Cost-effectiveness of Sacubitril/Valsartan (Entresto) for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction.

The NCPE has issued a recommendation regarding the cost-effectiveness of sacubitril/valsartan (Entresto). Following NCPE assessment of the applicant's submission, sacubitril/valsartan (Entresto) is considered cost-effective for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Novartis Ireland Ltd.) economic dossier on the cost effectiveness of sacubitril/valsartan (Entresto). 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 **July 2016**

Summary

In March 2016 Novartis Ireland Ltd submitted an economic dossier on the cost-effectiveness of sacubitril/valsartan (Entresto) for the treatment of symptomatic chronic heart failure in adult patients with a reduced ejection fraction. The product was approved by the EMA through the centralised procedure. The European Commission decision was adopted on the 19th November 2015. This combination product inhibits neprilysin via LBQ657, the active metabolite of the pro-drug sacubitril and blocks the angiotensin II receptor (AT1) via valsartan. There are three oral formulations of the product including 24/26mg, 49/51mg and 97/103mg. The recommended starting dose of sacubitril/valsartan for patients previously treated with an ACE inhibitor or an ARB is one tablet of 49/51mg twice daily. The dose should be doubled after 2 to 4 weeks to the target maintenance dose of one tablet of 97/103mg twice daily as tolerated by the patient. For patients not currently being treated with an ACE or ARB or those taking a lower dose of these agents a starting dose of 24/26mg twice daily is recommended followed by gradual titration to the maintenance dose of 97/103 mg twice daily as tolerated. Sacubitril/valsartan is being positioned to replace current first line treatment i.e. ACE inhibitors or ARBs in adult patients with heart failure and reduced ejection fraction.

1. **Comparative effectiveness**

The clinical study programme included two phase II studies TITRATION and PARAMOUNT-HF and the pivotal phase III trial PARADIGM-HF which was a double blind trial where 8442 patients with class II, III or IV heart failure and an ejection fraction of 40% or less (later reduced to ≤ 35%) were randomised to receive sacubitril/valsartan at a dose of 200mg twice daily or enalapril 10mg twice daily in addition to recommended therapy. Patients were required to have a BNP level of at least 150pg/ml or an NT-proBNP ≥ 600pg/ml. Baseline characteristics demonstrated a mean age of 63.8 years, 21% of participants were female, 70.9% had a history of hypertension, 43.4% had a previous myocardial infarction, 34.7% had diabetes mellitus and 36.2% had atrial fibrillation.

The primary endpoint was a composite of death from cardiovascular causes or hospitalisation for heart failure. After a median follow-up of 27 months the primary

outcome had occurred in 914 patients (21.8%) in the sacubitril/valsartan group and in 1117 patients (26.5%) in the enalapril treatment group (HR 0.80; 95% CI, 0.73-0.87;P<0.001). A total of 711 patients (17%) receiving sacubitril/valsartan died as compared with 835 patients (19.8%) who were treated with enalapril (HR;0.84;95% CI, 0.76-0.93;P<0.001). As compared with enalapril, sacubitril/valsartan also reduced the risk of hospitalisation for heart failure by 21% (P<0.01) and decreased the symptoms and physicial limitations of heart failure (P<0.001).

2. Safety

During the single blind, run in phase of PARADIGM-HF 12% of patients discontinued therapy due to an adverse event: 5.6% during the enalapril run-in mainly due to renal dysfunction (1.7%), hyperkalaemia (1.7%) and hypotension (1.4%) and 5.9% in the sacubitril/valsartan group including adverse effects such as renal dysfunction (1.8%), hypotension (1.7%) and hyperkalaemia (1.3%). After randomisation patients in the sacubitril/valsartan group were more likely to have symptomatic hypotension (14%) as compared with the enalapril group (9.2%) P<0.001. In contrast, adverse effects seen more frequently in patients treated with enalapril included, cough (14.3% vs 11.3%), a serum creatinine level ≥ 221 µmol/l (2% vs 1.5%) and a serum potassium over 6 mmol/l (4.3% vs 5.6%). The most frequently reported serious adverse events in the sacubitril/valsartan and enalapril groups included cardiac failure (14% and 15%) and pneumonia (3.7% and 4.3%) respectively. There were a total of 19 cases of angioedema in the sacubitril/valsartan group as compared with 10 cases in the enalapril group. Overall fewer patients in the sacubitril/valsartan group stopped their study medication due to adverse events (10.7% vs 12.3%) or because of renal impairment (0.7% vs 1.4%).

