Cost-effectiveness of Ivacaftor (Kalydeco®) for the treatment of cystic fibrosis in patients aged 18 years and older who have an R117H mutation in the CFTR gene

The NCPE has issued a recommendation regarding the cost-effectiveness of Ivacaftor (Kalydeco®). Following NCPE assessment of the applicant's submission, Ivacaftor (Kalydeco®) is not considered cost-effective for the treatment of cystic fibrosis in patients 18 years and older who have an R117H mutation in the CFTR gene and therefore it is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Vertex Pharmaceuticals, Europe) economic dossier on the cost effectiveness of Ivacaftor (Kalydeco®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **January 2017**

Summary

In April 2016 Vertex Pharmaceuticals submitted an economic dossier on the cost-effectiveness of Ivacaftor (Kalydeco®) for the treatment of cystic fibrosis in patients aged 18 years and older who have an R117H mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The product obtained European marketing approval on the 19th November 2015 for the license extension. The recommended dose is 150 mg orally every 12 hours. Ivacaftor is described as a CFTR potentiator as it modulates CFTR function enhancing the open probability of the CFTR protein at the cell surface thereby increasing chloride ion transport.

1. Comparative effectiveness

The pivotal clinical trial data for ivacaftor in patients aged 18 years or older who have the R117H mutation is provided by one placebo controlled phase 3 clinical trial of 24 weeks duration (KONDUCT) and a 104 week extension study (KONTINUE) evaluating the long term safety of ivacaftor treatment. In the ivacaftor and placebo arms of KONDUCT and the ivacaftor arm of KONTINUE patients continued on their usual CF management as clinically indicated. The KONDUCT study evaluated the safety and efficacy of ivacaftor in 69 CF patients aged 6 years or older with the R117H CFTR mutation. Twenty four patients (71%) in the ivacaftor + standard of care (SoC) arm and 26 patients (74%) in the placebo + SoC arm of KONDUCT were aged 18 years or older. Participants were randomly assigned in a 1:1 ratio to receive ivacaftor 150mg or placebo every 12 hours for 24 weeks. The primary endpoint was absolute change from baseline in percent predicted FEV1 (ppFEV1) through week 24. Secondary endpoints in the KONDUCT study included change from baseline in sweat chloride, body mass index (BMI) and Cystic Fibrosis Questionnaire – Revised (CFQ-R) through week 24. Time to first pulmonary exacerbation and safety was also assessed.

After 24 weeks of treatment the difference in mean absolute change in ppFEV1 between ivacaftor and placebo was 2.1% (p=0.20). In the adult subpopulation 54.2% of the ivacaftor + SoC group had at least a 5% absolute change in ppFEV1 as compared with 15.4% in the placebo + SoC group. In relation to secondary endpoints the reduction in sweat chloride and the improvement CFQ-R in the ivacaftor + SoC group were statistically significant. Ivacaftor

treatment in KONDUCT did not have a significant impact on the event rate for pulmonary exacerbations, pulmonary exacerbations requiring hospitalisation and pulmonary exacerbations requiring intravenous antibiotics. The KONTINUE study was a multicentre phase 3 study of 104 weeks duration which included 65 patients who received ivacaftor 150 mg twice daily. The primary objective was the evaluation of the long term safety of ivacaftor therapy. A secondary objective was to evaluate the efficacy of ivacaftor during long term treatment. Following a washout period both the placebo + SoC and the ivacaftor + SoC groups showed an improvement in ppFEV1 in both the overall and adult population, the absolute change in ppFEV1 at week 12 was 5.1% points in the adult population. There was an improvement in sweat chloride and CFQ-R however BMI or time to first pulmonary exacerbation were not evaluated in the interim analysis of KONTINUE.

2. Safety

The incidence of adverse events was similar between the ivacaftor + SoC and placebo + SoC arms in KONDUCT. The most commonly reported adverse events included pulmonary exacerbations, cough and headache. There were fewer adverse events in the ivacaftor + SoC group and most adverse events were mild or moderate. In KONTINUE twelve serious adverse events occurred in eight patients. Nine serious adverse events were infective pulmonary exacerbations the remaining serious adverse events were due to influenza and angioedema and urticaria in a patient with a history of allergy.

