New Medicine Recommendation

Insulin glargine / lixisenatide 100 units/ml + 33 micrograms/ml and 100 units/ml + 50 micrograms/ml solution for injection in pre-filled pens (Suliqua®▼)

Indication: 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

Recommendation: BLACK RAG rating

- None of the studies in the study program for insulin glargine /lixisenatide compare the combination preparation with GLP-1 receptor agonists and basal insulins given together but as separate injections. LixiLan-O compared insulin glargine/lixisenatide with insulin glargine alone and lixisenatide alone.
- Insulin glargine / lixisenatide (Suliqua®▼) does not currently fit into any locally or nationally defined pathways.
- Switch from GLP-1 receptor agonist to GLP-1 receptor agonist plus insulin combination has not been studied.
- Suliqua®▼ has not been studied in combination with DPP-4 inhibitors, sulfonylureas, meglitinides, pioglitazone and SGLT-2 inhibitors.
- The NICE Guidelines for the management of T2DM state the following, “only offer a glucagonlike peptide-1 (GLP-1) analogue in combination with insulin in a specialist care setting”[5,6]
- Insulin glargine plus lixisenatide, with its fixed ratio dosing, offers less flexibility to titrate the individual components and manage interruption of treatment, and at the initiation of treatment does not allow the prescriber to understand how the patient responds to or tolerates each component.
- Potential for medication errors with two pen types / doses

Summary of supporting evidence:

Two pivotal Phase III studies including patients with Type 2 Diabetes Mellitus (T2DM) support the licence for Suliqua®▼:

EFC12404 (LixiLan-O)

The changes from baseline to week 30 in HbA1c were -1.63% for the Suliqua®▼ group, -1.34% for the insulin glargine group and -0.85% for the lixisenatide group, reaching mean HbA1c values of 6.5%, 6.81% and 7.31% respectively at week 30.

Body weight decreased in the Suliqua®▼ and lixisenatide groups and increased in the insulin glargine group, with least squares (LS) mean changes from baseline to week 30 of -0.3, -2.3 and +1.1kg for each group respectively.[11,12]

EFC12405 (LixiLan -L)

The changes in HbA1c from baseline to week 30 were - 1.13% for the Suliqua®▼ group and -0.62% for the insulin glargine group, reaching mean HbA1c levels of 6.94% and 7.48%

respectively. The difference between the two groups was 0.52% (95% CI: -0.633%, -0.397%). Statistical superiority of Suliqua®▼ over insulin glargine was demonstrated (p<0.0001).

A change in bodyweight was also observed, with a mean body weight decrease in the Sulqiua®▼group of 0.67kg whilst there was a mean body weight increase in the insulin glargine group of 0.7kg. The LS mean treatment difference (-1.37kg) between the two groups was statistically significant (95% CI -1.808 to -0.930, p<0.0001).[11,13]

Details of Review

Name of medicine (generic & brand name)**:** Insulin glargine / lixisenatide (Suliqua®▼)

Strength(s) and form(s): 100 units/ml + 33 micrograms/ml and 100 units/ml + 50 micrograms/ml solution for injection pre-filled pens

Dose and administration:[1,2]

Suliqua®▼ is to be injected subcutaneously in the abdomen, deltoid, or thigh.

Suliqua®▼ is available in two pens, providing different dosing options:

- Suliqua®▼ 100 units/ml + 50 micrograms/ml pre-filled pen delivers dose steps from 10-40 units of insulin glargine in combination with 5-20 mcg lixisenatide (Suliqua®▼ (10-40) pen)
- Suliqua®▼ 100 units/ml + 33 micrograms/ml pre-filled pen delivers dose steps from 30-60 units of insulin glargine in combination with 10-20 mcg lixisenatide (Suliqua®▼ (30-60) pen)

To avoid medication errors, the prescriber must make sure that the correct strength and number of dose steps is stated in the prescription. The term dose steps is used instead of units to highlight the fact that Suliqua®▼ consists of two active substances. This is in line with the terminology used for the insulin degludec / liraglutide combination (Xultophy).

Therapy with basal insulin or oral glucose lowering medicinal product other than metformin should be discontinued prior to initiation of Suliqua®▼.

