Cost-effectiveness of Lumacaftor/Ivacaftor (Orkambi) for cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene

The NCPE has issued a recommendation regarding the cost-effectiveness of lumacaftor/ivacaftor (Orkambi). Following NCPE assessment of the applicant's submission, lumacaftor/ivacaftor (Orkambi) is not considered cost-effective for the treatment of cystic fibrosis in patients 12 years and older who are homozygous for the F508del mutation in the CFTR gene and therefore 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 lumacaftor/ivacaftor (Orkambi). 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 **June 2016**

Summary

In March 2016 Vertex Pharmaceuticals submitted an economic dossier on the cost-effectiveness of lumacaftor + ivacaftor (Orkambi) for cystic fibrosis in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The product obtained European marketing approval on the 19th November 2015. The recommended dose is two tablets, orally every 12 hours i.e. four tablets daily giving a total daily dose of lumacaftor 800mg + ivacaftor 500mg. Lumacaftor is described as a CFTR corrector as it enhances the stability of the protein and improves its quantity. 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 clinical study programme consisted of three phase 2 studies to assess the safety and pharmacokinetics of ivacaftor monotherapy, lumacaftor monotherapy and lumacaftor + ivacaftor in combination in addition to two pivotal phase 3 studies to assess the safety and efficacy of lumacaftor + ivacaftor in combination. The two phase 3 studies included TRAFFIC (n=549) and TRANSPORT (n=559) where the study design and methods of data analysis were identical with the exception of the inclusion of ambulatory electrocardiography (TRAFFIC only) and adolescent pharmacokinetic assessment (TRANSPORT only) for a subgroup of patients. In both studies patients were randomly assigned to receive either lumacaftor (600mg once daily or 400mg every 12 hours) in combination with ivacaftor 250mg every 12 hours or matched placebo for 24 weeks. The primary endpoint was the absolute change from baseline in the percentage of predicted forced expiratory volume in 1 second (ppFEV1) at week 24. In both studies, there were significant improvements in the primary endpoint where the mean absolute improvement in the ppFEV1 ranged from 2.6% to 4%. Pooled analysis showed that the rate of pulmonary exacerbations was 30 to 39% lower in the lumacaftor + ivacaftor groups as compared with placebo. The rate of events leading to hospitalisation or the use of intravenous antibiotics was lower in the lumacaftor + ivacaftor groups.

2. Safety

Overall, the proportion of patients reporting adverse events was similar across the lumacaftor + ivacaftor and the placebo groups in the pivotal clinical trials. In the phase 3 clinical trials TRAFFIC and TRANSPORT serious adverse events were reported in 28.6% of patients in the placebo group versus 17.3% to 22.8% in the lumacaftor + ivacaftor groups. In all groups infective pulmonary exacerbation was the most common serious adverse event occurring in 24.1% of patients in the placebo group and 11.1% of those in the lumacaftor + ivacaftor (400mg lumacaftor 12 hourly + 250mg ivacaftor 12 hourly) group.The proportion of patients who discontinued therapy was greater in the lumacaftor + ivacaftor group (4.2%) as compared with the placebo group (1.6%). In the patients receiving lumacaftor + ivacaftor the adverse events that led to treatment discontinuation included elevated creatine kinase (CK) levels, haemoptysis, dyspnoea, pulmonary exacerbation and skin rash.

3. Cost effectiveness

The population in the economic model reflects the therapeutic indication. The intervention under assessment was the recommended dose of lumacaftor 400mg plus ivacaftor 250mg 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 lumacaftor + ivacaftor was assessed using an individual patient simulation model. A cohort of 1000 patients is simulated by drawing from the pool of patients who participated in TRAFFIC or TRANSPORT. Each simulated patients baseline characteristics are those measured in the corresponding patient in the clinical trial. Each patient is progressed through the model twice, once treated with lumacaftor + ivacaftor + standard of care and once treated with standard of care. The model is run over a lifetime with a 4 week cycle length for the first two years followed by an annual cycle length. Treatment progression is informed by patient characteristics.

Costs and utilities are linked to lung function (ppFEV1), pulmonary exacerbation and lung transplantation. Lumacaftor + ivacaftor is assumed to positively impact on ppFEV1, risk of pulmonary exacerbations and weight-for-age z score. These benefits have an implicit effect

on mortality, quality of life and lung transplant rate. Background mortality for CF patients is derived from the Irish CF registry. A parametric curve was fitted to the 1985-2004 birth cohort and a Gompertz distribution was chosen based on best-fit statistics and clinical reasoning. Each individual patients mortality risk is adjusted using a Cox proportional hazard model incorporating nine risk factors identified by Liou et al including ppFEV1, pulmonary exacerbations, weight-for-age z score, diabetes, certain respiratory infections, pancreatic insufficiency, age and gender. The NCPE review group considered the structure of the model appropriate to model the progression of CF in Ireland. However all treatment benefits were extrapolated for post trial duration effects and this introduced a high level of uncertainty into the model.

Using the manufacturers basecase assumptions the model estimates an incremental QALY gain of 2.45 at an incremental cost of € 903,947 resulting in an incremental cost effectiveness ratio (ICER) of € 369,141/QALY. The probabilistic results were similar at € 370,754/QALY. The model effects are mainly driven by mortality and the incremental life years gained are estimated to be 2.47, resulting from a median increase in overall survival of 7.4 years. The NCPE preferred scenario increased the ICER to € 649,624/QALY.

A one way sensitivity analysis highlighted that the rate of decline on lumacaftor + ivacaftor was the main driver in the analysis. As expected the discount rate and drug acquisition cost also impacted the ICER. Probabilistic analysis demonstrated little uncertainty in terms of costs but a large variability around incremental QALYs. The probability of lumacaftor + ivacaftor being a cost-effective treatment was 0% up to a cost effective threshold of €200,000/QALY. The price-ICER relationship indicates that the drug acquisition price would have to fall below € 30,000 per patient per year to satisfy the current cost-effectiveness threshold.

4. Budget impact

The F508del is the most prevalent mutation of the CFTR gene and it is estimated that some 505 persons are homozygous for the mutation and therefore potential candidates for the combination therapy of lumacaftor plus ivacaftor (Orkambi). The price to wholesaler for a pack including a 28 day supply of lumacaftor + ivacaftor is €12,144. The annual cost of

lumacaftor + ivacaftor is €158,306 or €159,050 including the patient care fee. The manufacturer estimates the 5 year gross budget impact of lumacaftor + ivacaftor at €352,281,736. The NCPE estimate of the 5 year budget impact is €391,892,681.

5. Conclusion

The manufacturer has failed to demonstrate the cost-effectiveness of lumacaftor + ivacaftor (Orkambi) for the treatment of cystic fibrosis patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. In addition, the budget impact is significant with an associated opportunity cost. We do not recommend the reimbursement of lumacaftor + ivacaftor (Orkambi) at the submitted price.