



Type 2 diabetes: insulin degludec/liraglutide (Xultophy)

Evidence summary

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www.nice.org.uk/guidance/esnm60

Key points from the evidence

The content of this evidence summary was up-to-date in July 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In people who are insulin-naïve, insulin degludec/liraglutide (Xultophy) was non-inferior to insulin degludec alone and superior to liraglutide alone for reductions in HbA1c (with a difference of 0.64% compared with liraglutide). In people previously treated with basal insulin, insulin degludec/liraglutide was superior to insulin degludec alone for reducing HbA1c with a difference of 1.1%. The safety profile and long-term safety concerns of insulin degludec/liraglutide are broadly in line with those of the 2 included components.

Regulatory status: Insulin degludec/liraglutide ([Xultophy](#)) was launched in the UK in November 2014. It is the first fixed-ratio combination basal insulin and glucagon-like

peptide-1 [GLP-1] receptor agonist preparation to be licensed in the UK. Insulin degludec (Tresiba: 100 units per ml and 200 units per ml) and liraglutide (Victoza) are available in the UK as the individual component preparations.

Effectiveness	Safety
<ul style="list-style-type: none">• Insulin degludec/liraglutide was non-inferior to insulin degludec alone (treatment difference –0.47% points) and superior to liraglutide alone (treatment difference –0.64% points) for change in HbA1c from baseline (1 RCT; n=1663; 26 weeks).• Insulin degludec/liraglutide was superior to insulin degludec alone (treatment difference –1.1% points) for change in HbA1c from baseline (1 RCT; n=413; 26 weeks).	<ul style="list-style-type: none">• The <u>European public assessment (EPAR) report</u> concluded that the safety profile is in general similar to that of the 2 included components. Long-term safety concerns are the same as for the other GLP-1 receptor agonists and long-acting insulin analogues.• The most commonly reported adverse reactions listed in the <u>summary of product characteristics (SPC)</u> are hypoglycaemia, decreased appetite, nausea, diarrhoea, vomiting constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension and injection site reactions.• Cases of confirmed hypoglycaemia were 32% with insulin degludec/liraglutide, 39% with insulin degludec and 7% with liraglutide (1 RCT; n=1663; 26 weeks).

Patient factors	Resource implications
<ul style="list-style-type: none"> Insulin degludec/liraglutide is given by once-daily subcutaneous injection which for some people may be preferable to giving basal insulin and GLP-1 receptor agonist injections separately. The dose is administered in 'dose-steps'. One dose-step contains 1 unit of insulin degludec and 0.036 mg of liraglutide. People will be unable to titrate the dose of basal insulin and GLP-1 receptor agonist separately because insulin degludec/liraglutide is a fixed-ratio combination product. Average weight loss was 2.22 kg to 2.5 kg with insulin degludec/liraglutide compared with insulin degludec alone. However there was 2.44 kg less weight loss from baseline with insulin degludec/liraglutide compared with liraglutide alone. 	<ul style="list-style-type: none"> Annual cost ranges from £387 for a daily dose of 10 dose-steps (10 units insulin degludec and 0.36 mg liraglutide) to £1987 for a daily dose of 50 dose-steps (50 units insulin degludec and 1.8 mg liraglutide). The cost of a GLP-1 receptor agonist and basal insulin given separately will depend on the preparations chosen and insulin dosage. With an insulin dose of 20 units daily, the annual cost for a combination of a GLP-1 receptor agonist and basal insulin would range from £802 to £1533. With an insulin dose of 50 units daily it would range from £947 to £2058.

Introduction and current guidance

The NICE guideline on [type 2 diabetes](#), which is being [updated](#) (publication date to be confirmed) states that managing people with type 2 diabetes is complex. It involves individualising a multifactorial approach, addressing blood pressure, blood lipids and lifestyle issues, as well as blood glucose. Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The current NICE guideline on [type 2 diabetes](#) recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to HbA1c levels

below 48 mmol/mol (6.5%) should be avoided.

[Full text of introduction and current guidance.](#)

Product overview

Insulin degludec/liraglutide ([Xultophy](#)) is a solution for subcutaneous injection containing both insulin degludec (a long-acting insulin analogue) and liraglutide (a GLP-1 receptor agonist). It is licensed for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering treatments when these alone or combined with basal insulin do not provide adequate glycaemic control. The SPC recommends that when it is being used as an add-on to oral glucose-lowering drugs the starting dose is 10 dose-steps once a day (10 units insulin degludec and 0.36 mg liraglutide). When transferring from basal insulin the recommended starting dose is 16 dose-steps once a day. The maximum dose is 50 dose-steps once a day (50 units insulin degludec and 1.8 mg liraglutide).

[Full text of product overview.](#)

Evidence review

- The study programme for insulin degludec/liraglutide includes 7 phase III randomised controlled trials (RCTs). This evidence summary is based on the 2 phase III studies that have been published in full: [DUAL I](#) and [DUAL II](#). All of the studies in the study program have change from baseline in HbA1c as primary outcomes. As with the other GLP-1 receptor agonists and long-acting insulin analogues, there are limited data from RCTs of insulin degludec/liraglutide relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events.
- [DUAL I](#) compared insulin degludec/liraglutide with insulin degludec alone and liraglutide alone in adults with type 2 diabetes who were insulin-naïve and taking metformin with or without pioglitazone. [DUAL II](#) compared insulin degludec/liraglutide with insulin degludec alone in adults with type 2 diabetes who had previously used basal insulin and were also taking metformin. In the DUAL II study, the insulin degludec alone group could be titrated to a maximum of 50 units.
- In DUAL I insulin degludec/liraglutide was non-inferior to insulin degludec alone and superior to liraglutide alone for change in HbA1c from baseline. After 26 weeks'

treatment HbA1c was reduced to 6.4% (46 mmol/mol) with insulin degludec/liraglutide, 6.9% (52 mmol/mol) with insulin degludec and 7% (53 mmol/mol) with liraglutide (from a baseline of 8.3% [67mmol/mol] in all 3 groups). Insulin degludec/liraglutide reduced HbA1c by an additional 0.47% points compared with insulin degludec (95% confidence interval [CI] -0.58 to -0.36; $p < 0.0001$) and an additional 0.64% compared with liraglutide (95% CI -0.75 to -0.53; $p < 0.0001$).

