New Medicine Assessment

OGLUO (GLUCAGON)

Recommendation: Green (restricted) for the following indications:

Treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.

Prescribing of Ogluo devices should be reserved for patients for whom the preparation and administration of conventional glucagon kits presents a barrier to effective treatment of hypoglycaemia and a risk to patient welfare.

Summary of supporting evidence:

- Pre-filled device; no reconstitution or assembly necessary for administration.
- Licensed in adults and children.
- Can be stored at room temperature (GlucaGen Hypokits have to be stored in a fridge).
- The pivotal study demonstrated that Ogluo was non-inferior when compared to GlucaGen HypoKit (HK) based on analysis of positive plasma glucose response: 99% for Ogluo patients and 100% for HK patients in the mITT Population and 100% of subjects in both treatment groups in the PP Population achieved positive plasma glucose response (PGR) within 30 minutes post-dose.
- However, the time to achieve positive PGR as of administration of study drug was 4-4.5 minutes longer (14.5-15 versus 10.5 minutes) for Ogluo versus HK and more HK subjects achieved positive PGR earlier than Ogluo.
- For more than 20% of Ogluo patients there was a delay of 5 to 20 minutes which can put them at risk of serious consequences. The SmPC of GlucaGen HK mentions that if the patient does not respond within 10 minutes, intravenous glucose should be given. If this was applied to Ogluo patients, it would mean that 63% would need to receive IV glucose.
- Resolution of hypoglycaemia symptoms was similar between the groups, across the studies. Consequently, it may be concluded that any differences between Ogluo and glucagon kits with respect to pharmacodynamic parameters, including mean time to plasma glucose >70 mg/dL, had no effect on resolution of symptoms.
- The pivotal study did not include any patients with Type 2 diabetes and only included a small number of elderly patients.
- Time required from a decision to dose to complete preparation and administration of study drug was statistically significantly faster in the Ogluo group compared to the HK group.
- The majority of adverse events were judged as mild or moderate, and all events were self-limiting, and resolved fully by the end of the studies. The most frequently reported adverse reactions are nausea (30%) and vomiting (16%).
- Immunogenicity is a relevant aspect regarding safety and tolerability of peptides and proteins.
- One Ogluo device is more than six times the cost of one GlucaGen Hypokit.
- GMMMG agreed that there may be benefits associated with the use of pre-filled pens when considering the reconstitution process required with Glucagen Hypokit. To replace the existing product would add around £383k per year to the prescribing budget for GM with little evidence to support the product being safer or more effective for any patient, however CRG members found it was very difficult to define which groups are most likely to benefit from the product.
  It was proposed that due to licensing and the availability of a 0.5mg pre-filled injection, that patients aged 2-6 years old who have a weight of less than 25kg could be considered eligible to reduce the potential for dosing errors with Glucagen. It was recognised that a clear GM-wide position is required to enable use in the groups which stand to benefit the most and to ensure fair access (NB. Position not

yet published).

Details of Review

Name of medicine (generic & brand name)**:**

Ogluo (glucagon)

NB. Ogluo is also marketed under the names Gvoke PFS and Gvoke HypoPen (granted approval by the FDA in September 2019)

Strength(s) and form(s):

Ogluo 0.5 mg glucagon solution for injection in pre-filled pen (0.1ml)

Ogluo 1 mg glucagon solution for injection in pre-filled pen (0.2ml)

Dose and administration:1

Adults and adolescents (≥6 years)

The recommended dose is 1 mg, administrated by subcutaneous injection.

Paediatric population (≥2 to <6 years)

• The recommended dose for paediatric patients who weigh less than 25 kg is 0.5 mg administered by subcutaneous injection.

• The recommended dose for paediatric patients who weigh 25 kg or greater is 1 mg administered by subcutaneous injection.

