Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Resubmission

ivacaftor 150mg film-coated tablets (Kalydeco®) SMC No. (827/12)
Vertex Pharmaceuticals UK Ltd

10 May 2013

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 resubmission

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

Indication under review: treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Ivacaftor has demonstrated superiority over placebo measured by absolute change in forced expiratory volume in one second (FEV_1) % predicted in two phase III, double-blind randomised studies.

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 economic assessment to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Dosing Information

The recommended dose is 150mg taken orally every 12 hours (300mg total daily dose).

Ivacaftor should be taken with fat-containing food. Meals and snacks recommended in CF guidelines or in standard nutritional guidelines contain adequate amounts of fat. Examples of meals that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats. Food containing grapefruit or Seville oranges should be avoided during treatment with ivacaftor.

Ivacaftor should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the *G551D* mutation in at least one allele of the *CFTR* gene before starting treatment.

Product availability date

3 September 2012. Ivacaftor was designated as an orphan medicinal product in July 2008.

Summary of evidence on comparative efficacy

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. The G551D mutation causes a defect in CFTR channel opening. 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 has a new mode of action: it is a selective potentiator of the CFTR protein. It is the first drug to target the genetic abnormality that causes CF.[1]

Evidence to support the use of ivacaftor comes from two similarly designed, randomised, double-blind, placebo-controlled, multi-centre, phase III studies, STRIVE and ENVISION. In both studies, patients had CF and a G551D-CFTR mutation in at least one allele. Patients were randomised equally to receive ivacaftor 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_1) % predicted. STRIVE evaluated the efficacy and safety of ivacaftor in patients aged 12 years and older, and ENVISION evaluated the efficacy and safety in patients aged 6 to 11 years.[1-3]

In STRIVE, all patients had a FEV_1 % predicted of 40 to 90 for age, gender and height. Randomisation was stratified according to age and pulmonary function. At baseline, the mean age was 26 years and the mean FEV_1 % predicted was 64. At week 24, the FEV_1 % predicted

increased from baseline by 10.4 in the ivacaftor group (n=83) and decreased by 0.2 in the placebo group (n=78), a treatment effect of 10.6 (95% Confidence Interval [CI]: 8.6 to 12.6, p<0.001). The treatment effect was maintained at week 48 with a difference in FEV_1 % predicted of 10.5 between the ivacaftor and placebo groups (95% CI: 8.5 to 12.5, p<0.001).

At week 48, 67% and 41% of ivacaftor and placebo-treated patients had not experienced a pulmonary exacerbation, hazard ratio 0.46 (95% CI: 0.28 to 0.73), p=0.001. Patients had gained 3.1kg and 0.4kg in the ivacaftor and placebo groups respectively at week 48, a treatment effect of 2.7kg (95% CI: 1.3 to 4.1), p<0.001. At week 24, the change in sweat chloride from baseline was -49mmol/L and -0.8mmol/L in the ivacaftor and placebo groups respectively, a treatment effect of -48mmol/L, p<0.001. This treatment effect was maintained at week 48 (-48mmol/L, p<0.001).

Patients reported respiratory symptoms at week 24 and week 48 using the respiratory domain of the Cystic Fibrosis Questionnaire-revised (CFQ-R). This is a 100-point scale with higher numbers indicating a lower effect of symptoms on quality of life with four points considered to be the minimal clinically important difference. From baseline to week 48, the scores increased by 5.9 points in the ivacaftor group and decreased 2.7 points in the placebo group giving a treatment effect of 8.6 points, p<0.001.

In ENVISION, patients were required to have a FEV_1 % predicted of 40 to 105 for age, gender and height, and weight ≥15kg at screening. Randomisation was stratified according to pulmonary function. The mean FEV_1 % predicted at baseline was 84 and the mean age of included patients was 9 years old. At week 24, the FEV_1 % 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% CI: 6.6 to 18.3, p<0.0001). The treatment effect was similar at week 48 with a difference in FEV_1 % predicted of 10.0 between the ivacaftor and placebo groups (95% CI: 4.5 to 15.5, p=0.0006).

