Cost effectiveness of dapagliflozin (Forxiga®) for the treatment of adult patients with Type 2 Diabetes Mellitus (T2DM).

The NCPE has issued a recommendation regarding the use of dapagliflozin in patients with Type 2 Diabetes Mellitus (T2DM). The NCPE does not recommend reimbursement of dapagliflozin.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturers (Bristol Myers Squibb and Astra Zeneca) economic dossier on the cost effectiveness of dapagliflozin (Forxiga®) for the treatment of adult patients with Type 2 Diabetes Mellitus (T2DM). 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 examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

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 **December 2013**

Summary

1. In August 2013, Bristol Myers Squibb (BMS), in conjunction with Astra Zeneca (AZ) submitted a dossier for dapagliflozin (Forxiga®) to support the application for reimbursement on the community drug schemes for the treatment of adults with *Type 2 Diabetes Mellitus (T2DM)*.

2. The economic evaluation compared dapagliflozin 10mg once daily in a dual therapy regimen (as add-on to metformin) versus the sulphonlyureas (as add-on to metformin), the dipeptidyl peptidase-4 inhibitors (DPP-4s) (as add-on to metformin) and the glucagon-like peptide-1 analogues (GLP-1s) (as add-on to metformin). Scenario analyses also considered the cost effectiveness of dapagliflozin in a triple therapy regimen (as add-on to metformin and a sulphonylurea) versus the DPP-4s and the GLP-1 analogues. The cost effectiveness of dapagliflozin in addition to a sulphonylurea or as add-on to metformin and insulin was not considered.

3. The evidence to support the use of dapagliflozin as dual therapy in combination with metformin is derived from three randomised, double-blind, controlled phase III studies: a non-inferiority study in comparison with glipizide and two placebo-controlled studies. Network meta-analyses were used to compare dapagliflozin to the DPP-4s and the GLP-1 analogues.

4. The primary outcome measure used in most studies for dapagliflozin is change in $HBA1_c$. Dapagliflozin provided similar improvements to a sulphonylurea in reducing $HBA1_c$ levels when combined with metformin. The change in $HBA1_c$ level in the active comparator trial was approximately -0.52% in both groups, giving a mean difference of 0.00% (95% CI: -0.11 to 0.11).

5. Additionally, a primary outcome measure in one of the placebo-controlled trials was reduction in weight. Dapagliflozin, in combination with metformin was associated with weight loss comparable to that seen with non-pharmacological interventions such as lifestyle modification and dietary intervention (Norris et al., 2005).

6. The review group noted a number of limitations with the clinical evidence presented in the submitted dossier. These included no direct clinical outcome data to demonstrate that dapagliflozin in combination with metformin reduces micro-vascular and/or macro-vascular complications, some bias in handling missing clinical outcome data for dapagliflozin which was not addressed, and differences in the clinical trial population versus the proposed population in which dapagliflozin would be used.

7. A discrete event simulation model was used to project costs and outcomes over a lifetime (40 year) horizon. The model structure, which was the same for each analysis and similar to other economic models in diabetes, used changes in clinical outcomes ($HbA1_c$, weight, systolic blood pressure and cholesterol levels) to predict changes in longer term micro-vascular and macro-vascular complications.

8. Estimates of effect were obtained from the network meta analysis at 24 weeks and 52 weeks. Resource use was from a variety of UK and Irish sources. Utility data associated with complications were derived from UKPDS 62 data. The impact of weight changes on quality of life (a key driver in the model) was derived from Bagust *et al.,* 2005. The majority of QALY gains in the model are derived from the direct impact of weight change on health related quality of life, rather than from a reduction in diabetic complications or other adverse events.

9. The manufacturer presented a comprehensive set of results with accompanying sensitivity analyses, which showed that the results were particularly sensitive to four parameters; the utility associated with weight change, the results of the 52 week network meta-analysis, the $HBA1_c$ thresholds for switching therapy and the impact of applying baseline clinical history from an observational study of UK patients who have a higher baseline prevalence of co-morbidities. Revised analyses were requested by the NCPE review group to show the combined impact of these four parameter changes

(*listed above*) in the model, which gave a revised set of base case results as follows;

- There was little difference in costs and effects between dapagliflozin (as add-on to metformin) and the DPP-4s (as add-on to metformin).
- Dapagliflozin (as add-on to metformin) is less costly & less effective than the GLP-1 analogues (as add-on to metformin).
- The ICER for dapagliflozin (as add-on to metformin) vs the sulphonlyureas (as add-on to metformin) was €30,026/QALY. The ICER for dapagliflozin (as add-on to metformin) vs the sulphonlyureas (as add-on to metformin), analysing the impact on $HBA1_c$ only was €66,609/QALY for dapagliflozin.

10. Based on the evidence submitted, the uncertainty associated with it, and recent evidence (Look Ahead Research Group 2013) highlighting that weight loss in patients with T2DM does not necessarily reduce the rate of cardiovascular events, the NCPE do not consider dapagliflozin to be a cost effective intervention for use in patients with T2DM at this time. Furthermore, the NCPE do not consider the evidence submitted to support the use of dapagliflozin in a triple therapy regimen to be robust and cannot assess cost effectiveness at present. In conclusion, based on the results of the pharmacoeconomic evaluation, the NCPE cannot recommend the reimbursement of dapagliflozin in a dual therapy regimen, in the Irish healthcare setting at this point in time.