The starting dose of Suliqua®▼ is based on previous anti-diabetic treatment, and in order not to exceed the recommended lixisenatide starting dose of 10 mcg:

		Previous therapy		
		Oral anti-diabetic treatment (insulin naïve patients)	**Insulin glargine (100 units/ml)** ≥20 to <30 units**	**Insulin glargine (100 units/ml)** ≥30 to ≤60 units**
Starting dose and pen	**Suliqua (10-40) pen**	10 dose steps (10 units/5 mcg)*	20 dose steps (20 units/10 mcg)*	
	Suliqua (30-60) pen			30 dose steps (30 units/10 mcg)*

* units insulin glargine (100 units/ml) / mcg lixisenatide

** If a different basal insulin was used:

- For twice daily basal insulin or insulin glargine (300 units/ml), the total daily dose previously used should be reduced by 20% to choose the Suliqua starting dose.
- For any other basal insulin the same rule as for insulin glargine (100 units/ml) should be applied

The maximum daily dose is 60 units insulin glargine and 20 mcg lixisenatide corresponding to 60 dose steps.

Suliqua®▼ should be 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.

Dosage titration

Suliqua®▼ is to be dosed in accordance with the individual patient's need for insulin. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.

Close glucose monitoring is recommended during the transfer and in the following weeks.

- If the patient starts with the Suliqua®▼ (10-40) pen, the dose may be titrated up to 40 dose steps with this pen.
- For doses >40 dose steps/day titration must be continued with Suliqua®▼ (30-60) pen.
- If the patient starts with the Suliqua®▼ (30-60) pen, the dose may be titrated up to 60 dose steps with this pen.
- For total daily doses >60 dose steps/day, Suliqua®▼ must not be used.

Patients adjusting the amount or timing of dosing should only do so under medical supervision with appropriate glucose monitoring

BNF therapeutic class / mode of action:

Endocrine system / Diabetes Mellitus

Licensed indication(s)[1,2]

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

Proposed use (if different from, or in addition to, licensed indication above):

As per licenced indication.

The main target population for Suliqua®▼ is expected to be patients eligible for initiation or intensification of treatment, (who are failing on metformin ± other oral glucose lowering products/ basal insulin) and where there is a need to avoid (further) weight increase.

Course and cost:[3]

Suliqua 100 units/ml + 50 micrograms/ml - 3 x 3ml SoloStar pre-filled pen=£67.50.

Suliqua 100 units/ml + 33 micrograms/ml - 3 x 3ml SoloStar pre-filled pen=£51.30.

Current standard of care/comparator therapies:[4]

- Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices 5 x 3ml pre filled pens = £37.77 (GREEN RAG rating)
- Insulin glargine 300units/ml solution for injection 1.5ml pre-filled disposable devices 3 x 1.5ml pre filled pens = £33.13 (AMBER 0 RAG rating)
- Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices 1 x 3ml pre filled pens = £31.67 (GREEN RAG rating)
- Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices 2 x 3ml pre filled pens = £57.93 (GREEN RAG rating)

- Insulin degludec 100units/ml / Liraglutide 3.6mg/ml solution for injection 3ml pre-filled disposable devices (Xultophy) 3 x 3ml pre filled pens = £95.53 (BLACK RAG rating)

Relevant NICE guidance

NICE pathway 'Type 2 diabetes in adults' (last updated June 2019)[5], and NICE Guideline NG28 Type 2 diabetes in adults: management (last updated May 2017)[6] both state that *"in adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant led multidisciplinary team"*

Type 2 diabetes: lixisenatide - Evidence summary [ESNM26] [7] Published date: September 2013

Type 2 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) - Evidence summary [ESNM65][8] Published date: December 2015

Type 2 diabetes: insulin degludec/liraglutide (Xultophy) - Evidence summary [ESNM60][9] Published date: July 2015

SMC/AWMSG

SMC – no review

AWMSG - Reference No. 2464[10] In the absence of a submission from the holder of the marketing authorisation, lixisenatide/insulin glargine (Suliqua®▼) cannot be endorsed for use within NHS Wales 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.

