Cost-effectiveness of Ivacaftor (Kalydeco) for children with cystic fibrosis aged 2 years and older and weighing less than 25kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

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 children aged 2 years and older and weighing less than 25kg who have one of the relevant gating (class III) mutations in the CFTR gene and therefore it is not recommended for reimbursement.

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 relevant for the decision; the final decision on reimbursement is made by the HSE. For cancer drugs the NCPE recommendation is also considered by (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 **October 2016**

Summary

In March 2016 Vertex Pharmaceuticals submitted an economic dossier on the cost-effectiveness of ivacaftor (Kalydeco) for the treatment of children with cystic fibrosis aged 2 years and older and weighing less than 25kg who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. European marketing authorisation was obtained on the 18th November 2015 for the extension of the ivacaftor license to include two new presentations i.e. the 50 mg and the 75 mg granule sachets. The recommended dose of ivacaftor for patients aged 2 to 5 years is weight based at doses of 50 mg every 12 hours for patients less than 14 kg and ivacaftor 75 mg every 12 hours for patients weighing 14 kg or more. 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 data supporting the use of ivacaftor in children aged between 2 and 5 years weighing less than 25 kg is provided by two studies i.e. KIWI and KLIMB. The KIWI study was primarily designed to evaluate the pharmacokinetics and safety of ivacaftor in patients aged 2 to 5 years and the KLIMB study (an extension study of KIWI) was primarily designed to evaluate long term safety rather than demonstrating efficacy, although positive effects were observed in secondary and tertiary health outcomes. The patient numbers in the KIWI study were small (n=9 in part A and n=34 in part B) and the primary endpoints for the KIWI study included adverse events, clinical laboratory assessments, clinical evaluation of vital signs, 12 lead ECG, physical examination and ophthalmological examination. Efficacy outcomes were secondary or tertiary endpoints. The mean reduction in sweat chloride at week 24 in the KIWI study was – 46.9 mmol/l. The ppFEV1 is usually the primary efficacy endpoint in CF studies as the rate of decline in this parameter has been correlated with survival and is a predictor of mortality. No evidence was presented to the NCPE demonstrating an impact of ivacaftor on the ppFEV1 in children aged 2 to 5 years. An assumption was made that the benefit seen in patients aged six years or older would be experienced in patients aged 2 to 5 years. The manufacturer highlighted the supportive studies conducted in older populations including STRIVE, ENVISION and KONNECTION.

2. Safety

Ivacaftor was generally well tolerated in the clinical studies. In terms of safety the NCPE review group noted that 15 patients in the KIWI study had a total of 35 pulmonary exacerbations although this was dependent on the definition of pulmonary exacerbation. In addition, over 25% of patients in the long term follow-up study (KLIMB) developed elevated liver function tests (ALT/AST) over 8 times the upper limit of normal. Six of those patients had elevated liver function tests over two times the upper limit of normal at baseline. It is also noted that there have been case reports of non-congenital lens opacities in paediatric patients treated with ivacaftor and that a possible risk attributable to ivacaftor cannot be excluded.

3. Cost effectiveness

The intervention is ivacaftor for the treatment of CF patients with the relevant mutations in the CFTR gene. Patients aged 2 – 5 years receive weight based dosing of ivacaftor (oral granules); ivacaftor 50 mg every 12 hours (patients less than 14kg) or ivacaftor 75 mg every 12 hours for patients at or above 14 kg and below 25 kg in weight. There is no active comparator as ivacaftor is first in class. The economic evaluation considered three treatment arms including (1) early treatment initiation i.e. standard of care plus ivacaftor initiated at 2 years of age (2) late ivacaftor treatment initiation i.e. standard of care plus ivacaftor initiated at 6 years of age and (3) standard of care alone. An individual patient level simulation model was constructed in MS Excel and the perspective was that of the HSE and costs and benefits were discounted at a rate of 5%.

The model is divided into two components including a late treatment model and an early treatment model. In the early treatment model patients were assumed to start treatment at the age of 2 years and modelled for 4 years.The efficacy parameter estimates were adapted from the clinical trial data in patients with the same mutation aged over 6 years. Early costs and QALYs were simply calculated using the results of the late treatment model using a number of assumptions.

The late treatment model is based on the model that was previously submitted to support the use of ivacaftor in CF patients aged 6 years and older. The treatment benefit estimated

with ivacaftor is driven by the short term improvements in lung function (ppFEV1) observed in the ENVISION study which studied patients between 6 and 11 years. The survival predictors 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. A number of assumptions were made regarding the clinical benefit of early ivacaftor at the start of the late stage model including the assumption that patients who receive early ivacaftor experience no decline in ppFEV1 for 20 years following treatment initiation at two years of age. The NCPE review group highlights the fact that there is no evidence to support this assumption.

In terms of cost-effectiveness, early ivacaftor treatment plus standard of care versus standard of care alone for children aged 2 to 5 years is not cost-effective with a basecase ICER of € 465,546/QALY or € 502,529/LYG which greatly exceeds the current thresholds of interest to the Health Service Executive. The ICER for early ivacaftor treatment versus late ivacaftor treatment was € 636,237/QALY. As expected there was considerable uncertainty around the ICER. The price –ICER relationship indicated that the price of ivacaftor would have to fall below € 25,000 per patient per annum to bring the ICER close to the € 45,000/QALY threshold.

4. Budget impact

For the purpose of budget impact calculations the manufacturer estimates that there will be 18 patients eligible for early ivacaftor treatment. The 5 year gross budget impact was estimated at just over € 21 million with the 5 year net budget impact ranging from € 15.3 million to € 22.7 million.

5. Conclusion

The manufacturer has failed to demonstrate that ivacaftor is a cost-effective treatment in the Irish healthcare setting for CF patients aged 2 years and older and weighing less than 25 kg who have one of the specific gating mutations. The budget impact is significant with an

associated opportunity cost. Therefore the NCPE recommends that ivacaftor should not be reimbursed for this indication at the submitted price.