Is Xultophy® (insulin degludec/liraglutide) a match for basal bolus therapy? Learnings from the DUAL™ VII trial

Dr Harsha Kasetty
Medical affairs Manager
Novo Nordisk UK

This meeting is organised and funded by Novo Nordisk. Prescribing information and adverse event reporting are available at this meeting.
Insulin degludec and Liraglutide prescribing information

**Xultophy®**

Insulin degludec and Liraglutide.

**Please consult the full Summary of Product Characteristics (SmPC) before prescribing**

**Xultophy®** is a pre-filled dial-a-dose pen. 1 mL solution contains 100 units insulin degludec and 3.6 mg liraglutide. One pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 10.8 mg liraglutide. Each dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide.

**Indication:** Xultophy® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes.

**Posology and administration:** Xultophy® is given once daily by subcutaneous administration. Xultophy® can be administered at any time of the day, preferably at the same time of the day. A minimum of 8 hours between injections should always be ensured. Xultophy® is to be dosed in accordance with the individual patient’s needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. Xultophy® is administered as dose steps. The pre-filled pen can provide from 1 up to 50 dose steps in one injection. The maximum daily dose of Xultophy® is 50 dose steps. The recommended starting dose should not be exceeded. The recommended starting dose of Xultophy® as add-on to oral antidiabetes drugs (OADs) is 10 dose steps, and 16 dose steps when transferring from GLP-1 receptor agonist or basal insulin therapy. If transferring from a long-acting GLP-1 receptor agonist (e.g. once-weekly dosing), the prolonged action should be considered. Close glucose monitoring is recommended during the transfer and in the following weeks when transferring from either GLP-1 receptor agonist or basal insulin. In elderly patients, in patients with mild, moderate or severe renal impairment and in patients with mild or moderate hepatic impairment, glucose monitoring is to be intensified. Xultophy® cannot be recommended for use in patients with end-stage renal disease or severe hepatic impairment. No studies have been performed with Xultophy® in children and adolescents below 18 years of age.

**Contraindications:** Hypersensitivity to the active substance or to any of the excipients.

**Special warnings and precautions for use:** Please consult the full Summary of Product Characteristics (SmPC) for details of special warnings and precautions for use. Xultophy® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Higher than required dose, omission of a meal, or unplanned strenuous physical exercise may lead to hypoglycaemia. In combination with sulfonylurea, the risk of hypoglycaemia may be lowered by a reduction in the dose of sulfonylurea. Inadequate dosing and/or discontinuation of antidiabetic treatment may lead to hyperglycaemia and potentially to hyperosmolar coma. Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin medicinal products, especially in patients with risk factors for development of cardiac failure. If the combination of pioglitazone and Xultophy® is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists, including liraglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Xultophy® should be discontinued. If severe acute pancreatitis is confirmed, Xultophy® should not be restarted. Thyroid adverse events such as goitre have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, and in particular in patients with pre-existing thyroid disease. Xultophy® should therefore be used with caution in these patients. There is no experience in patients with inflammatory bowel disease and diabetic gastroparesis. Xultophy® is therefore not recommended in these patients. Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, a component of Xultophy®.

Patients treated with Xultophy® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between Xultophy® and other injectable diabetes medicinal products. Transfer to Xultophy® from doses of basal insulin 100 U/mL and >50 U/mL has not been studied. There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and Xultophy® is therefore not recommended for use in these patients. Patients must be advised to take precautions to avoid hypoglycaemia while driving.

**Fertility, pregnancy and lactation:** There is no clinical experience with the use of Xultophy® in pregnant women. If a patient wishes to become pregnant, pregnancy occurs or is breast feeding; treatment with Xultophy® should be discontinued. There is no clinical experience with Xultophy® in relation to fertility.

**Undesirable effects:** The Summary of Product Characteristics should be consulted for a full list of side effects.

**Very common (≥1/10):** Hypoglycaemia. Common (≥1/100 to <1/10): Decreased appetite, nausea, diarrhoea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, gastrointestinal reflux disease, abdominal distension, increased lipase, increased amylase and injection site reactions.

**Uncommon (≥1/1000 to <1/100):** Urticaria, hypersensitivity, dehydration, rash, pruritis, and increased heart rate, eructation, flatulence, lipodystrophy acquired, cholelithiasis and cholecystitis. Unknown (cannot be estimated from the available data): Anaphylactic reactions, pancreatitis (including necrotising pancreatitis) and peripheral oedema.