Background and context

Type 2 diabetes mellitus (T2DM) is characterised by a gradual deterioration in β cell function; this occurs even when standard of care antidiabetic therapy is used, including concurrent use of multiple oral antidiabetic drugs (OADs). In the last decade, several new therapeutic classes have become available, enabling a patient centred approach and moving T2DM management towards appropriate dual therapy at an earlier point in the disease. The fixed combination of insulin glargine and lixisenatide may provide a benefit to patients since simultaneous once daily injection of a dual anti-hyperglycaemic therapy may improve treatment compliance.

Suliqua®▼ is a fixed ratio combination of the basal insulin glargine and the glucagon like peptide – 1 (GLP-1) analogue lixisenatide.

Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Insulin glargine is a human insulin analogue with a prolonged duration of action. After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Lixisenatide is a selective GLP-1 receptor agonist. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.

Lixisenatide stimulates insulin secretion when blood glucose is increased but not at normoglycaemia, which limits the risk of hypoglycaemia. In parallel, glucagon secretion is suppressed. In case of hypoglycaemia, the rescue mechanism of glucagon secretion is preserved.

Lixisenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

When administered once daily, lixisenatide improves glycaemic control through the immediate and sustained effects of lowering both post-prandial and fasting glucose concentrations in patients with type 2 diabetes.

According to the manufacturer of Suliqua, the majority of the target population for the fixed dose combination is expected to require a daily dose of insulin glargine between 10-60u. In order to cover the range of 10 to 60u of insulin glargine while limiting the maximum lixisenatide dose to 20 µg, two pens with two different fixed ratios and dose ranges were used in the Phase III studies. The lower end of the lixisenatide dose range is the minimum dose for glycaemic efficacy as defined in a Phase II dose ranging study.

Summary of evidence

Summary of efficacy data in proposed use:

There were two pivotal Phase III studies both of which included patients with T2DM diagnosed for at least 1 year before the screening visit. Patients in each study were provided with protocol specified training on the pen-injector devices, treatment schedules and dosing algorithms.

The fixed ratio combination (Suliqua®▼) was administered subcutaneously once daily within 1 hour before breakfast. The fixed ratio combination dose was individualised based on the clinical response and was titrated based on the patients need for insulin. During titration, the choice of Pen A or Pen B was based on the required daily dose of Suliqua®▼. Pen A was to be used for daily doses below 40U and Pen B for doses between 41U and 60U. The maximum daily dose was 60U / 20µg. If a daily dose > 60U / 20µg was required to maintain FPG or HbA1c below thresholds defined for rescue therapy, the dose was kept at 60U / 20µg and a rescue therapy initiated. The recommended rescue therapy was the addition of a short / rapid acting insulin to be started as a single daily dose given at the main meal of the day. No other GLP-1 receptor agonist, DPP-4 inhibitor or basal insulin was allowed as rescue therapy.

In each of these studies Suliqua®▼ and insulin glargine treatments were both titrated to a fasting self measured plasma glucose (SMPG) target of 4.4 – 5.6mmol/l in a treat to target approach with once weekly titration

EFC12404 (LixiLan-O)[11,12]

This study was a 1170 patient randomised 30 week, active controlled, open label, 3 treatment arm, parallel group, multicentre study comparing the efficacy and safety of insulin glargine / lixisenatide fixed ratio combination (Suliqua®▼) to insulin glargine alone and to lixisenatide alone on top of metformin in patients with T2DM. The primary objectives were to demonstrate the superiority of Suliqua®▼ to lixisenatide and the non-inferiority of the fixed ratio combination to insulin glargine in HbA1c change from baseline to week 30.

Insulin naïve patients inadequately controlled on metformin ± a second OAD (at least 3 months of treatment) were randomised in a 2:2:1 ratio to Suliqua®▼ (469), insulin glargine (467) and lixisenatide (234). Inclusion criteria at the end of the 4 week run in period were HbA1c ≥ 7% and ≤ 10%, fasting plasma glucose (FPG) ≤ 13.9mmol/l and a maximum tolerated metformin dose of ≥ 1500mg / day

Treatments:

Fixed ratio combination treatment group

The recommended daily starting dose of insulin glargine in insulin naïve patients is 10u. Therefore, the daily starting dose of the fixed ratio combination in patients inadequately controlled on OADs

was 10u of insulin glargine / 5µg of lixisenatide. This daily dose was maintained during the first week of treatment. During titration, patients needing a daily dose of more than 40U were switched to Pen B.

