

# Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis

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## Scientific summary

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# Scientific summary

## Background

Cystic fibrosis (CF) is one of the most common genetic diseases, with over 9000 cases in the UK. It is caused by a single faulty gene which controls movement of salt and water across cells. Most of the illness caused by CF is from diseases of the lungs and repeated infections. The treatment burden associated with this condition is significant, with patients undertaking a minimum of twice-daily chest physiotherapy augmented by nebulised therapies, prophylactic antibiotics, fat-soluble vitamins and pancreatic enzyme supplements. These therapies are time-consuming but non-curative, targeting the symptoms rather than the cause of disease. Median survival of the current UK cohort with CF is estimated as 41 years.

A large number of different mutations have been identified in the gene that causes CF. New treatments are being developed that target specific mutations. Ivacaftor (Kalydeco<sup>®</sup>, Vertex Pharmaceuticals) is the first of these drugs and targets patients with the G551D (glycine to aspartate change in nucleotide 1784 in exon 11) mutation. Around 5.7% of patients with CF in the UK have this mutation. Ivacaftor has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with CF (aged  $\geq 6$  years) who have the G551D mutation. There are currently no similar drugs that target the underlying protein defect in CF on the market.

## Objectives

This review aims to appraise the clinical effectiveness and cost-effectiveness of ivacaftor for the treatment of CF in patients aged  $\geq 6$  years who have at least one G551D mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. We will aim to determine the category of patients most likely to benefit from ivacaftor by assessing whether or not the effects vary according to disease severity and age.

## Methods

### *Methods for assessing clinical effectiveness*

Ten databases, including MEDLINE and EMBASE, were searched without language, date or publication status restrictions from inception to July 2012. Supplementary searches were undertaken to identify unpublished and ongoing studies and relevant conference proceedings were searched. Studies that evaluated ivacaftor for the treatment of adults and children ( $\geq 6$  years) with at least one G551D mutation were eligible. The primary outcome was lung function. For the review of clinical effectiveness, only randomised controlled trials (RCTs) with at least 3 months' follow-up were included. Criteria were relaxed for consideration of adverse events and longer-term outcomes ( $> 12$  months), for which open-label studies were also eligible.

The results of the searches were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. RCTs were assessed for methodological quality using the Cochrane risk of bias tool. There were insufficient data to conduct a formal meta-analysis. Data were tabulated and discussed in a narrative review. Dichotomous data were summarised as relative risks and continuous outcomes were summarised as mean differences between treatment groups together with 95% confidence intervals (CIs). Publication bias was not formally assessed owing to the very small number of trials included.

### Methods for reviewing cost-effectiveness

A comprehensive search of multiple databases was undertaken to identify literature that might inform the cost-effectiveness study of ivacaftor. We identified cost studies, utility studies and full economic evaluations, that is to say those that explicitly compared different decision options. Studies were included if they contained information that had the potential to inform parameters within the de novo analysis of cost-effectiveness (information on care processes in UK setting, focus on CF population, reported longer-term effect, recent data and relevant outcomes).

## Results

### Results of clinical effectiveness review

Three studies fulfilled the inclusion criteria: a RCT conducted in adults ( $n = 167$ ) ( $\geq 12$  years) ('adults' study'), a RCT in children ( $n = 26$ ) (6–11 years) ('children's study'), and an open-label extension study of the two included RCTs. All studies were funded by Vertex Pharmaceuticals and were conducted in centres across the USA, Australia and Europe. Ivacaftor tablets were administered at a dose of 150 mg every 12 hours. Both RCTs were 48 weeks in duration. The open-label study is ongoing and is intended to run for 96 weeks. The adults' study was rated as low risk of bias for all criteria. Fewer details were available for the study in children as this has not yet been published in full.

Both RCTs reported significantly greater changes from baseline in all measures of lung function in patients receiving ivacaftor compared with those receiving placebo at all time points assessed. The mean difference in change in percentage predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) was 10.5 (95% CI 8.5 to 12.5) percentage points in the adults' study and 10.0 (95% CI 4.5 to 15.5) percentage points in the children's study at 48 weeks. Improvements were maintained in the open-label trial. Subgroup analysis based on age, sex, study region and lung function suggested that improvements in lung function were seen across all subgroups investigated and that there were no significant differences in treatment effect between subgroups. For the children's study, the small number of participants in each subgroup meant that the study may have lacked power to detect significant differences.

