Cost Effectiveness of *insulin degludec (Tresiba®)* for the treatment of diabetes mellitus in adults, adolescents and children aged greater than one year.

The NCPE has issued a recommendation regarding the use of *insulin degludec* for this indication. The NCPE *does not recommend* reimbursement of *insulin degludec*.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturer's (*Novo Nordisk*) economic dossier on the cost effectiveness of *insulin degludec*. 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 that 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 that 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 ***Date 4th May 2015***

Summary

Novo Nordisk submitted a dossier for *insulin degludec (Tresiba®)* on *November 1st 2014*. *Insulin degludec (*Tresiba®) is indicated for *the treatment of diabetes mellitus in adults, adolescents and children aged greater than one year*. *Tresiba®* contains *insulin degludec,* a long acting basal insulin. Insulin degludec is a specific and full agonist at the human insulin receptor and the mode of action is identical to that of human insulin and other insulin analogues.

1. **Comparative Effectiveness**

- The comparator included in the pharmacoeconomic evaluation was insulin glargine as it is the most widely used long acting basal insulin in Ireland. Insulin detemir was considered in a separate scenario analysis in patients with Type 1 diabetes mellitus (T1DM). Neutral Protamine Hagedorn (NPH) insulin was not included by the applicant.

- The efficacy and safety of insulin degludec was investigated in an extensive clinical program comprising nine confirmatory trials in both patients with T1DM and patients with type 2 diabetes mellitus (T2DM). The T1DM trials included 1,578 patients and the T2DM trials included 4,076 patients. Efficacy in terms of HbA1c lowering effect was confirmed in both T1DM and T2DM patients in clinical trials of 26 to 52 weeks duration. Insulin degludec was shown to be non-inferior to the insulin comparator in all trials. In one trial in T2DM patients, sitagliptin was used as a comparator and in this trial insulin degludec showed superiority. Clinically relevant HbA1c reductions were achieved (0.6% in T1DM trials and 1.2% in T2DM trials). The occurrence of hypoglycaemia was included as a secondary endpoint.

- For the secondary outcome of hypoglycemia, a prospectively planned meta-analysis, pooling all therapeutic confirmatory trials (T1DM and T2DM) with insulin degludec and insulin glargine as comparator was

performed. The analysis were based on the full analysis set, which included a total of 2,899 subjects treated with insulin degludec and 1,431 subjects treated with insulin glargine. The analysis confirmed that no differences were observed in the rates of severe hypoglycaemia within the T1DM or T2DM populations. The meta-analysis further showed a lower risk for hypoglycaemia with insulin degludec, which was driven by the T2DM trials, whereas for T1DM the point estimates were in favour of the comparator (insulin glargine). Regarding nocturnal hypoglycaemia (captured from patient diaries), the result was consistent for both T1DM and T2DM populations showing a lower risk with insulin degludec treatment.

2. Safety

- In the 41 completed clinical trials constituting the clinical development program for insulin degludec, a total of 5,624 subjects were exposed to insulin degludec. The assessment of safety in subjects with T1DM and T2DM was mainly based on 11 completed therapeutic confirmatory trials, representing the major part of the exposure. Overall, the incidence of adverse events (AEs), serious adverse events (SAEs), AEs assessed as possibly or probably related to insulin degludec and AEs leading to withdrawal was slightly higher in the insulin degludec group than in the comparator group. However the vast majority of AEs were mild or moderate in severity and the distribution of AEs was similar between groups. Hypoglycaemia episodes were only recorded as AEs if they fulfilled the definition of a SAE or severe hypoglycaemia (according to the CHMP guideline). Serious events of hypoglycaemia (mainly in T2DM) were slightly more common in the insulin degludec group than in the comparator group. Discontinuations due to hypoglycaemia were slightly more common in the insulin degludec group than in the comparator group in patients with T1DM, while withdrawals were comparable between insulin degludec and comparator in T2DM patients. Interim results of the cardiovascular outcomes trial 'DEVOTE' are due out later in 2015.

3. Cost-Effectiveness analysis

- A cost utility analysis comparing insulin degludec with insulin glargine was submitted by the company. The perspective of the HSE (payer) was presented.

- The main efficacy outcome used in the model was the hypoglycaemic event rate.