At week 24, the change in sweat chloride from baseline was -55.5mmol/L and -1.2mmol/L in the ivacaftor and placebo groups respectively, treatment effect -54.3mmol/L (95% CI: -61.8 to -46.8, p<0.0001. This treatment effect was maintained at week 48 (-53.5mmol/L, 95% CI: -60.9 to -46.0, p<0.0001). At week 48, patients had gained 5.9kg and 3.1kg in weight in the ivacaftor and placebo groups respectively, treatment effect 1.9kg (95% CI: 0.9 to 2.9), p=0.0004.

From baseline to week 48, the scores measuring the respiratory symptoms using the respiratory domain of the CFQ-R increased by 6.1 points in the ivacaftor group and 1.0 points in the placebo group giving a treatment effect of 5.1 points. This difference was not statistically significant (95% CI: -1.6 to 11.8, p=0.1354).

Participation in an extension study (PERSIST) has been offered to all patients who completed the STRIVE and ENVISION studies and interim results are available. All patients have received ivacaftor in this study. Patients previously treated with ivacaftor in STRIVE had a mean absolute change from baseline in FEV_1 % predicted of 10.3 and 9.5 after an additional 24 and 48 weeks of ivacaftor treatment respectively. For patients previously treated with placebo, the results were similar, 10.0 and 8.0 at 24 and 48 weeks respectively. The patients previously treated with ivacaftor in ENVISION had a mean absolute change from baseline in FEV_1 % predicted of 10.1 at week 24; patients previously treated with placebo had an increase of 7.5. Week 48 results are not yet available for patients in ENVISION.[1]

Summary of evidence on comparative safety

In STRIVE there was a similar incidence of adverse effects in each treatment group; most patients experienced an adverse event. A serious adverse event was reported by 24% and 33% of ivacaftor and placebo-treated patients respectively. An adverse event led to study drug interruption in more ivacaftor-treated patients (13% versus 6%), however more placebo-treated patients discontinued the study drug due to an adverse effect (1.2% versus 5.1%). Common adverse events that occurred more frequently in the ivacaftor group compared with the placebo group were headache, upper respiratory tract infection, nasal congestion, rash and dizziness.

In ENVISION there was also a similar incidence of adverse events in each treatment group with most patients experiencing an adverse event. A serious adverse event was reported by 19% and 23% of patients in the ivacaftor and placebo group respectively. Common adverse events that occurred more frequently in the ivacaftor group compared with the placebo group were headache, oropharyngeal pain, upper respiratory tract infection, nasopharyngitis, otitis media, diarrhoea and increased eosinophil count.

Summary of clinical effectiveness issues

In patients with CF, the airways become congested with thick sticky mucus, impairing the clearance of microorganisms. Patients experience recurrent infection, inflammation, bronchial damage and bronchiectasis, leading to death from respiratory failure. Patients also commonly experience pancreatic insufficiency and failure to thrive. The current standard of care for CF patients is supportive, including antibiotics, medicines to reduce the viscosity of the secretions, pancreatic enzymes and nutritional support. Despite these treatments life expectancy is poor, with a median survival of 34 years.[4] Ivacaftor has been designated an orphan medicine for the treatment of CF.

Ivacaftor is the first medicine to target one of the genetic abnormalities that cause CF. CFTR mutations, including G551D, are currently tested for in CF patients in NHS Scotland. SMC clinical experts advise that approximately 12% of CF patients in Scotland have this mutation, which is higher than the UK estimate of 6%. Clinical experts also advise that there is an unmet need for effective therapies for the treatment of CF, and that this is the first agent that potentially addresses one of the underlying problems as it corrects some of the function of the defective G551D gene in a small group of patients.

A clinically and statistically significant benefit for ivacaftor over placebo was demonstrated in the two pivotal phase III studies in CF patients with G551D mutation on at least one allele at 24 and 48 weeks, measured by FEV_1 % predicted. Although this is a surrogate marker, FEV_1 % predicted is the recommended primary clinical endpoint for efficacy studies in CF as the rate of decline in FEV_1 has been demonstrated to correlate with survival and is the strongest clinical predictor of mortality.

