Long-acting insulin analogue is recommended for people with type 2 diabetes when they have difficulty with isophane insulin or they need fewer daily doses. In 2009, NICE recommended insulin glargine or insulin detemir, since when insulin degludec (Tresiba) has been introduced as a basal insulin.

Xultophy, a formulation combining insulin degludec and the GLP-1 agonist liraglutide has now been introduced. NICE guidance limits the use of liraglutide to triple therapy in overweight or obese people, or as part of dual therapy with metformin or a sulfonylurea when one of these, a glitazone and/or a DPP-4 inhibitor is unsuitable. The maximum recommended dose of liraglutide is 1.2mg/day, although the maximum licensed dose for diabetes is 1.8mg/day. Liraglutide is also licensed for use together with a basal insulin.

**Xultophy**

Xultophy is a combination of insulin degludec 100 units/ml and liraglutide 3.6mg/ml in a prefilled pen of 3ml. It is licensed for the treatment of adults with type 2 diabetes in combination with oral glucose-lowering drugs when these alone, or combined with basal insulin, do not provide adequate glycaemic control. The dose of a sulfonylurea may need to be reduced when Xultophy is initiated.

Xultophy is given once daily. Doses can be dialled in increments of 1 unit/0.036mg. When prescribed as add-on therapy to oral treatment, the recommended starting dose is 10 units/0.36mg. When transferring from another basal insulin, the initial dose is 16 units/0.6mg. The maximum dose is 50 units/1.8mg.

The prescribing cautions and contraindications for Xultophy are the same as for the component drugs. There is no experience of transferring patients from basal insulin at doses >40 units or from GLP-1 receptor agonists, or of combining Xultophy with a DPP-4 inhibitor, nateglinide (Starlix) or repaglinide. There is limited experience in patients with congestive heart failure.

**Clinical trials**

As add-on to single or dual therapy, Xultophy has been compared with insulin degludec and liraglutide separately, with placebo and with insulin degludec in patients transferred from another basal insulin. The first trial was not blinded. A total of 1663 patients (mean age 55, mean
BMI 31.3kg/m²) with HbA₁c 7–10 per cent (mean 8.3 per cent) despite treatment with metformin (plus pioglitazone in 17 per cent) were randomised to additional treatment with Xultophy, insulin degludec or liraglutide. The doses of Xultophy and insulin degludec were titrated to achieve a plasma glucose concentration of 4–5mmol/L before breakfast; the dose of liraglutide was 1.8mg/day.

After 26 weeks, Xultophy reduced mean HbA₁c by 1.9 per cent to 6.4 per cent; this was non-inferior to insulin degludec (1.4 per cent lower to 6.9 per cent) and significantly greater than liraglutide (1.3 per cent lower to 7 per cent; see Figure 1).

The proportions of patients in whom HbA₁c was <7 per cent were 81 per cent with Xultophy, 65 per cent with insulin degludec and 60 per cent with liraglutide. The incidence of confirmed hypoglycaemia was 32 per cent with Xultophy and 39 per cent with insulin degludec.

The insulin dose in patients using Xultophy plateaued at 38 units/day at 12 weeks but continued to increase in those using insulin degludec alone to 53 units/day. Mean change in weight was -0.5kg with Xultophy, +1.6kg with insulin degludec and -3.0kg with liraglutide.

A total of 1311 patients entered a 26-week extension phase of this trial. Differences between the treatment arms changed little except that the difference in insulin dose between Xultophy and insulin degludec increased to 23 units/day.

The placebo-controlled trial included 435 patients (mean age 60, mean BMI 31.5kg/m²) with HbA₁c 7–9 per cent (mean 7.9 per cent) despite treatment with a sulfonylurea; 89 per cent of patients were also taking metformin. They were randomised to receive either Xultophy (starting dose 10 units/0.36mg, titrated twice weekly to target a pre-breakfast plasma glucose concentration of 4–5mmol/L) or placebo.