- Two patient groups were considered:
    - Patients with T1DM who used a basal-bolus regimen with a basal insulin analogue ($T1DM_{BB}$).
    - Patients with T2DM who used a basal oral therapy regimen with a basal insulin analogue ($T2DM_{BOT}$).

  For each of the groups modelled, a simple model was constructed to show the costs and outcomes associated with a hypoglycaemic event, over a one year time horizon. The review group consider that the model which mainly models the benefit in terms of hypoglycaemia may be over-simplistic for a multi-faceted condition such as diabetes mellitus.

- The applicant carried out a study which used the time trade-off method in an international sample of the general population to estimate the disutility associated with different hypoglycaemic events. The Review Group considered alternative estimates of utility in the model in light of the variability reported in the literature for disutilities associated with hypoglycaemic episodes. The disutility estimates are a key driver in the economic model, and the alternative estimates considered by the Review Group resulted in higher ICERs being generated by the model, than those submitted by the applicant.

Results

- An incremental analysis was conducted by the applicant for both the T1DM and T2DM cohorts, with deterministic ICERs presented. The ICER for the $T1DM_{BB}$ and $T2DM_{BOT}$ cohorts were €6,284/QALY and €3,010/QALY respectively.
- Several changes were made to the applicant's assumptions using the Review Group's preferred set of model inputs, which were based on alternative estimates for hypoglycaemic event rates and the proportion which occurred at night, costs associated with a hypoglycaemic episode and disutility estimates for a hypoglycaemic episode. Changes made to these parameters generated the following results:
    - In the $T1DM_{BB}$ cohort, the incremental analysis yielded a deterministic ICER of €50,697/QALY.
    - In the $T2DM_{BOT}$ cohort, the incremental analysis yielded a deterministic ICER of €108,203/QALY.

Scenario Analysis

- Using the Review Group's preferred set of model inputs, and applying the additional assumption of dose equivalence between insulin degludec and insulin glargine, the following results were generated:
    - In the $T1DM_{BB}$ cohort, the incremental analysis yielded a deterministic ICER of €101,532/QALY.
    - In the $T2DM_{BOT}$ cohort, the incremental analysis yielded a deterministic ICER of €161,372/QALY.

Sensitivity analysis

- A one way sensitivity analysis was conducted and the main driver was the hypoglycaemic event rate used. Several scenario analyses were conducted which examined populations from both groups who were experiencing recurrent hypoglycaemic episodes. The Review Group felt that the quality of

these analyses was compromised by the fact that no data is available for insulin degludec use in such populations.

- A probabilistic analysis was conducted however it is compromised by the fact that only statistically significant parameter values were included.

4. Budget Impact Analysis

- The price per pack of insulin degludec to the HSE, inclusive of wholesale margin, dispensing fee and rebate is €96.40. VAT (23%) is payable on insulin degludec as it is an injectable item, thus the cost including VAT is €118.57 per pack.

- To calculate the cost per patient per year, the applicant bases insulin use on the average daily insulin dose from the clinical trial programme. Based on the revised eligible population as outlined by the Review Group, the potential gross budget impact of insulin degludec (and associated cost of insulin aspart) over the 5 years could reach in year 1 to 5; €1,433,082, €2,939,244, €4,514,699, €6,155,950, €7,859,582 respectively. Given the uncertainty associated with insulin degludec dosing in clinical practice, applying a dose of 40.85units/day (the weighted average insulin glargine dose) would increase the gross budget impact in year 1 to 5 to: €1,583,657, €3,248,050, €4,989,061, €6,802,759, €8,635,393.

- The net drug budget impact, taking into account the displaced insulin costs for insulin glargine, insulin detemir and insulin aspart could be in years 1 to year 5; €300,768, €616,869, €947,521, €1,291,979, €1,649,528. Assuming a higher dose of insulin degludec is used per day, would increase the net budget impact in year 1 to 5 to: €451,343, €925,695, €1,421,883, €1,938,788, €2,475,339. A one way sensitivity analysis was conducted and showed that the cost of insulin degludec, when varied ± 20% had the largest impact on the budget impact estimates.

5. Conclusion

Insulin degludec (Tresiba®) is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged greater than one year. Following NCPE assessment of the applicant's submission, insulin degludec (Tresiba®) is not considered cost-effective versus insulin glargine for the treatment of diabetes mellitus in adults, adolescents and children aged greater than one year and therefore is not recommended for reimbursement at the submitted price.