Cost effectiveness of Lixisenatide (Lyxumia®) for the treatment of adult patients with Type 2 Diabetes Mellitus.

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

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturers (Sanofi) economic dossier on the cost effectiveness of lixisenatide (Lyxumia®) for the treatment of adult patients with Type 2 Diabetes Mellitus. 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 **July 2014**

Summary

In December 2013, Sanofi submitted a dossier for lixisenatide (Lyxumia®) to support the application for reimbursement on the community drug schemes for the treatment of adults with *Type 2 Diabetes Mellitus (T2DM)*. The cost effectiveness of lixisenatide was evaluated in the following scenarios;

- In combination with oral antidiabetic agents.
  Lixisenatide was modelled as add-on to metformin and the comparator used was liraglutide 1.2mg and 1.8mg once daily and a weighted proportion of the two doses informed by post-reimbursement utilisation data.
- In combination with basal insulin.
  Lixisenatide was modelled as add-on to basal insulin and compared with exenatide, in the absence of any evidence supporting the use of liraglutide in this indication at the time.

Comparative Effectiveness of lixisenatide

The clinical trial programme for lixisenatide included trials covering use in monotherapy, dual therapy and triple therapy regimens. Trials relevant to both dual and triple therapy use, as well as add-on to basal insulin were considered for the purposes of this evaluation.

Lixisenatide in dual therapy

There were two placebo-controlled add-on to metformin studies (EFC 6014 and EFC 10743), performed primarily in Caucasian patients, where treatment with lixisenatide resulted in statistically significant reductions in HBA1c compared to placebo ranging from 0.37% to 0.49%. The assessment of the magnitude of effect in these studies was complicated by a large placebo effect (0.35 and 0.4%, respectively). Mean reductions in body weight were small and the difference compared to placebo was only statistically significant in one of the two studies.

Lixisenatide in triple therapy

Results from two 24 week, double-blind, placebo-controlled RCTs of lixisenatide were available, in which 81-84% of patients were receiving metformin in combination with pioglitazone (Study EFC 6017) or sulphonylurea (Study EFC 6015). EFC 6017 compared lixisenatide with placebo in people whose diabetes was poorly controlled on pioglitazone, with or without metformin. Study EFC 6015 included a large proportion (45%) of Asian (Taiwan, India, Japan, South Korea, Thailand) patients, with relatively lower body mass index (BMI), and in whom the placebo corrected glucose-lowering effect was somewhat more pronounced compared to Caucasian patients. The Review Group therefore questioned the relevance of these studies to the patients in Ireland when (a) pioglitazone is not used to any great extent in Ireland and (b) the generalisability of these studies to patients in Ireland.

Lixisenatide as add-on to basal insulin

Study EFC 6016, a double-blind placebo-controlled trial which evaluated the addition of lixisenatide to basal insulin was used to support the use of lixisenatide in this setting.

As the data directly comparing lixisenatide with liraglutide in T2DM patients in combination with oral antidiabetic medications was limited, a systematic review and network meta-analysis (NMA) utilising a Bayesian network analysis method were included in the company submission to evaluate the relative efficacy of these treatments. Reduction in HBA1c was the primary outcome measure, with reduction in weight being a secondary outcome measure. Results showed that liraglutide had a greater effect at lowering HBA1c than lixisenatide however, the Review Group noted some issues with the methodology used in the MTC and thus questioned the magnitude of the difference in the treatment effect size estimated between liraglutide and lixisenatide.

The company submission also included comparative evidence of lixisenatide in combination with basal insulin versus exenatide twice-daily. A Bucher pair-wise

indirect comparison of lixisenatide to exenatide twice daily in combination with basal insulin was presented. There were numerous significant sources of heterogeneity between the two studies and results show that there was no statistical difference in HBA1c reduction with lixisenatide compared to exenatide. However treatment effect sizes on for weight loss show that exenatide exhibited a significantly greater reduction in weight compared to lixisenatide.

Safety of lixisenatide

As for other GLP-1 agonists, the most common adverse events reported for lixisenatide are gastrointestinal side effects; e.g. nausea (26%), vomiting (10.5%) and diarrhoea (8.3%). The product information includes a recommendation concerning a gradual up-titration of the dose to reduce these symptoms. The incidence is gradually reduced with treatment duration. Hypoglycaemia is reported mainly in combination with a sulphonylurea and/or insulin. There was no mean increase in heart rate in the clinical studies but a tendency to transient increase in heart rate was reported in the phase 1 (TES 11807) study, which evaluated the effect of lixisenatide on cardiac safety. This has also been reported for other products in the class. More information with regard to cardiovascular (CV) effects will be obtained in the ongoing CV outcomes study (ELIXA, due to be reported in 2015). The proportion of patients developing antibodies was 70% for lixisenatide. The development of antibodies has been associated with a higher incidence of injection site reactions (also seen with other products in the class). However, the incidence of allergic reactions possibly associated with lixisenatide was low (0.4%) and the anaphylactic reactions reported were mostly low grade in severity. Hypersensitivity reactions are being reviewed and continually adjudicated in ongoing trials.

Cost effectiveness of lixisenatide

The IMS CORE model was used to simulate disease progression over a 50 year time horizon. Health benefits were measured in QALYs using utility values from Bagust & Beale (2005). Disutilities associated with nausea, diarrhoea and vomiting were included. Costs associated with the given health states in the

CORE model were derived from Casemix (Ireland). Costs for these complications were accounted for separately for the first and subsequent years. All costs were reported in 2012 Euros.

Incremental cost-effectivness ratios (ICERs) for lixisenatide were in the South-West quadrant (i.e. less costly and less effective).

Scenario 1: lixisenatide in combination with other oral agents.
The comparison of lixisenatide versus liraglutide (all doses) in the add-on to other oral agents population (based on indirect evidence) yielded 0.072 less QALYs and cost €3,537 less (i.e. less effective and less costly).

Scenario 2: lixisenatide as add-on to basal insulin.
The comparison of lixisenatide versus exenatide in the basal insulin population (based on indirect evidence) yielded 0.136 less QALYs and cost €268 less (i.e. less effective and less costly).

A probabilistic analysis was conducted for both treatment scenarios.
Comparison with liraglutide (all doses)
Seventy percent of outcomes were in the South-West quadrant (reduced effectiveness and lower costs) and 29% of outcomes were in the South-East quadrant (greater effectiveness and lower costs). The remaining 1% of outcomes were in the North East (more costly, more effective) quadrant.

Comparison with exenatide in the basal insulin population
Sixty-five percent of outcomes were in the South-West quadrant (reduced effectiveness and lower costs) and thirty percent of outcomes were in the North-West quadrant (reduced effectiveness and higher costs). The remaining 5% of outcomes were dispersed between the South-East (less costly, more effective) and North East quadrants.

In summary, based on the evidence submitted and the uncertainty associated with it, reimbursement of lixisenatide is not recommended for patients with T2DM at the submitted price.