ivacaftor 150mg film-coated tablets (Kalydeco®) SMC No. (1193/16)
Vertex Pharmaceuticals (Europe) Ltd

04 November 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 Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission considered under the ultra-orphan process

**ivacaftor (Kalydeco®)** is not recommended for use within NHS Scotland.

**Indication under review**: for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CF transmembrane conductance regulator (CFTR) gene.

Ivacaftor, compared to placebo, significantly increased percent predicted forced expiratory volume in one second (ppFEV₁) by 5.0% at 24 weeks in a subgroup of patients aged ≥18 years with CF and an R117H 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 sufficiently robust clinical and economic analyses to gain acceptance by SMC.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**
For the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CFTR gene.

**Dosing Information**
Ivacaftor 150mg orally every 12 hours taken with fat-containing food.

Ivacaftor 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 before starting treatment to confirm the presence of an R117H mutation in at least one allele of the CFTR gene. The phase of the poly-T variant identified with the R117H mutation should be determined in accordance with local clinical recommendations.

**Product availability date**
18 November 2015.
Ivacaftor was designated an orphan medicine by the European Medicine Agency on 8 July 2008 (EU/3/08/556). Ivacaftor meets SMC ultra-orphan criteria in this treatment setting.

**Background**

Cystic fibrosis (CF) 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. Ivacaftor is a potentiator of the CFTR protein and in vitro it increases CFTR channel gating to enhance chloride transport in specified gating mutations with reduced channel-open probability. Ivacaftor also potentiated the channel-open probability of R117H-CFTR, which has both low channel-open probability (gating) and reduced channel current amplitude (conductance). The exact mechanism of action is not completely understood. Ivacaftor tablets are licensed for the treatment of patients with CF aged ≥ six years and weighing ≥ 25 kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. Granules are available for children aged ≥ two years and weighing <25 kg. The marketing authorisation for ivacaftor has been extended to include use in adult patients with an R117H mutation.¹

Ivacaftor for use in adult patients with an R117H mutation has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

**Nature of condition**

In CF patients, the loss of chloride transport due to defects in the CFTR protein, results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction and elevated sweat chloride concentration. Although CF affects multiple organs, the leading cause of mortality is progressive loss of lung function. There are different defects in the CFTR protein caused by different genetic mutations and CF disease severity generally correlates with the severity of the loss of chloride transport. CF patients with an R117H mutation generally have a less severe form of the disease. It is associated with residual CFTR
function and a variable clinical presentation which often develops into symptomatic disease in late childhood or early adulthood. The median life expectancy of patients with R117H mutation is 50 years.² CF is treated by managing symptoms and complications, such as respiratory infections, impaired mucous clearance and nutritional status. Ivacaftor is the first medicine to be licensed in the UK for the treatment of CF in adults who have an R117H mutation in the CFTR gene. The R117H mutation occurs less frequently than other CFTR mutations and is present in 6.7% of CF patients in Scotland.⁵ The company submission estimates that there are 22 patients in Scotland aged ≥18 years with an R117H mutation who are suitable for ivacaftor. Ivacaftor meets SMC ultra-orphan criterion.

A patient and clinician engagement (PACE) meeting was held to consider the added value of ivacaftor in this patient group in the context of treatment currently available in NHS Scotland. At the PACE meeting, attention was drawn to the variable phenotype of patients with the R117H mutation, some having significant disease which is comparable to those with the G551D mutation. The heavy treatment burden for CF patients was also highlighted; this has a major impact on the daily life of patients and carers through frequent hospital attendance and the lengthy administration of daily maintenance treatments.

