The cost-effectiveness of ivacaftor/tezacaftor/elexacaftor (Kaftrio®) in a combination regimen with ivacaftor (Kalydeco) in cystic fibrosis (CF) patients aged 6 years and older who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Kaftrio plus ivacaftor for the treatment of CF patients aged 6 years and older who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the CFTR gene. Following assessment of the Applicant's submission, the NCPE recommends that Kaftrio plus ivacaftor be considered for reimbursement only if cost-effectiveness can be improved relative to best supportive care*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Vertex Pharmaceuticals (Europe) Limited) economic dossier on the cost effectiveness of Kaftrio plus ivacaftor. 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.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013

National Centre for Pharmacoeconomics **February 2023**

Summary

On the 21st December 2022 Vertex Pharmaceuticals (Europe) Limited submitted an economic dossier on the cost-effectiveness of ivacaftor/tezacaftor/elexacaftor (Kaftrio®) in a combination regimen with ivacaftor (Kalydeco) in cystic fibrosis (CF) patients aged 6 years and older who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cystic fibrosis is an autosomal recessive disease associated with mutations in the CFTR gene located on chromosome 7 which encodes the CFTR protein, an ion channel responsible for the transport of chloride and bicarbonate across cell membranes. The F508del mutation is the most common mutation and is present in up to 91.8% of Irish people with CF.

Mutations in both copies of the CFTR gene result in disordered expression and/or function of CFTR protein resulting in impaired salt and fluid transport across the epithelial lining of multiple organs. The disrupted ion concentration gradient results in thick mucus accumulating within the lungs and other organs. Mucus obstruction in the airways results in a chronic inflammatory response which is exacerbated by infection resulting in ongoing damage to the respiratory tract. Pulmonary complications account for most of the morbidity and mortality associated with cystic fibrosis and respiratory failure is the most common cause of death. Dysfunctional CFTR protein also results in progressive damage to the pancreas, intestinal tract and the liver. In addition to respiratory symptoms patients may experience malabsorption, constipation, CF-related diabetes mellitus and CF-related liver disease.

There are no Irish specific treatment guidelines for CF, however the European Cystic Fibrosis Society (ECFS) produces standards of care which outline best practice in the management of cystic fibrosis. The ECFS recommends that patients with CF aged six years and older, with one or two 508del variants, should have daily treatment with ivacaftor/tezacaftor/elexacaftor (Kaftrio) which is a combination therapy that includes two classes of CFTR modulators. The CFTR 'correctors' elexacaftor and tezacaftor increase the processing and transport of mutant CFTR proteins (including F508del-CFTR mutation) to the epithelial cell surface. Ivacaftor is a CFTR 'potentiator' which increases F508del-CFTR protein gating function (i.e. chloride

transport) by improving channel-open probability. Therefore the combination of two correctors and a potentiator increases the quantity and function of F508del-CFTR protein at the epithelial cell surface. Oral dosing for children aged 6 to less than 12 years is weight based with those weighing less than 30 kg receiving two tablets of the lower dose (i.e. ivacaftor 37.5mg + tezacaftor 25mg + elexacaftor 50mg) in the morning and one tablet of ivacaftor 75mg in the evening. For patients who weigh 30kg or more the dose is two tablets of ivacaftor 75mg + tezacaftor 50mg + elexacaftor 100mg in the morning and one tablet of ivacaftor 150 mg in the evening. Patients continue to receive symptom - based therapies as required.

1. Comparative effectiveness

The submitted dossier highlights four clinical trials of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor in CF patients aged 6 to 11 years with the F508del mutation and a minimal function mutation (F/MF genotype). The four trials include two completed phase 3/phase 3b studies and two ongoing open-label extension (OLE) studies i.e. GALILEO and GALILEO OLE in addition to the AURORA 6-11 and AURORA 6-11 OLE trials.

The GALILEO trial was a randomised, double-blind, placebo-controlled phase 3b study designed to evaluate the efficacy and safety of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor in children 6 through 11 years of age with the F/MF genotype. Children were randomised to receive either Kaftrio plus ivacaftor (n=60) or placebo (n=61) during a 24 week treatment period. The mean age for the treatment group at baseline was 9.1 years, 58% were female and the lung clearance index was 10.26 units. Mean values for ppFEV1, Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score and sweat chloride in the treatment group at baseline were 91.4%, 85.7 points and 102.8 mmol/l respectively. The primary endpoint was absolute change in lung clearance index$_{2.5}$ (LCI$_{2.5}$) from baseline through week 24. The lung clearance index (LCI) can detect early changes in lung function and small airway disease and is considered a more sensitive predictor of lung disease progression as compared with FEV1 in children with cystic fibrosis. Secondary endpoints included absolute changes in sweat chloride concentration, ppFEV1 and CFQ-R respiratory domain score from baseline through week 24.