Insulin glargine group

The starting dose was 10U. This daily dose was maintained during the first week of treatment.

Patients randomised to insulin glargine had to administer the same daily dose on the day of randomisation as the day before randomisation. Subsequently, the dose was titrated once a week using the same algorithm as used for the Suliqua®▼ group.

As the maximum daily dose of Suliqua®▼ was 60U/ 20µg, the comparative insulin glargine dose was capped at 60U.

Lixisenatide group

Lixisenatide was initiated with daily injections of 10µg for 2 weeks. The dose was then increased to a maintenance dose of 20µg daily through to the end of the treatment period. If the maintenance dose of 20µg daily was not tolerated then the dose could be reduced to 10µg daily.

Outcomes

The primary objectives of the study were met. The changes from baseline to week 30 in HbA1c were -1.63% for the Suliqua®▼ group, -1.34% for the insulin glargine group and -0.85% for the lixisenatide group, reaching mean HbA1c values of 6.5%, 6.81% and 7.31% respectively at week 30.

Body weight decreased in the Suliqua®▼ and lixisenatide groups and increased in the insulin glargine group, with least squares (LS) mean changes from baseline to week 30 of -0.3, -2.3 and +1.1kg for each group respectively.

EFC12405 (LixiLan -L)[11,13]

A 736 patient randomised 30 week, active controlled, open label, 2 treatment arm, parallel group, multicentre study comparing the efficacy and safety of insulin glargine / lixisenatide fixed ratio combination to insulin glargine with or without metformin in patients with T2DM. The primary objective of this study was to demonstrate the superiority of Suliqua®▼ to insulin glargine in HbA1c change from baseline to week 30.

Insulin treated patients inadequately controlled on established basal insulin (at least 6 months) ± 1 to 2 OADs were randomised in a 1:1 ratio to Suliqua®▼ (367) or insulin glargine (369). Inclusion criteria at the end of the 6 week run in period were HbA1c ≥ 7% and ≤ 10%, mean self measured plasma glucose (SMPG) for the 7 days prior to randomisation of ≤7.8mmol/l and an average insulin glargine daily dose ≥ 20u and ≤ 50u.

Treatments:

Fixed ratio combination treatment group

Patients switching from basal insulin to the fixed ratio combination began treatment at a recommended daily lixisenatide dose of 10 µg using either Pen A (20U glargine) or Pen B (30U) depending on the insulin glargine dose received on the day before randomisation as follows:

- If the dose was <30U, the starting dose of the fixed ration combination was 20U/10µg (Pen A)
- If the dose was ≥30U, the starting dose of the fixed ration combination was 30U/10µg (Pen B)

During titration, patients who initiated treatment with Pen A but subsequently needed a daily dose of more than 40U were switched to Pen B.

Insulin glargine group

Patients already treated with insulin glargine entered the run-in phase with the same dose they received prior to screening. Patients receiving a different basal insulin were switched to insulin glargine. Doses were adjusted based on daily fasting SMPG in order to improve fasting glycaemic control and obtain mean fasting SMPG ≤ 7.8mmol/l measured for 7 days before the randomisation visit, whilst avoiding hypoglycaemia.

Patients randomised to insulin glargine had to administer the same daily dose on the day of randomisation as the day before randomisation. Subsequently, the dose was titrated once a week using the same algorithm as used for the fixed ratio combination group.

As the maximum daily dose of Suliqua®▼ was 60U/ 20µg, the comparative insulin glargine dose was capped at 60U.

Outcomes

The primary objective of the study was met as statistical superiority of Suliqua®▼ over insulin glargine was demonstrated in change in HbA1c from baseline to week 30. The changes in HbA1c from baseline to week 30 were 1.13% for the Suliqua®▼ group and -0.62% for the insulin glargine group, reaching mean HbA1c levels of 6.94% and 7.48% respectively. The difference between the two groups was 0.52% (95% CI: -0.633%, -0.397%, p<0.0001).