The number and severity of pulmonary exacerbations were significantly reduced in the adults' study. The RR of an exacerbation in the ivacaftor group compared with the placebo group was 0.60 (95% CI 0.41 to 0.85) at 48 weeks. The study in children reported that exacerbations were uncommon in both groups. Other outcomes reported in the studies included quality of life (measured using the respiratory domain of the Cystic Fibrosis Questionnaire Revised), sweat chloride and weight. There were significantly greater improvements in the ivacaftor group compared with the placebo group for all outcomes at all time points (24 and 48 weeks) with the exception of quality of life in children, which failed to reach statistical significance.

Adverse events were mainly minor and comparable across treatment groups and studies. The most commonly reported adverse events were pulmonary exacerbation, cough, headache, upper respiratory tract infection and oropharyngeal pain. Both RCTs reported more overall withdrawals and withdrawals due to adverse events in the placebo group than in the ivacaftor group.

### Results of cost-effectiveness review

Twenty-three studies were included; these assessed health-care costs, cost-effectiveness and utility to inform the economic model. None of the included studies contained information that would inform social care costs. Included studies were used to validate and contextualise assumptions in the model. Three of the 23 included studies contributed to the model.

## Methods for assessing cost-effectiveness

The manufacturer of ivacaftor, Vertex Pharmaceuticals, submitted a deterministic patient-level simulation model for the assessment of the lifetime cost-effectiveness of ivacaftor for the treatment of CF in patients aged  $\geq 6$  years who have at least one G551D mutation in the *CFTR* gene. We used the manufacturer's model as the basis for our model, making modifications where values used by the manufacturer were not UK-specific or not recent, or where better estimates could be found. The only change made to the structure of the model was the addition of lung transplantations, which were included as ivacaftor has the potential to improve lung function which could lead to fewer lung transplantations. We changed utility values, annual decline in percentage predicted FEV<sub>1</sub>, and the baseline exacerbation rate. Additionally, we used data from the CF Registry to estimate the relation between costs, age and percentage predicted FEV<sub>1</sub>.

We took estimates of the treatment effect of ivacaftor from the results of the clinical effectiveness review. We modelled three possible scenarios for the longer-term effects of ivacaftor. In all scenarios the percentage predicted FEV<sub>1</sub> of ivacaftor-treated patients stayed stable for 96 weeks and then three alternatives were modelled for ivacaftor-treated patients:

1. Conservative scenario: percentage predicted FEV<sub>1</sub> declined by the same rate as in the standard-care population.
2. Intermediate scenario: percentage predicted FEV<sub>1</sub> declined at 66% of that of standard-care patients.
3. Optimistic scenario: percentage predicted FEV<sub>1</sub> stayed stable over lifetime.

In addition, we modelled a further 'optimistic' scenario for a subgroup of patients aged  $< 12$  years with little lung damage in whom treatment with ivacaftor was assumed to result in no disease progression, resulting in quality of life and mortality rates comparable with the general population and no or limited costs for treatment of CF.

The cost of ivacaftor given by the manufacturer and used in our model was £182,000. All costs and effects were discounted by 3.5% according to the National Institute for Health and Care Excellence methods guide. The model incorporated a lifetime time horizon to estimate outcomes in terms of quality-adjusted life-years (QALYs) and costs from the perspective of the NHS. The impact of uncertainties in the model was explored through probabilistic sensitivity analysis (PSA). We conducted a budget impact analysis to estimate the total cost to the NHS of introducing ivacaftor in England.

## Results of cost-effectiveness analyses

The economic evaluation of ivacaftor showed that the incremental cost-effectiveness ratio (ICER) varied between £335,000 (optimistic scenario) and £1,274,000 (conservative scenario) per QALY gained. The variation in ICERs was mostly due to large differences in QALY gains (range 1.27–5.26, discounted) between the scenarios. The additional scenarios for the subgroup of patients aged  $< 12$  years with little lung damage resulted in an ICER of between £154,000 and £201,000 per QALY gained. The results of the PSA suggested that the impact of the remaining parameter uncertainty was small compared with the uncertainty caused by the long-term extrapolation.

We explored the budget impact for England of introducing ivacaftor to all eligible CF patients. We found that the total additional lifetime costs (discounted) for this cohort would amount to £438M to £479M, whereas the lifetime costs for standard care only would amount to £72M.

