Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2235

insulin glargine plus lixisenatide (Suliqua®), 100 units/mL plus 50 microgram/mL and 100 units/mL plus 33 micrograms/mL solution for subcutaneous injection in pre-filled pens

Aventis Pharma Limited, trading as Sanofi

06 March 2020

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

insulin glargine/lixisenatide (Suliqua®) is accepted for restricted use within NHSScotland.

Indication under review: In combination with metformin for the treatment of adults with type 2 diabetes mellitus, to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose-lowering medicinal product or with basal insulin.

SMC restriction: for use in patients who are uncontrolled on basal insulin (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 analogues.

Insulin glargine/lixisenatide improved glycaemic control compared with insulin glargine alone in adults with inadequately controlled type 2 diabetes mellitus.

Chairman
Scottish Medicines Consortium

Indication

In combination with metformin for the treatment of adults with type 2 diabetes mellitus (T2DM), to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another oral glucose-lowering medicinal product or with basal insulin.

Dosing Information

Insulin glargine/lixisenatide should be subcutaneously injected once a day within one hour prior to a meal. It is preferable that the prandial injection is performed before the same meal every day, when the most convenient meal has been chosen.

The dose must be individualised based on clinical response and is titrated based on the patient's need for insulin. The lixisenatide dose is increased or decreased along with the insulin glargine dose and also depends on which pen is used.

Insulin glargine/lixisenatide is available in two pens, providing different dosing options, i.e. a (10-40) pen and a (30-60) pen. The differentiation between the pen strengths is based on the dose range of the pen.

• Insulin glargine plus lixisenatide (100 units/mL plus 50 micrograms/mL) pre-filled pen delivers dose steps from 10 to 40 units of insulin glargine in combination with 5 to 20 micrograms lixisenatide.

• Insulin glargine plus lixisenatide (100 units/mL plus 33 micrograms/mL) pre-filled pen delivers dose steps from 30 to 60 units of insulin glargine in combination with 10 to 20 micrograms lixisenatide.

Please see summary product characteristics for full dosing information.[1]

Product availability date

September 2019

Summary of evidence on comparative efficacy

Suliqua® is a fixed ratio combination product consisting of two medicines: insulin glargine (basal insulin analogue) and lixisenatide (glucagon-like peptide 1 (GLP-1) receptor agonist). These medicines have a complementary mechanism of action to target both fasting and postprandial glucose levels.[1]

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers this product when positioned for use for the treatment of patients with type 2 diabetes mellitus (T2DM) uncontrolled on basal insulin (glycosylated haemoglobin [HbA1c] >7.5% [59mmol/mol]), for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy to basal insulin analogues.

Evidence relevant to the proposed positioning comes from a phase III, multicentre, randomised, open-label, parallel group study (LixiLan-L) in 736 patients with T2DM treated with basal insulin. The study design included a 6-week run-in phase to assess and optimise glycaemic control followed by a 30-week open-label treatment period and a final 3-day safety follow-up period. Recruited patients could have received concomitant treatment with stable doses of oral antidiabetic medicines including metformin (≥1,500mg/day), sulfonylureas, meglitinides, sodium-glucose co-transporter 2 (SGLT-2) inhibitors or dipeptidyl peptide 4 (DPP-4) inhibitors. Fasting plasma glucose was required to be ≤10 mmol/L for patients receiving basal insulin in combination with two oral antidiabetic medicines or with one other than metformin and ≤11.1 mmol/L for those receiving basal insulin with or without metformin. During the 6-week run-in phase, any oral antidiabetic medicine other than metformin was stopped and patients receiving other basal insulin were switched to insulin glargine. At the end of the 6-week run-in phase, patients meeting the following inclusion criteria were eligible for randomisation: HbA1c 7% to 10% (53 to 86 mmol/mol), a mean fasting self-measured plasma glucose (SMPG) ≤7.8mmol/L, insulin glargine dose daily dose of 20 to 50 units, calcitonin of ≤ 20picograms/mL (5.9picomol/L) and amylase and/or lipase levels <3 times the upper limit of normal. [2, 3]

Eligible patients were randomised equally to receive once daily insulin glargine/lixisenatide or insulin glargine for 30 weeks. Randomisation was stratified by HbA1c value (<8%, ≥8% [<64, ≥64 mmol/mol]) at week-1 and metformin use at screening (yes/no).[2, 3]

Insulin glargine/lixisenatide was supplied using one of two SoloStar® pen injectors according to the insulin requirement. The pens allowed for the insulin dose range (20 to 60 units) while avoiding doses higher than the recommended daily dose for lixisenatide (20 micrograms). The starting dose of insulin was determined by the last dose prior to randomisation. The dose was not changed for the first 2 weeks and was then titrated on a weekly basis according to a pre-specified algorithm to a maximum dose of 60 units (60 dose steps) to maintain a fasting SMPG of 4.4 to 5.6mmol/L. Insulin glargine was supplied in a prefilled Lantus SoloStar® pen (100 units/mL).