A change in bodyweight was also observed, with a mean body weight decrease in the Sulqiua®▼ group of 0.67kg whilst there was a mean body weight increase in the insulin glargine group of 0.7kg. LS mean treatment difference was -1.37kg (95% CI -1.808 to -0.930, p<0.0001). Compared to insulin glargine, a greater effect on HbA1c was achieved without weight gain and at a comparable rate of hypoglycaemias.

Other efficacy data:

Unpublished study EFC13794 (LixiLan–G)[14,15]

This was a 26 week randomised, open label, active controlled, 2 treatment arm, parallel group study assessing the efficacy and safety of the insulin glargine / lixisenatide fixed ratio combination (Suliqua®▼) in adults with T2DM inadequately controlled on GLP-1 receptor agonist and metformin (alone or with pioglitazone and / or SGLT2 inhibitors), followed by a fixed ratio combination (Suliqua®▼) single arm 26 week extension period.

Its primary objective is to demonstrate the superiority of the insulin glargine / lixisenatide fixed ratio combination vs GLP-1 receptor agonist in HbA1c change from baseline to week 26. The objective of the extension period was to evaluate safety, efficacy and other endpoints and pharmacokinetics of Suliqua®▼ up to week 52.

The study recruited 514 patients (257 patients per group) during the open label randomised treatment period, with approximately 230 patients having been estimated to enter the single arm extension period.

GLP-1 receptor agonists used as controls were liraglutide, exenatide, albiglutide and dulaglutide. Patients randomised to the GLP-1 receptor agonist group continued the same daily dose and regimen of GLP-1 as prior to randomisation.

The results have yet to be published, but interim results were presented as an oral presentation at the American Diabetes Association (ADA) meeting on the 9th June 2019.

After 26 weeks, patients who switched to Suliqua®▼ saw a 0.6% greater reduction in HbA1c vs continuing treatment with a GLP-1 receptor agonist. More patients who switched to Suliqua®▼ achieved an HbA1c below the 7% target recommended by the ADA vs those treated with GLP-1 receptor agonists.

The study showed a safety profile consistent with previous studies: 22% of patients who switched to Suliqua®▼ experienced gastrointestinal events (nausea, diarrhoea and vomiting), compared to 10% of patients who continued previous treatment with GLP-1 receptor agonists. Rates of hypoglycaemia were also consistent with the established safety profiles of the treatments: 9% of patients treated with Suliqua®▼ experienced at least 1 event, compared with <1% who remained on previous GLP-1 therapy.

The results from the 26 week extension period have not been published.

Summary of safety data:[1,2,11]

The safety of Suliqua®▼ compared to insulin glargine alone and lixisenatide alone in T2DM was studied in one active controlled, open label, 24 week, Phase II study (ACT12374) [11] and the two Phase III studies (EFC12404 /12405).

In the Phase III study pool the percentage of patients experiencing at least one treatment emergent adverse event (TEAE) was comparable in the Suliqua®▼ and insulin glargine group (55% vs 50%) but slightly lower in subjects on Suliqua®▼ compared to subjects on lixisenatide (57% vs 67%).

There were no new or unexpected adverse events in any of the treatment groups.

The main difference in TEAE between the treatment groups was that subjects in the Suliqua®▼ group compared to the subjects on insulin glargine experienced more GI symptoms – nausea 10% vs 2.3%, diarrhoea 7% vs 3.6%, vomiting 3.4% vs 1.1%. However, GI symptoms were less frequently reported among subjects on Suliqua®▼ compared to lixisenatide – nausea 9.6% vs 24% and vomiting 3.2% vs 6.4% respectively.

The overall most common (≥5%) TEAE reported in the studies were nausea (10%), diarrhoea (7%), nasopharyngitis (7%), upper respiratory tract infection (5.5%) and headache (5.4%).

Hypoglycaemia

There were similar percentages of patients experiencing at least one documented hypoglycaemic episode among insulin naïve patients (EFC12404) in both the Suliqua®▼ and insulin glargine groups (25.6% and 23.6% respectively). The corresponding percentage compared to lixisenatide was lower (6.4%). Most of the subjects, both on Suliqua®▼ and insulin glargine, experienced 1-3 documented hypoglycaemic episodes.

