East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, North East Hampshire & Farnham CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	**Xultophy (insulin degludec/liraglutide)** *(Novo Nordisk)* **for type 2 diabetes**, *Licensed indication* is 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. *Local consultants* wish to use in patients with type 2 diabetes who are currently treated with basal analogue insulin, who require intensification, and who would be considered for addition of GLP-1 receptor agonist according to NICE guidance/local policy
Requested by	Professor Russell-Jones, Royal Surrey Count Hospital

SUMMARY

Clinical Effectiveness

- The study programme for insulin degludec/liraglutide includes 7 phase III randomised controlled trials (RCTs). Only 2 phase III studies have been published in full: DUAL I and DUAL II. The clinical development programme for Xultophy included approximately 1,900 patients (1).
- DUAL I study included 1663 patients who were insulin naïve (most of whom were only on metformin), the DUAL II study included 413 patients already treated with basal insulin plus metformin (cohort of patients local specialists are interested in). In both DUAL I and DUAL II the mean BMI of participants was below the NICE recommended threshold for initiation of GLP-1 receptor agonists (31 kg/m^2, and 33.7 kg/m^2 respectively).
- Change from baseline in HbA1c is the primary outcome in all the studies. Secondary outcomes included effect of treatment on insulin dose, % of participants with HbA1c less than 7% (53 mmol/mol) at week 26, hypoglycaemic episodes and weight control.
- 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.
- In the DUAL I study, 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).
- More patients achieved the secondary outcome of HbA1c less than 7% (53 mmol/mol) at week 26 with insulin/degludec compared with insulin degludec or liraglutide (81% vs 65% vs 60%).
- In the DUAL II study, people previously treated with basal insulin, insulin degludec/liraglutide was superior to insulin degludec alone for reducing HbA1c with a difference of 1.1% (95% CI -1.3 to – 0,8%; p <0.0001). In the Xultophy group the mean body weight decreased by 2.7Kg, there was no change in the insulin degludec group (Estimated mean treatment difference (-2.5kg [95% CI -3.21 to -1.82]; p<0.0001)).
- At the end of the DUAL II study the mean daily dose on insulin degludec in both arms was 45 Units, and for liraglutide was 1.62mg
- More patients achieved the secondary outcome of HbA1c less than 7% (53 mmol/mol) at week 26 with insulin/degludec compared with insulin degludec (60.3% vs 23.1%).

Comments

- The DUAL II study included patients who were not well controlled on basal insulin at baseline, however in both treatment arms (Xultophy and insulin degludec) the insulin dose was restricted to a maximum of 50 Units a day, and there was no further optimisation of insulin treatment in the insulin degludec arm of the study, for example by changing insulin regimens or using an alternative insulin. This made the study an assessment of the benefit of the addition of liraglutide to insulin degludec, which does not reflect best clinical practice.
- Xultophy is a fixed-ratio combination where the dose is of the individual components cannot be individually titrated. The dose of Xultophy is adjusted based on the insulin component which could result in higher doses of

liraglutide agonist being used (i.e. above 1.2 mg per day), with potential for more side-effects e.g. nausea, but which offer only small improvements in HbA1c control over 1.2mg per day.

- The reduction in bodyweight seen in DUAL II did not meet the NICE threshold for continuing GLP-1 receptor agonist treatment of 3% (2.85kg) reduction.
- There are no studies comparing Xultophy with other GLP-1 receptor agonist and insulin combinations.

