

insulin degludec/liraglutide 100 units/mL / 3.6mg/mL solution for injection pre-filled pen (Xultophy®) SMC No. (1088/15)

Novo Nordisk A/S

4 September 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

insulin degludec/liraglutide (Xultophy®) is accepted for restricted use within NHS Scotland.

Indication under review: 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 with basal insulin do not provide adequate glycaemic control.

SMC restriction: for use in 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.

In two phase III studies treatment with insulin degludec/liraglutide resulted in a significant reduction from baseline to week 26 in HbA1c compared with the basal insulin comparators.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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 with basal insulin do not provide adequate glycaemic control.

Dosing Information

Insulin degludec/liraglutide is given once daily by subcutaneous (SC) administration, administered at any time of the day, preferably at the same time of the day.

Insulin degludec/liraglutide is to be dosed in accordance with the individual patient's needs. It is administered as dose steps. One dose step contains 1 unit of insulin degludec and 0.036mg of liraglutide. The pre-filled pen can provide from 1 up to 50 dose steps in one injection in increments of one dose step. The maximum daily dose of insulin degludec/liraglutide is 50 dose steps (50 units insulin degludec and 1.8mg liraglutide). The dose counter on the pen shows the number of dose steps.

Transfer from basal insulin

Therapy with basal insulin should be discontinued prior to initiation of insulin degludec/liraglutide. When transferring from basal insulin therapy, the recommended starting dose of insulin degludec/liraglutide is 16 dose steps (16 units insulin degludec and 0.6mg liraglutide). The recommended starting dose should not be exceeded. Close glucose monitoring is recommended during the transfer and in the following weeks.

Add-on to oral glucose lowering medicinal products

The recommended starting dose of insulin degludec/liraglutide is 10 dose steps (10 units insulin degludec and 0.36mg liraglutide). Insulin degludec/liraglutide can be added to existing oral anti-diabetic treatment. When insulin degludec/liraglutide is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered.

Product availability date

November 2014

Summary of evidence on comparative efficacy

Insulin degludec/liraglutide (Xultophy[®]) is the first combination product containing a basal insulin plus glucagon-like peptide 1 (GLP-1) receptor agonist for the treatment of type 2 diabetes mellitus that has gained marketing authorisation.¹ The submitting company has requested that SMC considers insulin degludec/liraglutide when positioned for use in 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. Liraglutide has been accepted for use in NHS Scotland for use in combination with basal insulin whereas insulin degludec has not been recommended for use by SMC.

Evidence relevant to the positioning is from two randomised, double-blind (DUAL II) or open-label (DUAL V) phase III studies, conducted in patients aged ≥18 years with inadequately

controlled type 2 diabetes (HbA1c of 7.5% to 10.0%) and a body mass index (BMI) $\geq 27\text{kg/m}^2$. Patients were required to be inadequately controlled on basal insulin (stable dose of 20 to 40 units) plus metformin, with or without sulfonylurea/glinides (in DUAL II only). DUAL II randomised patients equally, stratified according to pre-study treatment (with or without sulfonylurea/glinide), to SC treatment with insulin degludec/liraglutide (starting dose 16 units/0.6mg) or insulin degludec (starting dose 16 units) for 26 weeks. DUAL V randomised patients equally to SC treatment with insulin degludec/liraglutide (dose as for DUAL II) or insulin glargine (pre-study dose) for 26 weeks. All patients received oral metformin at the pre-study dose and discontinued other oral anti-diabetic drugs. Doses of SC treatments were adjusted twice weekly according to a predefined titration algorithm, based on a pre-breakfast, fasting plasma glucose target of 4.0 to 5.0mmol/L. The maximum dose of insulin degludec/liraglutide was 50 units/1.8mg, of insulin degludec was 50 units (DUAL II) and there was no maximum for insulin glargine (DUAL V). The primary endpoint was the mean change in HbA1c from baseline to week 26; primary and some secondary endpoints are reported in table 1.²⁻⁶

Table 1: Primary and some secondary endpoints from the DUAL II and DUAL V studies^{2,4,6}