Timing of the once daily injection was not specified but was to remain at the same time throughout treatment. For patients with elevated plasma glucose for 3 consecutive days despite the maximum dose of insulin glargine (60 units), rescue medication with a short/rapid acting insulin was added to the main meal. [2, 3]

The primary outcome was change in HbA1c from baseline to week 30 measured in the modified intention to treat population (mITT) which included all randomised patients who had a baseline assessment and at least one post-baseline assessment. At week 30, there was a significantly greater improvement from baseline in HbA1c in the insulin glargine/lixisenatide group compared with the insulin glargine group. The results are detailed in Table 1. [2, 3]

Table 1. Primary outcome from the LixiLan-L study in the mITT population[2, 3]

	Insulin glargine/lixisenatide (n=366)	Insulin glargine (n=365)
Baseline mean HbA1C (%)	8.1	8.1
Week 30 mean HbA1c (%)	6.9	7.5
LS mean change from baseline to week 30	-1.1	-0.6
LS mean difference versus insulin glargine (95% CI)	-0.5 (-0.6 to -0.4)	
p-value	<0.001	

HbA1c=glycosylated haemoglobin; CI=confidence interval; LS = least squares

Categorical secondary outcomes found a greater percentage of patients in the insulin glargine/lixisenatide group than the insulin glargine group had achieved an HbA1c of <7% (54mmol/mol) 55% versus 30% and ≤6.5% (48mmol/mol) 34% versus 14% at week 30.

A hierarchical statistical testing strategy was applied to continuous secondary outcomes, following the order listed in Table 2 below, and there was no formal testing after the first non-significant outcome in the hierarchy, with further results descriptive only and not inferential (no p-values reported). Insulin glargine/lixisenatide demonstrated significant advantages over insulin glargine from baseline to week 30 in the outcomes listed in Table 2.[2, 3] There was no statistical difference between insulin glargine/lixisenatide and insulin glargine groups in the secondary outcomes of mean change in dose of insulin glargine at week 30 (10.6 units and 10.9 units respectively) or in the mean change of fasting plasma glucose (-0.4 mmol/L and -0.5mmol/L respectively). [2, 3]

Table 2. Secondary outcomes from the LixiLan-L study in the mITT population[2, 3]

Baseline to week 30		Insulin glargine/lixisenatide (n=366)	Insulin glargine (n=365)
2 hour plasma glucose excursion during a standardised liquid meal test (mmol/L)[A]	Baseline	7.0	7.1
	LS mean change	-3.9	-0.5
	LS mean difference (95% CI)	-3.4 (-3.9 to -2.9) p<0.001	
Bodyweight (kg)	Baseline	87.8	87.1
	LS mean change	-0.7	0.7
	LS mean difference (95% CI)	-1.4 (-1.8 to -0.9) p<0.001	
Average 7-point SMPG (mmol/L)[B]	Baseline	9.2	9.1
	LS mean change	-1.5	-0.6

	LS mean difference (95% CI)	-0.9 (-1.2 to -0.6) p<0.001	
HbA1c < 7% (53mmol/mol) without weight gain	%(n)	34 (125)	13 (49)
	Proportion difference (%) (95% CI)	21 (15 to 27) p<0.001	

HbA1c=glycosylated haemoglobin, LS = least squares, SMPG = self-monitored plasma glucose, CI = confidence interval
A = Plasma glucose excursion is 2-hour postprandial glucose (PPG) minus plasma glucose value obtained 30 minutes prior to the start of the meal and before investigational medicinal product (IMP) administration, if IMP was injected before breakfast. Change in plasma glucose excursions was calculated by subtracting baseline value from Week 30 value.[4]
B= Participants recorded a 7-point plasma glucose profile measured before and 2-hours after each meal and at bedtime, two times in a week before baseline, before visit Week 12 and before visit Week 30 and the average value across the profiles performed in the week before a visit for the 7 time points was calculated. Change in average 7 point SMPG was calculated by subtracting baseline value from Week 30 value. The analysis included all scheduled measurements obtained during the study. The missing data were handled by mixed effect model with repeated measures (MMRM) approach.[4]