Safety

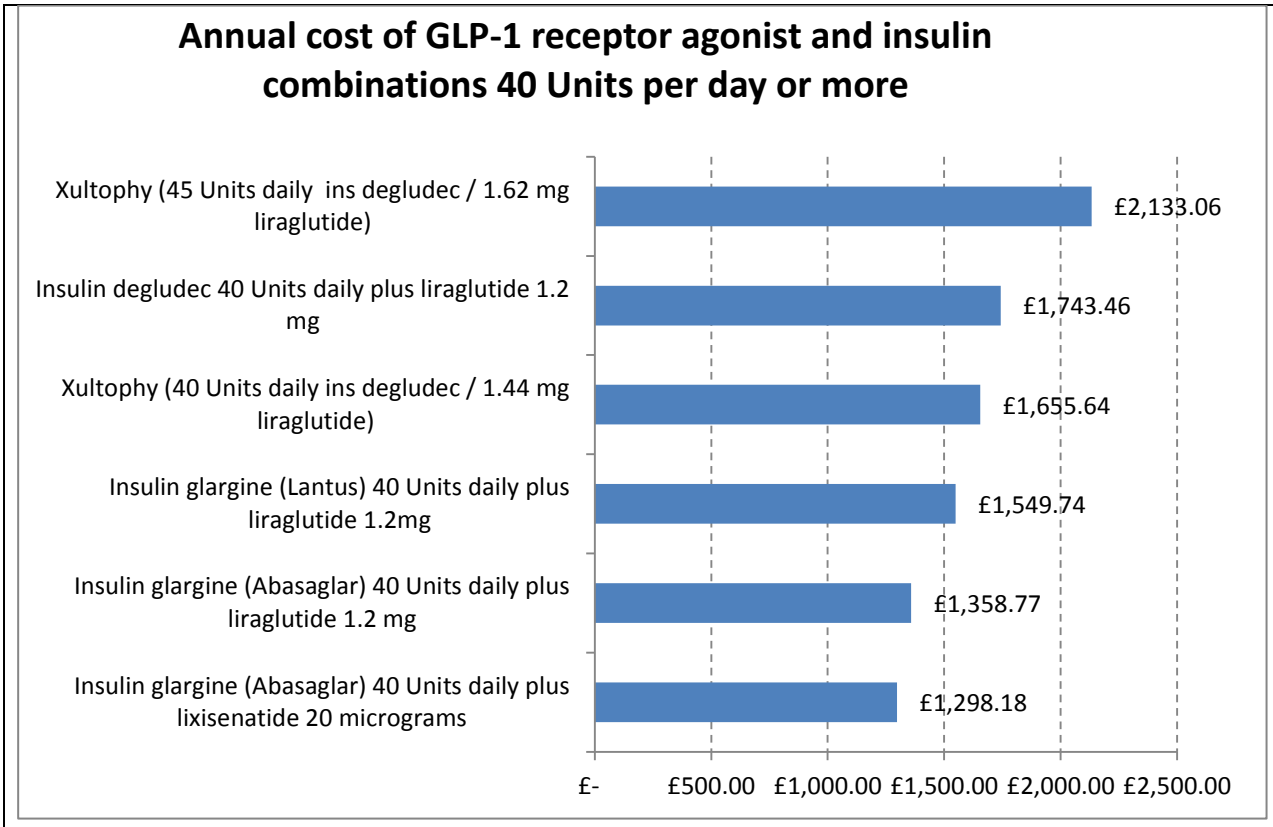
- In DUAL I cases of confirmed hypoglycaemia were statistically significantly higher with insulin degludec/liraglutide compared with liraglutide (32% compared with 7%; estimated rate ratio [RR] 7.61; 95% CI 5.17 to 11.21; p<0.0001) but lower compared with insulin degludec (32% compared with 39%; estimated RR 0.68; 95% CI 0.53 to 0.87; p=0.0023).
- In DUAL II the incidence of confirmed hypoglycaemia was similar (not statistically significant) between treatment groups. There were too few episodes of severe hypoglycaemia to provide any useful analysis.
- 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.
- The most commonly reported adverse reactions listed in the summary of product characteristics (SPC) are hypoglycaemia, decreased appetite, nausea, diarrhoea, vomiting constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesphageal reflux disease, abdominal distension and injection site reactions.
- 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.
- Xultophy is one of 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.