**Marketing Authorisation Numbers (MA) and Basic NHS Price:**

3 x 3 mL U/mL, EU/1/14/947/002, £95.53

**Xultophy® pre-filled dial-a-dose pen.**

**Legal category:** POM.

**Full prescribing information can be obtained from:**

Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA.

**MA Holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

**Date last revised:** October 2019

---

**Adverse events should be reported.** Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055).** Calls may be monitored for training purposes.

**Xultophy®, NovoTwist® and NovoFine®** are trademarks owned by Novo Nordisk A/S, Denmark.
Disclosures

- I have not received honorarium from Novo Nordisk for presenting at this meeting
- *I am an employee of Novo Nordisk since February 2013*
Therapeutic indication

**IDegLira**
Xultophy® (Insulin degludec + liraglutide) is indicated for the treatment of adults with insufficiently controlled type 2 diabetes to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes.
Agenda

1. Definition & need for insulin intensification
2. Concept of combining GLP-1 RA & basal insulin
3. Clinical evidence for IDegLira
4. Practical considerations on how to initiate IDegLira
Diabetes is a progressive disease
Decline in beta cell function over time

Type 2 diabetes is characterised by the progressive loss of beta cell function in addition to certain levels of insulin resistance

This article was published in *Endocrinology*, Bergenstal RM et al., 821–35, Copyright Elsevier 2001
Insulin optimisation and intensification
Should follow disease progression

- **Beta cell function (%)**
  - **Lifestyle + medication**
  - **Basal insulin + other medication**
  - **Titrate dose to reach/maintain glycaemic targets**
  - **Basal and 1-4 bolus or premix**
  - **Intensify for mealtime insulin coverage**

Reasons for lack of insulin intensification

- Hypoglycaemia
- Weight gain
- Complex regimens
- Increased need for HCP resources
- Lack of patient adherence

New strategies are required to aid patients in achieving glycaemic control, whilst minimising side effects.

1. Definition & need for insulin intensification
2. Concept of combining GLP-1 RA & basal insulin
3. Clinical evidence for IDegLira
4. Practical considerations on how to initiate IDegLira
Complementary actions of GLP-1 RA and insulin target underlying pathophysiology of type 2 diabetes

GLP-1 receptor agonist

- **Heart**: Cardiac function
- **Pancreas**: Glucose-dependent insulin and glucagon secretion, Insulin synthesis
- **Liver**: Hepatic glucose output
- **GI tract**: Gastric emptying

**Brain**
- Energy intake
- Satiety
- Neuroprotection

**Basal insulin**

- **Skeletal muscle**: Glucose disposal
- **Liver**: Hepatic glucose production
- **Adipose tissue**: Insulin receptor activation

GLP-1, glucagon-like peptide-1
**Rational drug design**

Formulation feasible due to distinct, stable association forms

- Properties of the liraglutide and insulin degludec co-formulation compared with its mono-components alone:
  - Glycaemic control throughout the day with FPG reduction and PPG coverage at all meals\(^1,2\)
  - Steady titration and similar tolerability profiles in patients not controlled on OADs and basal insulin\(^1,2\)
  - Once-daily administration in a single pen device

---

FPG, fasting plasma glucose; PPG, postprandial plasma glucose; OADs, oral antidiabetic drugs

Agenda

1. Definition & need for insulin intensification
2. Concept of combining GLP-1 RA & basal insulin
3. Clinical evidence for IDegLira
4. Practical considerations on how to initiate IDegLira
IDegLira clinical development programme

Uncontrolled on OADs

**DUAL™ I and ext.**\(^1,2\)
- Met ± pio
- IDegLira
- IDeg
- Liraglutide

**DUAL™ IV\(^3\)**
- SU ± met
- IDegLira
- Placebo

**DUAL™ VI\(^4\)**
- Met ± pio
- IDegLira 1WT titration
- IDegLira 2WT titration

Uncontrolled on GLP-1 RA

**DUAL™ III\(^5\)**
- GLP-1 RA + 1-3 OADs
- IDegLira
- GLP-1 RA

Uncontrolled on basal insulin

**DUAL™ II\(^6\)**
- Basal insulin (20-40 U) + 1-2 OADs
- IDegLira
- IDeg

**DUAL™ V\(^7\)**
- IGlary U100 (20-50 U) + 1 OAD
- IDegLira
- IGlary U100

**DUAL™ VII\(^8\)**
- IGlary U100 (20-50 U) + 1 OAD
- IDegLira
- IGlary U100+IAsp

ext., extension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlary U100, insulin glargine U100; Met, metformin; OAD, oral antidiabetic drug; Pio, pioglitazone; SU, sulphonylurea; 1WT, once-weekly titration; 2WT, twice-weekly titration