After 26 weeks, HbA₁c decreased by 1.45 per cent to 6.4 per cent with Xultophy, significantly more than with placebo (0.46 per cent to 7.4 per cent).

The proportions of patients with HbA₁c <7 per cent were 79 and 29 per cent for Xultophy and placebo respectively. The mean final dose of Xultophy was 28 units/1.0mg/day.

The third trial included 398 patients (mean age 57, mean BMI 33.7kg/m²) with mean HbA₁c 8.8 per cent while using basal insulin 20–40 units/day plus metformin + a sulfonylurea (eight were also taking repaglinide/nateglinide). They were randomised to treatment with Xultophy or insulin degludec alone, with the dose titrated to achieve a plasma glucose concentration of 4–5mmol/L before breakfast.

After 26 weeks, HbA₁c was reduced by 1.9 per cent to 6.9 per cent with Xultophy, which was significantly more than with insulin degludec (0.9 per cent to 8.0 per cent). The proportions of patients with HbA₁c <7 per cent were 60 and 45 per cent for the Xultophy and insulin degludec groups respectively. The mean dose of insulin was 45 units/day (plus 1.6mg/day liraglutide) and the incidence of confirmed hypoglycaemia was 24 per cent in both groups. By contrast, mean weight change was -2.7kg with Xultophy and zero with insulin degludec.

Adverse effects
The adverse events reported in clinical trials were as expected from the component drugs, with a lower incidence of gastrointestinal effects compared with liraglutide (nausea 10 per cent vs 22 per cent with liraglutide). The incidence of injection site reactions was similar to that associated with insulin degludec (about 3 per cent).

References

Declaration of interests
Steve Chaplin has none to declare.

*Steve Chaplin is a pharmacist who specialises in writing on therapeutics*
Place in therapy

Vinod Patel

In the diabetes world there is excitement once again with the launch of Xultophy (Xultophy). This is a combination of liraglutide and longest-acting insulin analogue to date in the form of degludec. This is the only treatment to target both beta cell replacement providing direct insulin action and GLP-1 agonist action with a well known injectable incretin. The “ideal” of insulin action, reduced glucagon synthesis, reduced hepatic gluconeogenesis, increased satiety and reduced stomach emptying are all therefore promised by Xultophy.

The clinical trials results are worthy of note and will persuade many clinicians to try this agent in the “difficult” patient. This may be considered as a patient with significant personal and clinician problems with being very obese, problems with hypoglycaemia and difficulty in titrating insulin dosages sufficiently safely and effectively. Xultophy appears easy to use being provided in a formulation that has 100 units of insulin per mL and 3.6mg of liraglutide.

It is cost-effective? Xultophy provides the usually more expensive insulin degludec at the same unit price as glargine with the liraglutide being the usual current price. In patients who are currently being considered for a combination of glargine and liraglutide, Xultophy is cost neutral at a dose of 33 units per day. There will be the additional advantage of ease of use and a single injection. Titration of the dose is also more simple, aiming for a target pre-breakfast glucose level in most cases and avoiding hypoglycaemia.

The most impressive study is the one that used an average dose of 38 units and showed an HbA1c reduction of 1.9 per cent vs 1.4 per cent with degludec alone and 1.3 per cent reduction with liraglutide alone. Clinically very important was the fact that there were fewer hypoglycaemia events with Xultophy. Weight loss was impressive but similar to that expected with liraglutide alone.

I think Xultophy deserves being added to the “glycaemia-control” team alongside our old favourites. However, as with all new drug technologies it will be essential to conduct local audits to accumulate sufficient data to ensure that the purported clinical benefits are realised and found to be important for both patients and the local health economy to optimise cost-efficiencies.

Declaration of interests

Dr Patel has worked with most major pharmaceutical companies with regard to diabetes. This is in relation to lecture fees and occasional conference travel.

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