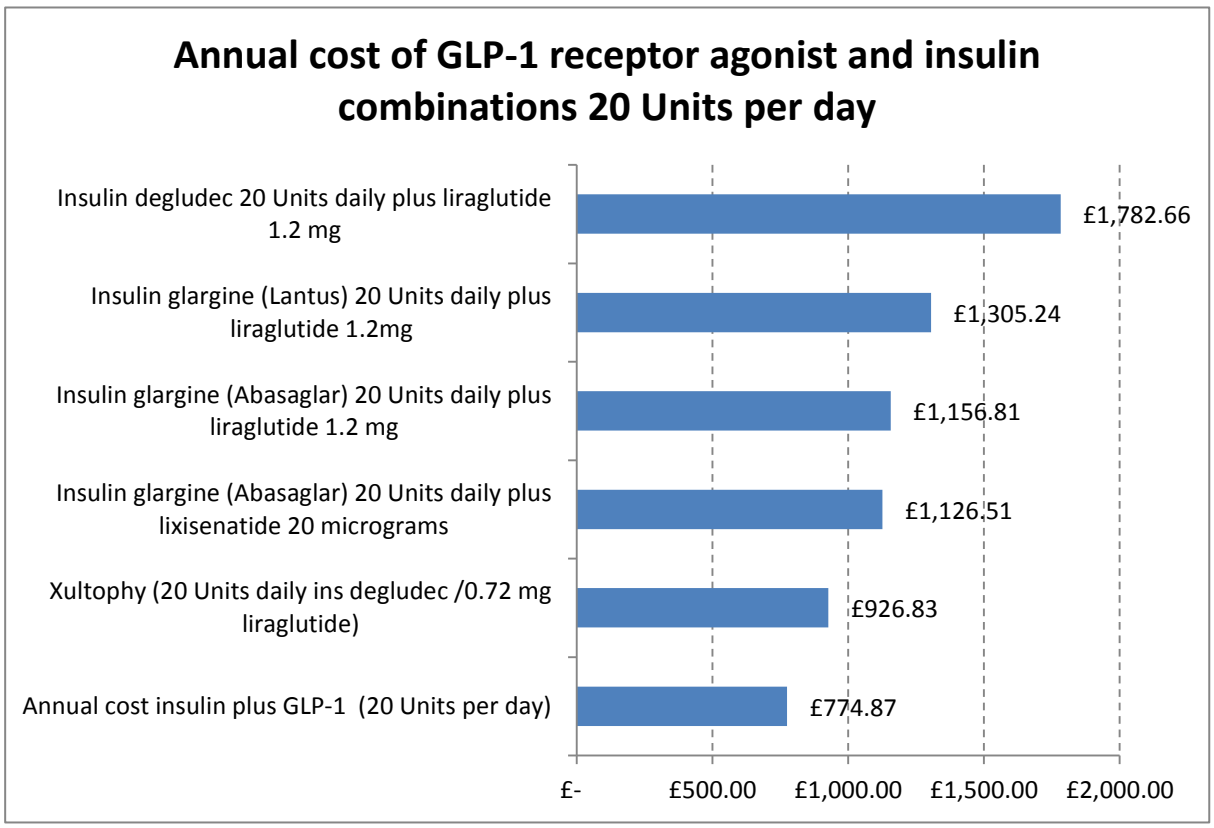
Patient factors

- Reduced number of injections, in patients requiring dual injectable therapy by using a combination product.
- The fixed-ratio of the combination product does not allow for the insulin analogue doses to be titrated separately in order to optimise individual patient diabetes control. Neither does it allow assessment of which element of the combination may be benefiting the patient.
- Patients will require education and support that follows MHRA guidance on minimising risk of medication errors for high strength, fixed combination insulin products (which includes Xultophy)

Cost implications

- Annual cost of Xultophy ranges 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).





Relevant guidance / reviews

- Recently published NICE guidance NG28 on type 2 diabetes advises that insulin degludec is not recommended as there was strong evidence it is not cost-effective. However the price of Xultophy is lower than the individual components. There was a lack of evidence for combinations of GLP-1 receptor agonists and insulin, and therefore agreed that this option should only be offered in a specialist care setting.
- SMC and AWMSG have both recommended the use of Xultophy in a selected cohort of patients. Other Area Prescribing Committees have not recommended the use of Xultophy.