	DUAL II		DUAL V	
	insulin degludec/ liraglutide (n=199)	insulin degludec (n=199)	insulin degludec/ liraglutide (n=278)	insulin glargine (n=279)
Primary endpoint				
Change from baseline in HbA1c at week 26				
Baseline HbA1c	8.8%	8.9%	8.4%	8.2%
Change at week 26, %	-1.9%	-0.9%	-1.8%	-1.1%
Estimated treatment difference (95% CI), p-value	-1.1% (95% CI: -1.3 to -0.8) p<0.0001		-0.59% (95% CI: -0.74 to -0.45), p<0.001	
Secondary endpoints				
Dose of insulin at week 26				
Dose, units	45 units	45 units	41 units	66 units
Treatment difference (95% CI), p-value	-0.02 units (95% CI: -1.88 to 1.84)		-25.47 units (95% CI -28.90 to -22.05) p<0.001	
Responders, HbA1c <7.0% at week 26				
Responders, %	60%	23%	72%	47%
Odds ratio, (95% CI), p-value	5.44, (95% CI: 3.42 to 8.66), p<0.0001		3.45 (95% CI: 2.36 to 5.05) p<0.001	
Responders, HbA1c ≤6.5% at week 26				
Responders, %	45%	13%	55%	31%
Odds ratio, (95% CI), p-value	5.66, (95% CI: 3.37 to 9.51), p<0.0001		3.29 (95% CI: 2.27 to 4.75) p<0.001	
Mean change from baseline in weight at week 26				
Change at week 26, kg	-2.7kg	0kg	-1.4kg	+1.8kg
Estimated treatment difference (95% CI), p-value	2.5kg, (95% CI: -3.2 to -1.8), p<0.0001		-3.20kg (95% CI: -3.77 to -2.64) p<0.001	

CI=confidence interval

In DUAL II and DUAL V, the proportions of responders with HbA1c <7.0% or HbA1c $\leq$ 6.5% plus no hypoglycaemia; no weight gain; or no hypoglycaemia and no weight gain were significantly higher for insulin degludec/liraglutide than the comparator.^{2,6}

Quality of life was assessed in the DUAL V study only, using the treatment related impact measure for diabetes (TRIM-D) and short-form 36 version 2 (SF-36 v2) questionnaires. For TRIM-D, a total score was calculated by summing five sub-domains with the total score and the sub-domains transformed to a 1 to 100 scale. The change from baseline was significant in favour of insulin degludec/liraglutide for total score (treatment difference 2.8, 95% CI: 0.9 to 4.7, $p=0.003$) and the sub-domains of treatment burden (treatment difference 3.7, 95% CI: 0.7 to 6.8, $p=0.017$) and diabetes management (treatment difference 7.2, 95% CI: 4.2 to 10.2, $p<0.001$). The SF-36 v2 is a generic non-disease specific measure which contains 36 items covering eight domains of functional health and well-being, as well as two component summary scores of physical and mental health. Scores were transformed to a 1 to 100 scale. There were significant improvements in the physical component summary (treatment difference 1.9, 95% CI: 0.8 to 3.1, $p<0.001$) and three of the physical domain scores (physical functioning [treatment difference 1.4, 95% CI: 0 to 2.7, $p=0.045$], bodily pain [treatment difference 2.0, 95% CI: 0.4 to 3.6, $p=0.012$] and general health [treatment difference 1.7, 95% CI: 0.4 to 2.9, $p=0.008$]), in favour of insulin degludec/liraglutide. Mental component scores and the mental domain scores were similar between the two groups.^{6,7}

Summary of evidence on comparative safety

In DUAL II, the rates of adverse events per patient-year of exposure were similar between the groups: 4.0 versus 3.6 in the insulin degludec/liraglutide and insulin degludec groups respectively. Adverse events leading to withdrawal occurred in one patient (<1%) in the insulin degludec/liraglutide group and three patients (1.5%) in the insulin degludec group; none was considered related to study medication. Confirmed hypoglycaemia comprised episodes confirmed by plasma glucose <3.1mmol/L (56mg/dL), regardless of symptoms, or severe episodes (requiring assistance of another person) and occurred in a similar proportion of patients in both groups (24.1% versus 24.6%). However, the rate of confirmed hypoglycaemic episodes was 153.4 events per 100 patient-years of exposure for insulin degludec/liraglutide and 263.3 events per 100 patient-years of exposure for insulin degludec. Nocturnal confirmed hypoglycaemia (defined as a confirmed hypoglycaemic episode that occurred between 0:01 and 5:59am [inclusive]) occurred in 6.0% of patients in the insulin degludec/liraglutide group and 8.5% of patients in the insulin degludec group.^{2,3}