Time to respond and additional doses

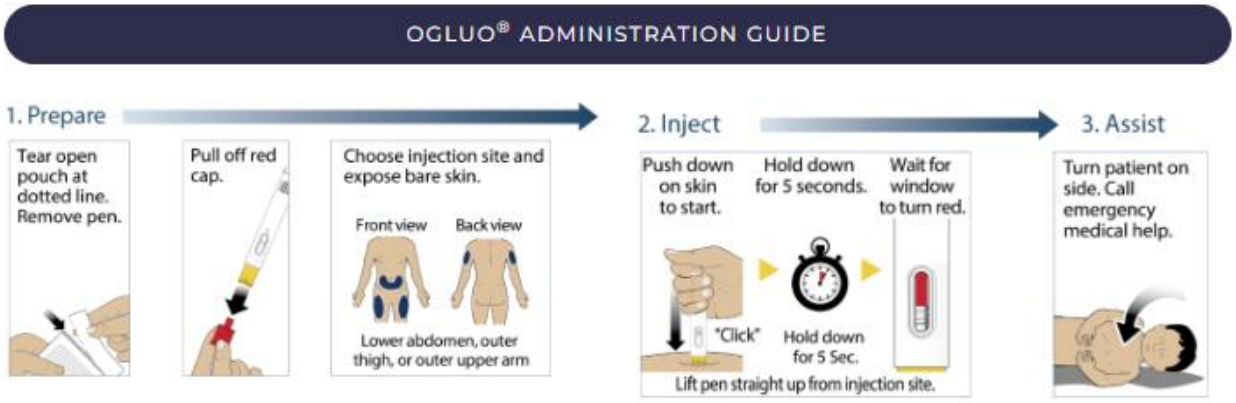
The patient will normally respond within 15 minutes. When the patient has responded to the treatment, give an oral carbohydrate to restore the liver glycogen and prevent relapse of hypoglycaemia. If the patient does not respond within 15 minutes, an additional dose of Ogluo from a new device may be administered while waiting for emergency assistance. It is recommended that patients are prescribed two Ogluo devices.

Method of administration

Ogluo pre-filled pen and pre-filled syringe are for subcutaneous injection only.

Patients and their caregivers should be instructed on the signs and symptoms of severe hypoglycaemia. As severe hypoglycaemia requires the help of others to recover, the patient should be instructed to inform those around them about Ogluo and its package leaflet. Ogluo should be administered as soon as possible when severe hypoglycaemia is recognised.

The patient or caregiver should be instructed to read the package leaflet at the time they receive a prescription for Ogluo.



Each device contains a single dose of glucagon and cannot be reused.

BNF therapeutic class / mode of action:

Glycogenolytic hormones

Licensed indication(s):[1]

Ogluo is indicated for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.

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

As licensed

Course and cost:

£73 per pen (single dose device)

It is recommended that patients are prescribed two Ogluo devices = £146 /prescription

Frequency of use variable. Shelf life of product 2 years.

Prices as per drug tariff Jan 2023

Current standard of care/comparator therapies:

How to treat a hypo[2]

Treat the hypo immediately. You can do this by eating or drinking 15 to 20g of a fast-acting carbohydrate.

You should test your blood sugar again after 10 to 15 minutes to check it is back above 4mmol/l. If it is still less than 4, you should have some more fast-acting carbohydrate and retest after 10 minutes. Fast-acting carbohydrates for people for low blood sugar include:

- five glucose or dextrose tablets
- five jelly babies
- a small glass of a sugary (non-diet) drink
- a small carton of pure fruit juice
- two tubes of a glucose gel such as GlucoGel®.

What to do when someone is having a severe hypo[2]

Do not give you any food or drink because the patient won't be able to swallow.

You need to:

- Put the patient into the recovery position (on their side, with their head tilted back and knees bent)

- Give the patient a glucagon injection – if there is one and you or someone else knows how to use it
- Call an ambulance – if they don't have a glucagon injection or if they haven't recovered 10 minutes after the injection.