- In DUAL I there was more weight loss from baseline with insulin degludec/liraglutide compared with insulin degludec alone (-0.5 kg compared with +1.6 kg, treatment difference -2.22 kg; 95% CI -2.64 to -1.80; $p < 0.0001$). However there was less weight loss from baseline with insulin degludec/liraglutide compared with liraglutide alone (-0.5 kg compared with -3.0 kg, treatment difference 2.44 kg; 95% CI 2.02 to 2.86; $p < 0.0001$). At week 26, mean insulin dose was 38 units in the insulin degludec/liraglutide group and 53 units in the insulin degludec group. The mean liraglutide dose was 1.4 mg in the insulin degludec/liraglutide group and 1.8 mg in the liraglutide group.
- In the DUAL I study more participants achieved a HbA1c of less than 7.0% (53 mmol/mol) without weight gain or hypoglycaemia with insulin degludec/liraglutide compared with insulin degludec alone (36% compared with 14%; odds ratio [OR] 3.56; 95% CI 2.59 to 4.90; $p < 0.0001$). However, fewer people achieved this with insulin degludec/liraglutide compared with liraglutide alone (36% compared with 52%; OR 0.49; 95% CI 0.38 to 0.63; $p < 0.0001$).
- In DUAL II insulin degludec/liraglutide was superior to insulin degludec alone for change in HbA1c from baseline. After 26 weeks' treatment HbA1c was reduced to 6.9% (52 mmol/mol) from a baseline of 8.8% (73 mmol/mol) with insulin degludec/liraglutide and to 8.0% (64 mmol/mol) from a baseline of 8.9% (74 mmol/mol) with insulin degludec. Insulin degludec/liraglutide reduced HbA1c by an additional 1.1% (95% CI -1.3 to -0.8; $p < 0.0001$) compared with insulin degludec. At the end of the study the mean daily dose of insulin degludec was the same in both groups (45 units).
- In DUAL I cases of confirmed hypoglycaemia were statistically significantly higher with insulin degludec/liraglutide compared with liraglutide (32% compared with 7%; estimated rate ratio [RR] 7.61; 95% CI 5.17 to 11.21; $p < 0.0001$) but lower compared with insulin degludec (32% compared with 39%; estimated RR 0.68; 95% CI 0.53 to 0.87; $p = 0.0023$).
- In DUAL I the most frequently reported adverse events were headache, nasopharyngitis and gastrointestinal disorders. Headache and nasopharyngitis were similarly reported across the groups but gastrointestinal disorders occurred more

frequently with insulin degludec/liraglutide compared with insulin degludec but less frequently compared with liraglutide. For example, nausea occurred in 9%, 4% and 20% of participants, respectively, for insulin degludec/liraglutide, insulin degludec and liraglutide.

- The [European public assessment \(EPAR\) report for Xultophy](#) concluded that the safety profile for insulin degludec/liraglutide is in general similar to the 2 included components, with no indications of additive toxicity. It further states that the long-term safety concerns are the same as for the other GLP-1 receptor agonist and long-acting insulin analogues; in particular, there is an identified risk of pancreatitis and potential risk of malignancies for example, pancreatic and thyroid tumours.
- There are no data available on the use of insulin degludec/liraglutide in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides (such as nateglinide or repaglinide) or prandial insulin. There are also no published data on initiating insulin degludec/liraglutide in people who are already taking a GLP-1 receptor agonist. The use of insulin degludec/liraglutide in people taking basal insulin doses greater than 40 units has not been studied.
- There are now several new insulin products (high strength, fixed combination and biosimilar insulin products) which have recently been launched or are soon to be launched in the UK. In April 2015 the [MHRA](#) issued [advice](#) on how to minimise the risk of medication errors such as the wrong insulin dose being given.

[Full text of evidence review.](#)

Context

Insulin degludec/liraglutide is the first combination basal insulin and GLP-1 receptor agonist preparation to be licensed in the UK. It is available in packs of 5×3 ml prefilled pens at a cost of £159.22 per pack ([MIMS](#) June 2015). Annual costs range from approximately £387 for a daily dose of 10 dose-steps to £1937 for a daily dose of 50 dose-steps.

In addition to liraglutide, 3 other GLP-1 receptor agonists are licensed in the UK: exenatide, lixisenatide and dulaglutide. Liraglutide and lixisenatide are administered once daily, exenatide is administered twice daily or once a week depending on the preparation, and dulaglutide is administered once a week. In addition to insulin degludec, there are 2 other long-acting insulin analogues currently licensed in the UK: insulin detemir and insulin

glargine.

The cost of a GLP-1 receptor agonist and basal insulin given separately will depend on the preparations chosen and insulin dosage.

Full text of context.

Estimated impact for the NHS

Insulin degludec/liraglutide has been shown to be non-inferior to insulin degludec alone and superior to liraglutide alone for reducing HbA1c in the DUAL I study (with a difference of 0.64% compared with liraglutide).

Compared with insulin degludec alone, the combination preparation may have other potential advantages such as weight loss, reduced insulin dose and less hypoglycaemia, but these potential advantages were not seen for the combination product compared with liraglutide alone. The DUAL I population had an average HbA1c of 8.3% (67 mmol/mol) at baseline on oral therapy alone, were insulin-naïve, and had not been treated with GLP-1 receptor agonists. Although this approach to blood glucose control is within the licensed indication for insulin degludec/liraglutide, other less intensive treatment options are available as options for individuals.

The manufacturer suggests that a potential place in therapy for insulin degludec/liraglutide is for adults with type 2 diabetes who are uncontrolled on basal insulin. For this group of people for whom the use of basal insulin and a GLP-1 receptor agonist in combination is being considered, the alternative treatment option would be to add a separate GLP-1 receptor agonist. This treatment option would allow flexible titration of the insulin and GLP-1 receptor agonist doses, but could increase the complexity of the administration regimen.

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

The NICE guideline on [type 2 diabetes](#); which is being [updated](#) (publication date to be confirmed) states that managing type 2 diabetes is complex. It involves individualising a multifactorial approach, addressing blood pressure, blood lipids and lifestyle issues, as well as blood glucose. Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The current NICE guideline on [type 2 diabetes](#) recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided. For 2015/16 the [Quality and Outcomes Framework](#) (QOF) allocates points for achieving 3 levels of glucose control in people with type 2 diabetes: HbA1c of 75 mmol/mol (9%) or less, 64 mmol/mol (8%) or less and 59 mmol/mol (7.5%) or less; thresholds for payments vary between 92% and 35% of patients.