- PCN does not recommend the use of insulin degludec, and the combination of insulin and GLP-1 receptor agonists is restricted to specialist initiation using Amber shared care documentation.
- An evidence review for Dulaglutide, a once weekly GLP-1 receptor agonist will be presented to PCN in March.

Likely place in therapy relative to current treatments

PCN has approved the use of GLP-I receptor agonists with insulin initiated by specialists in a small cohort of patients. This is in line with NICE which advises that due to the lack of good evidence for insulin/GLP-1 receptor agonist combinations, their use should be restricted to small cohorts of patients in a specialist care setting. Wider use of GLP-1 receptor agonist and insulin combinations has not been demonstrated.

Local specialists see a place for the use of analogue insulin and GLP-1receptor agonist use in patients who are not achieving sufficient glycaemic control on basal insulin analogues. However we do not know how this would compare to a different insulin regimen e.g. biphasic regimen, and we do not know how the combination in Xultophy compares with insulin analogue and a GLP-1 receptor agonist given separately. For example is one less injection a week a potential advantage (if once weekly GLP-1 agonist preparation used.

Recommendation to PCN

Black – Fixed dose combination of GLP-1 receptor agonist and insulin is not recommended, due to absence of evidence of benefit over current therapies, increased cost, and the inability to optimise the dose of separate components of treatment to achieve maximal effect.

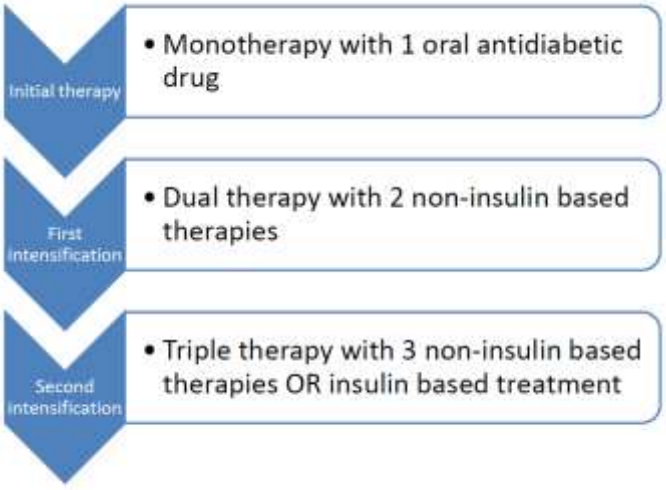
Medicine details	
Name and brand name	Fixed-ratio combination of insulin degludec and liraglutide - Xultophy
Licensed indication, formulation and usual dosage	• Licensed for type 2 diabetes, in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control • Presented as a 3mL prefilled pen, containing 100 units/mL insulin degludec and 3.6mg/mL liraglutide • One dose step contains 1 unit of insulin degludec and 0.036mg liraglutide • Recommended starting dose (if not on prior basal insulin or GLP-1 agonist) is 10 dose steps (10 units insulin degludec and 0.36mg liraglutide) • Maximum daily dose is 50 dose steps (50 units insulin degludec and 1.8mg liraglutide) • Administered once daily by subcutaneous injection. • Fixed dose combination reduces flexibility of dosing which may be important in patients with changing insulin requirements
Summary of mechanism of action, and relevant pharmacokinetics	• Xultophy is a combination of the long-acting insulin analogue, insulin degludec, and the GLP-1 receptor agonist, liraglutide which both improve glycaemic control with complementary mechanisms of action. • Not recommended for use in patients with moderate or severe renal impairment
Important drug interactions	Same as those reported with insulin and liraglutide as mono components
Monitoring requirements	HbA1c and blood glucose
Prescribing considerations	GPs are familiar with prescribing insulin (although not insulin degludec) and GLP-1 receptor agonists including liraglutide
Other considerations	• Xultophy has not been studied in patients on DPP-4 inhibitors (a potentially large patient group), glinides or prandial insulin (1). • Shelf life after opening is 21 days, which is different to liraglutide (1 month) or insulin degludec (8 weeks).

