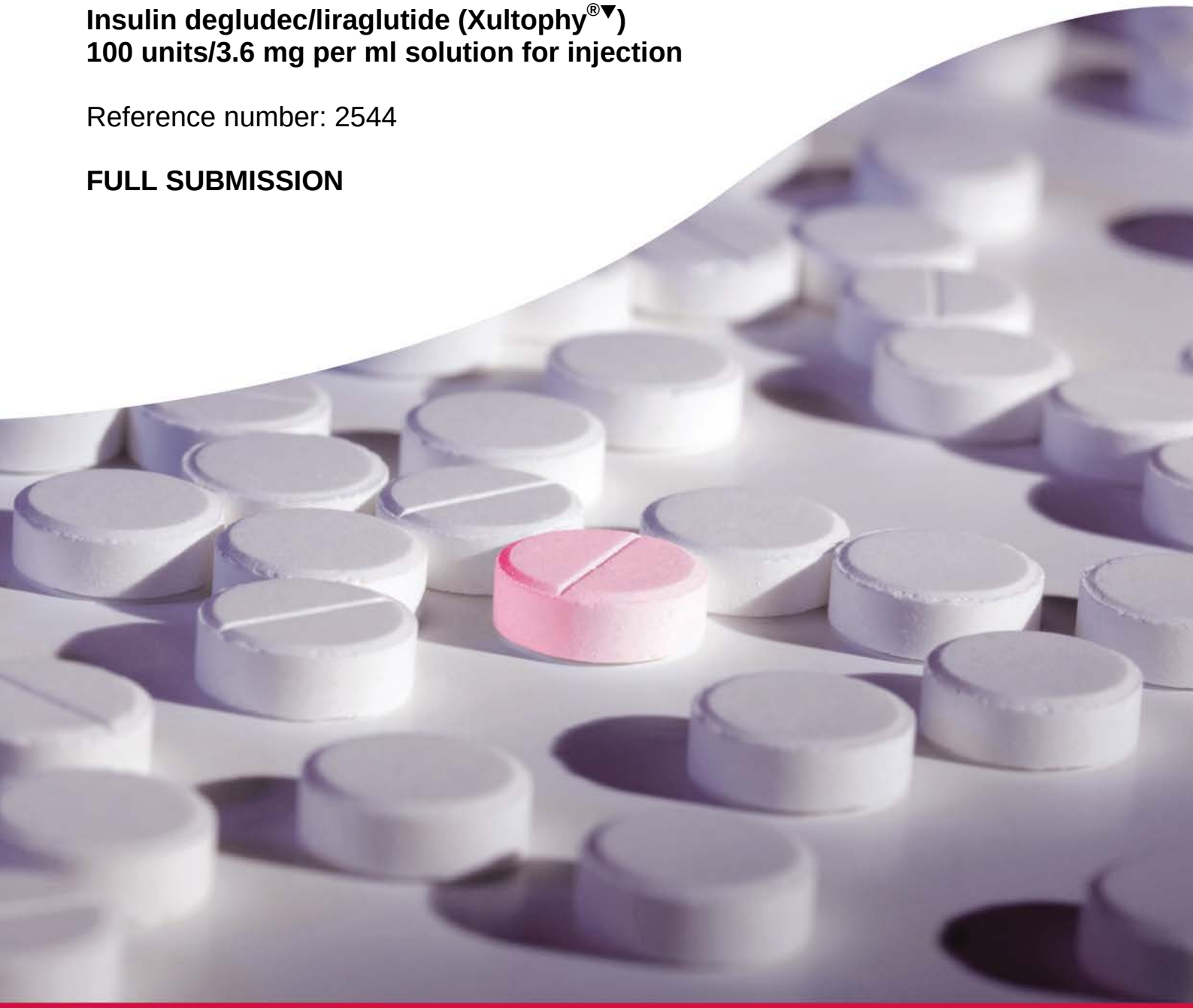
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Insulin degludec/liraglutide (Xultophy®▼)
100 units/3.6 mg per ml solution for injection

Reference number: 2544

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Insulin degludec/liraglutide (Xultophy®▼) 100 units/3.6 mg per ml solution for injection