In DUAL II, treatment-emergent adverse events occurring in $\geq 5\%$ of patients in either group included nausea (6.5% versus 3.5%), diarrhoea (6.5% versus 3.5%), headache (6.0% versus 2.0%), nasopharyngitis (2.5% versus 6.0%) and increased lipase (6.0% versus 3.5%) in the insulin degludec/liraglutide and insulin degludec groups respectively. No patients discontinued from the study because of gastrointestinal adverse events.^{2,3}

In DUAL V, rates of confirmed hypoglycaemia and nocturnal hypoglycemia (definitions as in DUAL II) were significantly lower with insulin degludec/liraglutide, titrated to a capped maximum dose of 50 units/1.8mg than insulin glargine, which could be titrated with no capped maximum dose. The most frequently occurring adverse events ($\geq 5\%$) for insulin degludec/liraglutide and insulin glargine, respectively, were nausea (9.4% and 1.1%), diarrhoea (7.2% and 2.5%), vomiting (5.0% and 1.8%), and headache (4.0% and 5.0%).^{4,6,8}

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers insulin degludec/liraglutide for use in patients who are uncontrolled on basal insulin analogues and for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy to basal insulin. SMC has previously accepted liraglutide, exenatide and lixisenatide, for use in combination with basal insulin. Basal insulins which have been accepted for use by SMC include insulin glargine and insulin detemir, while insulin degludec has not been recommended. Liraglutide plus basal insulin is considered the key comparator by the submitting company. The Scottish Intercollegiate Guidelines Network (SIGN) notes several options added to metformin and/or sulfonylurea for third-line treatment of type 2 diabetes mellitus, which include GLP-1 receptor agonists or commencement of insulin although order or preference is not stated. SIGN notes that GLP-1 receptor agonists should be used in patients with BMI $>30\text{kg/m}^2$, with a desire to lose weight and usually <10 years from diagnosis.⁹ Experts consulted by SMC considered that in patients with type 2 diabetes mellitus uncontrolled on oral anti-diabetic drugs, GLP-1 receptor agonists may be commenced first and then basal insulin if uncontrolled.

In the pivotal studies, in patients receiving concomitant metformin, the decrease in HbA1c was significantly superior for insulin degludec/liraglutide versus the basal insulin comparators. Responder rates confirmed this benefit. European Medicines Agency (EMA) guidance recommends justification of the clinical relevance of the treatment effect by presenting responder analyses (HbA1c $\leq 7\%$ and/or 6.5%) across the different treatment groups.¹⁰

However, the studies have limitations. Both compared insulin degludec/liraglutide with basal insulin, which is not a relevant comparator for the current submission. Additionally, in DUAL II, the maximum dose of insulin degludec was 50 units; therefore, the study does not fully reflect the glucose lowering or adverse events of fully titrated basal insulin. Consequently, conclusions that can be drawn in terms of direct comparisons with real-life treatment with insulin degludec are limited. Patients received concomitant oral anti-diabetic treatment with metformin and there are no data on use with other oral treatments. The open-label design of DUAL V may have introduced bias, and in this study the capped dose for insulin degludec versus no maximum dose for insulin glargine may account to some extent for the differences in rates of hypoglycaemia and nocturnal hypoglycaemia.