Relevant NICE guidance:

Type 1 diabetes in adults: diagnosis and management (NG17)

1.10.10 Explain to adults with type 1 diabetes that a fast-acting form of glucose is needed for managing hypoglycaemic symptoms or signs in people who can swallow. [2004, amended 2015]

1.10.11 Adults with type 1 diabetes who have a decreased level of consciousness because of hypoglycaemia and so cannot safely take oral treatment should be:

• given intramuscular glucagon by a family member or friend who has been shown how to use it (intravenous glucose may be used by healthcare professionals skilled in getting intravenous access)

• checked for response at 10 minutes, and then given intravenous glucose if their level of consciousness is not improving significantly

• then given oral carbohydrate when it is safe to administer it, and put under continued observation by someone who has been warned about the risk of relapse. [2004, amended 2015]

Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18)

1.2.87 Explain to children and young people with type 1 diabetes and their families or carers that they should always have access to an immediate source of fast-acting glucose and blood glucose monitoring equipment, so that they can check for hypoglycaemia and manage it safely. [2004, amended 2015]

1.2.88 Train and equip families, carers, and (if appropriate) school nurses and other carers to give intramuscular glucagon for severe hypoglycaemia in an emergency. [2004, amended 2015]

1.2.89 Immediately treat mild to moderate hypoglycaemia in children and young people with type 1 diabetes as follows.

• Give oral fast-acting glucose (for example, 10 to 20 g) (liquid carbohydrate may be easier to swallow than solid).

• Be aware that fast-acting glucose may need to be given in frequent small amounts, because hypoglycaemia can cause vomiting.

• Recheck blood glucose levels within 15 minutes (fast-acting glucose should raise blood glucose levels within 5 to 15 minutes), and give more fast-acting glucose if they still have hypoglycaemia.

• As symptoms improve or blood glucose levels return to normal, give oral complex long-acting carbohydrate to maintain blood glucose levels, unless the child or young person is:

– about to have a snack or meal

– having a continuous subcutaneous insulin infusion. [2004, amended 2015]

1.2.91 For children and young people with type 1 diabetes who are not in hospital, or if rapid intravenous access is not possible, treat severe hypoglycaemia as follows.

• Use intramuscular glucagon or a concentrated oral glucose solution (for example Glucogel). Do not use oral glucose solution if they have reduced consciousness, because this could be dangerous.

• If using intramuscular glucagon:

– give 1 mg glucagon to children and young people who are over 8 years old, or who weigh 25 kg or more.

– give 500 micrograms of glucagon to children who are under 8 years old, or who weigh less than 25 kg.

• Seek medical assistance if blood glucose levels do not respond or symptoms continue for more

than 10 minutes.

• As symptoms improve or blood glucose levels return to normal, and once the child or young person is sufficiently awake, give oral complex long-acting carbohydrate to maintain normal blood glucose levels.

• Recheck blood glucose repeatedly in children and young people who have persistently reduced consciousness after a severe hypoglycaemic episode, to determine whether further glucose is needed. [2004, amended 2015]

1.2.94 Explain to children and young people with type 1 diabetes and their families or carers that when alcohol causes or contributes to hypoglycaemia, glucagon may be ineffective and they may need intravenous glucose. [2004]

Background and context

Hypoglycaemia (a hypo) happens when your blood glucose level is too low. A hypo needs to be treated if an individual's blood glucose falls below 4mmol/L.

This can happen when patients delay meals, have not had enough carbohydrate in their last meal, do lots of exercise without having the right amount of carbohydrate or reducing their insulin dose, take too much insulin, or drink alcohol on an empty stomach

Hypos come on fast and patients must be aware of the signs of a hypo so that they can treat it quickly.

The most common signs are:

- sweating
- being anxious or irritable
- feeling hungry
- difficulty concentrating
- blurred sight
- trembling and feeling shaky

The UK Hypoglycaemia Study Group reported an incidence of 110 severe hypoglycaemic episodes per 100 patient-years in patients with T1D treated with insulin for < 5 years, and an incidence of 320 episodes per 100 patient-years in those with T1D treated for > 15 years. Type 1 diabetics suffer an average of two symptomatic hypoglycaemic events per week, and a severe, temporarily disabling event approximately once a year. Insulin-using T2D patients typically have several hypoglycaemic episodes in a given year, one to two of these being severe episodes.[4]

Some people keep glucagon at home in case of an emergency. An injection of glucagon releases stored glucose from their liver.[3] Administration of glucagon with current products (i.e. Lilly Glucagon for Injection, and Novo GlucaGen) is a 9-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose.[4] Further downsides are the fact that the glucagon must be used immediately after reconstitution, and that it should be stored in the refrigerator. Under a stressed environment, the complexity of preparing the drug for administration may lead to drug administration failures due to either partial doses or missed doses all together: company-owned studies with currently marketed emergency glucagon kits have shown that only 6% to 31% of users were able to successfully prepare and administer the full dose of glucagon, while in a published study this was shown to be only 0% to 13%.