**Impact of new technology**

**Summary of evidence on comparative efficacy**
The evidence to support use in CF patients with an R117H mutation comes from one pivotal randomised, double-blind, phase III study (KONDUCT). Eligible patients were aged ≥six years and weighed ≥15kg, with a confirmed diagnosis of CF and at least one allele with the R117H-CFTR mutation. Patients aged six to 11 years were required to have a percent predicted forced expiratory volume in one second (ppFEV₁) of 40 to 105%, and patients aged ≥12 years, of 40 to 90%. They were randomised equally to receive ivacaftor (150mg every 12 hours) or placebo for 24 weeks, with stratification by age (six to 11 years; 12 to 17 years; ≥18 years) and ppFEV₁ (<70%; ≥70% to ≤90%; >90%). Patients continued to receive their usual prescribed CF treatment (standard of care).²³⁴ The primary outcome was the absolute change from baseline to week 24 in ppFEV₁, analysed in the full analysis set (all randomised patients who received at least one dose of study drug) using a mixed-effects model for repeated measures with adjustments for age and ppFEV₁. There was no significant difference between ivacaftor and placebo groups in the overall population (n=69). Pre-defined subgroup analyses found a significant treatment difference in the subgroup of study patients aged ≥18 years (ie the licensed population, n=50) but in the subgroup of patients aged 6 to 11 years (n=17), there was a significantly greater improvement with placebo than with ivacaftor. There were only two patients in the subgroup aged 12 to 17 years and no statistical analysis was performed. Secondary outcomes included change from baseline to week 24 in body mass index (BMI), in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and in sweat chloride concentrations. The KONDUCT study was stopped early and 59 of the 69 randomised patients completed 24 weeks of treatment. However, analysis in the population of patients who completed 24 weeks (completed case) found results consistent with the primary analysis. Key results of primary and secondary outcomes are presented in the table below.²³
Table 1: primary and secondary outcomes of the KONDUCT study\textsuperscript{2,3}

<table>
<thead>
<tr>
<th></th>
<th>Ivacaftor</th>
<th>Placebo</th>
<th>Treatment difference (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome in overall population</strong></td>
<td>n=34</td>
<td>n=35</td>
<td></td>
</tr>
<tr>
<td>Baseline ppFEV(_1), %</td>
<td>75.7 (19.3)</td>
<td>70.2 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline in ppFEV(_1), %</td>
<td>2.6 (1.2)</td>
<td>0.5 (1.1)</td>
<td>2.1 (-1.13 to 5.35) p=0.20</td>
</tr>
<tr>
<td><strong>Primary outcome in subgroup ≥ 18years</strong></td>
<td>n=24</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>Baseline ppFEV(_1), %</td>
<td>67.0 (15.4)</td>
<td>62.2 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline in ppFEV(_1), %</td>
<td>4.5 (1.4)</td>
<td>-0.5 (1.3)</td>
<td>5.0 (1.15 to 8.78) p=0.01</td>
</tr>
<tr>
<td><strong>Secondary outcomes in subgroup ≥ 18years</strong></td>
<td>n=24</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>Baseline BMI, kg/m(^2)</td>
<td>26.9 (5.2)</td>
<td>24.9 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline in BMI, kg/m(^2)</td>
<td>0.53 (0.80)</td>
<td>0.22 (0.78)</td>
<td>0.31 (-1.90 to 2.51) p=0.78</td>
</tr>
<tr>
<td>Baseline sweat chloride concentration, mmol/L</td>
<td>69.3 (24.1)</td>
<td>73.0 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline in sweat chloride concentration, mmol/L</td>
<td>-25.9 (1.6)</td>
<td>-4.0 (1.5)</td>
<td>-21.9 (-26.46 to -17.28) p&lt;0.0001</td>
</tr>
<tr>
<td>Baseline respiratory domain of CFQ-R</td>
<td>68.4 (19.1)</td>
<td>59.9 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Absolute change from baseline in respiratory domain of CFQ-R</td>
<td>12.2 (2.7)</td>
<td>-0.5 (2.6)</td>
<td>12.6 (5.02 to 20.25) p=0.002</td>
</tr>
</tbody>
</table>

CI: confidence interval; ppFEV\(_1\): percent predicted forced expiratory volume in one second; BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised
Baseline values are reported as mean (standard deviation [SD]). Change from baseline values are reported as least squares mean (standard error [SE]).

In the licensed population (subgroup aged ≥18 years), a ≥5.0% in ppFEV\(_1\) was achieved by 54% and 15% of ivacaftor and placebo patients respectively by week 24.\textsuperscript{3}

Subgroup analysis by poly-T mutation status for the group of patients aged ≥18 years, found a larger treatment effect in patients with the R117H-5T variant than with the R117H-7T variant. However, there was only a small number of patients with confirmed R117-7T variant.\textsuperscript{1}

