $ppFEV_1$ from an observational UK study in which 401 adult patients with CF completed the CFQ-R, the EQ-5D and a demographical/clinical background form. No mapping from the phase III studies SF-6D utilities to EQ-5D utilities was attempted. A disutility specific to pulmonary exacerbations was also applied which was derived from EQ-5D data collected in the lumacaftor-ivacaftor clinical trials. Additionally, a treatment-related utility increment of 0.05 was assumed to apply in the treatment arm to reflect the more general treatment-related improvements to other organ systems, well-being and quality of life not related to respiratory outcomes. A post-lung transplantation utility of 0.81 was derived from a cross-sectional survey collecting EQ-5D data from patients regardless of previous treatment and clinical status prior to transplantation.

Costs included in the analysis were annual treatment costs and treatment monitoring costs, costs relating to adverse events, disease management costs, and lung transplant costs. These were informed from a range of public cost sources and observational studies. Treatment is assumed to reduce disease management costs, as measured through a proxy reduction derived in observational studies comparing the resource use before-and-after ivacaftor monotherapy in the USA. A treatment compliance of 80% was assumed throughout most of the time horizon of the model.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

Analysis results at list prices are presented separately for both populations under the licensed indication in the table below. 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.

Table 3: Base case results per patient at list price

Discounted outcome	Homozygous population			Heterozygous population		
	TEZA-IVA + SoC	SoC	Incremental	TEZA-IVA + SoC	SoC	Incremental
Total life year (LY)	14.65	10.67	3.97	17.65	12.18	5.47
Total quality adjusted life years (QALYs)	10.77	7.14	3.63	13.42	8.37	5.05
Total costs	£1,905,163	£376,452	£1,528,711	£2,204,663	£383,700	£1,820,962
Incremental cost per LY gained	-	-	£385,009			£332,761
Incremental cost per QALY gained	-	-	£421,173	-	-	£360,499

A range of optimistic scenario analyses were estimated which included: initiating treatment in patients aged 12 only, applying some heavy discounts on treatment costs after 12 years to reflect generic entrants to the market, doubling and tripling the 0.05 treatment-related utility increase, excluding disease management costs during the life extension period. The resulting incremental cost-effectiveness ratios (ICERs) in all these individual scenarios did not drop below £300,000 in the homozygous population and below £245,000 in the heterozygous population respectively. An extensive list of model parameters were varied in the one-way sensitivity analysis which showed the ICER to be most sensitive to, the treatment compliance rate assumed, the baseline utility scores and the assumed treatment-specific utility increase, as well as the treatment impact on long-term rate of decline in $ppFEV_1$ and pulmonary exacerbations rate. The resulting ICERs fall within the £310,000 to £730,000 range in the homozygous population and within the £240,000 to £720,000 range in the heterozygous population.

Table 4: Scenario sensitivity analysis at list price

	Homozygous population	Heterozygous population
Base case	£421,173	£360,499
Population aged 12 years at baseline	£389,688	£339,438
Incremental utility factor 0.10	£353,513	£307,142
Disease management costs excluded during life extension period	£396,627	£340,821

Utilising UK CF Registry data to derive the reference survival curve in the model	£417,666	£357,331
Extend discontinuation rates post-trial follow-up up to approximately 100 weeks	£427,543	£354,229
Utilising the trial-derived SF-6D utilities	£343,932	£299,662

The following limitations were identified in relation to the economic analysis presented:

- 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 and 30 days in the heterozygous population, there is still potential for overlapping and overestimating the long-term reduction in ppFEV1 decline. Additionally, the uncertainty in this estimated reduction in long-term ppFEV$_1$ decline is further propagated by the propensity-score matching methods utilized, the use of surrogate measures of treatment effect from other CFTR modulators and the mismatch of the populations compared. The one-way sensitivity analysis indicated this estimated reduction to be a key driver of model results (ICERs increase to approximately £450,000 in the homozygous population and £400,000 in the heterozygous population if the assumed reduction in long-term ppFEV$_1$ is lowered by 19%).
- 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 in 20% fewer tezacaftor-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 tezacaftor-ivacaftor 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 hence a compliance rate as high as the one observed in the trials may have been more appropriate. Based on the one-way sensitivity analysis submitted, applying a compliance rate of 100% increase the ICER to approximately £520,000 in the homozygous population and £450,000 in the heterozygous population.
- Baseline utilities: The value of the utilities used in the model and derived from an UK observational study may seem more plausible despite also being subject to response shift. However, their face-validity remains uncertain given the differences in clinical characteristics

and genotype mix between the population from which they were derived and the trial-based model population. A mapping of the trial-based SF-6D utilities onto EQ-5D utilities would have been helpful for comparability.

- Treatment-related utility increment: Finally, the treatment-specific utility increment is subject to uncertainty. This can have quite a substantial impact on the resulting ICER as it seems to be responsible for the accrual of 17% to 20% (depending on the genotype) of the overall incremental QALY gain in the treatment arm of the model over a patient's lifetime. Based on the one-way sensitivity analysis submitted, excluding this utility increment increases the ICER to approximately £520,000 in the homozygous population and £435,000 in the heterozygous population.

The Committee also considered the benefits of tezacaftor-ivacaftor in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of criteria were satisfied; absence of other treatments of proven benefit and a substantial improvement in quality of life. In addition, as tezacaftor-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 tezacaftor-ivacaftor for use in NHSScotland.

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

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published in 2017 the guideline '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 lists a series of recommendations on treating the most common infections in people with cystic fibrosis.[9]

Additional information: comparators

Supportive care

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Tezacaftor-ivacaftor and Ivacaftor	**One tablet (tezacaftor 100mg and ivacaftor 150mg) in the morning and one ivacaftor 150mg tablet in the evening**	**172,821**

Costs for tezacaftor-ivacaftor from eMC dictionary of medicines and devices and for ivacaftor from BNF online on 9 April 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimates there would be 320 patients eligible for treatment with tezacaftor-ivacaftor in year 1 increasing to 347 patients in year 5. All patients are assumed to be started on the new treatment and a 13.63% discontinuation rate is assumed.

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.