Ogluo is a soluble, liquid glucagon formulation that is stable for at least 2 years at room temperature. The stable liquid glucagon is loaded in a prefilled, ready-to-use autoinjector.[5]

Summary of evidence

Summary of efficacy data in proposed use:

European Medicines Agency (2021)[4]

The clinical development programme of Ogluo included 7 clinical trials involving 62 healthy subjects in one phase 1 study, and 300 adult and 31 paediatric subjects with T1D in two Phase 2 studies and four Phase 3 studies.

Since Ogluo is a synthetic glucagon formulation which contains the same amino acid sequence as native glucagon as well as to recombinant glucagon used in currently marketed glucagon emergency kits, distribution and elimination pathways are expected to be the same as for recombinant glucagon.

Study XSGP-304

Study XSGP-304 is a phase 3 multicentre, randomised, controlled, single-blind, 2-way crossover study to compare the efficacy and safety of Ogluo with GlucaGen HypoKit (Glucagon) (HK) for induced hypoglycaemia rescue in adults with T1DM.

Hypoglycaemia was induced through an insulin induction procedure to a target glucose level of <54 mg/dL (3.0 mmol/L). An insulin dosing algorithm was used in order to maintain a steady state of hypoglycaemia. After a hypoglycaemic steady state was obtained, the subject was administered the study drug SC to the abdomen with either Ogluo or HK per the randomised assignment. However, study glucagon was not administered in more severe hypoglycaemic episodes (if the PG was below 42 mg/dL).

Of the 132 patients that were randomised, 123 patients completed the study. Nine (9/132; 6.8%) subjects withdrew early from the study (5/66 [7.6%] subjects in the Ogluo arm and 4/66 [6.1%] subjects in the GlucaGen HypoKit arm).

No patients with T2DM were included in the study population while the intended indication is both T1DM and T2DM patients with severe hypoglycaemia. The number of elderly patients included in the clinical trial was small (only six patients [4.5%]); taking into account their increased hypoglycaemia risk, their reduced ability to recognise hypoglycaemia symptoms and communicate their needs it would have been relevant for the intended population to include more elderly patients.

The numbers of subjects achieving a plasma glucose >70 mg/dL or rise ≥20 mg/dL within 30 minutes of dosing were similar between treatment groups: 99% for Ogluo subjects and 100% for HK subjects for the modified intent to treat (mITT) population, and 100% of subjects in both treatment groups for the per protocol population.

Overall Ogluo and HK were similar for mean plasma glucose concentration at 30 minutes post-dose and both groups had mean and median values that were well above 70 mg/dL. Positive symptomatic response was defined as relief of neuroglycopenic symptoms within 30 minutes from a decision to dose. Rates of positive symptomatic response from time of decision to dose were similar between treatment groups at all time points for the mITT Population. At 30 minutes post dose, 34/39 subjects (87.2%) in the Ogluo group and 29/35 subjects (82.9%) in the GlucaGen HypoKit group had achieved positive symptomatic response. Mean time to achieving plasma glucose of ≥70 mg/dL or ≥20 mg/dL increase in plasma glucose concentration within 30 minutes of study drug administration was greater in the Ogluo treatment group compared to the HK treatment group. However, all were well within the clinically meaningful timeframe of 30 minutes of study drug administration.

Mean time to achieving PG of ≥70 mg/dL or ≥20 mg/dL increase in PG within 30 minutes of study drug administration (minutes)	mITT		PP	
	Gvoke	HK	Gvoke	HK
	14.8 min (±5.3)	10.4 min (±1.8)	14.57 min (±4.9)	10.45 min (±1.9)

Time required from a decision to dose to complete preparation and administration of study drug was statistically significantly faster in the Ogluo group compared to the HK group. These findings have important ramifications during real-world use of the product by laymen caregivers of diabetic patients who would likely need even more time to prepare HK than the licensed and trained pharmacists in this study. Additionally, the rate of successful preparation and delivery of full dose glucagon by caregivers in pre-hospital, emergency situations is low.