# IDegLira clinical development programme

## Uncontrolled on OADs

<table>
<thead>
<tr>
<th>DUAL™ I and ext.¹,²</th>
<th>Uncontrolled on GLP-1 RA</th>
<th>Uncontrolled on basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met ± pio</td>
<td>DUAL™ III⁵</td>
<td>DUAL™ II⁶</td>
</tr>
<tr>
<td>IDegLira</td>
<td>IDegLira</td>
<td>IDegLira</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 RA + 1-3 OADs + GLP-1 RA</td>
<td>Basal insulin (20-40 U) + 1-2 OADs</td>
</tr>
<tr>
<td>IDegLira 1WT titration</td>
<td>IDegLira</td>
<td>IDegLira</td>
</tr>
<tr>
<td>IDegLira 2WT titration</td>
<td>GLP-1 RA</td>
<td>GLP-1 RA</td>
</tr>
</tbody>
</table>

## Uncontrolled on GLP-1 RA

<table>
<thead>
<tr>
<th>DUAL™ IV³</th>
<th>Uncontrolled on OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU ± met</td>
<td>DUAL™ VI⁴</td>
</tr>
<tr>
<td>IDegLira</td>
<td>Met ± pio</td>
</tr>
<tr>
<td>Placebo</td>
<td>IDegLira 1WT titration</td>
</tr>
</tbody>
</table>

## Uncontrolled on basal insulin

<table>
<thead>
<tr>
<th>DUAL™ V⁷</th>
<th>Uncontrolled on GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGlar U100</td>
<td>DUAL™ VII⁸</td>
</tr>
<tr>
<td>(20-50 U) + 1 OAD</td>
<td>IDegLira</td>
</tr>
<tr>
<td>IGlar U100+IAsp</td>
<td>GLP-1 RA</td>
</tr>
</tbody>
</table>

---

ext., extension; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; Met, metformin; OAD, oral antidiabetic drug; Pio, pioglitazone; SU, sulphonylurea; 1WT, once-weekly titration; 2WT, twice-weekly titration

**DUAL™ VII: Trial design**

506 patients with T2D diabetes

<table>
<thead>
<tr>
<th>Screening</th>
<th>Randomisation (1:1)</th>
<th>26</th>
<th>27</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment</td>
<td>1st FU</td>
<td>2nd FU</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Trial information**
- Non-inferiority
- Treat-to-target
- Open label

**Key inclusion criteria**
- Age ≥18 years
- HbA1c 7.0–10.0% (53–85.8 mmol/mol)
- IGlar U100 20–50 units + metformin
- BMI ≤40 kg/m²

**IDegLira + metformin (n=252)**

**IGlar U100 + IAsp (≤4 times) + metformin (n=254)**

**Primary endpoint:**
- Change in baseline in HbA1c after 26 weeks of treatment

IDegLira is a fixed-ratio combination. 1 U IDegLira = 1 U IDeg/0.036 mg liraglutide
BMI, body mass index; FU, follow-up; HbA1c, glycosylated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; T2D, type 2 diabetes; U, units

Billings et al. Diabetes Care 2018;41:1009–1016
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IDegLira</th>
<th>IGlar U100 + IAsp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full analysis set, n</td>
<td>252</td>
<td>254</td>
</tr>
<tr>
<td>Male, %</td>
<td>43.7</td>
<td>46.1</td>
</tr>
<tr>
<td>Age, years</td>
<td>58.6</td>
<td>58.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87.2</td>
<td>88.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td><strong>31.7</strong></td>
<td><strong>31.7</strong></td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>13.2</td>
<td>13.3</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>8.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Daily insulin dose, units</td>
<td><strong>34</strong></td>
<td><strong>33</strong></td>
</tr>
<tr>
<td>Daily metformin dose, mg</td>
<td>2049</td>
<td>2091</td>
</tr>
</tbody>
</table>

BMI, body mass index; FPG, fasting plasma glucose; HbA₁c, glycosylated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml

Billings et al. Diabetes Care 2018;41:1009–1016
Primary endpoint: $\text{HbA}_1\text{c}$ over time

Mean observed values with error bars (standard error mean) based on full analysis set. ETD is based on change from baseline LSMeans from full analysis set, using mixed model for repeated measurement treatment, region and visit as factors, and baseline value as covariate. Interactions between visit and all other factors and covariate are included.