A clinically significant improvement from baseline in quality of life, measured using the respiratory domain of the CFQ-R, was seen in ivacaftor-treated patients in both studies. The results were statistically significant over placebo in STRIVE, and numerically higher in ENVISION. Weight gain was significantly higher in the ivacaftor-treated patients compared with placebo-treated patients in both studies, suggesting an improvement in nutritional status.

Long term efficacy and safety data are necessary for chronic conditions and data for ivacaftor beyond 48 weeks are currently limited. The open-label extension study PERSIST is currently ongoing, with an interim analysis providing safety and efficacy data for a total of 96 weeks treatment for patients aged 12 years and older and 72 weeks for patients aged 6 to 11 years.[1]

The ENVISION study was small and was not sufficiently powered to detect significant differences between the treatment groups. However, this is an orphan indication so patient numbers are expected to be small.

Patients with severe pulmonary disease (FEV_1 % predicted <40) and those colonised with bacteria associated with an increased decline in lung function (*Burkholderia cenocepacia, Burkholderia dolosa* or *Mycobacterium abcessus*) were excluded from the pivotal studies so there is limited efficacy and safety information for these patients. Hypertonic saline use was not permitted in STRIVE or ENVISION but it was permitted in the open-label extension study PERSIST. SMC clinical experts advise that some patients use hypertonic saline in NHS Scotland; however, its exclusion from the pivotal studies would be unlikely to affect the generalisability of the study results to clinical practice.

This oral medication, in addition to standard of care, to be taken with a high calorie meal or snack, would not be expected to have any implications for service delivery or the patient. Younger children may have problems swallowing the tablet whole and the tablets cannot be chewed, broken or dissolved.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ivacaftor plus standard care against standard care alone to treat patients with CF caused by a G551D mutation and aged 6 years and older. Standard care consisted of CF-related medication (mainly pancreatic enzymes, dornase alfa, inhaled corticosteroids, bronchodilators, prednisone and antibiotics) and devices (oxygen vests, nebulizers and other airway clearance and respiratory devices). Inhaled hypertonic saline use was not assumed to be part of standard care. A lifetime horizon was adopted in the analysis.

A patient-level survival model with time varying risk factors was used. Baseline data for each of 213 patients analysed in STRIVE and ENVISION were entered using data from these studies and the UK CF Registry.

Patients in each treatment arm were modelled individually and, at three-monthly intervals, the characteristics updated by applying parameter values from a survival risk equation and efficacy rates for the intermediate endpoints observed in the studies. The main treatment benefit was increased survival. This was modelled by applying the values from the risk equation which identified the key clinical features of CF and the relationship of each with survival. The equation was developed using multivariate logistic regression on data for 5,820 patients from the American CF Registry in 1993. Only FEV_1 % predicted, weight-for-age z-scores and exacerbations were assumed responsive to ivacaftor.

Utility values were taken from a recent NICE assessment report and used values of 0.864, 0.81 and 0.641 for patients classified as having normal/mild, moderate and severe disease

respectively. Costs for all hospital and community care were taken from a Department of Health (DH) study in 2011/12. This collected costs of CF from specialist centres in England and analysed them over seven bands of increasing treatment complexity. Each patient was allocated to a treatment band. As patients on ivacaftor were modelled to have better health status, this will have resulted in the cost-effectiveness results taking into account any potential cost-offsets associated with other aspects of health care resource use e.g. reduced hospitalisations.

A patient access scheme 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 discount is offered on the medicine. As SMC has not recommended use of the medicine, however, the PAS cannot be implemented in NHS Scotland. The incremental cost per quality adjusted life year (QALY) with the PAS was £277,011 over standard care alone. This was based on an incremental cost of £1,491,707 and incremental QALYs of 5.4. The associated modelled survival benefit when ivacaftor was added to standard care was estimated at a mean of 17.8 years (i.e. remaining lifespan increased from 16.1 years to 34.0 years from baseline).