For patients who had previously been treated with basal insulin (EFC12405) the percentages of at least one documented hypoglycaemic episode were higher in both treatment groups (Suliqua®▼ 40% and insulin glargine 42.5%).

Severe hypoglycaemia was reported in study EFC12405 - Suliqua®▼ 1.1% and insulin glargine 0.3%

Special warnings and precautions for use

Suliqua®▼ should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment e.g. change in the injection area, missed meals, unaccustomed, increased or prolonged physical activity.

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. Caution should be exercised in patients with a history of pancreatitis.

Suliqua®▼ is not recommended in patients with severe gastrointestinal disease.

Suliqua®▼ is not recommended in patients with severe renal impairment or end-stage renal disease.

The delay of gastric emptying with lixisenatide may reduce the rate of absorption of orally administered medicinal products. Suliqua®▼ should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption, require careful clinical monitoring or have a narrow therapeutic ratio.

No interaction studies with Suliqua®▼have been performed, the information available is based on studies with the monocomponents.

Suliqua®▼ is not recommended in women of childbearing potential not using contraception.

Suliqua®▼ should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Suliqua should be discontinued.

Suliqua®▼ should not be used during breast-feeding.

The manufacturer of Suliqua®▼ has produced Risk Materials alongside the SPC for use by both HealthCare Professionals and Patients.[16,17]

Undesirable effects

Related adverse reactions from clinical investigations and detailed in the SPC are as follows:

System organ class	Frequency		
	Very common	Common	Uncommon
Infections and infestations			Nasopharyngitis Upper respiratory tract infection
Immune system disorders			Urticaria
Metabolism and nutrition disorders	Hypoglycaemia		
Nervous system disorders		Dizziness	Headache
Gastrointestinal disorders		Nausea Diarrhoea Vomiting	Dyspepsia Abdominal pain
General disorders and administration site conditions			Fatigue Injection site reactions

(very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100)

Strengths and limitations of the evidence:

Strengths:

Multicentre studies with substantial patient numbers

Suliqua showed greater efficacy than each of the combination's individual components

Limitations:

Open label / Rescue treatment allowed

Lack of long term data beyond 30 weeks

No study directly compares the fixed ratio combination (Suliqua®▼) with the combined use of its individual components.

Patients below 18 years of age were not included in the studies.

In the studies Suliqua®▼ was administered subcutaneously once daily within 1 hour before breakfast. However, the SPC does not specify time of injection but states that Suliqua®▼ should be 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.

Summary of evidence on cost effectiveness:

Fixed Combination (Suliqua)

Suliqua®▼ 100 units/ml + 50 micrograms/ml - 3 x 3ml SoloStar pre-filled pen=£67.50.

Suliqua®▼ 100 units/ml + 33 micrograms/ml - 3 x 3ml SoloStar pre-filled pen=£51.30.

The recommended starting dose of Suliqua®▼ dependent on previous therapy is either:

10U/5µg or 20U/10µg given using 100 units/ml + 50 micrograms/ml pre-filled pen

10U/5µg = 0.1ml, 3 x 3ml = 90 doses= £67.50,

1 x 0.1ml dose = £0.75 (30 days treatment = £22.50)

20U/10µg = 0.2ml, 3 x 3ml = 45 doses = £67.50

1 x 0.2ml dose = £1.50 (30 days treatment = £45.00)

The maximum daily dose of Suliqua®▼ is 60U/ 20µg given using the 100 units/ml + 33 micrograms/ml pre-filled pen.