Insulin degludec/liraglutide ([Xultophy](#)) is a solution for subcutaneous injection containing both insulin degludec (a long-acting insulin analogue) and liraglutide (a glucagon-like peptide-1 [GLP-1] receptor agonist). Insulin degludec/liraglutide is the first combination basal insulin and GLP-1 receptor agonist preparation to be licensed in the UK. It was launched in the UK in November 2014. Liraglutide ([Victoza](#)) and insulin degludec ([Tresiba](#): [100 units per ml](#) and [200 units per ml](#)) were already available in the UK as the individual component preparations. Liraglutide ([Victoza](#)) was granted a licence extension for use in combination with basal insulin (with or without oral glucose lowering drugs) in April 2014.

In addition to liraglutide, there are 3 other GLP-1 receptor agonists currently licensed and available in the UK: exenatide ([Byetta](#) and [Bydureon](#)), lixisenatide ([Lyxumia](#)) and

dulaglutide ([Trulicity](#)). An evidence summary on [lixisenatide for type 2 diabetes](#) and [dulaglutide for type 2 diabetes](#) has been published. With the exception of [Bydureon](#), all of the currently available GLP-1 receptor agonist preparations are licensed for use in combination with insulin (see [summaries of product characteristics](#) for details). Dulaglutide ([Trulicity](#)) has only been studied in combination with prandial insulin.

The current NICE guideline on type 2 diabetes does not include any recommendation on the use of any GLP-1 receptor agonists in combination with insulin. The [scope](#) for the updated NICE guideline for the management of type 2 diabetes includes both GLP-1 receptor agonists and insulin as management options but not specifically the insulin degludec/liraglutide combination product.

The current NICE guideline on type 2 diabetes recommends that, when insulin therapy is necessary, human NPH (isophane) insulin is the preferred option. Long-acting insulin analogues can be considered in some people, in certain circumstances. In addition to insulin degludec, there are 2 other long-acting insulin analogues currently licensed and available in the UK: insulin detemir ([Levemir](#)) and insulin glargine ([Lantus](#)). An evidence summary on [insulin degludec for type 2 diabetes](#) has been published.

See the [type 2 diabetes](#) key therapeutic topic and the NICE pathway on [diabetes](#) for more information.

Product overview

Drug action

Insulin degludec/liraglutide ([Xultophy](#)) is a solution for subcutaneous injection containing both insulin degludec and liraglutide. Insulin degludec is a long-acting insulin analogue and liraglutide is a GLP-1 receptor agonist.

Licensed therapeutic indication

Insulin degludec/liraglutide ([Xultophy](#)) is licensed for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control. Liraglutide ([Victoza](#)) and insulin degludec (Tresiba: [100 units per ml](#) and [200 units per ml](#)) were already available in the UK as the individual component

preparations. Liraglutide (Victoza) was granted a licence extension for use in combination with basal insulin (with or without oral glucose lowering drugs) in April 2014.

Insulin degludec/liraglutide has been studied in combination with metformin (with or without pioglitazone) and in combination with a sulfonylurea (with or without metformin).

In May 2015, insulin degludec/liraglutide received a [positive opinion](#) for an extension to the existing indication as follows: Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

Course and cost

Insulin degludec/liraglutide is given once a day by subcutaneous injection via a multidose, pre-filled pen containing 100 units insulin degludec and 3.6 mg liraglutide per ml. The dose is administered in 'dose-steps'. One dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide.

The [summary of product characteristics](#) (SPC) recommends that when insulin degludec/liraglutide is being used as an add-on to oral glucose-lowering drugs, the starting dose is 10 dose-steps (10 units insulin degludec and 0.36 mg liraglutide) once a day.

When transferring from basal insulin, the recommended starting dose is 16 dose-steps (16 units insulin degludec and 0.6 mg liraglutide) once a day. The SPC states that the recommended starting dose should not be exceeded when transferring from basal insulin. Treatment with basal insulin should be stopped before starting insulin degludec/liraglutide and glucose levels should be monitored closely during initiation and in the following weeks.

The maximum daily dose is 50 dose-steps (50 units insulin degludec and 1.8 mg liraglutide). One pre-filled pen contains 300 units insulin degludec and 10.8 mg liraglutide (300 dose-steps). The pre-filled pen can provide from 1 to 50 dose-steps in 1 injection in increments of 1 dose-step. The dose counter on the pen shows the number of dose-steps.

Insulin degludec/liraglutide is available in packs of 5×3 ml prefilled pens at a cost of £159.22 per pack ([MIMS](#), June 2015). Annual costs range from approximately £387.43 for a daily dose of 10 dose-steps to £1937.17 for a daily dose of 50 dose-steps.

Evidence review

This evidence summary is based on the following 2 phase III studies that have been published in full:

- [DUAL I](#) compared insulin degludec/liraglutide with insulin degludec alone and liraglutide alone in adults with type 2 diabetes who were insulin-naïve and taking metformin with or without pioglitazone (Gough et al. 2014; see table 1)
- [DUAL II](#) compared insulin degludec/liraglutide with insulin degludec alone in adults with type 2 diabetes who had previously used basal insulin and were also taking metformin (Buse et al. 2014; see table 2).

The [European public assessment report for Xultophy](#) includes data from an extension phase of DUAL I and this is also discussed in the clinical effectiveness section of this evidence summary.

Three other phase III studies have been completed but have not been published in full:

- DUAL III ([NCT01676116](#)) compared insulin degludec/liraglutide with exenatide or liraglutide in adults with type 2 diabetes who were also taking oral glucose-lowering drugs (metformin, pioglitazone or sulfonylureas). Participants had been previously treated with GLP-1 receptor agonists.
- DUAL IV ([NCT01618162](#)) compared insulin degludec/liraglutide with placebo in adults with type 2 diabetes who were also taking sulfonylureas with or without metformin.
- DUAL V ([NCT01952145](#)) compared insulin degludec/liraglutide with insulin glargine in adults with type 2 diabetes who were also taking metformin. Participants had been previously treated with insulin glargine.

A further 2 phase III studies are not yet completed:

- DUAL V extension study ([NCT02100475](#)) compared insulin degludec/liraglutide plus insulin aspart with further dose increases of insulin degludec/liraglutide in adults with type 2 diabetes mellitus, previously treated with insulin degludec/liraglutide and metformin and in need of further intensification.
- DUAL VI ([NCT02298192](#)) compared insulin degludec/liraglutide once weekly titration with insulin degludec/liraglutide twice weekly titration in adults with type 2 diabetes

who were also taking metformin with or without pioglitazone.

All of the studies in the study program have change from baseline in HbA1c as primary outcomes.

