ivacaftor 50mg and 75mg granules in sachet (Kalydeco®)  SMC No. (1134/16)  
Vertex Pharmaceuticals (Europe) Ltd.

08 April 2016

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

**ADVICE**: following a full submission assessed under the ultra orphan medicine process

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

**Indication under review**: treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25kg who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

In an open-label single-arm study, acceptable safety was demonstrated in children aged 2 to 5 years.

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

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**

Treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25kg who have one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

**Dosing Information**

Children aged 2 years and older should be dosed according to table 1.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose</th>
<th>Total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14 kg</td>
<td>50mg granules taken orally every 12 hours with fat containing food</td>
<td>100mg</td>
</tr>
<tr>
<td>≥14 kg to &lt;25 kg</td>
<td>75mg granules taken orally every 12 hours with fat-containing food</td>
<td>150mg</td>
</tr>
</tbody>
</table>

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 to confirm the presence of one of the above-listed gating (class III) mutations in at least one allele of the CFTR gene before starting treatment.

**Product availability date**

January 2016. Ivacaftor has been designated an orphan medicine by the European Medicines Agency (EMA). Ivacaftor granules meets SMC ultra orphan criteria.

**Background**

Cystic fibrosis (CF) is a genetic condition caused by mutations in the CFTR protein, an epithelial ion channel that contributes to the regulation of absorption and secretion of salt and water in the lung, sweat glands, pancreas and gastrointestinal tract. CF is an incurable condition with a high morbidity and mortality. Current treatments target the symptoms and sequelae of CF such as respiratory infections, impaired mucociliary clearance and nutritional status.

Ivacaftor is a potentiator of the CFTR protein and targets the genetic abnormality that causes CF. Ivacaftor tablets are currently indicated for the treatment of CF in patients aged 6 years and older and weighing 25kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. SMC issued not recommended advice for ivacaftor tablets in June 2013; at that time the marketing authorisation for this formulation included only the G551D mutation, the most common gating mutation on the CFTR gene.

The formulation under review in this submission (ivacaftor granules) is indicated for younger children aged 2 years and older and weighing less than 25kg. Ivacaftor has been designated an orphan medicine for the treatment of CF. Ivacaftor granules meets SMC ultra-orphan criteria.
Lumacaftor-ivacaftor (Orkambi®) is also currently under review by SMC for treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

### Nature of condition

In children with CF the lungs appear normal at birth; however, they quickly become congested with mucus leading to recurrent infection and inflammation. Pulmonary insufficiency is the main cause of CF-related death. In addition, most infants rapidly develop pancreatic insufficiency which can lead to malnutrition. Malnutrition is associated with decline in pulmonary function and is an independent predictor of mortality.

The current standard of care for CF patients aged 2 years and older and weighing less than 25kg is supportive treatment, including antibiotics, medicines to reduce the viscosity of the secretions, pancreatic enzymes and nutritional support. Despite these treatments, life expectancy is poor; in 2014, the median predicted survival was 40 years.

Ivacaftor targets the genetic abnormality that causes CF. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely the lack of treatments available to target the underlying genetic condition for the age group under review.

PACE participants highlighted that CF also impacts on the function of other organs and can lead to a range of conditions including diabetes, liver disease and arthritis. They noted that current treatment options are complex and time consuming for patients and their families.

### Impact of new technology

#### Summary of evidence on comparative efficacy

Evidence to support the marketing authorisation came from several phase III studies of ivacaftor in patients with CF. The KIWI study and the KLIMB extension study evaluated the use of ivacaftor granules in children aged 2 to 5 years. Additional studies evaluated the use of ivacaftor tablets in older patients and provided supporting evidence.

KIWI was a phase III, two-part, open-label, single-arm study of ivacaftor granules in patients aged 2 to 5 years with a confirmed diagnosis of CF and a CFTR gating mutation in at least one allele (G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D). Part A was designed to evaluate the safety and pharmacokinetics of ivacaftor, part B was designed to evaluate safety, pharmacokinetics, pharmacodynamics and efficacy. In part B, patients received ivacaftor weight-based dose every 12 hours for 24 weeks. Patients weighing <14kg received ivacaftor 50mg (n=10) and patients weighing ≥14kg received ivacaftor 75mg (n=24). The granules were mixed with approximately one teaspoon of soft food and given with a high calorie and high fat meal or snack.