A pulmonary exacerbation (a tertiary outcome) was defined as a new or change in antibiotic therapy for ≥4 of the following reasons: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise; fatigue or lethargy; temperature >38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical chest examination; ≥10% decrease in pulmonary function; radiographic changes indicative of pulmonary infection. In the overall population, at least one pulmonary exacerbation was reported in 32% (11/34) of ivacaftor patients and 37% (13/35) of placebo patients: these were all patients aged ≥18 years.\textsuperscript{2,3} There was no significant difference between treatments in time to first pulmonary exacerbation (hazard ratio 0.93). Hospitalisation was required by two ivacaftor patients (two events) and six placebo patients (seven
events), and intravenous antibiotics were required by two ivacaftor patients (two events) and six placebo patients (eight events).³

Patients who completed the KONDUCT study, after a three to four week washout, could enrol in the open-label, extension KONTINUE study to assess the longer-term safety and efficacy of up to 104 weeks of ivacaftor treatment. KONTINUE also included patients from two other studies in patients with different mutations. Results of interim analysis in patients who continued from the KONDUCT only, showed a mean increase in ppFEV₁ from post-washout baseline to week 12 of 5.5% in the overall population (n=65) and 5.15% in the subgroup of patients aged ≥18 years (n=49).²³

Summary of evidence on comparative safety
No comparative safety data are available other than versus placebo. The safety profile of ivacaftor in CF patients with R117H mutations was consistent with studies in patients with gating mutations and no new safety concerns were observed.²

In the licensed population (subgroup aged ≥18 years) of the KONDUCT study, an adverse event was reported by 96% (23/24) of ivacaftor patients and 100% (26/26) of placebo patients. No adverse events led to discontinuation of study drug. Serious adverse events were reported in 8.3% (2/24) and 23% (6/26) of patients respectively. The most frequently reported adverse events in the ivacaftor and placebo groups respectively were: pulmonary exacerbation (46% and 50%); cough (38% and 27%); headache (17% and 12%); increased sputum (21% and 15%); nasal congestion (21% and 3.8%); oropharyngeal pain (1% and 0%); diarrhoea (17% and 12%); abdominal pain (8.3% and 0%); wheezing (17% and 3.8%) and CF lung pathogen colonisation (4.2% and 3.8%). The most common serious adverse event in both treatment groups was infective pulmonary exacerbation. One patient in the ivacaftor group had a serious adverse event of cellulitis. No serious adverse events were considered to be related to study treatment.²³

Summary of clinical effectiveness issues
The KONDUCT study assessed efficacy of ivacaftor in addition to standard of care using the primary outcome of absolute change from baseline in ppFEV₁ to week 24 which is recommended for CF studies given that lung function declines with age and is considered a significant predictor of mortality.² However KONDUCT failed to meet its primary outcome with no significant difference between ivacaftor and placebo in the overall population. A pre-specified subgroup analysis demonstrated a significant treatment effect in patients aged ≥18 years (n=50) which was considered clinically relevant. However, the placebo-corrected absolute change in ppFEV₁ of 5.0% was smaller than seen in studies of ivacaftor in other mutations (eg G551D: 10.6% to 12.5%).¹³

The European Public Assessment Report notes that although the evidence is based on positive results from a subgroup analysis when the primary outcome of the pivotal study failed, further analyses supported a positive effect of ivacaftor in the adult subgroup when all other evidence was considered.² Results of the primary outcome in the licensed subgroup (≥18 years) are supported by secondary outcomes of sweat chloride concentration and the respiratory domain of the CFQ-R. There was no significant difference in the rate of pulmonary exacerbations between ivacaftor and placebo, which was low in both groups.²³ There was no difference in BMI between ivacaftor and placebo groups at week 24 in the overall population or in the subgroup aged ≥18 years. However, study patients were considered to have normal body weight at baseline and the majority of patients were pancreatic sufficient.²

The placebo-controlled treatment duration of the KONDUCT study was 24 weeks. Although this is considered sufficient by the European Medicines Agency to assess treatment effect on lung function, it is too short to determine longer-term effects on rate of decline, pulmonary exacerbations and mortality. The study was stopped early and eight patients did not complete the 24-week treatment period.
However, analysis of outcomes in a complete case population of the overall population found consistent results.\textsuperscript{2,3}

Adult patients were excluded from KONDUCT if they had ppFEV\textsubscript{1} <40\% or >90\% at screening. This may limit application of results to patients with a marked reduction of pulmonary function and to those whose disease has had little effect on FEV\textsubscript{1}.\textsuperscript{2,3}