3. Cost effectiveness

The population in the economic model reflects the therapeutic indication. The intervention under assessment was ivacaftor 150mg orally twice daily administered as an add on to the current standard of care. The comparator was standard of care treatment and the perspective was that of the HSE.

The cost effectiveness of ivacaftor was assessed using an individual patient simulation model. A cohort for the purpose of the simulation is built by drawing patients from the pool of patients who participated in the KONDUCT study. The survival predictors in the model are based on underlying survival estimates derived from CF Registry Ireland data and a Cox proportional hazards model which links survival to nine risk factors including age, gender,

ppFEV1, annual number of pulmonary exacerbations, infections, diabetes mellitus, weight for age z-score and pancreatic sufficiency status in patients with CF. The ppFEV1 and annual number of pulmonary exacerbations change over time and differ between the treatment arms. The model assumes that ivacaftor continues to impact ppFEV1 after the study period. In the absence of long term data the NCPE Review Group questions the validity of such an assumption.

To calculate the frequency of pulmonary exacerbations for patients treated with SoC an age dependent equation relating ppFEV1 to the annual expected rate of pulmonary exacerbation is used. The beneficial treatment effect on pulmonary exacerbation is applied for the duration of the model. The NCPE Review Group question this assumption as there was no significant impact of ivacaftor treatment on pulmonary exacerbations in the KONDUCT trial. In relation to lung transplantation the model assumes that once a patients ppFEV1 falls below 30% the patient becomes eligible for a lung transplant.

For patients who have not received a lung transplant the model estimates individual patient risk of death in each cycle using a two part calculation; first the age specific background mortality hazard derived from Irish CF Registry data is calculated and secondly the hazard is adjusted in each cycle to account for individual patient characteristics that predict survival in CF based on a published Cox proportional hazards model. The economic model predicts an incremental median survival gain of 7.99 years in patients aged 18 years or older with the R117H mutation following treatment with ivacaftor.

Health outcomes were expressed as Quality Adjusted Life Years (QALYs). The health related quality of life of CF patients in the model is dependent on the patients ppFEV1, history of pulmonary exacerbation and treatment arm. A utility equation was developed following an analysis of the STRIVE study population. Costs were stratified by ppFEV1 in the model as the literature indicates higher disease management costs for patients with lower lung function. The cost data included hospitalisations, mucolytics, pancreatic enzymes, beta agonists and antibiotics. A cost of € 15,719 was applied for mild disease (ppFEV1 > 70%), € 31,877 for moderate disease (ppFEV1 40% - 69%) and € 53,938 for severe lung disease (ppFEV1 < 40%). A reduction in hospitalisation costs of 45% for patients treated with ivacaftor + SoC is

assumed for the basecase. Lung transplantation costs were obtained from UK data. The NCPE review group were satisfied that the relevant costs were included in the model. Costs and benefits were discounted at a rate of 5% per annum.

The price of ivacaftor included in the economic dossier was € 18,000 per 28 day supply. The annual cost of ivacaftor was calculated at € 234,803 per patient. The basecase incremental cost-effectiveness ratio (ICER) for ivacaftor treatment + SoC versus SoC was € 444,466/QALY or € 609,270/LYG (life year gained) which exceeds the current thresholds of interest to the HSE. A deterministic sensitivity analysis indicated that the model is most sensitive to the discount rates, adherence to ivacaftor and mean absolute change in ppFEV1 associated with ivacaftor + SoC during the trial. The price - ICER relationship demonstrates that the annual price of ivacaftor would have to fall to € 34,692 to give an ICER of € 45,000/QALY i.e. a 6.7 fold price reduction.

4. Budget impact

For the purpose of budget impact calculations the manufacturer estimates that there will be 58 patients eligible for ivacaftor treatment in year one increasing to 65 patients in year five. This would result in a maximum gross budget impact of € 13,618,574 in year one increasing to € 15,262,195 in year 5. The 5 year gross budget impact may be estimated at € 72,554,127. The manufacturer estimates the 5 year gross budget impact at € 54,055,681.

5. Conclusion

The manufacturer has failed to demonstrate the cost-effectiveness of ivacaftor (Kalydeco®) for the treatment of cystic fibrosis patients aged 18 years and older who have an R117H mutation in the CFTR gene. In addition, the budget impact is significant with an associated opportunity cost. We do not recommend the reimbursement of ivacaftor at the submitted price for this indication.