The primary outcome of part B was safety. The mean absolute change from baseline at 24 weeks in sweat chloride, weight, stature and body mass index (BMI) were measured as secondary outcomes and the results are presented in table 1. The tertiary efficacy endpoints, absolute change from baseline in mean weight-, stature- and BMI-for-age z scores supported the above secondary outcomes and are also presented in table 1. The measures of pancreatic function, faecal elastase-1 and immunoreactive trypsinogen, were generally improved from baseline.
Table 1. Secondary and tertiary outcomes. Mean absolute change from baseline at 24 weeks\textsuperscript{2,3}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>Mean absolute change at 24 weeks (standard deviation)</th>
<th>p values (post hoc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweat chloride (n=25)</td>
<td>97.9mmol/L</td>
<td>-46.9mmol/L (26.19)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Weight (n=33)</td>
<td>15.5kg</td>
<td>1.4kg (0.56)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Stature (n=32)</td>
<td>98.4cm</td>
<td>3.3cm (1.17)</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>BMI (n=32)</td>
<td>15.98kg/m\textsuperscript{2}</td>
<td>0.32kg/m\textsuperscript{2} (0.538)</td>
<td>p=0.0021</td>
</tr>
<tr>
<td>Weight-for-age z score (n=33)</td>
<td>-0.16 units</td>
<td>0.20 units (0.250)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Stature-for-age z score (n=32)</td>
<td>-0.34 units</td>
<td>-0.01 units (0.327)</td>
<td>p=0.848</td>
</tr>
<tr>
<td>BMI-for-age z score (n=32)</td>
<td>0.13 units</td>
<td>0.37 units (0.424)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

KLIMB\textsuperscript{4,5} is an ongoing 88-week extension study to the KIWI study. Efficacy data will be assessed as secondary outcomes. Interim analyses after 48 weeks of treatment in the KLIMB study demonstrated that the efficacy results achieved in the KIWI study were maintained.

Supporting evidence for the use of ivacaftor granules came from ENVISION,\textsuperscript{6} a phase III study evaluating the efficacy and safety of ivacaftor tablets in patients aged 6 to 11 years with CF and a G551D-CFTR mutation in at least one allele. Patients were randomised equally to receive ivacaftor tablets 150mg every 12 hours or placebo for 48 weeks in addition to their pre-study medications, excluding hypertonic saline. The primary efficacy endpoint, measured in the full analysis set (all patients who received at least one dose of study medication) was the absolute change from baseline at week 24 in forced expiratory volume in one second (FEV\textsubscript{1}) percent predicted. The mean FEV\textsubscript{1} percent predicted at baseline was 84% and the mean age of included patients was 9 years old. At week 24, the FEV\textsubscript{1} percent predicted increased from baseline by 12.6% in the ivacaftor group (n=26) and 0.1% in the placebo group (n=26), a treatment effect of 12.5% (95% Confidence Interval [CI]: 6.6 to 18.3, p<0.0001). The treatment effect was similar at week 48 (10.0 [95% CI: 4.5 to 15.5, p=0.0006]).\textsuperscript{6,7} Ivacaftor was also associated with improvements in sweat chloride tests and body weight and in health-related quality of life as measured by the respiratory domain of the child version of Cystic Fibrosis Questionnaire-revised (CFQ-R).\textsuperscript{6}

PERSIST was a 96-week extension study to two phase III studies including ENVISION. Patients who completed 48 weeks of treatment could enrol in this open-label extension study designed to evaluate the safety and efficacy of long term treatment with ivacaftor tablets 150mg twice daily. Of the 48 patients who entered from ENVISION, 94% (45/48) completed 96 weeks of treatment. For patients previously treated in ENVISION, the mean absolute change in FEV\textsubscript{1} percent predicted (standard deviation) at the end of the study was 10.3% (12.4) and 10.5% (11.5) in ivacaftor (n=25) and placebo (n=21) previously treated patients respectively.\textsuperscript{8}
Summary of evidence on comparative safety

In the KIWI study, 89% (8/9) of patients in part A and 97% (33/34) of patients in part B experienced at least one adverse event. Seven serious adverse events occurred in six patients: two cases of infective pulmonary exacerbation of CF and one case each of device-related sepsis, positive Pseudomonas aeruginosa culture, increased transaminases, vomiting and convulsion. One patient discontinued treatment because of severe transaminase elevation.\textsuperscript{2}

Adverse events that occurred in more than 10% of patients in part B were cough (56%), vomiting (29%), nasal congestion (26%), upper respiratory tract infection (24%), rhinorrhea (21%), pyrexia (18%), bacterial test positive (18%), infective pulmonary exacerbation of CF (15%), increased hepatic enzymes (15%), constipation (12%) and rash (12%).\textsuperscript{2}