This assessment report is based on evidence from a full submission by Novo Nordisk Ltd on 20th April 2015.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Insulin degludec/liraglutide (Xultophy®▼) 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 glucagon-like peptide protein-1 (GLP-1) receptor agonist or basal insulin do not provide adequate glycaemic control[1].
Dosing	Dosing is by dose steps, once daily by subcutaneous injection. One dose step contains 1 unit of insulin degludec and 0.036 mg liraglutide. The maximum daily dose is 50 dose steps (50 units of insulin degludec and 1.8 mg liraglutide). Dose should be adjusted based on fasting plasma glucose in accordance with the individual patient's needs. Refer to the Summary of Product Characteristics for further information regarding missed doses, method of administration and special populations[1].
Marketing authorisation date	18 September 2014[2]

2.0 DECISION CONTEXT

2.1 Background

Type 2 diabetes mellitus (T2DM) is a chronic condition in which the pancreas either stops producing enough insulin or the body becomes resistant to the effects of insulin produced, resulting in elevated blood glucose levels (hyperglycaemia)[3–5] which, if left untreated can lead to macrovascular disorders (ischaemic heart disease, peripheral artery disease and stroke) and microvascular complications (eye damage, kidney damage and nerve damage). In Wales the number of patients diagnosed with diabetes mellitus in 2013 was 173,299, a prevalence of 6.7%[3]. T2DM accounts for approximately 90% of all cases of diabetes, equating to approximately 156,000 patients in Wales in 2013[3–5].

T2DM can often be managed initially with diet and exercise, however, over time most patients will require oral drugs and/or insulin[4,6]. The current National Institute for Health and Care Excellence (NICE) pathway for blood glucose lowering therapy for T2DM recommends use of insulin if glycated haemoglobin (HbA_{1c}) is ≥ 58 mmol/mol (7.5%) or agreed target despite dual and/or triple oral anti-diabetic therapy[7]. If HbA_{1c} continues at ≥ 58 mmol/mol (7.5%) or agreed target, intensification of the insulin regimen or addition of other medicines is the final stage in the treatment pathway[6,7].

Insulin degludec/liraglutide (IDegLira) (Xultophy®▼) is a fixed ratio combination of the long acting basal insulin analogue insulin degludec with liraglutide, a glucagon-like peptide protein-1 receptor agonist (GLP-1 RA)[8]. The mechanism of action of the GLP-1 RAs is to mimic the effects of the endogenous incretin hormone, increasing insulin secretion and inhibiting glucagon release when glucose levels are elevated[9].

IDegLira is licensed for use in patients with T2DM in combination with oral antidiabetic medicines when these alone or combined with a GLP-1 RA or basal insulin do not provide adequate glycaemic control. The company have focused their submission on the use of IDegLira as an add-on therapy for patients whose glucose levels are uncontrolled on basal insulin; this is a narrower population than the licensed indication.

2.2 Comparators

The comparators included in the company submission were:

- Liraglutide (Victoza®) plus insulin glargine (IGlar) (Lantus®)
- Exenatide (Byetta®) plus IGlar (Lantus®)
- Lixisenatide (Lyxumia®▼) plus IGlar (Lantus®)

The comparators considered by the company were identified through the review of prescribing data and results of a physician survey for Wales which suggested that insulin glargine plus liraglutide is the most popular intensification option[8]. Lixisenatide is however the only GLP-1 RA recommended in combination with insulin for use in Wales[10]. In the absence of a submission from the holder of the marketing authorisation, exenatide (Byetta®) and liraglutide (Victoza®) are not endorsed for use in Wales in combination with insulin[11,12].

AWTTC-sought clinical expert opinion, confirmed that the most widely used intensification regimen in Wales is insulin glargine plus a GLP-1 RA and liraglutide is currently the most common choice of GLP-1 RA in Wales (see section 3.5).