Overall, times to symptom relief after a decision to dose were generally similar between treatment groups. However, for the Per-Protocol Population, subjects who received Ogluo had statistically significantly faster neuroglycopenic symptom relief compared to subjects who received HK (10.51 minutes vs.13.98 minutes, respectively; P=0.023). Mean time to complete resolution of overall feeling of hypoglycaemia from a decision to dose was similar between treatment groups.

In summary, the study demonstrated that Ogluo was non-inferior when compared to GlucaGen HypoKit based on analysis of positive PGR (plasma glucose response): 99% for Ogluo patients and 100% for HK patients in the mITT Population and 100% of subjects in both treatment groups in the PP Population achieved positive PGR within 30 minutes post-dose. However, the time to achieve positive PGR as of administration of study drug was 4-4.5 minutes longer (14.5-15 versus 10.5 minutes) for Ogluo versus HK and more HK subjects achieved positive PGR earlier than Ogluo. The gain considering no reconstitution is necessary is estimated to be only 1 minute which would mean that there still is a delay of 3 to 3.5 minutes. Moreover, the time to recovery of 14.8 minutes (versus 10.4 minutes for HK) is only a mean value with important variability as the standard deviations were respectively 5.4 and 1.9 minutes.

When looking at the responders per time interval for Ogluo (mITT): 18 (14.2%) patients took 15 to 20 minutes, 5 patients (3.9%) took 20 to 25 minutes, 4 patients (3.1%) took 25 to 30 minutes and 1 patient

(0.8%) took 30 to 35 minutes to recover. This is in contrast to the HK patients who all took maximum 15 minutes to recover (and 88.6% took only up to 10 minutes, which was the case for merely 37% of Ogluo patients). This means that for more than 20% of Ogluo patients there was a delay of 5 to 20 minutes which can put them at risk of serious consequences. The SmPC of GlucaGen HK mentions that if the patient does not respond within 10 minutes, intravenous glucose should be given. If this would be applied to Ogluo patients, this means that 63% of them would need to receive IV glucose.

XSGP-301 and XSGP-303

In general, the treatment administration procedure in studies XSGP-301 and XSGP-303 was similar to the one in study XSGP-304. However, there were also some differences including a different comparator (Glucagon Emergency Kit – GEK) and the target plasma glucose concentration after the insulin induction procedure at which administration of glucagon could occur: 50 mg/dL in studies XSGP-301 and XSGP-303 versus 54 mg/dL in study XSGP-304.

Of the 161 randomised subjects in studies XSGP-301 and XSGP-303, 153 (95.0%) completed the studies. There were 2 discontinuations in XSGP-301, and there were 6 discontinuations in XSGP-303. None of the discontinuations was due to an adverse event (AE) or intolerance to study drug.

Of subjects treated with Ogluo, 97.4% of subjects in the mITT Population and 98% of subjects in the PP Population achieved a plasma glucose level >70 mg/dL within 30 minutes of dosing, comparable to treatment with GEK in which 100% of subjects achieved the primary endpoint. Of the subjects treated with Ogluo within these studies, the mean time to achieve plasma glucose >70 mg/dL or increase in plasma glucose >20 mg/dL was 13.8 minutes versus 10.0 minutes for GEK.

The analyses of the Adult Phase 3 Subjects with Type 1 Diabetes Pool demonstrated that Ogluo was comparable to GEK based on achieving relief of neuroglycopenic symptoms within 30 minutes after dosing. For the mITT analysis, 85.1% (131/154) of the subjects on Ogluo had symptom relief within 30 minutes after dosing, while 82.2% (129/157) on GEK experienced relief within 30 minutes.

In XSGP-301 Ogluo did not satisfy the criterion for non-inferiority to GEK based on analysis of failure scores for the ITT Population for the primary endpoint (increase in plasma glucose concentration from below 50 mg/dL to >70 mg/dL within 30 minutes after receiving study drug). Contributing to the difference in mean failure scores were 4 subjects in the Ogluo arm who did not achieve a plasma glucose >70 mg/dL within 30 minutes, but, rather, within an average time of 43.2 minutes without receiving glucose or additional intervention beyond Ogluo. It was noted that these 4 subjects had a nadir glucose in the range of 26.2 to 40.6 mg/dL, well below the protocol-defined plasma glucose target of just under 50 mg/dL.