At the 48-week interim analysis of KLIMB, most adverse events reported were mild to moderate in severity and generally respiratory, gastrointestinal or liver related. The serious adverse events reported were: pulmonary exacerbation (n=4), increased alanine aminotransferase (n=2), increased aspartate aminotransferase (n=2), enterovirus infection (n=1), respiratory syncytial virus infection (n=1), Staphylococcal infection (n=1), subcapsular cataract (n=1), pyrexia (n=1) and anoxic seizure (n=1). From baseline at the start of the KIWI study, eight patients had liver transaminases greater than eight times the upper limit of normal. Six patients had a treatment interruption then re-started ivacaftor and two patients permanently discontinued study treatment.\textsuperscript{4,5}

No comparative safety data are available for patients aged 2 to 5 years. The adverse event profile of ivacaftor has been characterised in previous studies of patients aged 6 years and older. Refer to the summary of product characteristics for details.\textsuperscript{1}

Summary of clinical effectiveness issues

The pivotal KIWI study demonstrated acceptable safety and improvement in selected efficacy outcomes (sweat chloride, nutritional markers) associated with ivacaftor granules compared with baseline in patients aged 2 to 5 years. The 48-week interim analyses of the KLIMB extension study supports the KIWI study results. Supporting evidence in patients aged 6 years and older demonstrated a treatment effect for ivacaftor tablets measured by accepted respiratory surrogate outcomes for CF.\textsuperscript{2}

The pivotal KIWI study in patients aged 2 to 5 years is a single-arm, pharmacokinetic, pharmacodynamic and safety study that is, as yet, unpublished. Efficacy outcomes were secondary or tertiary endpoints. Because of the small sample size, no statistical tests were planned; post hoc p-values have been presented. Sweat chloride results were only reported in 25 of the 34 patients enrolled in the KIWI study due to the difficulty in sampling sweat chloride in young children. The European Medicines Agency (EMA) does not consider sweat chloride a surrogate for clinical outcome in patients with CF. There were positive results related to the effect of ivacaftor granules on nutritional status but the absence of a placebo group makes it difficult to interpret the data. Faecal elastase-1 is used clinically to diagnose pancreatic insufficiency in patients with cystic fibrosis: 26 of the 27 patients with baseline values had pancreatic insufficiency. The company suggested that the results indicated that some patients experienced an improvement in pancreatic function but the EMA considered this to be premature based on the current data. Data regarding pulmonary exacerbations were collected during the study but the small number of patients included limits the interpretation. In addition, few events would be expected in this young age group.\textsuperscript{2}
FEV$_1$ percent predicted is usually the primary efficacy endpoint to measure treatment effect in patients with CF since rate of decline in FEV$_1$ has been correlated with survival and is the strongest clinical predictor of mortality. There is a lack of evidence regarding potential improvements in lung function associated with ivacaftor in children aged 2 to 5 years since cooperation is required to measure FEV$_1$ percent predicted and this is difficult in young children. Furthermore, pulmonary function tests are not considered sensitive enough to detect early manifestations of lung disease and the effect of interventions in young children with CF. Therefore, respiratory outcome data used to support the economic case are based on an unpublished subgroup analysis of children aged 6 to 9 years enrolled in the ENVISION study.

Clinical experts consulted by SMC considered that ivacaftor is a therapeutic advancement. It appears to correct the underlying biochemical defect of CF in the target group and is associated with a clinical benefit.

Genetic mutation testing is performed routinely for patients with CF in NHSScotland. Clinical experts consulted by SMC considered that the introduction of this medicine would have limited service impact, though some additional pharmacy resource may be required. Elevated transaminases have been commonly reported in patients taking ivacaftor, and cataracts have also been reported in paediatric patients taking ivacaftor. Regular liver function monitoring and ophthalmology examinations are therefore recommended. Palatability of the ivacaftor granules for the age group under review was explored in the KIWI study: administration of ivacaftor granules in soft food was acceptable.

**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 ivacaftor, as an ultra-orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- **Cystic fibrosis (CF)** is a progressive, life limiting disease that results in a decline in lung function and a significantly reduced life expectancy due to respiratory failure.

- **CF** puts an enormous emotional and psychological strain on families and carers where anxiety and depression are frequently reported. The condition also adds financial strain in view of the impact on employment; costs associated with travelling to specialist centres; and the additional dietary expenses.

- **CF in children aged 2-5 years** is currently managed with supportive treatment, and ivacaftor is the first treatment that targets the underlying cause and not just the symptoms of CF.