2.3 Guidance and related advice

- NICE pathway. Blood-glucose-lowering therapy for type 2 diabetes. Updated 2015[7].
- NICE technology appraisal (TA) 248. Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. 2012[13].
- NICE TA203. Liraglutide for type 2 diabetes mellitus[14].
- NICE clinical guideline 87. Type 2 diabetes. The management of type 2 diabetes. 2009[15]. (Update due August 2015).
- Welsh Assembly Government. Designed for the management of adults with diabetes mellitus across Wales: consensus guidelines. 2008[16].

AWMSG has previously issued advice not recommending the use of insulin degludec (Tresiba®)[17]. Lixisenatide (Lyxumia®) is recommended as an option for restricted use[10]; exenatide (Byetta®) and liraglutide (Victoza®) (both in combination with basal insulin with/without oral glucose-lowering medicines) have been issued with statements of advice (SOAs) and cannot be endorsed for use in NHS Wales[11,12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company have focused their submission on the treatment of T2DM patients uncontrolled on basal insulin. Details regarding the most relevant studies included in the submission are discussed below. These include two phase III studies comparing the safety and efficacy of IDegLira versus insulin degludec (IDeg) (DUAL II) and IDegLira versus insulin glargine (IGlar) (DUAL V) both in T2DM patients uncontrolled on basal insulin[8]. A systematic review, network meta analysis and pooled analysis of patient level data were provided to address the lack of head-to-head comparative data[8].

3.1 DUAL II (NN9068-3912)

DUAL II was a phase III randomised, double-blind multi-centre treat-to-target study in patients with T2DM uncontrolled* on basal insulin and metformin with or without a sulphonurea or glinides[8,18]. The primary efficacy outcome was the change in HbA_{1c} from baseline after 26 weeks of treatment. Secondary outcomes included the effect of treatment on insulin dose, hypoglycaemic episodes and weight control[8,18].

Patients (n = 398) were randomised 1:1 to receive once-daily subcutaneous injections of either IDegLira or IDeg, all glucose-lowering drugs except for metformin were discontinued at randomisation[18]. The initial dose was 16 units IDeg or 16 dose steps IDegLira (16 units IDeg plus 0.6 mg liraglutide), the dose was adjusted biweekly based on a self-measured prebreakfast fasting plasma glucose (FPG) (mean of three consecutive days) with the aim of reaching a mean FPG concentration of 4.0–5.0 mmol/l. The maximum dose was 50 units IDeg or 50 dose steps IDegLira (50 units IDeg plus 1.8 mg liraglutide)[18].

At 26 weeks the primary endpoint of change in HbA_{1c}, was statistically significantly greater in the IDegLira treatment group compared with the IDeg group. The estimated treatment difference was -12 mmol/mol (95% confidence interval [CI] -14 to -9) (−1.1% [95% CI −1.3 to −0.8]), $p < 0.0001$, demonstrating superiority of IDegLira over IDeg[8,19]. The mean HbA_{1c} at 26 weeks was 52 mmol/mol (6.9%) in the IDegLira group and 64 mmol/mol (8.0%) in the IDeg group[18]. After 26 weeks of treatment the mean actual daily insulin dose was 45 units in both treatment groups. In the IDegLira group 65.3% reached a daily dose of 50 dose steps and 67.3% of the IDeg group reached a daily insulin dose of 50 units[19]. Incidence of hypoglycaemia was similar between treatments groups, the difference in rates was not statistically significant. In the IDegLira group mean body weight decreased by 2.7 kg, there was no change in body weight in the IDeg group, the estimated mean treatment difference was statistically significant, −2.51 kg (95% CI −3.21 to −1.82, $p < 0.0001$)[8,19].

3.2 DUAL V (NN9068-3952)

DUAL V was a phase III randomised, open-label, multicentre, treat-to-target study in patients with T2DM uncontrolled* on insulin glargine (IGlar) and metformin[8,20]. The primary efficacy outcome was the change in HbA_{1c} from baseline after 26 weeks of treatment; the pre-defined non-inferiority limit was 0.30% for IDegLira versus IGlar. Secondary outcomes included; HbA_{1c} responder endpoints, insulin dose at 26 weeks, hypoglycaemic episodes, weight control and patient reported outcomes[8].