There are three poly-T variants of the CFTR gene: the R117H-5T mutation is associated with more severe disease than R117H-7T, and R117-9T is highly unlikely to cause disease.\textsuperscript{2} The summary of product characteristics notes that there is less evidence of a positive effect of ivacaftor in patients with an R117H-7T mutation. Whenever possible, the phase of the poly-T variant identified with the R117H mutation should be determined as this may be informative in considering treatment of patients with an R117H mutation.\textsuperscript{1}

The introduction of ivacaftor for CF patients with an R117H mutation would offer a specific treatment option for use in addition to standard of care. It is the only available medicine to target the genetic abnormality that causes CF. Alternative management is supportive. However, there is currently a lack of evidence on the longer-term efficacy and safety of ivacaftor in this patient population and results of the KONTINUE extension study are awaited.

At the PACE meeting, it was noted that short-term study outcomes are anticipated to lead to reduced exacerbations, hospitalisations, courses of intravenous antibiotics and overall burden of treatment. Patients described how any reduction in the burden of treatment would be associated with an improved quality of life. Experience in patients who have the G551D mutation indicates that ivacaftor can reduce maintenance therapy and may allow patients to return to a full and more normal life.

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

**Patient and clinician engagement (PACE)**

A patient and clinician engagement (PACE) meeting with patient group and clinical specialist representation was held to consider the added value of ivacaftor, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- CF is a multi-system progressive, debilitating disease resulting in a decline in lung function and a significantly reduced life expectancy. The psychological impact of CF and its heavy treatment burden can result in stress, insecurity, anxiety and depression for patients and their carers.

- Patients with the R117H mutation have a variable phenotype, those with poly-T 5 mutational status have significant disease which is similar in severity to those with the G551D mutation.

- CF has a significant and increasing impact on health-related quality of life due to poor lung function, frequent respiratory infections, exacerbations (and associated hospitalisations) and inevitable progressive respiratory failure. Symptoms such as cough, sputum production and breathlessness negatively affect patients on a daily basis and the condition has an extremely high treatment burden.

- There are no other treatments available that target the R117H mutation or offer disease modification.
• Ivacaftor offers the potential for improvements in health-related benefits including modest improvement/reduced decline in lung function and reduced exacerbation rate. Experience from patients with the G551D mutation indicates that this may translate to fewer hospitalisations and reduced overall treatment burden. Patients described how any reduction in the burden of treatment would be associated with an improved quality of life and how ivacaftor may allow a return to a full and more normal life.

• Ivacaftor is available for patients with other mutations in the CFTR gene (via Health Board procedures where it is considered for use in particular patients). PACE participants supported a consistent approach to access across mutation types.

Additional Patient and Carer Involvement
We received patient group submissions from the Ivacaftor Patient Interest Group (iPIG) and the Cystic Fibrosis Trust. iPIG has not received any pharmaceutical company funding in the last two years. Cystic Fibrosis Trust has received <3% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the Cystic Fibrosis Trust also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement. iPIG did not participate in the PACE meeting; however, many of the key points of their submission were covered in the PACE statement.

Value for money

The company submitted a cost-utility analysis comparing ivacaftor plus standard of care (patient’s usual prescribed CF treatment) to standard of care alone for the treatment of patients with CF aged 18 years and older who have an R117H mutation in the CFTR gene. A lifetime horizon was used in the analysis. SMC clinical experts have indicated that there is currently no specific treatment available for patients with the R117H gene mutation; therefore, standard of care is considered to be the appropriate comparator.

An individual patient level micro-simulation model was used in the analysis. A cohort of patients was created using data from the pre-defined subgroup of patients aged ≥18 years in the KONDuct study, where patients were ascribed baseline characteristics from the study (age, gender, mean weight-for-age Z score, mean ppFEV1) and modelled individually according to the treatment received. The model updated each patient profile at the end of each 4 week cycle, and accounted for the risk of experiencing adverse events, probability of treatment discontinuation, patient age and the probability of receiving a lung transplant. The company estimated median survival for each patient using a Cox proportional hazards model and published CF Registry data. The key clinical variable driving the model result was the rate of reduction in decline of ppFEV1.