DUAL I (Gough et al. 2014)

- Design: open-label, 26-week, randomised controlled trial (RCT). The global study was conducted across 271 sites in 19 countries (around 5% of participants were recruited from the UK). Allocation was concealed.
- Population: 1663 adults (mean age 55 years; 50% female; 62% white) with type 2 diabetes (BMI of 40 kg/m² or less and HbA1c between 53–86 mmol/mol [7.0–10.0%]) who had been taking metformin with or without pioglitazone for at least 3 months. Participants were insulin-naïve and had not been treated with GLP-1 receptor agonists, gliptins or sulphonylureas within the previous 90 days. All oral glucose lowering drugs were stopped at randomisation apart from metformin or pioglitazone. About 83% were taking metformin prior to randomisation and around 17% were taking metformin plus pioglitazone. At baseline the median daily dose of metformin was 2000 mg and the median daily dose of pioglitazone was 30 mg. Mean HbA1c was around 67 mmol/mol (8.3%) and mean BMI was around 31 kg/m².
- Intervention and comparison: participants were randomised 2:1:1 to once-daily injections of insulin degludec/liraglutide, insulin degludec or liraglutide. Insulin degludec/liraglutide was started at a daily dose of 10 dose-steps (10 units insulin degludec plus 0.36 mg liraglutide). Insulin degludec was started at a daily dose of 10 units. Doses of insulin degludec/liraglutide and insulin degludec were titrated on an individual basis twice a week to achieve a pre-breakfast plasma glucose of 4–5 mmol/litre. The dose of insulin degludec/liraglutide could be titrated to a maximum of 50 dose steps once a day (50 units insulin degludec and 1.8 mg liraglutide). No maximum dose was specified for insulin degludec alone. Liraglutide was started at a dose of 0.6 mg per day and was increased by 0.6 mg per week to a maximum of 1.8 mg per day.
- Outcomes: The primary outcome was change in HbA1c from baseline after 26 weeks treatment. The study was designed to show the non-inferiority (with an upper 95% confidence interval margin of 0.3%) of insulin degludec/liraglutide to insulin degludec alone and the superiority of insulin degludec/liraglutide to liraglutide alone for the primary outcome. The primary outcome was conducted for the intention-to-treat population (defined as the full analysis set: which was all randomised participants

using a last observation carried forward method for missing data). Secondary and additional outcomes included achievement of HbA1c levels of less than 7.0% (53 mmol/mol) or 6.5% (48 mmol/mol) or less with or without hypoglycaemia or weight gain and change in bodyweight from baseline. Safety outcomes included hypoglycaemic episodes, standard laboratory analyses and vital signs. Adverse events of special interest included gastrointestinal symptoms, pancreatitis, neoplasms, thyroid disease, severe hypoglycaemia, allergic reactions and major cardiovascular adverse events.

Table 1 Summary of DUAL I (Gough et al. 2014)

	Insulin degludec/liraglutide (titrated to a maximum of 50 dose-steps daily)	Insulin degludec (no maximum dose)	Liraglutide (titrated to a maximum of 1.8 mg daily)	Analysis
Randomised	n=834	n=414	n=415	
Efficacy Full analysis set ^a (ITT group)	n=833	n=413	n=414	

Primary outcome: change in HbA1c from baseline after 26 weeks treatment	-1.9% (SD 1.1) to 6.4% [46 mmol/mol] HbA1c was 8.3% [67mmol/mol] at baseline	-1.4% (SD 1.0) to 6.9% [52 mmol/mol] HbA1c was 8.3% [67mmol/mol] in at baseline	-1.3% (SD 1.1) to 7.0% [53 mmol/mol] HbA1c was 8.3% [67mmol/mol] at baseline	<p>Insulin degludec/ liraglutide compared with insulin degludec: estimated treatment difference in the ITT group -0.47% (95% CI -0.58 to -0.36; p<0.0001) confirms non-inferiority^b</p> <p>Estimated treatment difference in the per-protocol^c analysis -0.46% (95% CI -0.56 to -0.35) p value not reported.</p> <p>Insulin degludec/ liraglutide compared with liraglutide: estimated treatment difference in the ITT group -0.64% (95% CI -0.75 to -0.53; p<0.0001) confirms superiority</p>
Selected secondary and additional outcomes:				
Participants with HbA1c of less than 7.0% (53 mmol/mol) at week 26	81% (671/833)	65% (269/413)	60% (250/414)	<p>Insulin degludec/ liraglutide compared with insulin degludec: OR 2.38 (95% CI 1.78 to 3.18; p<0.0001)</p> <p>Insulin degludec/ liraglutide compared with liraglutide: OR 3.26 (95% CI 2.45 to 4.33; p<0.0001)</p>
Participants with HbA1c of less than 7.0% (53 mmol/mol) at week 26 without weight gain or hypoglycaemia	36% (296/833)	14% (58/413)	52% (215/414)	<p>Insulin degludec/ liraglutide compared with insulin degludec: OR 3.56 (95% CI 2.59 to 4.90; p<0.0001)</p> <p>Insulin degludec/ liraglutide compared with liraglutide: OR 0.49 (95% CI 0.38 to 0.63; p<0.0001)</p>

Mean change in body weight from baseline to week 26 (baseline weight around 87 kg in all 3 groups)	-0.5 kg (SD 3.5)	+1.6 kg (SD 4.0)	-3.0 kg (SD 3.5)	Insulin degludec/ liraglutide compared with insulin degludec: estimated treatment difference -2.22 kg (95% CI -2.64 to -1.80; p<0.0001) Insulin degludec/liraglutide compared with liraglutide: estimated treatment difference +2.44 kg (95% CI +2.02 to +2.86; p<0.0001)
Safety^d	n=825	n=412	n=412	
Serious adverse events	2% (19/825)	2% (8/412)	3% (14/412)	No statistical analysis presented
Adverse events leading to withdrawal	1% (10/825)	2% (8/412)	6% (24/412)	No statistical analysis presented
Confirmed hypoglycaemia ^e	32% (263/825)	39% (159/412)	7% (28/412)	Insulin degludec /liraglutide fewer episodes compared with insulin degludec (estimated rate ratio 0.68; 95% CI 0.53 to 0.87; p=0.0023) Insulin degludec/liraglutide more episodes compared with liraglutide (estimated rate ratio 7.61; 95% CI 5.17 to 11.21; p<0.0001)
Severe hypoglycaemic episodes ^e	0.36% (3/825)	0.49%(2/412)	0	No statistical analysis presented.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; OR, odds ratio.

^a Full analysis set: defined as all randomised participants using a last observation carried forward method for missing data. The primary analysis used the analysis of covariance (ANCOVA) method.

^b Pre-specified non-inferiority margin set at an upper 95% CI of +0.3%.