Patients (n = 557) were randomised 1:1 to receive once daily IDegLira plus metformin or IGlar plus metformin[8]. The initial dose of IDegLira was 16 dose steps (16 units IDeg plus 0.6 mg liraglutide), IGlar was initiated at the dose that patients were on prior to randomisation (average 32 units). Dose was titrated twice weekly to the FPG target of 4.0–5.0 mmol/l. The maximum dose of IDegLira was 50 dose steps (50 units IDeg plus 1.8 mg liraglutide), there was no maximum dose of IGlar[8].

The company report that at 26 weeks the primary endpoint of change in HbA_{1c}, was statistically significantly greater in the IDegLira treatment group compared with the IGlar group. The estimated treatment difference was −0.59% (95% CI −0.74 to −0.45, $p < 0.001$) demonstrating non inferiority of IDegLira over IGlar. Change in HbA1c was also tested for superiority and treatment with IDegLira was confirmed to be superior to IGlar. Secondary endpoints were supportive of the primary endpoint statistically significantly in favour of IDegLira for all HBA_{1c} responder rates, hypoglycaemic control and reduction in body weight compared to IGlar. Health related quality of life was assessed with the Short Form-36 (SF-36) questionnaire, statistically significant

*Uncontrolled T2DM was defined as a patient with HbA_{1c} of 7.5–10.0% (58–86 mmol/mol)[8,18].

improvements in overall physical score for IDegLira over IGlar were reported. There were no significant differences in scores for mental wellbeing[8].

3.3 Systematic review and pooled analysis

In the absence of head to head studies the company conducted a network meta analysis (NMA), this was not considered to be sufficiently robust due to the heterogeneous design of insulin-based clinical trials[8]. In the absence of a valid NMA the company have provided a systematic review and pooled analysis using trials within the Novo Nordisk clinical trial database[8]. Patient level data from five trials was combined and analysed as a single dataset to obtain an indirect estimate of relative treatment effects of comparator interventions for patients with T2DM uncontrolled on basal insulin. The interventions included were; IDegLira, basal plus bolus insulin (IGlar plus bolus insulin aspart), GLP-1 RA added to basal insulin (liraglutide plus IGlar or insulin detemir [IDet]) or basal insulin (IGlar) only. For the purposes of this analysis current standards of care were based on Welsh prescription data and the results of a survey completed by 15 physicians in Wales[8].

The results of the pooled analysis showed a greater reduction in HbA_{1c} with IDegLira versus all three comparators. Further results comparing IDegLira to liraglutide added to basal insulin showed no significant differences in daily basal insulin dose at end of trial, weight loss or hypoglycaemic events[8].

3.4 Safety

Comparative safety of IDegLira versus IDeg and IGlar was provided from the DUAL II and DUAL V studies. No new safety issues were identified for IDegLira, the most common adverse effects reported were gastrointestinal events due to the liraglutide component[8,19]. The Committee for Medicinal Products for Human Use (CHMP) note that the prevalence and severity of gastrointestinal side-effects were lower compared to liraglutide as monotherapy due to the lower starting dose and slower up-titration of dose of the liraglutide component in the combination product[19]. Although acute pancreatitis has been associated with other GLP-1 RAs, no confirmed episodes were reported with IDegLira, a precautionary warning is included in the Summary of Product Characteristics (SPC)[1,8,19].

3.5 AWTTC critique

- The company have focused their submission on the use of IDegLira as an add on intensification therapy for patients not adequately controlled on basal insulin[8]. This is a subpopulation of patients within the full licensed indication and does not include patients who are uncontrolled on oral glucose lowering medicines alone or combined with a GLP-1 RA[1].
- The comparators considered by the company (see section 2.2) were identified through the review of prescribing data and results of a physician survey for Wales which suggested that insulin glargine plus liraglutide is the most popular intensification option[8].
- Lixisenatide is currently the only GLP-1 RA recommended in combination with insulin for use in Wales[10]. Exenatide (Byetta®) and liraglutide (Victoza®) are not endorsed for use in Wales in combination with insulin[11,12].
- No head-to-head data for IDegLira versus insulin glargine plus lixisenatide, exenatide or liraglutide as separate agents was provided. DUAL II compared IDegLira versus IDeg; however IDeg is not widely used in Wales.
- AWTTC-sought clinical expert opinion confirmed that the most widely used intensification regimen in Wales is insulin glargine plus a GLP-1 RA and liraglutide is the most common choice of GLP-1 RA in Wales. Prescribing data obtained by AWTTC supports the clinical expert opinion that liraglutide is the most widely used GLP-1 RA. The data suggests that lixisenatide is prescribed by some clinicians although this is currently a very small proportion of the total