Potential patient group (if appropriate to include)	
Brief description of disease	• Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance, and insufficient pancreatic insulin production, resulting in high blood glucose levels. • It is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and increased cardiovascular risk. • It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy.
Potential patient numbers per 100,000	• Diabetes has a prevalence rate of 6.2% in England and 4.9% in Surrey, about 90% of cases are type 2 diabetes. • Obesity has a prevalence of 9.4% in England and 5.4% in Surrey • The manufacturer suggests that a potential place in therapy for Xultophy is for patients with type 2 diabetes who are uncontrolled on basal insulin. They estimate that approximately 50,427 adults with type 2 diabetes in the country are taking basal insulin and have an Hba1c >59 mmol/mol (7.5%), and that 9% of these people may be suitable for the addition of a GLP-1 receptor agonist.
Outcomes required	• Patient orientated outcomes: reduced microvascular and macrovascular complications, improved quality of life. • NICE type 2 diabetes guidelines make recommendations regarding required achievement at 6 months for HbA1c (11 mmol/mol, or 1%) and weight loss (3% initial body weight) in patients on GLP-1 mimetics in order for them to be considered cost-

	effective.

Summary of current treatment pathway

NICE has recently published an updated guideline for type 2 diabetes (3). Xultophy would potentially be placed at second intensification in the treatment pathway, or as a further step following second intensification using insulin.



Recommendations regarding GLP-1 receptor agonists:
For adults with type 2 diabetes who:

- have a BMI of 35 kg/m2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity

OR

- have a BMI lower than 35 kg/m2and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Only continue GLP-1 receptor agonist therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months).

Recommendations regarding insulin treatment:
Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens:

- Offer NPH insulin injected once or twice daily according to need.
- Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either:
  - Separately **or**
  - as a pre-mixed (biphasic) human insulin preparation.
- Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:
  - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily **or**
  - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes **or**
  - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:
  - a person prefers injecting insulin immediately before a meal **or**
  - hypoglycaemia is a problem **or**
  - blood glucose levels rise markedly after meals.

Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:

- who do not reach their target HbA1c because of significant hypoglycaemia **or**
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached **or**
- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made **or**
- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections

Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation).

Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate.

Relevant extracts from the full NICE guideline:

- The Guideline Development Group (GDG) noted there was a lack of evidence for combinations of GLP-1 receptor agonists and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The GDG also noted that such treatment combinations are normally prescribed in complex cases and would therefore benefit from specialist care advice and ongoing support from a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care.
- The GDG reviewed the insulin-based recommendations from NICE guidance CG87 and agreed that the updated evidence supported the use of insulin detemir and insulin glargine as alternatives to NPH insulin under certain circumstances. The GDG agreed that there was strong evidence to indicate that insulin degludec was not cost-effective and therefore was confident that this option should not be recommended.
- Regarding the use of GLP-1 receptor agonists in combination with oral hypoglycaemic agents the GDG considered that GLP-1 receptor agonist combinations may be a cost-effective option for people with high BMIs who would require high doses (and therefore costs) of insulin or for whom other treatment options were not tolerated or were contraindicated. However, the GDG noted the high costs of these treatment options and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. Given the lack of cost effectiveness of GLP-1s demonstrated in the health economic modelling, the GDG recommended that the starting and stopping rules from CG87 should be retained

Current PCN recommendations:

Insulin degludec (Feb 2013)

- Status is Black, NOT currently recommended. The group discussed the request from local consultants to use degludec for 4 defined cohorts of patients but considered that currently there is insufficient evidence available to support its use as a cost effective treatment option.

GLP-1 mimetics

- Status is Green for Exentatide (twice daily and weekly preparations), Liraglutide 1.2 mg, Lixisenatide

Combination insulin and GLP-1 mimetic (Feb 2012)

- Status is Amber

Evidence review

NICE have published an Evidence summary: new medicine for Xultophy in type 2 diabetes, which is attached that summarises the evidence for Xultophy (4). The All Wales Medicines Strategy Group has also published an Assessment Report for Xultophy (5).