^c Per protocol population: defined as all participants without any major protocol violations that may have affected the primary endpoint. Per-protocol population is presented to establish non-inferiority; this should be shown in both the ITT and per protocol population.

^d Safety analysis set: all participants who received at least 1 dose of the study drug.

^e Confirmed hypoglycaemia defined as episodes in which plasma glucose concentration was less than 3.1 mmol/l irrespective of symptoms. The occurrence of episodes requiring assistance was classed as a severe hypoglycaemic episode.

DUAL II (Buse et al. 2014)

- Design: double-blind, 26-week RCT. The study was conducted across 75 sites in 7 countries across Europe (which did not include the UK), India and the US. Allocation was concealed.
- Population: 413 adults (mean age 57 years; 45% female; 77% white) with type 2 diabetes (BMI 27 kg/m² or more) and HbA1c 58–86 mmol/mol (7.5–10.0%) who had been treated with basal insulin (at a stable dose of 20 to 40 units per day) plus metformin (at a dose of at least 1500 mg daily) with or without sulfonylureas or glinides for at least 90 days. All glucose lowering drugs and insulin were stopped at randomisation apart from metformin. About 48% were taking basal insulin plus metformin before randomisation and around 52% were taking basal insulin, metformin plus a sulfonylurea or glinide. Mean HbA1c was around 74 mmol/mol (8.9%) and mean BMI was around 33.7 kg/m².
- Intervention and comparison: participants were randomised 1:1 to once-daily injections of insulin degludec/liraglutide or insulin degludec. Insulin degludec/liraglutide was started at a daily dose of 16 dose-steps (16 units insulin degludec plus 0.6 mg liraglutide) and insulin degludec was started at a daily dose of 16 units. Doses of insulin degludec/liraglutide and insulin degludec were titrated on an individual basis twice a week to achieve a pre-breakfast plasma glucose of 4–5 mmol/litre. The dose of insulin degludec/liraglutide could be titrated to a maximum of 50 dose steps once a day (50 units insulin degludec and 1.8 mg liraglutide); insulin degludec could be

titrated to a maximum of 50 units a day.

- **Outcomes:** The primary outcome was change in HbA1c from baseline after 26 weeks treatment. The study was designed to show the superiority of insulin degludec/liraglutide to insulin degludec alone for the primary outcome. Secondary outcomes included achievement of HbA1c levels of less than 7.0% (53 mmol/mol) or 6.5% (48 mmol/mol) or less with or without hypoglycaemia or weight gain and change in bodyweight from baseline.

Table 2 Summary of DUAL II (Buse et al. 2014)

	Insulin degludec/liraglutide (titrated to a maximum of 50 dose-steps daily)	Insulin degludec (titrated to a maximum of 50 units daily)	Analysis
Randomised	n=207	n=206	
Efficacy Full analysis set ^a (ITT group)	n=199	n=199	
Primary outcome: change in HbA1c from baseline after 26 weeks treatment	-1.9% to 6.9% [52 mmol/mol] HbA1c was 8.8% [73 mmol/mol] at baseline	-0.9% to 8.0% [64 mmol/mol] HbA1c was 8.9% [74 mmol/mol] at baseline	Estimated treatment difference in the ITT group -1.1% (95% CI -1.3 to -0.8; p<0.0001) confirms superiority
Selected secondary and additional outcomes			
Participants with HbA1c of less than 7.0% (53 mmol/mol) at week 26	60.3%	23.1%	OR 5.44 (95% CI 3.42 to 8.66; p<0.0001)

Participants with HbA1c of less than 7.0% (53 mmol/mol) at week 26 without weight gain or hypoglycaemia	40.2%	8.5%	OR 7.44 (95% C 4.08 to 13.57; p<0.0001)
Mean change in body weight from baseline to week 26	-2.7 kg (baseline weight around 95 kg)	No weight change (baseline weight around 94 kg)	Estimated treatment difference: -2.5 kg (95% CI -3.2 to -1.8; p<0.0001)
Safety^b	n=199	n=199	
Serious adverse events	3.5%	5.5%	No statistical analysis presented
Adverse events leading to withdrawal	1% (1/199)	2% (3/199)	No statistical analysis presented
Confirmed hypoglycaemia ^c	24.1%	24.6%	No statistically significant difference between the 2 groups: estimated treatment ratio 0.66 (95% CI 0.39 to 1.13)
Severe hypoglycaemic episodes ^c	0.5% (1/199)	0	No statistical analysis presented

Abbreviations: CI, confidence interval; ITT, intention to treat; OR, odds ratio.

^a Full analysis set: defined as all randomised participants. Fifteen (8 in the insulin degludec/liraglutide group and 7 in the insulin degludec group) were excluded from analysis before unmasking of trial results owing to a breach in good clinical practice at a trial site). The primary analysis used the analysis of covariance (ANCOVA) method.

^b Safety analysis set: defined as all randomised participants (with 15 excluded as explained above).

^c Confirmed hypoglycaemia defined as the occurrence of episodes in which plasma glucose concentration was less than 3.1 mmol/l irrespective of symptoms. The occurrence of episodes requiring assistance was classed as a severe hypoglycaemic episode.

Clinical effectiveness

DUAL I and II both had HbA1c primary outcomes. The clinical significance of these needs to be judged in the context of the wider evidence base for the management of type 2 diabetes. As with the other GLP-1 receptor agonists and long-acting insulin analogues, there are limited data from RCTs of insulin degludec/liraglutide relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events. The current NICE guideline on [type 2 diabetes](#) recommends that people should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%), and that pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided. Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia.

DUAL I compared insulin degludec/liraglutide with insulin degludec alone and liraglutide alone in people also taking metformin or pioglitazone. DUAL II compared insulin degludec/liraglutide with insulin degludec alone (titrated to a maximum daily dose) in people also taking metformin. In DUAL I participants were insulin-naïve, in DUAL II participants had been previously treated with basal insulin. Mean baseline HbA1c was 8.3% (67 mmol/mol) in DUAL I and 8.9% (73.5 mmol/mol) in DUAL II. Within both studies, treatment groups were well balanced with regards to baseline characteristics.