GLP-1 RA prescribed. There are limitations with the prescribing data as it does not specify the subpopulation outlined in the company submission.

- The only comparison of IDegLira versus basal insulin plus liraglutide was provided by the pooled analysis (see section 3.3).
- No studies using lixisenatide or exenatide were included in the indirect comparison as only data from Novo Nordisk Ltd's own database was used in the pooled analysis.
- The methodology used in the pooled analysis is supported by the European Network for Health Technology Assessment (EUnetHTA) guidelines on how to conduct indirect analyses[21]. The company acknowledge that there were differences between trial design and patient characteristics[8]. Consequently, despite standard adjustment for heterogeneity between treatment arms a number of uncertainties were identified and, as with all such analyses results should be interpreted with caution.
- IDegLira is recommended as a once-daily dose independent of mealtimes at any time of the day (preferably at the same time each day)[1]. This involves fewer daily injections than insulin given with other GLP-1A RAs separately which may be preferable for patients with poor adherence[8].
- CHMP notes that in some patients it may be preferable to titrate the two components of IDegLira separately to monitor the initial patient response and tolerability to each, use of two components separately may also simplify the management of treatment interruption, this would not be possible with the IDegLira combination[19]. The separate components, liraglutide (in combination with insulin) and IDeg are not endorsed or recommended for use in NHS Wales, respectively[12,17].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of IDegLira in adults with T2DM uncontrolled on basal insulin analogues who are considered appropriate for intensification with a GLP-1 RA, this represents a subset of the wider licensed indication.

The company considered the comparators to be:

- Liraglutide (Victoza®) and IGlar (Lantus®) /IDet (Levemir®)
- Lixisenatide (Lyxumia®) and IGlar (Lantus®)
- Exenatide (Byetta®) and IGlar (Lantus®)

(see section 2.2)

The company uses the CORE diabetes model to estimate the incremental costs and health outcomes over a 40-year time horizon. The CORE diabetes model is a Markov-based simulation model based on the UK Prospective Diabetes Study (UKPDS). It uses a set of risk equations, which include HbA_{1c}, weight, systolic blood pressure and lipid parameters, to estimate the incidence of T2DM complications over time and cardiovascular and all-cause mortality. Patient baseline characteristics were derived primarily from the IDegLira arm of the DUAL II study and supplemented with UK-specific published estimates for smoking frequency, alcohol consumption and estimates on background retinopathy and amputation.

The company conducted a NMA to estimate treatment effects. However, the results of this were not used in the economic model as the company concluded that differences in both trial design and patient characteristics were potentially compromising the results. They stated that this was due to differences in both trial design and patient

characteristics between the trials and that the limited evidence base did not allow for mitigation of several potential biases. Instead, a pooled analysis was performed to obtain an indirect estimate of the relative treatment effects of interventions that have not been evaluated directly against each other.

There was no evidence submitted by the company to support the comparison of lixisenatide and exenatide. Effectiveness data were obtained from the results of an indirect comparison from a pooled analysis for IDegLira and liraglutide plus IGlar/IDet. It was assumed that the treatment effects for lixisenatide plus IGlar and exenatide plus IGlar were equal to those of liraglutide plus IGlar or IDet in the base case analysis. Alternative assumptions on treatment effects were considered in scenario analyses. The effectiveness of the subsequent treatment for all arms is based on the results from the pooled analysis for the basal/bolus insulin regimen.

Health state utility values for disease and treatment-related outcomes were identified through the findings of a recently published systematic literature review[22], supplemented with one paper published too late to be included in the review[23]. Costs included in the model were drug acquisition costs, consumable costs (strips, lancets and needles), patient management costs (concomitant medications, screening) and health state and event costs. The costs were obtained from standard costing sources and the published literature.