Bucher indirect treatment comparisons were performed to compare the efficacy and safety of insulin glargine/lixisenatide with basal insulins (± one or two oral antidiabetic medicines and GLP-1 receptor agonists, using basal insulin ± one oral antidiabetic medicines as the common comparator). The network consisted of 12 studies with outcomes including: differences in HbA1c change from baseline; difference in weight (kg) change from baseline; patients reaching target HbA1c% <7.0%; patients reaching target HbA1c% ≤6.5%; any symptomatic/documented hypoglycaemia; and severe hypoglycaemia. SMC is unable to present the results from the indirect treatment comparisons.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

During the LixiLan-L study, no new or unexpected adverse reactions were reported for either the insulin glargine/lixisenatide or insulin glargine groups. Patients reporting at least one treatment emergent adverse event (TEAE) in the insulin glargine/lixisenatide group and insulin glargine group were 53% (195/365) and 52% (191/365) respectively. Serious TEAEs were reported in 5.5% of the insulin glargine/lixisenatide group and 4.9% of the insulin glargine group. TEAEs leading to treatment discontinuation were 2.7% and 0.8% respectively.[2, 3]

The main differences in TEAEs were in gastrointestinal symptoms. Nausea (10% versus 0.5%), vomiting (3.6% versus 0.5%) and diarrhoea (4.4% and 2.7%) were reported more frequently in the insulin glargine/lixisenatide group than the insulin glargine group. Most gastrointestinal symptoms were mild with only 1.1% of patients having to discontinue treatment in the insulin glargine/lixisenatide group due to nausea.[2, 3]

Symptomatic hypoglycaemia (defined as typical symptoms of hypoglycaemia accompanied with a plasma glucose concentration of ≤3.9 mmol/L [70mg/dL]) was similar between groups affecting 40% of those receiving insulin glargine/lixisenatide and 42% of those receiving insulin glargine. Reports of severe hypoglycaemia (defined as all episodes in which neurological impairment was severe enough to prevent self-treatment, and which were thought to place patients at risk of injury to themselves or others) were low in both groups: 1.1% insulin glargine/lixisenatide and 0.3% in insulin glargine.[2, 3]

The number of major cardiac events reported in both groups was low during the on treatment period (1.4% insulin glargine/lixisenatide and 1.0% insulin glargine). [2, 3, 5]

Summary of clinical effectiveness issues

Type 2 diabetes mellitus is a chronic metabolic condition characterised by loss of beta cell activity leading to insulin resistance. The aim of pharmacological glucose lowering interventions is to prevent microvascular (e.g. retinopathy, neuropathy and nephropathy) and macrovascular (e.g. myocardial infarction, stroke and peripheral artery disease) complications. Blood glucose control is measured using HbA1c with a target of 7.0% (53 mmol/mol) to reduce microvascular and macrovascular disease. In accordance with the Scottish Intercollegiate Guidelines Network (SIGN) guideline, treatment with a GLP-1 receptor agonist in combination with basal insulin would be a fourth-line option in the treatment algorithm, and should only be considered in patients with a body mass index (BMI) of ≥30kg/m^2(or ethnicity-adjusted equivalent). There are a range of GLP-1 receptor agonists and basal insulins (isophane and longer-acting analogues) available as separate medicines or a fixed ratio combination of insulin degludec/liraglutide is also available for this indication. Suliqua® (insulin glargine/lixisenatide) is the second fixed ratio combination of a basal insulin plus GLP-1 receptor agonist to be licensed.[3, 6]

The submitting company has requested SMC considers insulin glargine/lixisenatide (Suliqua®) when positioned for the treatment of patients with T2DM uncontrolled on basal insulin (HbA1c >7.5% [59mmol/mol]), for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy to basal insulin analogues.

