Commissioning Support
Insulin Degludec
(Tresiba®▼)
For the treatment of diabetes

Commissioning guidance:
Commissioners may wish to bear the following in mind when considering the commissioning of insulin degludec:

- **MHRA guidance**: Insulin degludec is the first long-acting insulin to be available at a higher 200 units/mL dose formulation; giving rise to the potential for medication error. A Direct Healthcare Professional Communication on the correct use of Tresiba to minimise medication errors’ advises that:
  - Ensuring that the required strength of insulin degludec is included on the prescription
  - Asking the patient to visually identify the strength of insulin degludec dispensed, and confirm that they are able to read the dose counter on the pen.
  - Ensuring that patients are trained in the correct use of insulin degludec and identification of the different strengths (packaging and labelling), and have been provided with a patient brochure.
  - Patients must be advised to seek medical advice immediately if they administer an incorrect dose of insulin degludec.

- The lack of evidence of a greater clinical benefit of insulin degludec compared with insulin glargine.
- Insulin degludec is considerably more expensive than insulin glargine.
- The 200 units/mL formulation of insulin degludec may be a suitable option for use:
  - in patients on high insulin doses to reduce the volume of insulin injected
  - in patients at high risk of nocturnal hypoglycaemia

Prescribing guidance: Category B (Q4)
Insulin degludec should be initiated and the dose stabilised in secondary care. Following initiation and stabilisation, it is suitable for continued prescribing in primary care.

**Category B: suitable for restricted prescribing under defined conditions**

**Q4 rating**: The evidence for the efficacy of insulin degludec was considered to be relatively weak. In three short-term trials, insulin degludec was shown to be non-inferior to insulin glargine in adults with type 1 and type 2 diabetes. Insulin degludec has a lower place in therapy because there was no data comparing insulin degludec with NPH insulin, it has a greater cost and insufficient evidence of a substantial clinical advantage over insulin glargine.

The Q rating relates to the drug’s position on the effectiveness indicator grid.
The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.

**Description of technology**
Insulin degludec (Tresiba®▼) is a neutral, soluble, ultra-long-acting insulin analogue licensed for the treatment of diabetes mellitus in adults as basal insulin replacement therapy.² It has a terminal half-life of longer than 25 hours, and a duration of action longer than 40 hours. Insulin degludec is available in 100 units/mL and 200 units/mL strengths. Full advice relating to the higher strength (extract above) can be found on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Background**
Type 1 diabetes is treated with insulin replacement therapy in addition to diet and lifestyle choices. The NICE clinical guideline on type 1 diabetes (CG15; 2004) recommends that adults should have access to the types (preparation and species) of insulin they find allow them optimal wellbeing. Basal insulin supply should be provided by the use of NPH (isophane) insulin or a long-acting insulin analogue (insulin glargine, insulin detemir, insulin degludec).

Dietary and lifestyle modifications form the mainstays of therapy for type 2 diabetes, but 50 to 70% of patients will also require an anti-diabetic drug. Drug treatments currently available include sulphonylureas, metformin, pioglitazone, acarbose, repaglinide, nateglinide, DPP-4 inhibitors ("gliptins"), dapagliflozin, exenatide, liraglutide and insulin.

**Clinical evidence for efficacy and safety**

**Type 1 diabetes**: Two published, open-label, phase 3, non-inferiority trials³⁴ compared insulin degludec with insulin glargine, both administered as a once-daily subcutaneous (s/c) injection (doses adjusted to achieve plasma glucose target 3.9 to 5 mmol/L) in adults with type 1 diabetes. The 52-week BEGINS Basal-bolus Type 1 trial³ enrolled 629 patients with HbA1c levels of 61 to 86 mmol/mol (7.7 to 10%) and who had been treated with basal bolus insulin for at least a year. Patients also...
received mealtime s/c insulin aspart using a treat-to-target approach. The 26-week BEGIN FLEX T1 trial, compared insulin degludec injected at intervals that varied from 8 to 40 hours between doses, with insulin degludec and insulin glargine given at a fixed time every day. The primary outcome in both trials was the non-inferiority of insulin degludec to insulin glargine; measured as the mean change in HbA1c from baseline.