The procedure relied heavily on investigator discretion. In some cases, the investigators infused an excessive amount of insulin and even increased insulin infusion rates when the plasma glucose rate was on target at 1 mg/(dL*min). This undercut the ability to achieve the desired steady state. About a third of the procedures across the treatment groups had post-dose glucose concentrations less than 40 mg/dL, illustrating the lack of steady state. Nevertheless, only 4 subjects in the study failed to achieve the primary endpoint of plasma glucose above 70 mg/dL in 30 minutes, a testament to the effectiveness of both products.

Resolution of hypoglycaemia symptoms was similar between the groups. In almost all cases, the resolution of these clinical symptoms preceded the return of documented euglycemia. Average time to resolution of the global feeling of hypoglycaemia did not differ significantly between Ogluo and GEK. Consequently, it can be concluded that any differences between Ogluo and GEK with respect to PD parameters, including mean time to plasma glucose >70 mg/dL, had no effect on resolution of symptoms, an important consideration when comparing the clinical efficacy of the products, where restoration of neurologic function and oral intake is critical to further medically manage severe hypoglycaemia.

In XSGP-303 Ogluo satisfied the criterion for non-inferiority to GEK based on analysis of the primary endpoint (an increase in plasma glucose concentration from below 50 mg/dL to >70 mg/dL within 30 minutes after receiving glucagon) for both the ITT and PP Populations. The percentage of subjects meeting the primary endpoint was 100% for both groups within both analytical populations. Ogluo satisfied the criterion for non-inferiority to Ogluo based on analysis of the secondary endpoint of relief of neuroglycopenic symptoms by 30 minutes after study drug administration for both the ITT and PP Populations.

There are only limited data for Ogluo in paediatric patients (31). There are only very limited data for Ogluo in elderly patients 65 years and above, and none in elderly 75 years and above. Ogluo was not investigated

in patients with hepatic or renal impairment.

The CHMP recommended to perform an actual-use study to provide data in T2DM patients which were not included and in patient types that were excluded in the clinical studies, and in elderly patients.

XSGP-302 – Paediatric patients

There are only limited data for Ogluo in paediatric patients (31) with only 7 in the 2-<6, 13 in the 6-<12 and 11 patients in the 12≤18 years old group. Study XSGP-302 is an open-label, sequential treatment efficacy and safety Phase 3 study. Subjects were administered insulin to induce a low-normal glycaemic state and then received an age-appropriate dose of Ogluo.

Statistically significant increases from Baseline in mean plasma glucose were observed in each age group ($p < 0.001$ for all groups) at 30 minutes following administration of an age-appropriate dose of Ogluo. Age groups were generally similar to each other in mean plasma glucose AUC (0-90), Cmax, and tmax. There were no clinically meaningful differences between age groups.

Although the increase from baseline in mean plasma glucose at 30 minutes post-dose was statistically significant in all age groups, there are some unexpected observations in the age group 12-<18 years versus the other age groups even though the administered dose of 1 mg was the double of the 0.5 mg used in the other age groups:

- The glucose increase from baseline (54.0 mg/dL) was much lower than for the other age groups (2-<6 and 6-<12), (81.4 and 84.2 mg/dL), and this cannot only be explained by a higher baseline glucose level

- Only 81.8% of patients in this group achieved a glucose increase ≥25 mg/dL within 30 minutes while of those having received 0.5 mg (other age groups together with the second administration in age group 12-<18) 96.8% achieved this mean time to plasma glucose increase ≥25 mg/dL from baseline was also higher (23.6 minutes versus 16.4 and 16.2 minutes)

- lower glucose AUC (0-90) (6377.54 (2700.448) versus 8147.71 (2162.379) and 8001.59 (2510.799) min*mg/dL

- glucose response did not vary greatly after receiving the 0.5 mg dose compared to the 1 mg dose of Ogluo, and overall similar PD was observed.