Children given Kaftrio plus ivacaftor had a mean decrease in lung clearance index$_{2.5}$ of 2.29 units as compared with 0.02 units in the placebo group (between group difference, -2.26 units; 95% confidence interval (CI), -2.71 to -1.81:p<0.0001). Kaftrio plus ivacaftor treatment also resulted in improvements in the secondary endpoints of ppFEV1 (between group difference, 11%; 95% CI, 6.9 – 15.1), sweat chloride concentration (between group difference, -51.2 mmol/l; 95% CI, -55.3 to -47.1) and CFQ-R respiratory domain score (between group difference, 5.5 points; 95% CI, 1.0 to 10.0). The NCPE review group note that there is no established clinically meaningful change in lung clearance index however the 11% change in ppFEV1 and the 5.5 point change in CFQ-R respiratory domain score are clinically relevant. Pulmonary exacerbations and hospitalisations were not study endpoints in GALILEO.

An open-label extension study involving patients from the GALILEO trial is on-going. It will evaluate the long-term efficacy and safety of Kaftrio plus ivacaftor in subjects with CF who are 6 years or older with F/MF genotypes. It is anticipated that 108 patients may enrol in the extension study and the primary endpoint is safety and tolerability based on adverse events, clinical laboratory values, ECGs, vital signs and pulse oximetry. Secondary endpoints include absolute change in lung clearance index and sweat chloride as compared with baseline. Other endpoints include changes in ppFEV1 and CFQ-R.

The AURORA 6-11 trial was a 24 week, open-label phase 3 study including 66 children where the safety and pharmacokinetics of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor were studied. The mean age at baseline was 9.3 years and 59% of children were female. The mean values for ppFEV1, CFQ-R respiratory domain score and sweat chloride at baseline were 88.8%, 80.3 points and 102.2 mmol/l respectively. In terms of genotypes 56.1% of participants were F/MF with the remainder being F/F (homozygous for the F508del mutation). The primary endpoint was safety and tolerability. The safety and pharmacokinetic profiles of Kaftrio plus ivacaftor were consistent with those observed in older patients. Through week 24 treatment with Kaftrio in combination with ivacaftor improved the ppFEV1 by 10.2% (95% CI, 7.9% to 12.6%). The CFQ-R respiratory domain score increased by 7 points (95% CI, 4.7 to 9.2 points) and sweat chloride fell by 60.9 mmol/l. The lung clearance index fell by 1.71 units and the body mass index increased by 1.02 kg over the 24 week treatment period. No CF-related hospitalisations occurred. The NCPE review group noted the clinically meaningful

increases in the study endpoints i.e. increases in ppFEV1 ≥ 5% and CFQ-R ≥ 4 points.

Following participation in the AURORA 6-11 study patients had the option to enter AURORA 6-11 OLE which is an on-going phase 3, 196 week open-label extension study designed to evaluate the long term safety and tolerability of Kaftrio in combination with ivacaftor. Secondary endpoints include absolute change in ppFEV1, $LCI_{2.5}$, sweat chloride, CFQ-R respiratory domain and nutritional parameters from the parent study baseline. Other secondary endpoints include frequency of pulmonary exacerbation events and CF related hospitalisations. A total of 64 participants were enrolled and received at least one dose of Kaftrio plus ivacaftor and an analysis of safety and efficacy data was conducted when the last of the study participants completed week 96 (n=61). The week 96 outcome data demonstrated sustained and clinically meaningful improvements across the efficacy endpoints. The subgroup analysis by genotype indicated that there were clinically meaningful treatment benefits in patients with CF genotypes F/F and F/MF. Real world evidence was included as part of the HTA submission and while such evidence is still accumulating it does support the beneficial effects of ivacaftor/tezacaftor/elexacaftor (Kaftrio) in combination with ivacaftor as demonstrated in the clinical trial programme.

2. Safety

The clinical trials of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor in patients between the ages of 6 and 11 years demonstrated that treatment was generally safe and well tolerated in the paediatric population. In the GALILEO trial 80% of patients on the triple therapy regimen had adverse events but the majority were mild to moderate in severity and generally consistent with CF manifestations. The most common adverse events were headache (30%) and cough (23.3%). Serious adverse events were more common in the placebo group (14.8% versus 6.7%). Elevated serum transaminases over three times the upper limit of normal occurred in 13.6% of children treated with Kaftrio plus ivacaftor with 5.1% having concentrations over five times the upper limit of normal. Skin rashes were noted in 13.3% of children on active treatment and these were mild to moderate in severity. A single case of severe skin rash resolved after discontinuation of therapy. Small increases in blood pressure were noted in some subjects on triple therapy for CF. The safety of Kaftrio plus

ivacaftor in the AURORA 6-11 study was similar to that reported in GALILEO trial with cough, headache and pyrexia being the most common adverse events and the majority were mild to moderate in severity. Elevated transaminases and skin rashes were also noted.