60U/20µg = 0.6ml, 3 x 3ml = 15 doses = £51.30

1 x 0.6ml dose = £3.42 (30 days treatment = £102.60)

Individual Components

Insulin glargine

100units/ml solution for injection 3ml pre-filled disposable devices 5 x 3ml pre filled pens = £37.77

10U = 0.1ml dose, 5 x 3ml = 150 doses = £37.77,

1 x 0.1ml dose = £0.25 (30 days treatment = £7.50)

20U = 0.2ml dose, 5 x 3ml = 75 doses = £37.77

1 x 0.2ml dose = £0.50 (30 days treatment = £15.00)

300units/ml solution for injection 1.5ml pre-filled disposable devices 3 x 1.5ml pre filled pens = £33.13

60U = 0.2ml dose, 3 x 1.5ml = 22.5 doses = £33.13

1 x 0.2ml dose = £1.47 (30 days treatment = £44.10)

Lixisenatide

Of the 6161 lixisenatide prefilled pens dispensed over the last 12 months across LMMG, 313 were 10micrograms/0.2ml solution for injection and 5848 were the 20micrograms/0.2ml solution for injection.

Lixisenatide starting dose: dosing is initiated at 10 mcg once daily for 14 days.

Lixisenatide maintenance dose: a fixed maintenance dose of 20 mcg once daily is started on Day 15.

Lixisenatide 10micrograms/0.2ml solution for injection 3ml pre-filled disposable devices 1 x 3ml pre filled pens = £31.67

Lixisenatide 20micrograms/0.2ml solution for injection 3ml pre-filled disposable devices 2 x 3ml pre filled pens = £57.93

Using Lixisenatide 10micrograms/0.2ml solution for injection

5µg = 0.1ml dose, 1 x 3ml = 30 doses = £31.67

1 x 0.1ml dose = £1.06 (30 days treatment = £31.67)

10µg = 0.2ml dose, 1 x 3ml = 15 doses = £31.67

1 x 0.2ml dose = £2.11 (30 days treatment = £ 63.34)

Using Lixisenatide 20micrograms/0.2ml solution for injection

10µg = 0.1ml dose, 2 x 3ml = 60 doses = £57.93

1 x 0.1ml dose = £0.97 (30 days treatments = £28.96)

20µg = 0.2ml dose, 2 x 3ml = 30 doses =£57.93

1 x 0.2ml dose = £1.93 (30 days of treatment = £57.93)

Equivalent dose cost comparison

Suliqua®▼ 10U/5µg, 30 day treatment cost = £22.50

Insulin glargine 10U, 30 day treatment cost = £7.50 } combined cost = £39.17

Lixisenatide 5 µg, 30 day treatment cost = £31.67

Suliqua®▼ 20U/10µg, 30 day treatment cost = £45.00

Insulin glargine 20U, 30 day treatment cost = £15.00 } combined cost = £78.34 or

Lixisenatide 10µg, 30 day treatment cost = £ 63.34 or £28.96 } £43.96

Suliqua®▼ 60U/20µg, 30 day treatment cost = £102.60

Insulin glargine 60U, 30 day treatment cost = £44.10 } combined cost = £102.03

Lixisenatide 20µg, 30 day treatment cost = £57.93

There would appear to be little difference in the monthly total cost between Suliqua®▼ and its separate individual components. However, Suliqua®▼ does offer the convenience of one versus two separate injections (which may aid patient compliance / convenience).

The other available basal insulin / GLP1 combination – insulin degludec / liraglutide (Xultophy) is dosed in accordance with the individual patient's needs. However, the maximum daily dose of Xultophy is 50 units insulin degludec and 1.8 mg liraglutide = 0.5ml.

Xultophy 3 x 3ml pre filled pens = £95.53

1 x 0.5ml dose = £5.31 (30 days treatment cost = £159.30)

Therefore, if we compare the monthly cost of the maximum dose of Suliqua®▼ (£102.60) to the monthly cost of the maximum dose of Xultophy (£159.30), Suliqua®▼ would appear to be less

expensive if a fixed combination were to be required. However, following previous medicines reviews, liraglutide is the LMMG GLP-1 preferred product (if daily administration is required), whilst lixisenatide is not a preferred product in the LMMG antihyperglycaemics guideline.

Xultophy currently has a BLACK RAG rating from LMMG. However, over the last 12 months 2598 pens have been prescribed across LMMG at a cost of £82,729.52

Prescribing and risk management issues:

Potential for medication errors with two pens of different strengths and in most patients there will be a need to change from one pen to the other over time.