The results of the LixiLan-L study demonstrated the superiority of insulin glargine/lixisenatide plus metformin over insulin glargine plus metformin in the reduction of HbA1c after 30 weeks with an absolute difference in HbA1c of 0.5%. The European Medicines Agency considered the reduction in HbA1c at week 30 to be of borderline clinical relevance as the lixisenatide component contributes less to the glucose-lowering effect of the combination than the insulin glargine component. However, it also acknowledges that a similar reduction in HbA1c by an increased insulin dose would likely have resulted in weight gain and increased risk of hypoglycaemia.[2, 3]

There are a number of limitations in the study design. The LixiLan-L study was open-label which may have introduced the potential for bias although biochemical outcomes were assessed at a central laboratory. The study was limited by its 30-week duration and there is a lack of long-term safety and

efficacy data of the fixed combination of insulin glargine/lixisenatide. HbA1c has been linked to reductions in the long-term complications of diabetes but there are no direct health outcome data demonstrating the reduction in microvascular or macrovascular complications of this combination product. There are long-term safety data on the individual medicines and no new or unexpected issues presented in the study.[2, 3]

In the proposed positioning (patients uncontrolled on basal insulin) there is no evidence to support the use of insulin glargine/lixisenatide in patients on concomitant treatment with oral antidiabetic medicines other than metformin. When starting treatment with a GLP-1 receptor agonist, SIGN guideline 154 recommends that patients could be continued on metformin, sulphonylurea (consider dose reduction), pioglitazone or SGLT2 inhibitors. The majority of patients enrolled on the LixiLan-L study had a creatinine clearance >60mL/min; this may affect the generalisability to the Scottish type 2 diabetic population. [1, 2, 6]

In the LixiLan-L study, insulin glargine/lixisenatide was compared with insulin glargine alone. A basal insulin and GLP-1 receptor agonist given separately may also be considered as a relevant comparator. Experts consulted by SMC considered an alternative fixed ratio combination of basal insulin and GLP-1 receptor agonist Xultophy® (insulin degludec/liraglutide) as the most relevant comparator.

The dose of insulin glargine in the comparator arm of the LixiLan-L study was capped at 60 units daily. This may not be a fair comparison if the study dose reflects a suboptimal dose in clinical practice. However, at the end of the 30-week study period, insulin doses in both groups were approximately the same (47 units). There was a slightly higher proportion of patients (31%) in the insulin glargine group receiving the maximum 60 unit dose than in the insulin glargine/lixisenatide group (27%).[3] Therefore capping does not appear to have affected the outcome in this short-term study.

The indirect evidence was limited by heterogeneity in the design of the included studies, their duration and the study populations. There were a range of GLP-1 receptor agonists used as comparators, some of which may not be commonly prescribed in Scotland. One study included nateglinide which is not recommended in SIGN guideline 154 and has not been reviewed by SMC. These differences make comparisons uncertain. The outcomes for liraglutide 1.8mg + basal insulin compared to insulin glargine/lixisenatide have used been in a supplementary economic cost utility analysis.

The introduction of insulin glargine/lixisenatide as a fixed ratio combination may reduce the number of daily subcutaneous injections patients need to self-administer which may be an advantage. However, the fixed dose ratio restricts flexibility in prescribing and the availability of two pens for administration may increase the risk of dosing errors.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

A cost-utility analysis was presented evaluating insulin glargine/lixisenatide in its licensed indication. The submitting company has requested that SMC considers this product when positioned for use for the treatment of patients with T2DM uncontrolled on basal insulin (HbA1c >7.5% [59mmol/mol]), for whom a GLP-1 receptor agonist is appropriate as an add-on intensification therapy to basal insulin analogues.

The submitting company selected two comparators: insulin glargine plus metformin and a regimen of liraglutide 1.8mg plus insulin glargine and metformin. However, clinical expert input received by the SMC indicated that insulin degludec/liraglutide (Xultophy®) is the most likely comparator to be displaced, with dulaglutide 1.5mg and the lower dose liraglutide 1.2mg regimen as additional relevant comparators (both in combination with insulin glargine and metformin). Revised pairwise comparisons were obtained against the insulin degludec/liraglutide, dulaglutide 1.5mg and liraglutide 1.8mg regimens and are summarised below. A scenario was provided comparing insulin glargine/lixasenatide with the liraglutide 1.2mg regimen.

The economic analysis used the CORE diabetes model, which was developed to predict the long-term health outcomes and economic consequences of interventions in type one and type two diabetes mellitus. Patients were modelled to receive treatment with the relevant medicine until the HbA1c level reached 7.5%, at which point patients switched to a treatment intensification regimen (insulin glargine and insulin aspart). Long-term costs and consequences such as the occurrence of microvascular and macrovascular complications were assessed. The economic analysis initially presented results using a non-standard approach, involving the estimation of an efficiency frontier. However, SMC-preferred pairwise comparisons of the intervention with relevant comparators using cost per quality adjusted life years (QALYs) were obtained upon request, and subsequent discussion within the DAD focuses on these analyses. A lifetime time horizon (50 years) was applied, and the analysis took the perspective of NHS Scotland and social services.