3. Cost effectiveness

The manufacturer submitted a cost utility analysis in a regression based cohort model. The population considered in the economic model reflects the therapeutic indication i.e. chronic heart failure patients with reduced ejection fraction as studied in PARADIGM-HF. The intervention was sacubitril/valsartan administered orally with a target dose of 97/103 mg

twice daily. The relevant comparators were ACE inhibitors and ARBs in addition to the standard of care therapies. The model uses all cause mortality and all cause hospitalisations as observed in PARADIGM-HF. The primary outcome in the pivotal trial (composite of death from cardiovascular causes or hospitalisation for heart failure) was not used in the model.

Mortality was estimated using parametric survival curves, hospitalisation rates were estimated using a negative binomial regression model and quality of life (QoL) values were estimated through longitudinal analysis of EQ-5D values using a mixed effects regression model derived from patient level EQ-5D data from the pivotal trial. The model could be described as a two state Markov model in which patients transition from alive to dead. A monthly cycle length was selected and half cycle correction applied. A lifetime horizon of 20 years was used in the cost-effectiveness model. Transition probabilities between the alive and dead state were derived from parametric survival curves, assuming a Gompertz distribution. Hospitalisation rates, adverse event rates and decline in EQ-5D over time were not based on transitions between formal health states rather multivariate regression models were used to estimate hospitalisation rates, adverse events and QoL outcomes (EQ-5D) from PARADIGM-HF. All cause hospitalisation was expected to incorporate the costs of serious adverse events while the costs of less serious adverse events were considered independently.

Outcomes are expressed in quality adjusted life years (QALYs) where the relative mortality gain coupled with improved quality of life from a reduction in hospitalisations, fewer adverse events and a proportionately better EQ-5D score results in a higher expected QALY over the time duration of sacubitril/valsartan treatment. Costs included in the model were drug costs, costs associated with the management of heart failure patients including hospital costs, adverse event costs, outpatient and general practitioner costs. The ex-factory price of sacubitril/valsartan (Entresto) used in the HTA submission is € 136.92 per 28 day pack. When additional factors (such as wholesaler costs, rebates, pharmacy fees) are considered the annual total cost to the HSE was estimated at € 1,922.43. Since the HTA submission the ex-factory price of sacubitril/valsartan was reduced by 6% (reflecting the current reference EU countries) to € 128.71 per 28 day pack. Hospitalisation costs were

obtained from relevant DRG codes. The NCPE review group were satisfied that accurate and relevant costs were provided.

The NCPE review group highlighted the major assumption where the sacubitril/valsartan advantages are incorporated via a persistent HR of sacubitril/valsartan over the ACE inhibitor treatment arm. The assumption of a sustained treatment effect beyond the trial and throughout the time horizon was questioned. Similarly, the beneficial effect of sacubitril/valsartan on quality of life persists for the duration of the model time horizon.

In the basecase analysis of the submitted dossier sacubitril/valsartan was associated with an incremental cost effectiveness ratio (ICER) of € 27,080/QALY. In terms of life years gained (LYG) the basecase ICER was € 23,942/QALY. The cost-effectiveness of sacubitril/valsartan versus an ARB (Candesartan) was estimated at € 25,350/QALY or € 21,252/LYG. Univariate sensitivity analysis demonstrated that the most influential parameter related to mortality, the main driver of the model. Probabilistic sensitivity analysis indicated that the probability of sacubitril/valsartan being cost-effective at a € 45,000/QALY threshold was 92% (93.5% when the 6% price reduction is considered) and a probability of cost-effectiveness at the € 20,000/QALY threshold was less than 15% (22.3% when the 6% price reduction is considered). Sensitivity analysis demonstrated that altering the treatment effect had the greatest influence in the ICER. If it is assumed that all sacubitril/valsartan effects cease at 5 years following initiation of treatment the ICER increases to € 44,375/QALY and tapering the treatment effects from year 5 to 10 results in an ICER of € 36,308/QALY. The price ICER relationship indicates the ICER falls from € 27,080/QALY to € 25,234/QALY when the 6% price reduction is considered. A 24% price reduction from the submitted HTA ex-factory price (i.e. from € 136.92 to € 104.06 per 28 day pack) is required to reduce the ICER to approximately € 20,000/QALY.

4. Budget impact

The estimated number of heart failure patients in the budget impact analysis was 40,000 with approximately 50% of those considered to have heart failure with reduced ejection fraction. Other assumptions considered that 8% of patients may be unsuitable for therapy due to conditions such as severe renal or hepatic failure and hypotension. The rate of

increase in heart failure diagnosis was estimated at 6% per annum. The NCPE consider the net drug budget impact over 5 years could exceed € 50 million.

5. Conclusion

The NCPE considers that sacubitril/valsartan (Entresto) is cost-effective and supports reimbursement of the medicine. However, there could be a significant budget impact associated with the introduction of the drug and to optimise cost-effectiveness it is essential that appropriate patients e.g. with NYHA II to IV heart failure and a LVEF ≤ 35% receive the product. A reimbursement application system under the HSE-Medicines Management Programme could be considered.