The studies were of 26 weeks duration. While HbA1c has been linked with reductions in the long-term complications of diabetes, there are no direct health outcome data demonstrating that insulin degludec/liraglutide reduces micro- and/or macro-vascular complications. However, HbA1c is an established measure of glucose control over the preceding two to three months and has been shown in large well-controlled studies to be linked to risk of diabetic complications.¹⁰

In the UK, HbA1c results are expressed as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.0% are 48mmol/mol and 53mmol/mol in the new units.¹¹

There are no direct comparative data versus a treatment strategy of GLP-1 receptor agonist plus basal insulin in addition to oral antidiabetic medicines. The submitting company included a pooled analysis of five studies conducted by Novo Nordisk using patient level data.¹² The

purpose was to compare insulin degludec/liraglutide with alternative treatment regimens for intensifying basal insulin: liraglutide plus basal insulin (glargine or detemir), basal plus bolus insulin (insulin glargine + insulin aspart) and basal insulin only (up-titration of insulin glargine). Endpoints included change in HbA1c and weight, mean daily basal insulin dose and responder rates. The results suggest that insulin degludec/liraglutide is similar to liraglutide plus basal insulin, except for change in HbA1c where the difference was significant in favour of insulin degludec/liraglutide. These data were used in the economic model. The pooled analysis has some limitations, including use of Novo Nordisk sponsored studies only (to allow use of patient level data) so that a comparison with other GLP-1 receptor agonists was not possible. Other issues are that the comparison was not randomised, with the relative effect being ignored, and an assumption that the error for each arm was fixed meaning that variability will be underestimated. A network meta-analysis (NMA), also included in the submission to SMC, was considered by the company to have limitations and therefore was not used to inform the economic model. However, in the NMA liraglutide plus basal insulin was better than insulin degludec/liraglutide for HbA1c endpoints, and insulin degludec/liraglutide better than liraglutide plus basal insulin for hypoglycaemia and non-severe hypoglycaemia. Therefore, given the differences with the indirect data available from the pooled analysis and the NMA, a conclusion of similar efficacy between insulin degludec/liraglutide and liraglutide plus basal insulin is uncertain.

The availability of insulin degludec/liraglutide may offer some advantages for the patient in terms of one or two fewer subcutaneous injections per day, which will need to be balanced against the restrictions of a fixed dose combination product. Clinical experts consulted by SMC noted that fixed dose combination products have limited use due to inflexibility in individualising the patient's treatment regimen.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing insulin degludec/liraglutide with basal insulin (insulin detemir or insulin glargine) plus liraglutide in patients who are uncontrolled on basal insulin analogues and for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy. The economic analysis was based on the published CORE diabetes model which is based on a series of sub-models with a semi-Markov structure. The model simulates the various complications associated with diabetes over a lifetime (40-year) time horizon, including both cardiovascular and non-cardiovascular fatal and non-fatal events, and all cause mortality.

No direct study data were available comparing insulin degludec/liraglutide with basal insulin plus liraglutide. As noted above, a NMA was conducted but was found to have limitations such that the submitting company considered the results to be unreliable for use in the economic model. For this reason, a pooled naive indirect comparison approach was undertaken using patient-level data to estimate the relative effectiveness of the relevant treatments. The results of this analysis suggested that insulin degludec/liraglutide is similar to basal insulin plus liraglutide, except for change in HbA1c where the difference was statistically significant in favour of insulin degludec/liraglutide. There were no other statistically significant differences between the treatments but the numerical differences in other outcomes were included in the model.

The treatment effect was assumed to be applied in the model for 1 year. Beyond this period, long term effectiveness was based on UKPDS 68 risk equations for HbA1c progression, systolic

blood pressure progression and cardiovascular disease risk. For total cholesterol progression, HDL cholesterol and LDL cholesterol, the Framingham equation was used. For BMI progression the treatment effect was assumed to remain constant over the duration of time on treatment (up to 3 years) and then any treatment differences were removed.

The utility values were taken from a published study where utility values were estimated from UK patients with T2DM using EQ-5D. The disutilities associated with hypoglycaemia were taken from a separate published study as the company considered the values from this study to be more appropriate.

The analysis included medicines cost, costs of strips and lancets for self-monitoring of blood glucose levels, and needle costs. Costs associated with adverse events were not included but the exclusion of these costs would not introduce any bias in the model given the evidence suggests there is likely to be little difference between the treatments. Other costs included patient management costs (concomitant medications, screening for renal disease, retinopathy and diabetic foot complications) and post-complication management costs. Health state event costs were also included.

In the base case analysis, the company estimated that insulin degludec/liraglutide would dominate basal insulin plus liraglutide (i.e. it was more effective and less costly) with estimated savings of £698 and a QALY gain of 0.113.