The main clinical effectiveness inputs were obtained from Bucher indirect comparisons, as described in the clinical effectiveness section. The treatment effect of insulin glargine/lixisenatide on HbA1c was derived from the LixiLan-L study, applied for the first year to align with the duration of the trial, and the comparator mean difference applied from the indirect comparison. HbA1c was then modelled using the UKPD68 risk equation until treatment switch,[7] while progression of total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) was modelled using risk equations from the Framingham Heart Study.[8] The pairwise comparisons assumed no relative treatment effects on BMI, total cholesterol, HDL and LDL, triglycerides and adverse events. A baseline utility value of 0.785 was derived using EQ-5D data from the UKPDS study, with a number of disutility values applied for clinical events such as peripheral vascular disease, as appropriate.[9]

Costs of medicines acquisition were included, with mean daily dose of insulin glargine/lixisenatide derived from a survey of clinicians and either trial data or assumptions used for the other

comparators. The mean daily dose from the GetGoal-DUO study was used for the treatment intensification regimen.[10] Health state-specific costs were also included for downstream complications, such as cardiovascular and renal disease. These were obtained from previous published literature.

The base case results of the pairwise comparisons are shown in Table 3. Key scenario analyses are shown in Table 4. Against each comparator, insulin glargine/ lixisenatide was associated with lower lifetime costs but lower QALYs thus meaning the cost-effectiveness ratios were in the south-west quadrant of the cost-effectiveness plane. Key drivers of cost savings were the reduced cost of medicines acquisition, balanced by an increased cost of downstream complications (particularly renal). A reduction in QALY gains was likely due to the reduced effectiveness of insulin glargine/lixisenatide.

Table 3: Base case results

	Insulin glargine/ lixisenatide	**Insulin degludec/liraglutide**	**Liraglutide 1.8mg***	**Dulaglutide 1.5mg***
Quality-adjusted life years (QALYs)	8.636	8.665	8.697	8.668
Lifetime combined costs* (£)	37,006	39,498	39,893	38,297
Incremental Quality-adjusted life years (QALYs)	N/A	-0.030	-0.061	-0.032
Incremental lifetime combined costs (£)		-2,492	-2,887	-1,291
ICER[¥] (Suliqua versus comparator)		£80,071	£47,095 [§]	£40,334
NMB at £20k/QALY		£1,892	£1,667	£651
NMB at £30k/QALY		£1,592	£1,057	£331

SMC does not specify a formal willingness-to-pay threshold, and net monetary benefit estimates are indicative only, in the context of southwest quadrant results. Abbreviation: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio; NMB: net monetary benefit; *plus insulin glargine and metformin ¥ South-west quadrant of the cost effectiveness plane; N/A: Not applicable.

Table 4: Key scenario analyses

			Insulin degludec/liraglutide		Liraglutide 1.8mg*		Dulaglutide 1.5mg*	
			ICER(£/QALY)	**NMB (£)**	**ICER(£/QALY)**	**NMB (£)**	**ICER(£/QALY)**	**NMB (£)**
#	***Base-case results***		£80,071	£1,892	£47,095	£1,667	£40,334	£651
1.	**Comparator treatment effect**	Upper bound of 95% CI of applied to the HbA1c treatment effect	49,183	1,313	30,543	940	23,437	172
2.	**Lower liraglutide dose**	Liraglutide 1.2mg (clinical equivalence to 1.8mg)	N/A	N/A	19,190	-49	N/A	N/A
3.	**Dose of insulin glargine**	Obtained from trials supporting ITC	59,959	1,199	31,705	375	31,705	375
4.	**Cost of renal complications**	Increased by 50%	58,724	1,162	31,705	375	29,168	293
5.	**Body mass index**	Consideration of BMI treatment effect	30,501	830	23,961	463	20,757	48

SMC does not specify a formal willingness-to-pay threshold, and net monetary benefit estimates are indicative only, in the context of southwest quadrant results. Abbreviation: QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio; NMB: net monetary benefit; *plus insulin glargine and metformin ¥ South-west quadrant of the cost effectiveness plane; N/A: Not applicable.