Equity / Stakeholder views (if relevant)

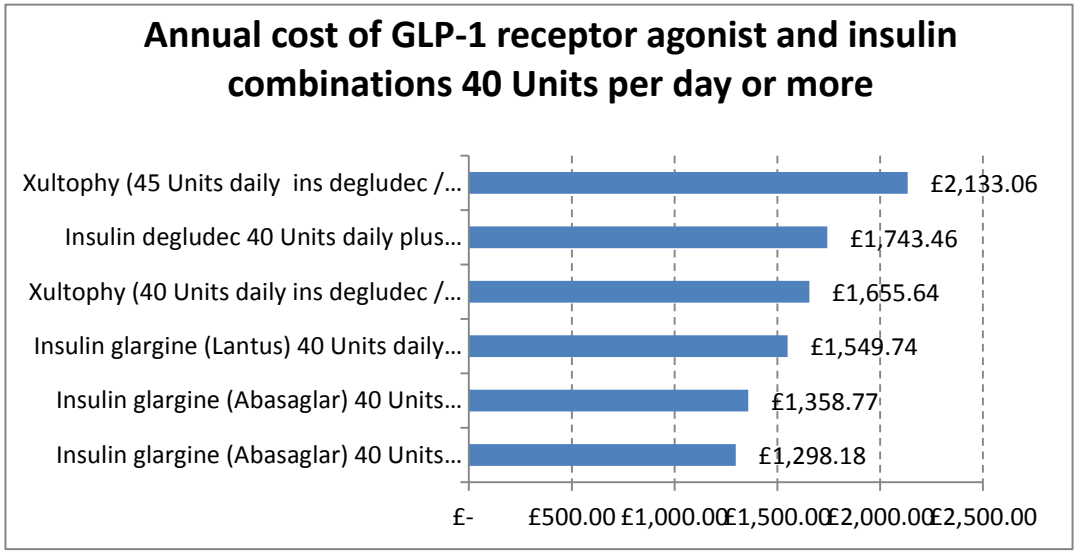
Decisions of local Trusts DTCs and neighbouring APCs	Approved by Royal Surrey County Hospital Drug and Therapeutics Committee with the view to using it in a small cohort of patients who are uncontrolled on basal insulin analogues (HbA1c > 59 mmol/mol (7.5%), and for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy to basal insulin to obtain glucose control. Epsom St Helier Drug and Therapeutics Committee: To add Xultophy® to the Trust formulary in line with its licensed indications for patients with poorly controlled type 2 diabetes who are on basal insulin and in whom addition of quick acting insulin is undesirable or contraindicated and in whom separate injection of a GLP-1RA is not tolerated. Initiation by Consultant Endocrinologist only with supplies from the hospital until further review
Recommendations from national / regional decision making groups	*SMC*: Agreed for restricted use 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. SMC has restricted its use to patients who are uncontrolled on basal insulin analogues (glycosylated haemoglobin [HbA1c] >7.5% [59mmol/mol]) and for whom a GLP-1