The clinical data used in the economic analysis were derived from the KONDuct study and other published studies.8,9 The results of KONDuct indicated that ivacaftor plus standard of care resulted in a significant increase in absolute change from baseline ppFEV1 of 4.5% compared to standard of care alone, and a treatment difference of 5.0% (p=0.01) in the subgroup of patients aged ≥18 years. In order to extrapolate these data over the model time horizon, different rates of ppFEV1 decline over time were applied to the treatment arms. For the standard of care arm, the annual rate of ppFEV1 decline over time was taken from CF registry data and was estimated to be -1.64 and -0.97 for patients aged 18-24 years and >25 years respectively. For the ivacaftor treatment arm, the rate of decline in ppFEV1 was assumed to be 71% lower based on data from a previously published study8 which resulted in rates of -0.48 and -0.28 for patients aged 18-24 years and >25 years respectively. Patients within this study were those aged >6 years with the G551D mutation. In the KONDuct
study, no significant differences in pulmonary exacerbations were identified between the treatments; however, the company assumed that ivacaftor treatment is associated with a lower rate of pulmonary exacerbations, with a hazard ratio of 0.446 (derived from previously published studies\(^8,9\)) applied in the model.

Utility values were derived using a published equation whereby a patient’s utility is estimated to be a function of ppFEV\(_1\) and history of pulmonary exacerbations. EQ-5D data used to populate the equation were taken from a published study\(^8\) and updated to account for the impact of ivacaftor on QoL using an unpublished study conducted by the submitting company (utility increment of 0.09). As examples, using the equation for values of ppFEV\(_1\) 50% and ppFEV\(_1\) 60% in patients without pulmonary exacerbations, resulted in utility scores of 0.97 and 0.90 for ivacaftor plus standard of care and standard of care respectively. A post transplant utility value of 0.81 was taken from published literature.

Drug acquisition costs were included in the analysis as well as the cost of disease management (for both treatment arms). Additional costs included lung transplant costs and the cost associated with adverse events. A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for the implementation in NHS Scotland. Under the PAS, a simple discount is offered on the list price of ivacaftor.

With the PAS, the base case results indicated that ivacaftor plus standard of care resulted in an incremental cost-effectiveness ratio (ICER) of £473,071 based on an incremental cost of £2,067,802 and a QALY gain of 4.37.

The company provided one-way, scenario and probabilistic sensitivity analysis. The results of analyses that gave the most upward uncertainty on the ICER are presented in the tables 2 and 3 below;

**Table 2: One-way sensitivity analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICER (with PAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discount rate on benefits 6%</td>
<td>£748,741</td>
</tr>
<tr>
<td>Discount rate on costs 0%</td>
<td>£880,326</td>
</tr>
<tr>
<td>Ivacaftor mean change in ppFEV(_1) during study using lower bound estimate</td>
<td>£573,016</td>
</tr>
</tbody>
</table>

**Table 3: Scenario analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICER (with PAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ivacaftor utility increment</td>
<td>£621,562</td>
</tr>
<tr>
<td>Utilities from Acaster et al</td>
<td>£530,016</td>
</tr>
<tr>
<td>Utilities from Whiting et al</td>
<td>£508,342</td>
</tr>
<tr>
<td>Utilities from Tappenden et al</td>
<td>£476,151</td>
</tr>
</tbody>
</table>

The company provided further analyses testing the key efficacy variables ie annual rate of reduction in ppFEV\(_1\), decline and annual rate of pulmonary exacerbations associated with ivacaftor. When the rate of ppFEV\(_1\) decline for ivacaftor plus standard of care was reduced to 53% (from 71%), the ICER increased to £524,723 with PAS. When the hazard ratio (0.446) for annual rate of pulmonary exacerbations was increased by 40%, the ICER increased to £490,062 with PAS. The company also provided a scenario analysis where the health benefits were discounted at a rate of 1.5% rather than the standard 3.5% rate used in the base case analysis, and also incorporating an estimate of the impact of generic pricing of ivacaftor upon patent expiry. This resulted in the with-PAS ICER reducing to £208,254.
There were a number of limitations with the analysis, including the following:

- The first weakness relates to the clinical data used to support the rate of decline in the ivacaftor plus standard of care arm. In the base case analysis, it was assumed that patients receiving ivacaftor plus standard of care declined 71% more slowly than patients receiving standard of care alone. These data were not derived from the KONDUCT, but from a previously published ivacaftor study. There are a number of issues with using efficacy data from this published study. The first concern is that these patients had a different gene mutation. As such, fundamental differences in the patient population and disease severity may exist, thus introducing uncertainty around the generalisability of efficacy data. Secondly, in terms of the treatment effect of ivacaftor in the published study, ivacaftor plus standard of care resulted in a 10.4% increase in ppFEV₁. However, in the KONDUCT study, ivacaftor is approximately half as effective (resulting in an increase in ppFEV₁ of 5%). Based on this observation, it is possible to conclude that assuming a rate of ppFEV₁ decline in line with what was observed in the previously published study, may not be appropriate as it may overestimate the benefit of ivacaftor. The company was asked to test uncertainty surrounding the rate of decline in ppFEV₁ for ivacaftor plus standard of care. When the rate of reduction was lowered to 53% from 71%, the ICER for ivacaftor plus standard of care (with the PAS) increased to £524,723 compared to standard of care alone.

- The economic analysis applies a hazard ratio of 0.446 to the ivacaftor plus standard of care arm in relation to exacerbations, based on data from previous ivacaftor studies. However, using pulmonary exacerbation rates from these studies may not be appropriate for the following reasons. Firstly, no significant differences in pulmonary exacerbations were identified between the two treatment arms in the KONDUCT study. Secondly, patients in the previous ivacaftor studies differed considerably from those in the KONDUCT study. The company provided some sensitivity analysis testing uncertainty surrounding pulmonary exacerbations by increasing the hazard ratio by 10% increments. When the hazard ratio was increased by 40% (to 0.62), ivacaftor plus standard of care resulted in an ICER of £490,062 with PAS.

- There were some concerns about the estimated utility values as the example values provided from use of the equation appeared to lack face validity and were considered to be high. When values from an alternative source was used in a scenario analysis, the ICER for ivacaftor plus standard of care increased to £476,151 (with PAS) compared to standard of care alone. Additionally, there is considerable uncertainty surrounding the incremental utility gain associated with ivacaftor (0.09), as this was derived from a published study which included younger patients with different disease severity. When this gain was removed, the ICER increased to £621,562 with PAS.

Other data were also assessed but remain commercially confidential.

### Impact beyond direct health benefits and on specialist services

At the PACE meeting, attention was drawn to experience of the use of ivacaftor in patients who have the G551D mutation indicating that patients may be able to return to a fuller and more normal life including full-time work. It was noted that reduced exacerbations and fewer courses of oral and intravenous antibiotics would reduce the burden on family and carers who would experience less disruption to daily life through reduced frequency of hospital attendance and reduced administration of daily maintenance treatment.

The economic analysis does not incorporate these wider effects.
Costs to the NHS and Personal Social Services

The company estimated there would be 22 patients eligible for treatment with ivacaftor in year 1, increasing to 26 patients in year 5.

Without PAS
The gross impact on the medicines budget was estimated to be £4.05m in year 1, rising to £4.78m in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is the same as the gross.

The submitting company did not estimate any costs outside of the NHS.

Other data were also assessed but remain commercially confidential.*

Conclusion

The Committee also considered the benefits of 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 ivacaftor is an orphan medicine, SMC can accept greater uncertainty in the economic case.

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

Additional information: guidelines and protocols

There are no national guidelines specific to this indication.

The European Cystic Fibrosis Society (ECFS) published Best Practice Guidelines in 2014. The guidelines include a section on treatments which target the underlying defect in CF, and recommend that “In patients with the G551D mutation ivacaftor should be part of standard of care.” This guideline makes no recommendation on patients with an R117H mutation in the CFTR gene.

The CF trust has published standards for the clinical care of children and adults with CF in the UK based on consensus. Diagnosis of CF should be confirmed by a sweat test and genetic mutation analysis. Patients should receive antibiotic prophylaxis in addition to early and aggressive treatment of lung exacerbations with high dose antibiotics. Other respiratory treatments that may be considered for patients include dornase alfa and hypertonic saline. Patients with pancreatic insufficiency will require pancreatic replacement therapy and fat-soluble vitamin supplements.

Additional information: comparators

Ivacaftor is likely to be used in addition to the current standard of care.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
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<tbody>
<tr>
<td>ivacaftor</td>
<td>150mg orally every 12 hours</td>
<td>182,000</td>
</tr>
</tbody>
</table>

Costs from eMIMs on 3 August 2016. Costs do not take any patient access schemes into consideration.
References

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


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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug 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 NHS Scotland 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 NHS Scotland 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.