A range of one-way and probabilistic sensitivity analyses (PSA) were conducted. In the one-way sensitivity analysis, insulin degludec/liraglutide remained dominant in the majority of scenarios and the highest cost per QALY was £6k when the comparator cost was changed to reflect the cost of lixisenatide. A key sensitivity analysis was the exclusion of the non-significant differences between the treatments, but this did not alter the conclusion of dominance. The PSA showed there was a 98% probability of insulin degludec/liraglutide being cost-effective at a willingness to pay threshold of £20k per QALY.

The following limitations were noted:

- The base case analysis estimates that insulin degludec/liraglutide is more effective than basal insulin plus liraglutide based on the results of the pooled indirect comparison analysis. However, there are several weaknesses with the indirect comparison approach used to estimate the relative treatment effects and using an alternative NMA approach resulted in contradictory results. Therefore, the clinical data used to derive the base case estimates are uncertain.
- The analysis included some differences in outcomes from the pooled indirect comparison analysis that were not statistically significant and, given the limitations with the indirect evidence, a cost-minimisation analysis was requested. This analysis showed insulin degludec/liraglutide was cost-saving compared to basal insulin plus liraglutide based on mean doses from the pooled analysis with estimated savings of £375 per year. Sensitivity analysis was also provided which assumed equivalent dosing in each arm and this analysis resulted in equivalent drug costs but an overall saving of £35 per year with insulin degludec/liraglutide due to a reduction in the number of needles required with the combination product.
- The analysis did not explore the cost-effectiveness of insulin degludec/liraglutide when compared to basal insulin used in combination with other GLP-1 receptor agonists used in practice, such as lixisenatide and exenatide. These treatments are available at a lower cost

than liraglutide. However, prescribing information indicates liraglutide has the largest market share.

Despite the limitations outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Diabetes Scotland, which is a registered charity.
- Diabetes Scotland has received pharmaceutical company funding in the past two years, including from the submitting company.
- Type 2 diabetes is not easy to live with, and has a big impact on the day to day lives of people with the condition, their carers and families. It is a progressive condition and it is often difficult for people to attain and maintain glycaemic targets. This puts them at risk of potentially devastating complications such as blindness, amputation, renal disease and reduced life expectancy due often to coronary heart disease and stroke. The anxiety associated with diabetes can be 'socially isolating' and the balancing act of managing diabetes is, for some, overwhelming.
- There is evidence that this dual treatment is effective at lowering blood glucose levels with no increase in the risk of hypoglycaemia compared with basal insulin alone. One of the major impacts of starting insulin and injectables is the anxiety associated with hypoglycaemia. A single injection will be easier to adapt to, and there may also be reduced risk of insulin errors because of the pre-filled step dosing.
- Any treatment regimen which improves glycaemic control and improves the person's quality of life has the potential to positively impact on family members and or carers.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the "Management of diabetes" in March 2010.⁹ The guideline recommends that treatment targets should be individualised to balance the harms of hypoglycaemia and weight gain with the benefits in reducing the risk of microvascular and macrovascular disease. Target glycosylated haemoglobin (HbA1c) of 7.0% (53mmol/mol) is reasonable in people with type 2 diabetes mellitus, and in newly diagnosed patients, this target may be intensified to 6.5% (48mmol/mol). The treatment algorithm notes several options for second and third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Treatment should be continued if an individualised target is reached or the HbA1c falls at least 0.5% in 3 to 6 months. With respect to using insulin in patients with type 2 diabetes, oral sulphonylurea and metformin therapy should be continued when insulin is initiated to maintain or improve glycaemic control. Once daily, neutral protamine Hagedorn insulin is the first choice of insulin to be used, but basal insulin analogues can be considered if there are concerns regarding the risk of hypoglycaemia. The bedtime basal insulin should be

titrated against the morning or fasting glucose and if HbA1c targets are not reached then the addition of prandial insulin should be considered. SIGN currently recommend GLP-1 agonists (exenatide or liraglutide) may be used as a third line agent to further improve glycaemic control in obese adults (BMI $\geq 30\text{kg/m}^2$) with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia.