3. Cost effectiveness

The cost-effectiveness model evaluated ivacaftor/tezacaftor/elexacaftor (Kaftrio) in combination with ivacaftor for the treatment of patients with CF aged 6 to 11 years who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the CFTR gene. It was assumed that patients with CF who are heterozygous for the F508del mutation with a second allele that is unknown and/or has not yet been characterised as MF, RF or gating are captured in the modelling of the F/MF population. The baseline patient characteristics were derived from the GALILEO and AURORA 6-11 trials. A patient state-transition simulation model was developed to evaluate the cost-effectiveness of Kaftrio plus ivacaftor as compared with best supportive care. Survival predictions were based on the Cox proportional hazards model from Liou et al. that relates survival to the clinical characteristics of CF patients in the absence of CFTR modulator therapy. Predictors of patient survival included age, gender, ppFEV1, annual number of pulmonary exacerbations, infections, CF related diabetes, weight-for-age z-score and pancreatic sufficiency status. A total of 2,000 individual patient profiles were simulated for each treatment cohort. Survival differences between the treatment cohorts were achieved based on differences in ppFEV1, annual number of pulmonary exacerbations and weight-for-age z-scores. The simulated patients are tracked through the model in four-week cycles for the first two years and one-year cycles thereafter. After the microsimulation process is completed the model aggregates the clinical characteristics across the cohort (e.g. totalling the number of life years spent in each ppFEV1 disease strata across the cohort). The model assumed that there was no decline in ppFEV1 for patients treated with ivacaftor/tezacaftor/elexacaftor (Kaftrio) in combination with ivacaftor after the initial acute period. The occurrence of pulmonary exacerbations was predicted based on patients ppFEV1 and age.

The utility values in this economic evaluation were derived from real-world evidence studies presented by the Applicant. Utilities were obtained from CFQ-R data and these were stratified by ppFEV1. A disutility of 0.07 was applied for the occurrence of a pulmonary exacerbation requiring treatment with intravenous antibiotics and/or hospitalisation. The economic model assumes that a patient treated with ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor will have a utility score that is higher than that of a patient with the same ppFEV1 value who is receiving best supportive care. A utility value of 0.81 was applied to patients post-lung transplantation. Patients who initiate ivacaftor/tezacaftor/elexacaftor (Kaftrio) in combination with ivacaftor between the ages of 6 to 11 years are assumed to receive a utility increment up until they turn 12 years of age to capture the quality of life improvements in their caregivers. Resource use and costs considered in the model included drug costs, annual Kaftrio monitoring, disease management, lung transplantation and adverse event costs. Costs are then assigned to the cohort, rather than to individual patients. For the base case a discount rate of 4% was applied to both health outcomes and costs. The model reports life years, quality adjusted life years (QALY) and costs per treatment cohort as well as the incremental cost-effectiveness ratios (ICERs). The analysis was conducted over a lifetime horizon and the perspective was that of the Health Service Executive (HSE).

The median predicted survival in the F/MF ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor treated cohort aged 6 to 11 was 84.2 years, a 42.9 year increase to the median predicted survival for F/MF patients treated with best supportive care (41.3 years). A deterministic analysis of the cost-effectiveness of ivacaftor/texacaftor/elexacaftor (Kaftrio) plus ivacaftor versus best supportive care was associated with incremental costs of €2,594,631 and an incremental quality adjusted life-year (QALY) of 7.7 resulting in a base case incremental cost-effectiveness ratio (ICER) of €263,202/QALY. Probabilistic analysis resulted in an ICER of €269,110/QALY which was similar to the deterministic ICER. The probability of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor being cost-effective at the €45,000/QALY threshold was 0%. A deterministic sensitivity analysis was also presented. The parameters that impacted the cost-effectiveness of ivacaftor/tezacaftor/elexacaftor (Kaftrio) plus ivacaftor versus best supportive care to the greatest extent included: the discount rates for health outcomes and costs, post-trial compliance in patients aged ≥ 12 years, treatment-specific utility increment and the modelling of ppFEV1 decline.

4. Budget impact

The reimbursement price of ivacaftor/tezacaftor/elexacaftor (Kaftrio) is €9,819.18 for a pack size of 56 tablets for the higher and lower doses. The reimbursement price for ivacaftor (Kalydeco) with a pack size of 28 tablets is €6,217.06 for the 150mg dose and €6,099.50 for the 75mg dose. The manufacturer confirms that the annual drug treatment cost to the HSE for Kaftrio plus ivacaftor (at list price) for children aged 6 to 11 years with a body weight less than 30kg is €208,398 which increases to €209,931 for children aged 6 to 11 years with a body weight of 30kg or more. The estimated 5 year gross budget impact for the treatment of 35 patients aged 6 to 11 years who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the CFTR gene was estimated at €36.56 million. These estimates were based on the assumption that 35% and 65% of patients would be prescribed the higher and lower dose regimens respectively. The net budget impact was considered equal to the gross budget impact. When cost-offsets were taken into consideration the 5 year net healthcare budget impact was €36 million.

5. Patient submission

A patient organisation submission was received from Cystic Fibrosis Ireland.

6. Conclusion

This assessment demonstrates that Kaftrio plus ivacaftor is not cost-effective at the list price for the treatment of patients aged 6 to 11 years who are heterozygous for the F508del mutation and either a minimal function (MF) mutation or an unknown mutation in the CFTR gene. The NCPE recommends that Kaftrio in combination with ivacaftor be considered for reimbursement if cost-effectiveness can be improved relative to best supportive care*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.