4.1.2 Results

Results of the base case analysis suggest that IDegLira dominates liraglutide plus IGlar/IDet, and yields incremental cost effectiveness ratios (ICERs) of £8,789 and £6,340 per quality adjusted life year (QALY) gained compared to lixisenatide plus IGlar and exenatide plus IGlar in adult patients with T2DM, respectively (Table 1).

Table 1. Company-reported results of the base case analysis

Treatment	IDegLira	Liraglutide plus IGlar or IDet	Lixisenatide plus IGlar	Exenatide plus IGlar
Costs (£)*	47,643	48,028	46,651	46,927
-Treatment	17,527	17,786	16,409	16,685
-Management	1,914	1,903	1,903	1,903
-CVD	10,099	10,239	10,239	10,239
-Renal	3,311	3,237	3,237	3,237
-Ulcer/Amputation/Neuropathy	11,364	11,355	11,355	11,355
-Eye	2,690	2,729	2,729	2,729
-Hypoglycaemia	738	777	777	777
Life expectancy (years)[1]	12.571	12.491	12.491	12.491
QALYs[1]	8.009	7.896	7.896	7.896
Incremental results for IDegLira versus comparator		**Liraglutide + IGlar/IDet**	**Lixisenatide + IGlar**	**Exenatide + IGlar**
Δ Life expectancy (years)		0.08	0.08	0.08
Δ QALYs		0.113	0.113	0.113
Δ Cost (£)		-385	992	716
Cost / LY gained		Dominant	12,450	8,982
Cost / QALY gained		Dominant	8,789	6,340

*Discounted costs/effects over 40 year time horizon
CVD: cardiovascular disease; IDegLira: insulin degludec/liraglutide; IDet: insulin detemir; IGlar: insulin glargine; LY: life year; QALY: quality-adjusted life year

The company conducted one-way and probabilistic sensitivity analyses to address uncertainty in model parameters. In general, IDegLira was cost-effective in most scenarios compared to the comparator treatments. Of the analyses included in the one-way sensitivity analysis, the parameters having most impact on cost-effectiveness were the discount rate and HbA_{1c} difference. The sensitivity analyses that result in an ICER above £20,000 per QALY gained are presented in Table 2.

Table 2. Company-reported results of the sensitivity analyses with an ICER above £20,000 per QALY gained

	ICER (£/QALY)	Plausible
Comparison with Liraglutide plus+ IGlar/IDet:		
Base case	IDegLira dominates	
6% discount rate for costs and benefits	35,249	Base case uses preferred rate, no reason to deviate from this
Comparison with Lixisenatide plus IGlar:		
Base case	8,789	
6% discount rate for costs and benefits	49,819	Base case uses preferred rate, no reason to deviate from this
HbA_{1c} difference abolished	32,097	Plausible as difference in HbA1c not supported by robust evidence
Comparison with Exenatide plus IGlar:		
Base case	6,340	
6% discount rate for costs and benefits	46,894	Base case uses preferred rate, no reason to deviate from this
HbA_{1c} difference abolished	20,432	Plausible as difference in HbA1c not supported by robust evidence
HbA_{1c}: glycated haemoglobin;.IDegLira: insulin degludec/liraglutide; IDet: insulin detemir; IGlar: insulin glargine;;ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year.		

Scenario analyses were conducted using different treatment effects for the comparisons with lixisenatide plus IGlar and exenatide plus IGlar. A scenario analysis using the NMA results for IDegLira versus lixisenatide plus IGlar was conducted. This resulted in a cost per QALY gained of £6,137. Similarly, two scenario analyses were conducted using an RCT comparing liraglutide to exenatide[18] for IDegLira versus exenatide plus IGlar: (i) the full difference in HbA_{1c} treatment effect from the trial was applied to the exenatide plus IGlar base case inputs from the pooled analysis; and (ii) half of the difference in HbA_{1c} treatment effect from the trial was applied to the exenatide plus IGlar base case inputs from the pooled analysis. This resulted in costs per QALY gained of £800 and £2,644 for the full and half difference scenarios, respectively.

