Insulin degludec is a new long-acting insulin for use in type 1 and 2 diabetes. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse events, and Dr Frank Joseph discusses its place in diabetes treatment compared with other long-acting insulins.

NICE recommends NPH insulin over insulin analogues as the long-acting insulin of choice for a basal insulin regimen. Its guidance on the use of long-acting insulin analogues by patients with type 2 diabetes recommends insulin glargine (Lantus) or insulin detemir (Levemir) as alternatives when using NPH insulin presents practical difficulties or is associated with hypoglycaemia, or if target HbA1c cannot be achieved.1

Its 2004 guideline on type 1 diabetes (now being updated) recommends a long-acting insulin analogue (only insulin glargine was available at the time) when NPH insulin is associated with hypoglycaemia or when rapid-acting analogues are used at meal times.2

Long-acting insulin analogues rely on changes at the site of injection for their duration of action. Insulin glargine forms a slowly-absorbed microprecipitate after subcutaneous injection, allowing once-daily injection. Insulin detemir molecules link together and bind with albumin at the injection site; its slow distribution allows a once- or twice-daily dose regimen.

Insulin degludec
Insulin degludec (Tresiba – Novo Nordisk) is an ultra long-acting basal insulin. After subcutaneous injection it forms a depot of soluble multihexamers from which insulin is slowly absorbed, providing a prolonged glucose-lowering effect that is less variable than that of insulin glargine.3 Its elimination half-life is approximately 25 hours (compared with 12 hours for insulin glargine and seven hours for insulin detemir) and the duration of action of a single dose exceeds 42 hours.3

It is licensed for the treatment of type 1 and type 2 diabetes in adults. Administered once daily by subcutaneous injection, insulin degludec can be used as monotherapy or in combination with bolus insulin or oral glucose-lowering agents in patients with type 2 diabetes. In patients with type 1 diabetes, it must be combined with a rapid-acting meal-time insulin.
Insulin degludec has been compared with insulin glargine as part of a basal-bolus regimen with insulin aspart as add-on therapy to metformin and a DPP-4 inhibitor, or other oral glucose-lowering drugs, in insulin-naive patients; and in patients previously treated with insulin as add-on therapy to metformin and/or pioglitazone. It has also been compared with sitagliptin (Januvia) as add-on therapy to metformin/sulfonylurea/pioglitazone in insulin-naive patients.

All were nonblinded treat-to-target noninferiority trials (except the comparison with sitagliptin, which was a superiority trial), ranging in size from 435 to 1030 patients and lasting 26 or 52 weeks, with a primary end-point of change in HbA$_{1c}$. The mean age of participants was 56–59 and mean HbA$_{1c}$ at baseline was 8.2–8.9 per cent. Insulin degludec was noninferior to insulin glargine in insulin-naive patients and in those previously treated with insulin, with reductions in HbA$_{1c}$ of 1.06–1.30 per cent (insulin degludec) vs 1.19–1.35 per cent (insulin glargine) respectively.

It reduced HbA$_{1c}$ significantly more than sitagliptin (-1.56 vs -1.22 per cent). There were no differences in the proportions of patients with HbA$_{1c}$ <7.0 per cent without confirmed hypoglycaemia.

**Type 2 diabetes**

**Glycaemic control**

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**Hypoglycaemia**

The rates of observed hypoglycaemic episodes (plasma glucose <3.1mmol per litre or severe event) were approximately 4000–4500 episodes per 100 patient-years of exposure (PYE), with no differences between insulin degludec and insulin glargine or insulin detemir. However, insulin degludec was associated with significantly fewer observed nocturnal episodes in both trials (441 vs 586 and 414 vs 594 PYE, respectively).

**Weight gain**

There was no difference in weight gain between insulin degludec and insulin glargine (mean 1.79 vs 1.59kg) but weight gain was significantly greater than with insulin detemir (1.50 vs 0.42kg).

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The rates of severe hypoglycaemia were similar for insulin degludec and insulin glargine.3

Weight gain
Mean weight gain was similar for the two insulin analogues (range 1.29–3.61kg for insulin degludec and 1.41–3.97kg for insulin glargine), with greater increases occurring in patients previously treated with insulin. Sitagliptin was associated with a mean weight loss of 0.35kg compared with a weight gain of 2.28kg with insulin degludec.

Other adverse effects
There were no clinically significant differences between insulin degludec and insulin glargine in the rates of other adverse effects, including injection-site reactions, cardiovascular effects and immunological events.

References

Declaration of interests
None to declare.

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Place in therapy
The overall burden of hypoglycaemia, the additional risk of nocturnal hypoglycaemia and the limitations on the flexibility of timing of long-acting insulin injections still remain significant challenges in the management of insulin-treated patients.

While insulin degludec provides similar efficacy in terms of glycaemic control when compared to the current long-acting insulins, there are reservations from the Scottish Medicines Consortium on its widespread use, due to the current lack of data on its cost-effectiveness, and from the US Food and Drug Administration on the grounds of insufficient cardiovascular end-point data from a prospective cardiovascular outcomes trial.3 NICE is not currently planning to publish any guidance on the use of the drug.

Insulin degludec, however, does provide distinct advantages that would allow its use in specific individuals. These include:

- Lower reported rates of overall hypoglycaemia and nocturnal hypoglycaemia in people with type 1 and type 2 diabetes
  This benefit lends itself to the use of insulin degludec in people who are unable to achieve target HbA1c on a basal-bolus regimen due to hypoglycaemia. In such people with type 1 diabetes, replacing the long-acting insulin with insulin degludec could be a treatment strategy prior to considering continuous subcutaneous insulin infusion (CSII) and would be an option in those that might decline CSII.

- Ultra-long duration of action
  This allows once-daily dosing at different times from day-to-day, when administration at the same time of day is not possible such as in shift workers.

Novo FlexTouch pens
Insulin degludec U100 and U200 are available in prefilled pen devices that have dose-counter windows in which the dose shown is the number of units of insulin degludec that will be injected regardless of strength; there has, however, been a Medicines and Healthcare products Regulatory Agency (MHRA) warning advising practitioners to use caution when using the U200 formulation.

The increasing number of people with type 2 diabetes on higher doses of insulin would benefit from the U200 strength. Those who require more than 80 units of basal insulin per injection will be able to inject up to 160 units in one injection rather than administering the dose as two consecutive injections as is required for other basal insulin products.

There may also be benefit from better absorption of the smaller volume of injected insulin using the U200, as seen in some patients treated...
with U500 insulin, but with the added safety conferred by the design of the prefilled pen.

It is worth noting that, in comparison with insulin degludec, insulin glargine causes similar weight gain and insulin detemir causes less.2

Also, hypoglycaemia and minor self-resolving injection-site reactions were still the commonest side-effects in the insulin-treated degludec arms of the various comparator trials.

References
2. Scottish Medicines Consortium. Insulin degludec (Tresiba) 100units/mL solution for injection in pre-filled pen or cartridge and 200units/mL solution for injection in pre-filled pen. SMC No. 856/13. April 2013.

Declaration of interests
Dr Joseph has received honoraria from Novo Nordisk, Eli Lilly, Sanofi Aventis, Boehringer Ingelheim and MSD, and his department has received research grants from Sanofi Aventis and Eli Lilly.

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