Although the analysis utilised an economic model structure which has been extensively validated, a number of limitations remained regarding the methods used:

- No direct comparative evidence is available and the analysis relies upon a Bucher indirect treatment comparison. As noted in the clinical effectiveness section above, this was subject to limitations, in particular due to heterogeneity between studies and the absence of published data for the preferred Scottish dose of liraglutide (1.2mg) (Scenario 1).
- An assumption of clinical equivalence was made regarding several parameters, most importantly BMI. In the case of BMI (as indicated by weight change from baseline), the indirect comparison suggested that the analysis significantly favoured liraglutide 1.8mg, dulaglutide 1.5mg and insulin degludec/liraglutide relative to insulin glargine/lixisenatide. Consideration of BMI results in a greater reduction in health for insulin glargine/lixisenatide versus the key comparators (Scenario 5).
- Inconsistent approaches have been utilised to estimating insulin doses of the key comparators, which results in a separation of the clinical effectiveness and cost inputs and may overestimate the cost of comparators. Use of observed data from the respective trials contributing to the ITC results in reduced cost savings for insulin glargine/lixisenatide (Scenario 3).
- The scenario evaluating the lower dose of liraglutide 1.2mg utilises efficacy data from a

different population. Although the company believes effectiveness may be lower at reduced doses of liraglutide, the justification is not based on a systematic review of the evidence and may be biased. Clinical evidence from a previous SMC submission (585/09) suggests the difference in effectiveness between the doses may be minimal. An assumption of equivalence to liraglutide 1.8mg significantly influences the incremental QALY losses (Scenario 2).

- The costs of long-term renal complications were the greatest additional cost associated with the use of insulin glargine/lixisenatide relative to comparators. Although input data were referenced to a NICE clinical guideline, they were significantly lower than used in the source publication.[12] When a more consistent approach was taken, the cost saving associated with insulin glargine/lixisenatide reduced (Scenario 4).

Insulin glargine/lixisenatide was consistently estimated to result in a cost-saving relative to insulin degludec/liraglutide and other comparators. Despite the uncertainties noted above, and the challenges of evaluating ICERs within the south west quadrant of the cost effectiveness plane the economic case has been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Pharmacological management of glycaemic control in people with type 2 diabetes: A national clinical guideline (SIGN 154) in November 2017. This guideline recommends metformin or a sulphonylurea (if metformin contraindicated or not tolerated) as the first-line oral therapy for people with T2DM in addition to lifestyle measures. Treatment is then intensified in a stepwise approach in order to achieve an agreed target HbA1c. SIGN notes several options for second, third and fourth line treatment of T2DM including sulfonylureas, SGLT-2 inhibitors, DPP-4 inhibitors, pioglitazone, injectable GLP-1 agonists and basal insulin. Choice of pharmacological agent is guided by the patient profile.GLP1 receptor agonists are recommended as a 3rd line injectable option in pharmacological management following inadequate glycaemic control with two oral antidiabetic medicines whose BMI >30kg/m^2 (basal insulin recommended injectable agent if BMI <30kg/m^2). If not selected 3rd line it may be added as a fourth line option with specialist input.[6]

The National Institute for Health and Care Excellence (NICE) published Type 2 diabetes in adults: management (NG28) in December 2015 and updated August 2019. GLP1 receptor agonists are recommended as a third intensification in combination with metformin and a sulfonylurea in adults with type 2 diabetes who have a BMI of ≥35kg/m^2 and have specific psychological or medical problems associated with obesity or have a BMI <35kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. [13]

Additional information: comparators

Basal insulin plus a GLP-1 receptor agonist either separately or in combination.

Additional information: list price of medication under review

Medicine	Dose Regimen	Cost per year (£)
Insulin glargine/lixisenatide (Suliqua®)100units/50micrograms/ml	**10units/5micrograms to 40units/20micrograms by subcutaneous injection once daily**	**338 to 1,215**
Insulin glargine/lixisenatide (Suliqua®)100units/33micrograms/ml	**30units/10micrograms to 60units/20micrograms by subcutaneous injection once daily**	**632 to 1,215**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online [27 February 2020].

Additional information: budget impact

The submitting company estimated there would be 3,935 patients eligible for treatment with insulin glargine/lixisenatide in year 1 and 4,485 in year 5. The uptake rate was estimated to be 5% in year 1 and 13% in year 5, giving 197 patients in year 1 and 583 patients in year 5. A discontinuation rate of 2.7% was applied each year, leading to 191 patients treated in year 1 and 567 in year 5.

Based on these estimates, the gross impact on the medicines budget was estimated to be £181k in year 1 rising to £532k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £114k in year 1 and £343k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 20 February 2020.

**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*

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.