In DUAL I insulin degludec/liraglutide was non-inferior to insulin degludec alone and superior to liraglutide alone for change in HbA1c from baseline at 26 weeks. Insulin degludec/liraglutide reduced HbA1c by an additional 0.47% compared with insulin degludec (with no maximum dose) and an additional 0.64% compared with liraglutide. Compared with both insulin degludec alone and liraglutide alone, statistically significantly more participants achieved a HbA1c of less than 7.0% (53 mmol/mol) at week 26 with insulin degludec/liraglutide (see table 1 for details). Statistically significantly more participants achieved a HbA1c of less than 7.0% (53 mmol/mol) without weight gain or hypoglycaemia with insulin degludec/liraglutide compared with insulin degludec alone (36% compared with 14%). However, statistically significantly fewer participants achieved a HbA1c of less than 7.0% (53 mmol/mol) without weight gain or hypoglycaemia with insulin degludec/liraglutide compared with liraglutide alone (36% compared with 52%). In the insulin degludec/liraglutide group the difference in the mean change in body weight from baseline was -2.22 kg compared with the insulin degludec group. However there was less weight loss in the insulin degludec/liraglutide group compared with the liraglutide group (estimated treatment difference 2.44 kg). At week 26, the mean insulin dose was statistically significantly lower in the insulin degludec/liraglutide group compared with the

insulin degludec group (38 units compared with 53 units; $p < 0.0001$). The mean liraglutide dose was 1.4 mg in the insulin degludec/liraglutide group and 1.8 mg in the liraglutide group.

The [European public assessment report \(EPAR\) for Xultophy](#) includes data from a 26-week extension phase of DUAL I. After 52 weeks treatment, insulin degludec/liraglutide reduced HbA1c by 0.46% (95% CI -0.57 to -0.34; $p < 0.0001$) compared with insulin degludec and 0.65% (95% CI -0.76 to -0.53; $p < 0.0001$) compared with liraglutide.

In DUAL II the dose of insulin degludec was titrated to a maximum of 50 units in both the insulin degludec/liraglutide group and the insulin degludec alone group in a population of people who had been previously treated with basal insulin. At the end of the study (26 weeks), the mean daily dose of insulin degludec was the same in both groups (45 units). This study was therefore assessing the benefit of the addition of liraglutide. Insulin degludec/liraglutide was superior to insulin degludec alone for change in HbA1c, reducing HbA1c by an additional 1.1% compared with insulin degludec.

The EPAR states that although the additive effect on HbA1c of the 2 components in insulin degludec/liraglutide has been adequately shown, the benefit in terms of reduction in HbA1c may only be of moderate clinical relevance compared with insulin degludec or liraglutide alone. It states that there are other potential benefits of the combination product in terms of insulin dose requirements, weight control and hypoglycaemic risk. However, the EPAR does highlight that compared with liraglutide alone the benefits of insulin degludec/liraglutide are less obvious as there was more weight loss with liraglutide and there were more hypoglycaemic events with insulin degludec/liraglutide.

Safety and tolerability

The [EPAR](#) for Xultophy concluded that the safety profile for insulin degludec/liraglutide is in general similar to that of the 2 included components, with no indications of additive toxicity, and that that no new safety issues had been identified for the combination. It further states that the long-term safety concerns are the same as for the other GLP-1 receptor agonists and long-acting insulin analogues; in particular, the identified risk of pancreatitis and potential risk of malignancies for example, pancreatic and thyroid tumours.

In [DUAL I](#) treatment emergent adverse events occurred in 63% of participants in the insulin degludec/liraglutide group, 60% of the insulin degludec group and 73% of the liraglutide

group (no statistical analysis presented). Most of these events were reported to be mild or moderate in severity. The most frequently reported adverse events were headache (11%, 9% and 12% respectively for insulin degludec/liraglutide, insulin degludec and liraglutide) nasopharyngitis (9% in all 3 groups) and gastrointestinal disorders. Gastrointestinal disorders occurred more frequently with insulin degludec/liraglutide compared with insulin degludec but were less frequent compared with liraglutide. Nausea occurred in 9%, 4% and 20% of participants respectively for insulin degludec/liraglutide, insulin degludec and liraglutide. Vomiting occurred in 4%, 1% and 8% of participants respectively for insulin degludec/liraglutide, insulin degludec and liraglutide. Diarrhoea occurred in 8%, 5% and 13% of participants respectively for insulin degludec/liraglutide, insulin degludec and liraglutide. No statistical analysis was presented.

In DUAL II the most frequently reported adverse events again included nausea, diarrhoea, headache and nasopharyngitis. Nausea, diarrhoea and headache occurred more frequently with insulin degludec/liraglutide compared with insulin degludec (6.5%, 6.5% and 6.0% compared with 3.5%, 3.5% and 2.0%). No statistical analysis was presented.

In DUAL I cases of confirmed hypoglycaemia were statistically significantly higher with insulin degludec/liraglutide compared with liraglutide (32% compared with 7%; estimated rate ratio [RR] 7.61; 95% confidence interval [CI] 5.17 to 11.21; $p < 0.0001$) but lower in comparison with insulin degludec (32% compared with 39%; estimated RR 0.68; 95% CI 0.53 to 0.87; $p = 0.0023$). There were 5 severe hypoglycaemic episodes reported (3 in the insulin degludec/liraglutide group and 2 in the insulin degludec group). There was no statistically significant difference between insulin degludec/liraglutide and insulin degludec for cases of confirmed hypoglycaemia in DUAL II (24% compared with 25%; estimated RR 0.66; 95% CI 0.39 to 1.13); one case of severe hypoglycaemia was reported in the insulin degludec/liraglutide group.

In DUAL I serious adverse events were similar between all 3 groups (2% in both the insulin degludec/liraglutide and insulin degludec groups and 3% in the liraglutide group). In DUAL II serious adverse events occurred in 3.5% of participants in the insulin degludec/liraglutide group and 5.5% of participants in the insulin degludec group. Pancreatitis has been identified previously as a safety issue with GLP-1 receptor agonists and all these products have warnings in their summaries of product characteristics about a risk of developing acute pancreatitis. In DUAL I there was 1 confirmed case of acute pancreatitis in a participant receiving liraglutide. In DUAL II no adverse events relating to pancreatitis were confirmed. In both DUAL I and DUAL II there were no medullary thyroid carcinomas or thyroid neoplasms reported. In DUAL II 1 case of metastatic pancreatic carcinoma was

reported in the insulin degludec group. However, the studies were too short and underpowered to accurately assess the incidence of potential adverse events such as malignancies.

In DUAL I there were 18 cardiovascular adverse events reported in 14 participants. Three of these adverse events were assessed as major cardiovascular events: a cardiovascular death in the insulin degludec/liraglutide group and 2 cases of myocardial infarction (1 in the insulin degludec group and 1 in the liraglutide group). In DUAL II there were 3 major cardiovascular events: 2 cases of myocardial infarction (1 in each group) and 1 case of stroke in the insulin degludec group. However, the studies were too short and underpowered to accurately assess the incidence of cardiovascular events.