- **Extrapolating the benefits of ivacaftor** seen in some older patients is not unreasonable such that it offers the potential for reduced exacerbation frequency, for improved attendance at nursery/school, for improved play and for reduced in-patient stays.

- **The current psychological impact** on families of having to wait until the child is 6 years old for ivacaftor is highly significant especially where siblings/cousins also have CF and may already be on ivacaftor treatment.

- **Ivacaftor is available for younger children in other countries** so there is an equity issue that is distressing for parents.
Additional patient and carer involvement

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

Value for money

The company presented a cost-utility analysis which compared early ivacaftor treatment against two different treatment strategies: late ivacaftor treatment and standard of care (SoC) in the licensed population. Early ivacaftor treatment was defined as SoC + ivacaftor initiated at 2 years of age, and late ivacaftor treatment reflected SoC + ivacaftor initiated at 6 years of age.

The company used an individual patient level simulation to estimate the cost-effectiveness of early ivacaftor treatment versus the comparators. In terms of model structure, the model was split into two components: the late treatment model, and the early treatment model. The late treatment model was a patient level simulation which modelled patients who were at least 6 years old. The model was driven by short term improvement in lung function and assumptions regarding long-term rates of lung function decline and pulmonary exacerbation rates. Survival predictions within the analysis were based on underlying survival estimates derived from UK CF registry data and a published Cox proportional hazards model. To estimate long term outcomes for each comparator, parallel cohorts with identical baseline characteristics were simulated through the model and patients were assigned to one of the three treatment arms. At each three month cycle, patients were at risk of death and if patients remained alive they may receive a lung transplant. If a lung transplant was not required, patient characteristics and clinical parameters were updated alongside costs and quality adjusted life years (QALYs). All patients could experience pulmonary exacerbations in each model cycle, with the exception of patients who had received a lung transplant. The early treatment model focused on patients who were 2 to 5 years old. Costs and QALYs for the 2 to 5 year old patients were captured as a function of model results from the first 4 years of the late stage model. For example, in order to estimate QALYs for early ivacaftor in the early stage model, the QALYs were set equal to 111% of the average QALY from the first year of the late treatment model for late ivacaftor. In addition, costs for early ivacaftor in the early stage model were assumed to be equal to the late ivacaftor costs for patients aged 6-9 years old.

The main sources of the clinical data used in the model included the ENVISION study which informed baseline characteristics for the population included in the analysis. The treatment effect for late ivacaftor and disease progression for SoC and late ivacaftor were based on published study data. The economic model used an increase in FEV1 percent predicted of 10% for late ivacaftor versus SoC and the increase remained constant for 144 weeks while disease progression for SoC followed natural history rates. The treatment effect and disease progression for early ivacaftor were based on clinical assumption. The analysis assumed that patients who were initiated to early ivacaftor treatment would experience an increase in FEV1 percent predicted of 12.5% relative to SoC and that this effect would be maintained for 20 years. The published literature, clinical studies and clinical guidelines were also used to inform weight for age z-scores, pulmonary exacerbations and lung transplant rates.
Utilities were estimated in the model through an equation which was available in the published literature. The equation generated utility estimates as a function of lung function and pulmonary exacerbations.

Medicines costs were included in the analysis as were costs associated with disease management, hospitalisation and lung transplantation.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the cost of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The result indicated that the ICER for early ivacaftor versus SoC was £609,316 without PAS. This result was based on an incremental cost of £3,747,804 without PAS and an incremental QALY gain of 6.15. For the comparison versus late ivacaftor treatment, the ICER was £484,386 without PAS. This result was based on an incremental cost of £845,070 without PAS and an incremental quality adjusted life year QALY gain of 1.74. The company also provided deterministic sensitivity analysis which indicated that the model was sensitive to the discount rate, utility values and treatment efficacy.

The main weaknesses were:

- The economic analysis assumed that patients who were initiated to early ivacaftor treatment would experience an increase in FEV\(_1\) percent predicted of 12.5% relative to SoC, and that this effect would be maintained for 20 years. However, it did not appear that these efficacy assumptions were supported by clinical data and were instead informed by clinical opinion. In addition, when modelling QALYs for patients between the ages of 2-5, the results from the late ivacaftor treatment model for patients aged 6 and over were applied to this time period. However, as noted above, the analysis also included multipliers such as increasing the QALY value from the late treatment model for the 2-5 year time period for early ivacaftor. These multipliers were favourable to the company and also appeared to be based on limited evidence. The company response referenced published studies and additional evidence in order to support the efficacy assumptions used in the analysis. However, it should be noted that the SMC clinical experts did not reach a consensus clinical opinion regarding the face validity of the assumptions used in the economic evaluation. The company has provided a sensitivity analysis which used results from the early treatment model only, which increased the ICER to £2,369,999 versus SoC and late ivacaftor respectively. In addition, the company provided a sensitivity analysis which reduced the increase in FEV\(_1\) percent predicted to 10% and the duration of effect to 10 years for early ivacaftor. The results of this analysis increased the ICER to £700,738 and £1,023,073 versus SoC and late ivacaftor respectively.

