Cost Effectiveness of *canagliflozin (Invokana®)* for adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

The NCPE has issued a recommendation regarding the use of *canagliflozin* for this indication. The NCPE does *not recommend* reimbursement of *canagliflozin* under the pricing structure submitted.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (*Janssen*) economic dossier on the cost effectiveness of *canagliflozin*. 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. 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 ***August 2014***

Summary

Invokana® (100mg and 300mg) is indicated for use in adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or add-on therapy with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. *Invokana*® contains canagliflozin hemihydrate and works by inhibiting the sodium-glucose co-transporter 2 (SGLT2) in the kidney, thus leading to increased glucose excretion. *Janssen* submitted a dossier for *canagliflozin (Invokana®)* on *April 17th 2014*. Final submissions were received on July 11th 2014.

1. **Comparative Effectiveness**

The clinical trials used to support the clinical effectiveness were: DIA 3006, DIA 3009, DIA 3002, DIA 2012, DIA 3015 and DIA 3008.

- The comparators included in the pharmacoeconomic evaluation were the sulphonlyureas (SUs), the dipeptidyl peptidase 4 inhibitors (DPP4), the glucagon-like peptide (GLP 1) analogues, basal insulin and dapagliflozin as part of a dual (with metformin) or triple (with metformin and a SU) combination and as an add-on to insulin therapy.
- Direct comparative data were only available for canagliflozin (CANA) *vs* a SU or a DPP-4 inhibitor. To support the economic case, which compared CANA against a range of treatment options, evidence was synthesised using a network meta-analyses (NMA) of anti-hyperglycaemic agents in combination with; metformin, metformin and a SU or with insulin.
- Results from the clinical trial data for both CANA doses showed reductions in HbA1c (change from baseline) ranging from -0.63% to -0.89% (CANA 100mg) and -0.72% to -1.06% (CANA 300mg). The incremental difference in terms of HbA1c reduction between CANA 100mg and CANA 300mg ranged between 0.1% and 0.2%. Results for the NMA were presented by outcome measure and the main outcome measures of relevance to the economic analysis were HBA1c and BMI. Results from the NMA were used where there were no head to head studies vs CANA.
- Overall results from the NMA for CANA 100mg and 300mg were consistent with the direct evidence from the CANA pivotal trials.

2. Safety

- In the placebo-controlled trials, the most commonly reported adverse reactions during treatment with CANA in combination with insulin or a sulphonylurea, were hypoglycaemia, vulvovaginal candidiasis, urinary tract infection (UTI), and polyuria or pollakiuria (i.e., urinary frequency). Adverse reactions leading to discontinuation of ≥0.5% of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of women) and balanitis or balanoposthitis (0.5% of men).

- The overall incidence of adverse events with CANA in the active comparator studies (DIA3009 and DIA3015) was 64.4%, 68.5%, and 68.5% for CANA 100 mg and 300 mg and glimepiride 6 mg or 8 mg, respectively, for DIA3009; and 76.7% and 77.5% for CANA 300 mg and sitagliptin 100 mg, respectively, for DIA3015 (C0001, C0008).

3. Cost-Effectiveness analysis

- A cost utility analysis comparing *canagliflozin* with the sulphonlyureas (SUs), the dipeptidyl peptidase 4 inhibitors (DPP4), the glucagon-like peptide (GLP 1) analogues, basal insulin and dapagliflozin was submitted by the company. The perspective of the HSE (payer) was presented.
- The manufacturer chose the ECHO-T2DM model. Individual patient outcomes were simulated over time through health states capturing micro- and macrovascular complications and death. The model used a lifetime time horizon (40 years), the cycle length was 1 year and health benefits and costs were each discounted at 5%.
- The manufacturer mainly used published quality of life utility values derived from the CODE-2 study. Utility decrements were applied to the baseline quality-of life value for patient characteristics (for example, age and duration of disease), microvascular and macrovascular complications, hypoglycaemic events, obesity and adverse events.
- The main outcomes were change in HbA1c, weight, BMI and SBP, and incidence of hypoglycaemia. Other secondary outcomes such as fasting plasma glucose (FPG) were reported. The outcomes which had most influence in the economic model were HbA1c and BMI.

- In the base case analysis patients were initiated on CANA 100mg and were titrated to CANA 300mg as needed to maintain glycaemic control. Sensitivity analyses were conducted on both doses when modelled separately. The Review Group considered the most plausible results were those in which CANA was modelled separately, as per the clinical trial evidence.

4. *Results*

The manufacturer provided a comprehensive set of results which captured the incremental cost-effectiveness ratios (ICERs) of CANA *vs* all comparators in a dual therapy, triple therapy and as add-on to insulin setting. In the analyses presented by the company CANA was cost effective in most settings, with ICERs ranging from €4,939/QALY to €40,426/QALY and CANA 300mg dominating the GLP-1 analogues.

Sensitivity analysis

Approximately 28 sets of alternative assumptions were considered. The Review Group noted that the scenarios modelling the impact of CANA (i) on the Hba1c outcome only and (ii) all outcomes excluding the impact of BMI reduction, had greatest impact on the results.

The cost differential between the 100mg and 300mg CANA dose is significant, where the 100mg dose costs €50.05 (per 30 tablet pack) and the 300mg dose costs €66.59 (i.e. cost to the HSE). From the clinical trial data, the incremental benefit (in terms of HbA1c reduction) between CANA 100mg and CANA 300mg is small (between 0.1% and 0.2%). It is difficult to predict the proportion of patients who will require the 300mg dose or when this will occur. The manufacturer modelled CANA 100mg and 300mg doses separately. The Review Group conducted an additional incremental analysis of the 100mg to 300mg, based on the figures provided by the manufacturer. The analysis resulted in ICERs which were above €45,000/QALY, the accepted threshold to demonstrate cost-effectiveness in Ireland and ranged from €56,000/QALY to €156,846/QALY, except when compared to the GLP-1 analogues, in which case CANA 300mg was dominant.

5. Budget Impact Analysis

CANA is supplied as film-coated 100mg and 300mg tablets in a 30 tablet pack for oral administration. The cost per pack (to the HSE) of CANA 100mg and 300mg is €50.05 and €66.59, respectively. The estimated market share is difficult to predict for the $SGLT_2$ class of drugs as they are a new drug class. In the submission however the manufacturer assumes that CANA will be used in Ireland predominantly in the dual and triple settings, with shares increasing from 0.1% to 15.8% and 0.3% to 13.1% from 2014 to 2018, respectively. A small number of patients are assumed to receive CANA as an add-on therapy to insulin, with shares increasing from 0.0% to 5.0% from 2014 to 2018. A 50% split in usage between the 100mg dose and 300mg dose is assumed throughout. The estimated gross budget impact for CANA in dual, triple and add-on to insulin regimens ranges from €123,249 in 2014, €1,591,465 in 2015, €3,672,425 in 2016, €6,291,334 in 2017 to €9.5m in 2018, giving a 5 year cumulative gross budget impact of €21.1m. Assuming displacement of the DPP4s, SUs and to a lesser extent the GLP-1 analogues, the net budget impact of introducing CANA is estimated to be €4,046 in 2014 ranging to €1.5m in 2018. The Review Group highlight that these figures are subject to considerable uncertainty however, due to the difficulty in reliably predicting the uptake of this new class of agent.

6. Conclusion

Under the pricing structure proposed by the manufacturer CANA cannot be considered cost effective. The marginal benefit of the 300mg dose is insufficient to justify the price premium requested.