As well as insulin degludec/liraglutide there are now several other new insulin products (high strength and biosimilar insulin) which have recently been launched or are soon to be launched in the UK. In April 2015 the Medicines and Healthcare Products Regulatory Agency (MHRA) issued [advice](#) on how to minimise the risk of medication errors such as the wrong insulin dose being given. The advice recommends that healthcare professionals should consult the product literature and any relevant education material before starting treatment and that appropriate training on the correct use of the prescribed insulin product should be given to the patient. It also recommends that patients should be given an [insulin passport or safety card](#). At the time of production of this evidence summary (June 2015) the European Medicines Agency were consulting on guidance to minimise the risk of medication error with these new insulin products.

The insulin degludec/liraglutide summary of product characteristics (SPC, [Xultophy](#)) discusses a number of warnings and precautions for use, such as risk of hypoglycaemia, hyperglycaemia, dehydration, acute pancreatitis and thyroid adverse events, which reflect the safety concerns associated with the individual components.

The SPC highlights that there is limited experience in people with congestive heart failure New York Heart Association (NYHA) class I–II and therefore insulin degludec/liraglutide should be used with caution in this group of people. It also states that there is no experience in people with congestive heart failure NYHA class III–IV therefore insulin degludec/liraglutide is not recommended for these patients. The SPC also states that insulin degludec/liraglutide cannot be recommended for people with hepatic impairment as experience of use for this group of people is limited. It is also not recommended for people with moderate or severe renal impairment, or for people with inflammatory bowel disease and diabetic gastroparesis. Experience of use in people over the age of 75 years is also

limited.

The SPC reports that hypoglycaemia is a very common adverse reaction (1 in 10 people or more). Common adverse reactions (between 1 in 10 and 1 in 100 people) are: decreased appetite, nausea, diarrhoea, vomiting constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension and injection site reactions.

Evidence strengths and limitations

As with the other GLP-1 receptor agonists and long-acting insulin analogues, there are limited data from RCTs of insulin degludec/liraglutide relating to patient-oriented outcomes, such as rates of macrovascular or microvascular events. The evidence of efficacy relates solely to surrogate end points, chiefly reductions in HbA1c. The clinical significance of these needs to be judged in the context of the wider evidence base for the management of type 2 diabetes.

None of the studies in the study program for insulin degludec/liraglutide compare the combination preparation with GLP-1 receptor agonists and basal insulins given together but as separate injections. DUAL I compared insulin degludec/liraglutide with insulin degludec alone and liraglutide alone. The liraglutide alone group could be titrated to a maximum of 1.8 mg daily. However, NICE technology appraisal guidance on [liraglutide for the treatment of type 2 diabetes](#) does not recommend liraglutide at a 1.8 mg daily dose. In DUAL II insulin degludec/liraglutide was compared with insulin degludec titrated to a maximum daily dose of 50 units.

Participants in DUAL I were insulin naïve and participants in DUAL II were excluded if they were using a dose of basal insulin greater than 40 units. The SPC ([Xultophy](#)) states that the use of insulin degludec/liraglutide in people taking basal insulin doses greater than 40 units has not been studied. The SPC also states that there is no data available on the use of insulin degludec/liraglutide in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides (such as nateglinide or repaglinide) or prandial insulin, and transfer from GLP-1 receptor agonists has not been studied. A study of insulin degludec/liraglutide in people who were already taking a GLP-1 receptor agonist has been conducted (DUAL III: [NCT01676116](#)). DUAL III has not yet been published but in May 2015, insulin degludec/liraglutide received a [positive opinion](#) for an extension to the existing indication as follows: Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when

these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

The majority of participants in DUAL I and II were recruited from outside the UK. Around 5% of participants were recruited from the UK for DUAL I and no participants were recruited from the UK for DUAL II.

DUAL I was an open-label study; treatment was blinded for the safety committee, however participants and investigators were not blinded to treatment which may have introduced bias. DUAL I and II used the last observation carried forward (LOCF) approach to take account of missing data. In both DUAL I and DUAL II, the use of the analysis of covariance (ANCOVA) method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycaemic drugs and baseline HbA1c.

Context

Alternative treatments

Insulin degludec/liraglutide is the first combination basal insulin and GLP-1 receptor agonist preparation licensed in the UK.

Basal insulin supply for people with type 2 diabetes can be provided by:

- NPH (isophane) insulin (for example, [Insulatard](#), [Humulin I](#) or [Insuman Basal](#)) **or**
- the long-acting insulin analogues: insulin glargine ([Lantus](#)), insulin detemir ([Levemir](#)) or insulin degludec ([Tresiba](#)).

Currently licensed glucagon-like peptide-1 (GLP-1) receptor agonists are:

- exenatide
 - [Byetta 5 microgram and 10 microgram](#) solutions for injection in prefilled pens (twice-daily use).
 - [Bydureon 2 mg](#) powder and solvent for prolonged-release suspension for injection (once-weekly use).

- liraglutide
 - Victoza 6 mg/ml solution for injection in prefilled pen (once-daily use).
- lixisenatide
 - Lyxumia 10 microgram and 20 microgram solutions for injection in prefilled pens (once daily use)
- dulaglutide
 - Trulicity 0.75 mg and 1.5 mg solution for injection (once-weekly use).

With the exception of Bydureon, all of the currently available GLP-1 receptor agonist preparations are licensed for use in combination with insulin. Dulaglutide (Trulicity) has only been studied in combination with prandial insulin.

Costs of alternative treatments

GLP-1 receptor agonists	
Drug and usual dosage ^a	Approximate annual cost excluding VAT
Dulaglutide 0.75 mg once weekly	£1182.35 ^c
Dulaglutide 1.5 mg once weekly	£1182.35 ^c
Exenatide 5 micrograms twice daily	£830.25 ^b
Exenatide 10 micrograms twice daily	£830.25 ^b
Exenatide 2 mg once weekly	£953.68 ^c
Liraglutide 1.2 mg once daily	£954.84 ^c
Lixisenatide 20 micrograms once daily	£705.75 ^c

^a The doses shown are taken from the relevant summary of product characteristics, but do not represent the full range that can be used nor do they imply therapeutic equivalence. Liraglutide is also licensed at a dose of 1.8 mg once daily but this is not recommended in [NICE technology appraisal guidance 203](#).

^b Costs taken from [Drug Tariff](#) May 2015.

^c Costs taken from [MIMS](#) May 2015.

Prices given above do not include cost of needles (with the exception of dulaglutide which is a single use complete unit and exenatide 2 mg once weekly which includes needles).