The National Institute for Health and Care Excellence published NICE Clinical Guideline 87 – Type 2 diabetes - newer agents, in May 2009.¹³ The guideline considered sulfonylurea, DPP-4 inhibitors or pioglitazone as suitable second-line options to be used in combination with metformin and advised on cost effective use of exenatide as a third-line agent. The guideline recommended that patients using basal insulin regimens (e.g. neutral protamine Hagedorn or long-acting analogues) be monitored for the need to increase the dose and/or intensify the regimen using short-acting insulin before meals, or pre-mixed insulin. Patients using pre-mixed insulin should be monitored to determine if they need further injections of short-acting insulin before meals or conversion to a basal-bolus regimen. Combination of pioglitazone and insulin was considered appropriate for patients; who have inadequate glycaemic control despite high-dose insulin therapy; or who have had a significant response to thiazolidinedione therapy in the past.

Additional information: comparators

GLP-1 receptor agonist plus a long-acting insulin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
insulin degludec / liraglutide	16 units/0.6mg to 50 units/1.8mg by subcutaneous injection once daily	618 to 1,932
<i>GLP-1 receptor agonists</i>		
liraglutide	1.2 to 1.8mg by subcutaneous injection once daily	952 to 1,428
exenatide	5 to 10 micrograms by subcutaneous injection twice daily	828
lixisenatide	20 micrograms by subcutaneous injection once daily	657
<i>Long acting insulins</i>		
insulin glargine	dose according to requirements (eg 30 to 60 units per day) by subcutaneous injection once daily	302 to 604
insulin detemir	dose according to requirements (eg 30 to 60 units per day) by subcutaneous injection once daily	306 to 612
isophane insulin	dose according to requirements (eg 30 to 60 units per day) by subcutaneous injection once daily	139 to 278

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 25 June 2015.

Additional information: budget impact

The submitting company estimated there would be 3,567 patients eligible for treatment in each year. The estimated uptake rate was 5% in year 1 and 13% in year 5 with a discontinuation rate of 5% applied each year. This resulted in 169 patients estimated to receive treatment in year 1 rising to 441 patients in year 5.

The gross medicines budget impact was estimated to be £248k in year 1 rising to £646k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £14k in year 1 rising to £37k in year 5. The net budget impact estimated by the submitting company assumes displacement of liraglutide, exenatide and lixisenatide.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Summary of product characteristics for insulin degludec/liraglutide (Xultophy®). Nova Nordisk. 18 September 2014.
2. Buse JB, Vilsboll T, Thurman J, et al. Contribution of Liraglutide in the Fixed-Ratio Combination of insulin degludec and liraglutide (IDegLira). Diabetes Care 2014: 2926-33.
3. European Medicines Agency. European Public Assessment Report for insulin degludec/liraglutide (Xultophy®). EMA/CHMP/369341/2014. 24 July 2014.
4. Buse J et al. Insulin Degludec/Liraglutide (IDegLira) Is superior to insulin glargine (IG) in A1c reduction, risk of hypoglycaemia and weight change: DUAL V Study. Oral presentation (160-OR) at the 75th Scientific Sessions of the American Diabetes Association (ADA), 7 June 2015. Boston, MA.
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8. Website:<http://www.prnewswire.com/news-releases/new-ideglira-phase-3b-study-showed-statistically-significant-hba1c-reduction-body-weight-change-and-lower-rate-of-hypoglycaemia-versus-insulin-glargine-506406071.html>
9. Scottish Intercollegiate Guidelines Network. Guideline number 116; management of diabetes. March 2010 (revisions May 2011, May 2014).
10. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). 14 May 2012.
11. BNF June 2015.
12. Freemantle N, Mamdani M, Vilsbøll T et al. Ideglira versus other intensification strategies in patients with type 2 diabetes inadequately controlled on basal insulin- an indirect statistical comparison. Poster presented at the ISPOR 20th Annual International Meeting, 16–20 May 2015, Philadelphia, PA, USA.
13. National Institute for Health and Clinical Excellence. NICE Clinical Guideline 87 - Type 2 diabetes: the management of type 2 diabetes. May 2009 [online] Available from www.nice.org.uk

This assessment is based on data submitted by the applicant company up to and including 14 August, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.