When the population treated with ivacaftor was limited to patients  $< 12$  years with no or little lung damage, we found that the total additional lifetime costs (discounted) amounted to £51M to £113M, whereas the lifetime costs for standard care would amount to £9M to £17M.

## Discussion

### *Clinical effectiveness*

Ivacaftor is an effective treatment for adults and children with the G551D mutation, based on the results of two good-quality RCTs and an open-label follow-up study of participants from both trials. Patients treated with ivacaftor showed improvements in lung function and other outcomes, compared with placebo, at 24 and 48 weeks. Improvements were maintained after 48 weeks' open-label treatment.

The main area of uncertainty relates to the long-term clinical effectiveness of ivacaftor. The longest follow-up data currently available are for (commercial-in-confidence information has been removed) weeks' treatment with ivacaftor in adults and (commercial-in-confidence information has been removed) weeks' treatment in children. The open-label trial is intended to run for 96 weeks. When full data are available from this study, information will be available on the effectiveness for a total of 144 weeks' (just over 2.5 years') treatment with ivacaftor in adults and children. With regard to children, ivacaftor has been evaluated only in those  $\geq 6$  years old; its potential effect in children younger than this is unclear. The trials evaluated in this review were restricted to patients with the G551D mutation. An ongoing study, not included in this review, is investigating ivacaftor in combination with VX-809, an investigational CFTR corrector, in patients with CF and homozygous for the  $\Delta F508$  mutation. If this combination is proved to be clinically effective it would considerably expand the potential usage of ivacaftor as  $\Delta F508$  is the most common CF-causing mutation in the UK population.

### *Cost-effectiveness analysis*

Three out of four dimensions on which ivacaftor showed an effect (percentage predicted FEV<sub>1</sub>, weight and exacerbations) were taken into account in the model. However, the decrease in the number of exacerbations due to ivacaftor was included in the model only in so far as it affected the survival of the patients. It is reasonable to assume that a reduction in exacerbations also has a direct effect on quality of life and costs. A reduction in exacerbations would therefore lead to an increase in quality of life and a reduction in health-care costs. Owing to a lack of data we were not able to include these effects in the model. In the data source used as input for the cost of CF care by severity no distinction was made between costs for maintenance treatment and costs for exacerbations. If these effects on exacerbations had been taken into account, the gain in QALYs in the ivacaftor group might have been higher and the savings in CF-related health-care costs might have been higher, resulting in a lower ICER.

In the model, quality-of-life values and costs were assumed to be dependent on disease severity defined in terms of percentage predicted FEV<sub>1</sub>. However, this clinical measure explains only part of the variation in quality of life and costs. Further refinements of the health states considered would provide a better reflection of the heterogeneity among patients, but as a result it would likely become more difficult to find the data required to inform transitions between health states.

From a cost-effectiveness perspective the long-term effectiveness is an important uncertainty. The various scenarios explored for this long-term effectiveness show a wide range of ICERs. Only when longer-term data on ivacaftor become available will it be clear which of these ICERs is most relevant.

## Conclusions

### *Implications for service provision*

The available evidence suggests that ivacaftor is an effective treatment for patients with CF and the G551D mutation. The high cost of ivacaftor may prove an obstacle in the uptake of this treatment; however, given that ivacaftor is an orphan drug, there is no clear benchmark to indicate whether or not ivacaftor should be considered cost-effective. On 19 December 2012 the four Specialised Commissioning Groups in England (North of England, South of England, Midlands and East, and London) announced that

ivacaftor will be funded by the NHS in England for all patients aged  $\geq 6$  years with CF and the G551D mutation.

### ***Suggested research priorities***

The main priority for further research is the long-term effectiveness of ivacaftor. The main uncertainty in the economic model was how the long-term effects of ivacaftor were included in the model. The ongoing open-label trial will go some way to addressing this question but will provide data only on effects up to around 2.5 years of treatment. The effectiveness of ivacaftor in children aged  $< 6$  years is another important question although this may be difficult to address through clinical trials due to the difficulties in conducting trials in young children. The current evidence supports the use of ivacaftor only in patients with at least one G551D mutation. Such patients represent only around 5% of patients with CF. The potential benefit of ivacaftor in patients with other mutations is therefore also an important area for further research. Clinical trials in patients with other mutations are ongoing.

### **Study registration**

This study is registered as PROSPERO CRD42012002516.

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