Probabilistic sensitivity analysis undertaken for the base-case analysis indicates that the probability that IDegLira is cost-effective compared to liraglutide plus IGlar/IDet, lixisenatide plus IGlar and exenatide plus IGlar was 98%, 83% and 92%, respectively, at a cost-effectiveness threshold of £20,000 per QALY gained. However, this is dependent on the assumptions in the base case analysis as whilst the company later conducted probabilistic sensitivity on the alternative scenarios presented in the submission, they did not conduct probabilistic sensitivity analysis on all potentially plausible, alternative assumptions.

4.1.3 AWTTC critique

Strengths of the company's economic evidence include:

- The CORE diabetes model used in the economic analysis is an established, validated model which has been used for previous health technology assessments in the economic evaluation of T2DM treatments.

Limitations of the economic evidence include:

- The company's analysis is based on an indirect comparison of IDegLira versus liraglutide plus IGlar/IDet from a pooled analysis, the treatment effects for lixisenatide plus IGlar and exenatide plus IGlar were assumed to be equal to liraglutide plus IGlar/IDet. Due to the lack of direct evidence for the comparator treatments there is uncertainty in the evidence used in the model.
- The pooled analysis was limited to Novo Nordisk conducted trials and there are differences in design between the trials and in patient characteristics. Consequently, despite standard adjustment for heterogeneity between treatment arms a number of uncertainties were identified and, as with all such analyses results should be interpreted with caution.
- The company did not adequately address uncertainty with respect to the treatment effects in the economic analysis. The inputs relating to treatment effects were initially only varied in one way sensitivity analysis. Limited multi-way sensitivity analysis was later provided. Similarly, the probabilistic sensitivity analysis was limited to the assumptions in the base case analysis and scenario analyses, whereby other assumptions may also be plausible.
- The economic analysis was conducted for a subset of the licensed population i.e. patients uncontrolled on basal insulin analogues who are considered appropriate for intensification with a GLP-1 RA. The resulting ICER may therefore not be reflective of the whole licensed indication.
- The company has not adequately justified the dosing assumptions used in the base case analysis, which impacts on total costs. And this was not adequately addressed in the sensitivity analysis.
- Utility weights were obtained from different sources hence adding uncertainty to the analysis. This was not adequately addressed in the sensitivity analysis.
- Although the patient population in the economic analysis is a subgroup itself, the company has not attempted to identify any other meaningful sub-groups in whom cost-effectiveness may be differentiated.

4.2 Review of published evidence on cost-effectiveness

No studies were identified that assessed the cost-effectiveness of IDegLira compared to the identified comparators.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The budget impact was based on a population for Wales of 3,107,165[24], of which 79.5% are adults[25], approximately 6.7% are estimated to have diabetes[3], approximately 90% of those patients have T2DM[3], with approximately 3.2% of adults with T2DM treated with basal insulin analogues[8] and 69% of them uncontrolled on basal insulin[8]. Among this population, a physician survey for Wales consisting of ten general practitioners and five consultants, found that they would consider an intensification treatment for patients with an HbA_{1c} > 8.5%[8]. It was estimated through the use of Cegedim Strategic Data that 61% of T2DM patients on basal insulin have an HbA_{1c} > 8.5%[8]. This equates to 2,005 patients in year 1 rising to 2,037 in year 5.

The company estimates the overall proportion of eligible patients receiving IDegLira will range from 5.0% in year one to 13.0% in year five. Thus the number of patients receiving IDegLira is expected to increase from 100 in year one to 265 in year five. The budget impact analysis included drug acquisition costs and the cost of consumables (strips, lancets and needles).

5.1.2 Results

The company estimated the number of patients and costs for the use of IDegLira for the treatment of adult patients with T2DM. The estimated number of patients and the associated costs as described by the company in their budget impact analysis are summarised in Table 3. The total cost includes drug acquisition costs and the cost of consumables (strips, lancets and needles). The company assumes that the use of IDegLira will displace liraglutide plus basal insulin (69%), exenatide plus basal insulin (19%), and lixisenatide plus basal insulin (12%). Consequently, the overall net costs are based on this.