Need to ensure correct nomenclature when prescribing / dispensing eg Suliqua 100 units/ml + 33 micrograms/ml pre-filled pen is the same as Suliqua (30-60) pen, whilst Suliqua 100 units/ml + 50 micrograms/ml pre-filled pen is also known as Suliqua (10-40) pen. To avoid medication errors, the prescriber must make sure that the correct strength and number of dose steps is stated in the prescription.[1]

Product subject to additional monitoring requirement. Risk materials are available from the company/ Electronic Medicines Compendium i.e. HCP guide / letter and a patient guide which provide information on dosing.[16,17]

Indication restricted to the combination with metformin.

Only licensed in adult patients over the age of 18 years (insulin glargine 100U/ml licensed in patients over the age of 2 years)

Commissioning considerations:

Innovation, need and equity implications of the intervention:

N/A

Financial implications of the intervention:

N/A

Service Impact Issues Identified:

N/A

Equality and Inclusion Issues Identified:

N/A

Cross Border Issues Identified:

GMMMG - Suliqua®▼ is not recommended for use in Greater Manchester. The product is less costly than Xultophy but there was concern that the availability of two strengths may lead to dispensing or dosing errors.

Pan Mersey - the Pan Mersey Area Prescribing Committee does not currently recommend the prescribing of insulin glargine + lixisenatide solution for injection (Suliqua®▼) for the treatment of type 2 diabetes mellitus. (GREY RAG Rating 2017)

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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References

[1] SPC - Suliqua 100 units/ml + 33 micrograms/ml solution for injection in a pre-filled pen https://www.medicines.org.uk/emc/product/9871/smpc
[2] SPC - Suliqua 100 units/ml + 50 micrograms/ml solution for injection in a pre-filled pen https://www.medicines.org.uk/emc/product/9870/smpc
[3] MIMS online July 2019 https://www.mims.co.uk/drugs/diabetes/insulins/suliqua
[4] NHS Electronic Drug Tariff July 2019 http://www.drugtariff.nhsbsa.nhs.uk/#/00721581-DA/DA00721310/Home
[5] NICE Pathway Type 2 diabetes in adults https://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults
[6] NICE Guideline NG28 Type 2 diabetes in adults: management https://www.nice.org.uk/guidance/ng28
[7] Type 2 diabetes: lixisenatide ESNM26 https://www.nice.org.uk/advice/esnm26
[8] Type 2 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) ESNM65
[9] Type 2 diabetes: insulin degludec/liraglutide (Xultophy) ESNM60 https://www.nice.org.uk/advice/esnm60/chapter/Key-points-from-the-evidence
[10] AWMSG insulin glargine/lixisenatide (Suliqua®) Reference No. 2464 http://www.awmsg.org/awmsgonline/app/appraisalinfo/2464
[11] European Medicines Agency Assessment Report – Suliqua EMA/800280/2016 https://www.ema.europa.eu/en/documents/assessment-report/suliqua-epar-public-assessment-report_en.pdf
[12] Rosenstock et al; Diabetes Care 2016 Nov; 39(11): 2026-2035. Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial https://care.diabetesjournals.org/content/39/11/2026
[13] Aroda et al; Diabetes Care 2016 Nov; 39(11): 1972-1980. Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. https://care.diabetesjournals.org/content/39/11/1972
[14] Sanofi Press Release June 2019. Soliqua® Phase 3 results significantly lowered blood sugar levels compared to GLP-1 receptor agonist treatments. https://www.sanofi.com/en/media-room/press-releases/2019/2019-06-09-19-00-00
[15] Clinical Trials. Gov. Efficacy and Safety of the Insulin Glargine/Lixisenatide Fixed Ratio Combination (FRC) Versus GLP-1 Receptor Agonist in Patients With Type 2 Diabetes, With a FRC Extension Period (LixiLan-G) https://clinicaltrials.gov/ct2/show/NCT02787551
[16] Risk Materials Suliqua 100 units/ml + 33 micrograms/ml solution for injection in a pre-filled pen https://www.medicines.org.uk/emc/product/9871/rmms
[17] Risk Materials Suliqua 100 units/ml + 50 micrograms/ml solution for injection in a pre-filled pen https://www.medicines.org.uk/emc/product/9870/rmms