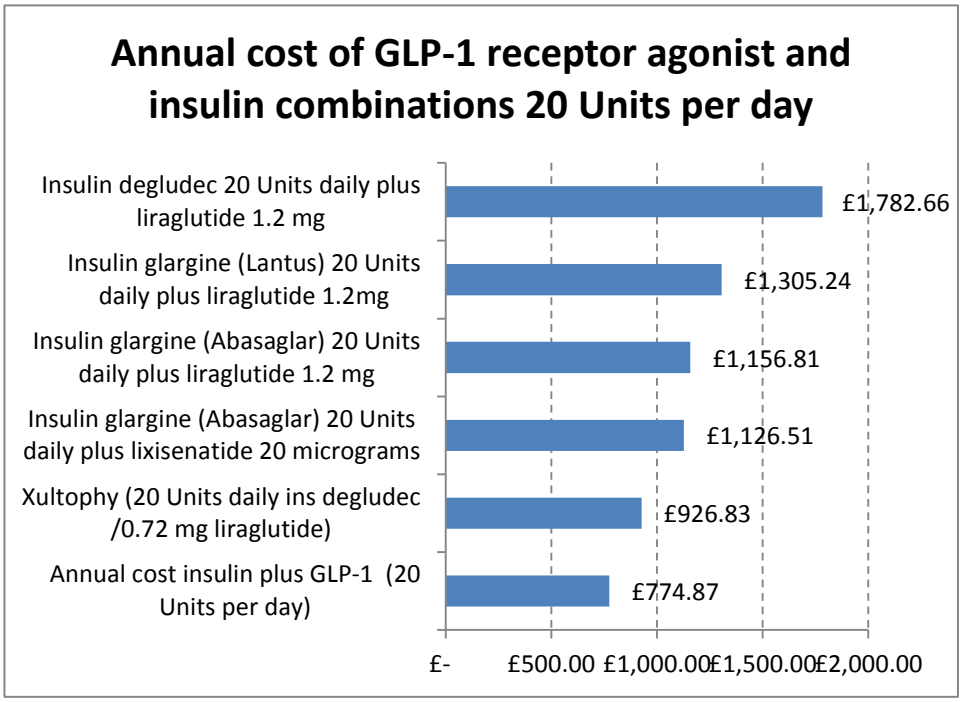
	receptor agonist is appropriate as an add-on intensification therapy to basal insulin to obtain glucose control. *All Wales Medicines Strategy Group:* Agreed for restricted for use in combination with oral glucose-lowering medicinal products when these combined with basal insulin do not provide adequate glycaemic control. Xultophy is not recommended for use within NHS Wales outside of this subpopulation. *Pan Mersey Area Prescribing Committee:* Black status – not recommended *Greater Manchester Medicines Group:* Not recommended *Portsmouth and South East Hampshire Area Prescribing Committee:* Not recommended – non-formulary *Crawley, Horsham and Mid Sussex CCGs:* Not recommended – non-formulary *Basingstoke, Southampton and Winchester District Prescribing Committee:* Not supported for routine local use currently. It may be suitable for exceptional use but should be reserved for specialist only prescribing (i.e. 'red') at this stage. *Oxfordshire Area Prescribing Committee*: Xultophy should only to be initiated by local diabetes consultants according to agreed criteria and following successful completion of a Prior Approval process *Leicestershire Health Community Formulary:* Restricted to specialist diabetology initiation at UHL. Primary care initiation conditional on appropriate competency. Otherwise simple amber.
Stakeholder views	See attached comments
CCG priorities	Diabetes is an important national priority. CCG Priorities for diabetes and obesity as set out in 2016/17 planning guidance are the diabetes prevention programme and reducing variation in management and care for people with diabetes.

Health economic considerations

Cost per year per patient

- Insulin degludec/liraglutide is available in packs of 5×3 ml prefilled pens at a cost of £159.22 per pack (BNF Dec 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).



Alternative treatments cost per patient per year	 Annual comparative doses given for 40 Units per day of insulin. Average daily insulin dose used in DUAL II study was 45 Units per day.
Health economic data (if available)	NICE was unable to do a health economic analysis of the combination of GLP-1 receptor agonists with insulin for it's recent type 2 diabetes guideline because of the lack of evidence for the combination.

References

1. Xultophy Summary of Product Characteristics updated 27 November 2015 http://www.medicines.org.uk/emc/medicine/29493
2. Public Health England, Public Health Profiles www.fingertips.phe.org.uk
3. National Institute for Health and Care Excellence (2015) Type 2 diabetes in adults: management. NICE guideline NG28
4. National Institute for Health and Care Excellence (2015) Type 2 diabetes: insulin degludec/liraglutide (Xultophy). ESNM 60
5. AWMSG Secretariat Assessment Report Sept 2015. Insulin degludec/liraglutide (Xultophy) 100 units/3.6mg per ml solution for injection. Reference number: 2544.

Date: December 2015

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