Table 3. Company-reported costs associated with use of IDegLira for the treatment of adults with T2DM

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients uncontrolled on basal insulin who intensify their treatment regimen (HbA_{1c}>8.5%)	2,005	2,013	2,021	2,029	2,037
Total % uptake of IDegLira	5.0%	7.0%	9.0%	11.0%	13.0%
Patients treated with IDegLira, n	100	141	182	223	265
Cost of IDegLira per patient, per annum	£1,465.51	£1,465.51	£1,465.51	£1,465.51	£1,465.51
Cost of consumables per patient, per annum	£150.12	£150.12	£150.12	£150.12	£150.12
Total cost of IDegLira plus consumables per annum	**£162,004**	**£227,700**	**£293,925**	**£360,664**	**£427,915**
Total cost of current scenario (without IDegLira) per annum	£3,110,709	£3,122,984	£3,135,441	£3,147,857	£3,160,231
Total cost of IDegLira endorsed in Wales scenario per annum	£3,117,177	£3,132,075	£3,147,177	£3,162,256	£3,177,316
Total incremental cost of IDegLira per annum	**£6,468**	**£9,091**	**£11,735**	**£14,400**	**£17,085**

The company also conducted sensitivity analysis. One sensitivity analysis assumed a higher proportion of T2DM patients on basal insulin have an HbA_{1c} > 8.5% (64.4% versus 61.0% in the base case analysis). Under this approach, the total incremental cost of IDegLira per annum increased to £6,829 in Year one, rising to £18,037 in Year five. Another sensitivity analysis assumed different market shares for the comparators. Under this approach, the total incremental cost of IDegLira per annum increased to £7,812 in Year one, rising to £20,635 in Year five.

5.1.3 AWTTC critique

The company estimated the eligible patient numbers based on prevalence rates and assumptions rather than attempt to estimate the actual number of eligible patients in Wales.

In addition:

- The company has made a number of assumptions about the existing therapies that will be displaced.
- The company has not incorporated discontinuation rates into their analysis.
- The company has not justified the dosing assumptions used in the estimation of drug acquisition costs.

5.2 Comparative unit costs

The costs of the potential treatments for adults with T2DM who are uncontrolled on basal insulin analogues and considered appropriate for intensification with a GLP-1 RA are highlighted in Table 4 below. This represents the costs of basal insulin as well as the additional costs over the basal insulin patients were already receiving. The additional cost for a GLP-1 RA per patient per year ranges from £706 for lixisenatide to £1,432 for liraglutide 1.8mg. The cost of basal insulin per patient per year, based on a defined daily dose of 40 units, ranges from £404 for insulin glargine to £701 for insulin degludec. The cost per patient per year for IDegLira is £1,466.

Table 4. Example of cost per patient per year for adult patients with T2DM uncontrolled on basal insulin

Regimen	Maintenance dose	Cost per year*
Liraglutide(Victoza®), 1.2mg dose, Solution for injection, 6mg/ml	1.2mg once daily	£955
Liraglutide(Victoza®), 1.8mg dose, Solution for injection, 6mg/ml	1.8mg once daily	£1,432
Exenatide (Byetta®), 10 micrograms, Solution for injection	10 micrograms twice daily	£830
Exenatide modified release (Bydureon®). 2 mg, Powder for reconstitution	2 mg once weekly	£954
Lixisenatide (Lyxumia®), 20 micrograms Solution for injection	20 micrograms once daily	£706
Insulin glargine (Lantus®), 5 x 3mL cartridge	40 units per day	£404
Insulin detemir (Levemir®), 5 x 3mL cartridge	40 units per day	£409
Insulin degludec (Tresiba®), 5 x 3mL cartridge	40 units per day	£701
*Costs based on British National Formulary, August 2015; This table does not imply therapeutic equivalence of medicines or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, IDegLira (Xultophy®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that IDegLira (Xultophy®▼) will be supplied by a home healthcare provider[8].

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[8].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 01 May 2015
Date range of evidence search: No date limits were applied to database searches.

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