CI, confidence interval; ETD, estimated treatment difference; $\text{HbA}_1\text{c}$, glycosylated haemoglobin; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; LSMean, least squares mean

Adapted from Billings et al. Diabetes Care 2018;41:1009–1016
Daily total insulin dose over time

Mean observed values with error bars (standard error mean) based on safety analysis set. ETD is based on observed data using MMRM with treatment, region and visit as factors and insulin dose at screening, and baseline HbA1c as covariates.

CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; MMRM, mixed-model repeated measures; U, unit.

Adapted from Billings et al. Diabetes Care 2018;41:1009–1016
Severe or BG-confirmed (<3.1 mmol/L) symptomatic hypoglycaemia over time

Mean cumulative function based on safety analysis set. Rate ratio analysed using a negative binomial model with a log-link function and the logarithm of the time period in which an episode occurred as offset, including treatment and region as fixed factors. Severe or BG-confirmed symptomatic: an episode that is severe according to the ADA classification or BG-confirmed by a plasma glucose value <3.1 mmol/L with symptoms consistent with hypoglycaemia. ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; PYE, patient years of exposure

Adapted from Billings et al. Diabetes Care 2018;41:1009–1016
IDegLira is not licensed for weight loss. LSMean values with error bars (standard error mean) based on full analysis set, using MMRM MMRM with treatment, region and visit as factors, and baseline value as covariate. Interactions between visit and all other factors and covariate are included CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; LSMean, least squares mean; MMRM, mixed-model repeated measures
Adapted from Billings et al. Diabetes Care 2018;41:1009–1016
# Treatment-emergent adverse events

<table>
<thead>
<tr>
<th></th>
<th>IDegLira</th>
<th>IGlar U100 + IAsp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>149</td>
<td>(59.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>12</td>
<td>(4.8)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>occurring in &gt;5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>(4.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>(6.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>18</td>
<td>(7.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28</td>
<td>(11.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
<td>(6.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>9</td>
<td>(3.6)</td>
</tr>
</tbody>
</table>

E, events; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide combination; IGlar U100, insulin glargine 100 units/ml; R, events per 100 years of exposure

Type 2 diabetes is a progressive disease, and there is often a need to intensify insulin therapy.

Combining basal insulin with GLP-1 is complementary and minimizes the risk of hypoglycaemia and weight gain compared with intensifying insulin alone.

DUAL™ VII demonstrates that IDegLira provides an efficacious intensification option with noninferior glycaemic control versus basal-bolus in patients with type 2 diabetes.

IDegLira is not licensed for weight loss.
## Agenda

<table>
<thead>
<tr>
<th></th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Definition &amp; need for insulin intensification</td>
</tr>
<tr>
<td>2</td>
<td>Concept of combining GLP-1 RA &amp; basal insulin</td>
</tr>
<tr>
<td>3</td>
<td>Clinical evidence for IDegLira</td>
</tr>
<tr>
<td>4</td>
<td>Practical considerations on how to initiate IDegLira</td>
</tr>
</tbody>
</table>
Licensed indication & administration

Xultophy® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes.

Xultophy® is given once-daily by subcutaneous administration. Xultophy® can be administered at any time of the day, preferably at the same time of the day. A minimum of 8 hours between injections should always be ensured.

Xultophy® Summary of Product Characteristics. Novo Nordisk Ltd.
Initiation of IDegLira in type 2 diabetes

**Add-on to OADs**

10 dose steps

When IDegLira is added to SU therapy, a reduction in the dose of SU should be considered

**Transfer from GLP-1 RA**

16 dose steps

Therapy with GLP-1 RAs should be discontinued prior to initiation of IDegLira

**Transfer from basal insulin**

16 dose steps

Therapy with basal insulin should be discontinued prior to initiation of IDegLira

GLP-1 RA, glucagon like peptide-1 receptor agonist; OAD, oral antidiabetic drug; SU, sulphonylurea

Xultophy® Summary of Product Characteristics. Novo Nordisk Ltd

IDegLira has not been studied in patients transferring from doses of basal insulin less than 20 and greater than 50 units
IDegLira titration

IDegLira is dosed in accordance with patients’ needs based on pre-breakfast (fasting) blood glucose.

- **Below target**: -2 dose steps
- **At individualised target**: Maintain dose
- **Above target**: +2 dose steps

In clinical trials a twice weekly titration algorithm was used. In the trial investigating IDegLira as add on to sulfonylurea the target was 4.0-6.0 mmol/L.

Xultophy® Summary of Product Characteristics. Novo Nordisk Ltd.
Insulin degludec and Liraglutide prescribing information

**Xultophy**®
Insulin degludec and Liraglutide.

Please consult the full Summary of Product Characteristics (SmPC) before prescribing

**Xultophy**® is a pre-filled dial-a-dose pen. 1 mL solution contains 100 units insulin degludec and 3.6 mg liraglutide. One pre-filled pen contains 3 mL equivalent to 300 units insulin degludec and 10.8 mg liraglutide. One dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide.