Basal insulin

	Cost of 5×3 ml cartridge (100 units/ml solution)	Cost of 5×3 ml pre-filled pen (100 units/ml solution)
Insulatard	£22.90	£20.40
Humulin I	£19.08	£21.70
Insuman Basal	£17.50	£19.80
Insulin glargine (Lantus)	£41.50	£41.50
Insulin detemir (Levemir)	£42.00	£42.00
Insulin degludec (Tresiba)	£72.00	£72.00 (£86.40 for 3×3ml 200 units/ml solution)

Costs are excluding VAT; taken from [MIMS](#) May 2015.

Prices given above do not include cost of needles.

Insulin degludec/liraglutide is available in packs of 5×3 ml prefilled pens at a cost of £159.22 per pack ([MIMS](#) June 2015). One pre-filled pen contains 300 units insulin degludec and 10.8 mg liraglutide (300 dose-steps). Annual costs range from £387.43 for a daily dose of 10 dose-steps (10 units insulin degludec and 0.36 mg liraglutide) to £1937.17 for a daily dose of 50 dose-steps (50 units insulin degludec and 1.8 mg liraglutide).

Annual costs of GLP-1 receptor agonists range from £705.75 to £1182.35 (the annual cost

for liraglutide 1.8 mg daily would be approximately £1432.26 [MIMS, May 2015] however this dose is not recommended in the NICE technology appraisal guidance on [liraglutide for the treatment of type 2 diabetes](#)). Annual costs of basal insulin (human NPH insulin or long-acting insulin analogues) will depend on the preparation chosen and dose. The cost of a combination of a GLP-1 receptor agonist and basal insulin given separately will depend on the preparations used and insulin dosage. With an insulin dose of 20 units daily, the annual cost for a combination of a GLP-1 receptor agonist and basal insulin would range from £802 to £1533. With an insulin dose of 50 units daily it would range from £947 to £2058.

Estimated impact for the NHS

Likely place in therapy

The current NICE guideline on type 2 diabetes does not include any recommendation on the use of any GLP-1 receptor agonist in combination with insulin. The [scope](#) for the updated NICE guideline for the management of type 2 diabetes includes both GLP-1 receptor agonists and insulin as management options but not specifically the insulin degludec/liraglutide combination product.

Insulin degludec/liraglutide ([Xultophy](#)) is licensed for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control.

[DUAL I](#) showed that insulin degludec/liraglutide was non-inferior to insulin degludec alone and superior to liraglutide alone for reducing HbA1c (with a difference of 0.64% compared with liraglutide).

The [EPAR](#) states that the benefit in terms of reduction in HbA1c with insulin degludec/liraglutide may only be of moderate clinical relevance compared with insulin degludec or liraglutide alone. It adds that there are other potential benefits of the combination product in terms of insulin dose requirements, weight control and hypoglycaemic risk. However, in [DUAL I](#), more participants in the liraglutide group achieved a HbA1c of less than 7% (53 mmol/mol) without weight gain or hypoglycaemia. The [DUAL I](#) population had an average HbA1c of 8.3% (67 mmol/mol) at baseline on oral therapy alone, they were insulin-naïve and had not been treated with GLP-1 receptor agonists. Although this patient

population is within the licensed indication for insulin degludec/liraglutide, other less intensive treatment options are available.

The summary of product characteristics (SPC) states that there are no data available on the use of insulin degludec/liraglutide in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides (such as nateglinide or repaglinide) or prandial insulin. The use of insulin degludec/liraglutide in people taking basal insulin doses greater than 40 units has not been studied. There are no published data on initiating insulin degludec/liraglutide in people who are already taking a GLP-1 receptor agonist. However, in May 2015 insulin degludec/liraglutide received a positive opinion for use in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

Insulin degludec/liraglutide is a fixed-ratio combination preparation and the insulin degludec and liraglutide components cannot be individually titrated. The SPC recommends that when insulin degludec/liraglutide is being used as an add-on to oral glucose-lowering drugs the starting dose is 10 dose-steps once a day (10 units insulin degludec and 0.36 mg liraglutide). When transferring from basal insulin the recommended starting dose is 16 dose-steps once a day (16 units insulin degludec and 0.576 mg liraglutide). Existing basal insulin treatment would have to be stopped before insulin degludec/liraglutide could be started. The maximum daily dose that insulin degludec/liraglutide can be titrated to is 50 dose steps once daily (50 units insulin degludec and 1.8 mg liraglutide). However, NICE technology appraisal guidance on liraglutide for the treatment of type 2 diabetes does not recommend liraglutide at a 1.8 mg daily dose.

DUAL II was conducted in a population of people who had previously been treated with basal insulin. DUAL II showed that insulin degludec/liraglutide was superior to insulin degludec alone for change in HbA1c, reducing HbA1c by an additional 1.1% compared with insulin degludec. In this study the insulin degludec alone group could only be titrated to a maximum of 50 units daily.

The manufacturer suggests that a potential place in therapy for insulin degludec/liraglutide is for adults with type 2 diabetes who are uncontrolled on basal insulin. For this group of people for whom the use of basal insulin and a GLP-1 receptor agonist in combination is being considered, the alternative treatment option would be to add a separate GLP-1 receptor agonist. This would allow individual titration of the insulin and GLP-1 receptor agonist doses, and possibly easier initiation of treatment because the existing basal insulin treatment would not need to be stopped to allow the introduction of the combination

product.

Insulin degludec/liraglutide is given as a single daily injection which may be preferable to giving basal insulin and GLP-1 receptor agonists as separate injections for some people. However, some GLP-1 receptor agonists are given as a weekly injection, which will also reduce the number of injections a person requires.

None of the studies in the study program for insulin degludec/liraglutide compare the combination preparation with GLP-1 receptor agonists and basal insulins given together but as separate injections; so it is unclear how they would compare.

Estimated usage

The manufacturer suggests that a potential place in therapy for insulin degludec/liraglutide is for adults with type 2 diabetes who are uncontrolled on basal insulin.

The manufacturer estimates that approximately 50,427 adults with type 2 diabetes are taking basal insulin and have a HbA1c greater than 7.5% (59 mmol/mol). They further estimate that 9% (4538) of these people may be suitable for the addition of a GLP-1 receptor agonist.

Relevance to NICE guidance programmes

NICE has published a clinical guideline on [type 2 diabetes](#), which is being [updated](#) (publication date to be confirmed).

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Paula Chattington: no relevant interests declared.

Dr Peter Hammond has received honoraria for lecturing on behalf of Medtronic, Abbott and Astra Zeneca in the last 12 months.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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