- The analysis estimated an undiscounted life year gain for early ivacaftor versus SoC of 21.56 life years, and 6.77 life years versus late ivacaftor treatment. However, it is worth noting that key covariates in the Cox proportional hazard model which was used to estimate survival included FEV\(_1\) percent predicted and number of exacerbations which were subject to uncertainty in the analysis. As a result it was unclear how plausible the survival benefit of early ivacaftor treatment may be. The company also referenced that median survival for CF patients is currently around 41 years; however, mean survival for SoC in the model was only 26.54 years. This result may suggest that mean survival for SoC patients was underestimated by the economic model.

- The utility values used in the analysis were derived from an equation which was available in the published literature and the utility values generated by the equation were high compared to other published estimates. In addition, a company response also indicated that the average
utility predicted by the model for each comparator was relatively high. However, the company did provide a sensitivity analysis using alternative utility values in the model which increased the ICER to £625,272 versus SoC and reduced the ICER to £470,051 versus late ivacaftor.

- The analysis included a number of assumptions which were not consistent with the required base case analyses reviewed by SMC. For example, the base case analysis and sensitivity analysis presented by the company used a discount rate of 1.5% as opposed to 3.5%. The company also assumed that all patients would switch to ivacaftor tablets at 6 years old and initially applied a discount to the tablet formulation in the analysis. As a result, revised analyses have been provided by the company which removed these assumptions and the results have been presented above.

- The economic analysis included late ivacaftor treatment as a comparator which represented the initial licence for ivacaftor before the licence extension. Usually health technology assessments compare treatments within an indication and, therefore, a comparison across licenses may not be appropriate.

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

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

Genetic mutation testing is already performed in Scotland and PACE participants and clinical experts consulted by SMC have advised that introduction of ivacaftor for use in children age 2-5 years will have limited service impact. Clinical experts noted the potential for minimal additional pharmacy resource requirements for supply of therapy.

PACE participants highlighted that ivacaftor may offer improved lung function and decreased exacerbation frequency, thus reducing further organ damage and, potentially, the burden of care and reliance on others. Another potential benefit is the opportunity to lower the financial impact of CF because parents will need less time off work for hospital visits or caring for their child during exacerbations. It may allow some parents the opportunity to return to full time employment.

**Costs to NHS and Personal Social Services**

The company assumed there would be 5 patients eligible for treatment in year 1 and year 5 respectively. Market share was assumed to be 100% and, therefore, the number of patients treated with ivacaftor was the same as the number of patients eligible for treatment.

Without PAS, the company estimated that the gross budget impact was £831k in year 1 and year 5 respectively. As no medicines were assumed to be displaced, the net budget impact was assumed to be the same as the gross.

The company estimated resource savings related to FEV% improvement. The net total budget impact was £815k in year 1 and year 5 respectively.

SMC expert responses suggested that the patient numbers may have been underestimated.

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

The Committee 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 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.”

The CF trust has published standards for the clinical care of children and adults with CF in the UK. 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 granules would be used in addition to standard of care which can include antibiotics, mucolytics, pancreatic enzymes and nutritional and vitamin supplements. Ivacaftor tablets are licensed for use in patients aged 6 years and older.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor granules in sachet</td>
<td>&lt;14 kg: 50mg orally every 12 hours ≥14 kg to &lt;25 kg: 75mg orally every 12 hours</td>
<td>182,000</td>
</tr>
<tr>
<td>Ivacaftor tablets</td>
<td>150mg orally every 12 hours</td>
<td>182,000</td>
</tr>
</tbody>
</table>

Cost for ivacaftor granules in sachet from the company submission and ivacaftor tablets from BNF online on 8 December 2015. 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.


3. Davies JC, Robertson S, Green Y, Rosenfeld M. On behalf of the KIWI study group. An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2 to 5 years with CF and a CFTR gating mutation: the KIWI study. North American Conference of the Cystic Fibrosis Foundation; October 9-11, 2014; Atlanta, GA.


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

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

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.