**Indication:** Xultophy® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise in addition to other oral medicinal products for the treatment of diabetes.

**Posology and administration:** Xultophy® is given once daily by subcutaneous administration. Xultophy® can be administered at any time of the day, preferably at the same time of the day. A minimum of 8 hours between injections should always be ensured. Xultophy® is to be dosed in accordance with the individual patient’s needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. Xultophy® is administered as dose steps. The pre-filled pen can provide from 1 up to 50 dose steps in one injection of one dose step. The maximum daily dose of Xultophy® is 50 dose steps. The recommended starting dose should not be exceeded. The recommended starting dose of Xultophy® as add-on to oral antidiabetes drugs (OADs) is 10 dose steps, and 16 dose steps when transferring from GLP-1 receptor agonist or basal insulin therapy. If transferring from a long-acting GLP-1 receptor agonist (e.g. once-weekly dosing), the prolonged action should be considered. Close glucose monitoring is recommended during the transfer and in the following weeks when transferring from either GLP-1 receptor agonist or basal insulin. In elderly patients, in patients with mild, moderate or severe renal impairment and in patients with mild or moderate hepatic impairment, glucose monitoring is to be intensified. Xultophy® cannot be recommended for use in patients with end-stage renal disease or severe hepatic impairment. No studies have been performed with Xultophy® in children and adolescents below 18 years of age.

**Contraindications:** Hypersensitivity to the active substance or to any of the excipients.

**Special warnings and precautions for use:** Please consult the full Summary of Product Characteristics (SmPC) for details of special warnings and precautions for use. These should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Higher than required dose, omission of a meal, or unplanned strenuous physical exercise may lead to hypoglycaemia. In combination with sulphonylurea, the risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea. Inadequate dosing and/or discontinuation of antidiabetic treatment may lead to hyperglycaemia and potentially to hyperosmolar coma. Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin medicinal products, especially in patients with risk factors for development of cardiac failure. If the combination of pioglitazone and Xultophy® is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists, including liraglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Xultophy® should be discontinued. If acute pancreatitis is confirmed, Xultophy® should not be restarted. Thyroid adverse events such as goitre have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, and in particular in patients with pre-existing thyroid disease. Xultophy® should therefore be used with caution in these patients. There is no experience in patients with inflammatory bowel disease and diabetic gastroparesis. Xultophy® is therefore not recommended in these patients. Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in clinical trials with GLP-1 receptor agonists including liraglutide, a component of Xultophy®. Patients treated with Xultophy® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion. Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between Xultophy® and other injectable diabetes medicinal products. Transfer to Xultophy® from doses of basal insulin 20 and >50 units has not been studied. There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and Xultophy® is therefore not recommended for use in these patients. Patients must be advised to take precautions to avoid hypoglycaemia while driving.

**Fertility, pregnancy and lactation:** There is no clinical experience with the use of Xultophy® in pregnant women. If a patient wishes to become pregnant, pregnancy occurs or is breast feeding; treatment with Xultophy® should be discontinued. There is no clinical experience with Xultophy® in relation to fertility.

**Undesirable effects:** The Summary of Product Characteristics should be consulted for a full list of side effects.

**Very common (≥ 1/10):** Hypoglycaemia. *Common (1/100 to < 1/10):* Decreased appetite, nausea, diarrhoea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, gastroesophageal reflux disease, abdominal distension, increased lipase, increased amylase and injection site reactions. *Uncommon (1/1000 to < 1/100):* Urticaria, hypersensitivity, depression, rash, pruritus and increased heart rate, erythema, flushing, hypoglycaemia, cholelithiasis and cholecystitis. *Unknown (cannot be estimated from the available data):* Anaphylactic reactions, pancreatitis (including necrotising pancreatitis) and peripheral oedema.

**Marketing Authorisation Numbers (MA) and Basic NHS Price:** 3 x 3 mL U/mL, EU/1/1947/002, £95.53

Xultophy® pre-filled dial-a-dose pen.

**Legal category:** POM.

Full prescribing information can be obtained from:
Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA.
MA Holder: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

**Date last revised:** October 2019

---

**Adverse events should be reported.** Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**Adverse events should also be reported to** Novo Nordisk Limited (Telephone: 0808 4000000). Calls may be monitored for training purposes.

**Xultophy®, NovoTwist® and NovoFine® are trademarks owned by Novo Nordisk A/S, Denmark.**