In the BEGIN Basal-bolus Type 1 trial, for the primary outcome, mean decreases in HbA1c of 4.3 to 4.4 mmol/mol (0.39% and 0.4%) were recorded in the insulin glargine and degludec treatment groups respectively (p < 0.0001, treatments were non-inferior). In the BEGIN-FLEX T1 trial, mean HbA1c decreased by 4.4 mmol/mol (0.4%) with variable injection time insulin degludec, and by 4.5 and 6.4 mmol/mol (0.41% and 0.58%) for doses of insulin degludec and glargine treatment groups respectively, given at fixed times. The incidence of nocturnal hypoglycaemia, a secondary endpoint, was significantly lower in patients given insulin degludec than insulin glargine in both trials. In the BEGIN Basal-bolus Type 1 trial, incidences were 72% vs. 74% for insulin degludec vs. insulin glargine (p = 0.021), resulting in about 1.5 fewer episodes per patient per year of exposure.

Type 2 diabetes: Two published, open-label phase 3, non-inferiority trials (BEGIN Basal-bolus Type 2, and BEGIN-FLEX) evaluated insulin degludec in patients previously treated with insulin. A third phase 3 trial (BEGIN Once Long) was not included because it evaluated insulin naive patients, which the NICE evidence summary for this product considered to be an unlikely target patient group. The included trials compared insulin degludec with insulin glargine, both administered as a once-daily subcutaneous (s/c) injection (doses adjusted to achieve plasma glucose target 3.9 to 5 mmol/L) in adults with type 2 diabetes.

BEGIN Basal-bolus Type 2 was a 52-week trial that enrolled 1,006 patients with inadequate HbA1c control despite treatment with insulin (with or without oral antidiabetic drugs [OADs]) for at least three months. Metformin or pioglitazone were permitted concomitant treatments during the trial. The 26-week, open-label BEGIN-FLEX trial compared the same treatments but varied the insulin degludec injection time (8 to 40 hour intervals between doses). This trial enrolled patients who were either insulin-naive and taking OADs (HbA1c 53 to 97 mmol/mol [7 to 11%]), or previously on basal insulin with or without OAD(s). The primary outcome in both trials was non-inferiority of insulin degludec to insulin glargine; measured as the mean change in HbA1c from baseline.

BEGIN Basal-bolus Type 2: After 52 weeks’ treatment, there was no significant difference in the mean decrease HbA1c between treatment groups (primary outcome). Insulin degludec was shown to be non-inferior to insulin glargine (-12.1 mmol/mol [-1.1%] for insulin degludec vs. -13 mmol/mol [-1.18%] for insulin glargine). BEGIN-FLEX: After 26 weeks’ treatment, HbA1c values had decreased by 14 mmol/mol, [1.28%], 11.8 mmol/mol [1.07%] and 13.9 mmol/mol [1.26%] in the insulin degludec (variable injection time), insulin degludec (fixed injection time) and insulin glargine (fixed injection time) groups, respectively. Insulin degludec given at variable dose intervals was shown to be non-inferior to insulin glargine given at fixed times.

Adverse events
In patients with type 1 diabetes, rates of hypoglycaemic episodes were not significantly different between treatment groups. There was a sudden death in the insulin glargine group that was judged to be related to trial products by the investigator, and two fatal myocardial infarctions in the insulin degludec group that were not judged to be related to trial products. In patients with type 2 diabetes, rates of severe hypoglycaemia were similar between the treatment groups. Compared with insulin glargine, insulin degludec significantly reduced confirmed episodes of hypoglycaemia (81% vs. 82% for insulin glargine; 2.5 fewer episodes per patient per year of exposure), and nocturnal hypoglycaemia (40% vs. 47%; 0.5 fewer episodes per patient per year of exposure) specifically.

Considerations for cost impact
- The estimated number of patients with diabetes mellitus in the West Midlands is 298,514.
- The current prices of insulin degludec are:
  - Polefill 100 Units/mL £72 (5 x 3 mL cartridges)
  - Flexitouch (pre-filled pen) 100 Units/mL £72 (5 x 3 mL cartridges)
  - Flexitouch (pre-filled pen) 200 Units/mL £86.40 (3 x 3 mL cartridges)

References
2. Tresebia FlexTouch 100U Pre-filled Pen. Available at: http://www.medicines.org.uk.