The results were not sensitive to gender or disease severity but were responsive to age (range for age 6 to 10 years, £266,364 with PAS; and £321,904 with PAS for those aged 51 to 55 years). Residual survival was, however, sensitive to disease severity. Those with severe disease gained an extra 6.1 years (total residual life of 12.4 years) with ivacaftor whilst those with mild disease gained 25.6 years (total residual life of 48.1 years) from commencing the medication.

Further sensitivity analysis showed the results were highly sensitive to the long term trend in FEV_1 % predicted. The baseline assumed patients receiving ivacaftor experienced no annual decline in FEV_1 % predicted over their lifetime. A second scenario assumed patients experienced a decline at 50% of the rate of the standard care group. This resulted in an incremental cost/QALY of (£373,964 with PAS. A third scenario assumed the slope of FEV_1 % predicted versus age curve declined at the same rate as standard care, with the only benefit of ivacaftor being a one-off 10% gain in the FEV_1 % predicted rate. This resulted in an incremental cost/QALY of £562,617 with PAS.

The main strengths of the economic evaluation related to the design of the study, use of data from valid sources including the relevant trials and the UK CF Registry. The main weaknesses are:

- A lifetime horizon was adopted in the model but there is currently an absence of long-term survival data on the benefit of ivacaftor in maintaining FEV_1 % predicted and reducing exacerbations. As such, the true magnitude of survival gains are based on extrapolation and, as shown above, the results showed considerable upward uncertainty when changes were made to the assumptions surrounding FEV_1 %.
- The survival risk equation was developed in 1993 when survival was lower and medication regimens different, and was developed from an American population.

Utility values were available from the clinical trial but concerns were expressed that these seemed high and lacked face validity. As such, the base case results reported above use lower utility values from a recent NICE report in order to address this concern.

The reported incremental cost/QALY is well above acceptable thresholds and sensitivity analyses suggest the results are subject to considerable uncertainty, particularly around the long-term trend in FEV_1 % predicted for patients maintained on ivacaftor.

SMC considered the likely range of cost-effectiveness ratios for ivacaftor and the remaining uncertainties in the economic case. The committee considered the benefits of ivacaftor in the context of the SMC decision modifiers and agreed that the following criteria were relevant: evidence of a substantial improvement in life expectancy; evidence of substantial improvement in quality of life; and absence of other therapeutic options of proven benefit. Despite this, however, the committee was unable to accept ivacaftor due to the high cost per QALY with the additional upwards uncertainty.

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

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Cystic Fibrosis Trust
- Ivacaftor Patient Interest Group

Additional information: guidelines and protocols

There are no guidelines relating to the treatment of CF patients with G551D mutations in the CFTR gene or any guidelines regarding the use of ivacaftor.

The CF trust has published standards for the clinical care of children and adults with cystic fibrosis in the UK.[4] 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

There are no comparator treatments for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ivacaftor	**150mg orally every 12 hours**	**182,000**

Cost from www.dmd.medicines.org.uk [accessed 28 February 2013].

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 53 in year 1 rising to 55 in year 5, with an estimated uptake rate of 90% in all years.

Without PAS: The gross impact on the medicines budget was estimated to be £7.989m in year 1 and £8.237m in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact is expected to remain as £7.989m in year 1 and £8.237m in year 5.

There should be no increase in diagnostic testing as currently over 95% of patients are tested for this genotype.

The company estimates of patient numbers are low as experts indicate that up to 70 patients may be recommended for treatment with ivacaftor in NHS Scotland.

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

References

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

1. The European Medicines Agency European Public Assessment Report. Ivacaftor (Kalydeco®). 06/08/12, EMEA H-C-2494. www.ema.europa.eu

2. Ramsey BW, Davies J, McElvaney G et al. A CFTR potentiator in patients with Cystic Fibrosis and the G551D mutation. N Eng J Med 2011;365(18):1663-72

3. Study of Ivacaftor in Cystic Fibrosis Subjects Aged 6 to 11 Years with the G551D Mutation (ENVISION). www.clinicaltrials.gov

4. Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. Second Edition. December 2011 www.cftrust.org.uk

This assessment is based on data submitted by the applicant company up to and including 12 April 2013.

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. These have been confirmed from the eVadis drug database. 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.