The applicant was requested to explain and to discuss whether this is due to outliers or not. According to the applicant the differences could be explained as follows: subjects (2 to <6 years and 6 to <12 years) likely received more glucagon by weight-based exposure. The difference in success rates is likely due to the administration of excess residual insulin from the insulin pumps during the 1 mg treatment visits, related to the individual study procedures. No outliers were identified.

Human Factors Study (2019)[5]

Simulated-use human factors usability study

The comparative usability study was conducted with a group of 16 participants consisting of 8 caregivers of patients with diabetes or first responders who were experienced with using GEKs, and 8 adults with no relationship to a diabetes patient and naïve to GEKs. Half of each participant group received training and the other half received no training.

The room was set up with a mannequin in the middle of the room on the floor, to represent a patient with diabetes experiencing a hypoglycaemic emergency. A tote bag containing the glucagon rescue device (kit or autoinjector) was placed on the floor next to the mannequin. Trained participants received a short, representative training from the moderator on how to prepare and administer a glucagon injection. Glucagon-experienced participants only received training on the glucagon autoinjector (GAI), while the glucagon-naïve participants received training on both the GAI and a GEK. Training included an overview of the device and a verbal walk-through of the procedure. Untrained participants did not receive any form of training from the moderator. All participants performed one unaided rescue injection with a GEK and one unaided rescue injection with the GAI (counter balanced order). After each rescue attempt, participants provided post interaction feedback on their experience.

Overall, 14 of 16 participants (88%) were able to successfully administer a rescue injection using the GAI compared with 5 of 16 participants (31%) with the GEK (chi-square test=10.49,P<0.05). The observed causes of failure for the GAI included the following: (1) could not remove device cap and (2) injected

through clothing. The observed causes of failure for the GEK included the following: (1) bent needle, (2) injected through clothing, (3) injected diluent only, (4) did not fully reconstitute, and (5) did not inject entire volume. Furthermore, while some participants may have correctly followed the GEK reconstitution and injection procedure, it was observed that many vials still contained solution or powder. In fact, only 6/16 (38%) of the GEK vials were empty following the injection procedure.

Summative human factors validation study

The summative human factors validation study consisted of two sessions. In the first session, participants either received training or underwent self-familiarisation with glucagon administration procedures. In the second session, participants administered the GAI under simulated emergency conditions with assessment of their skills and experiences. The study included 75 participants divided into 3 user groups. All First responders (n=15) received training before performing an unsupervised glucagon rescue attempt. In addition, half of the Naïve Caregivers (n=15) and all Naïve Adolescent Caregivers (n=15) received training. To test the worst-case scenario, all Experienced Caregivers (n=15) and the remaining Naïve Caregivers (n=15) received no training before performing an unaided rescue attempt.

Overall, 74 of 75 participants (98.7%) successfully administered the rescue injection using the GAI. Overall, there were no patterns of differences between trained versus untrained participants, between care givers versus first responders or between adults versus adolescents. One participant, an untrained Naïve Adult Care giver, failed to administer the full dose.

Summary of safety data:

European Medicines Agency (2021)[4]

The overall incidence of TEAEs was higher across the Ogluo groups versus comparator groups in the pooled Phase 3 Studies (46.1% Ogluo vs 33.1% GEK) and in Study XSGP-304 (52.8% Ogluo vs 46.3% HK). The higher incidence was partially driven by the incidences of nausea and vomiting, both known adverse class effects of glucagon. The insulin induction procedure itself likely was a cause of nausea.

The most commonly occurring TEAEs in adult studies were nausea (29.9%, Ogluo vs 22.9%, GEK [pooled studies] and 42.5%, Ogluo vs 44.7%, HK [Study XSGP-304]); vomiting (16.2% vs 9.6%, pooled studies and 12.6% vs 13.8%, Study XSGP-304); and headache (5.2% vs 3.8%, pooled studies and 5.5% vs 7.3%, Study XSGP-304).

There were 2 incidences of tachycardia (2 [1.6%] and 1 incidence of supraventricular extrasystoles (1 [0.8%]) after treatment with Ogluo 1 mg. However, glucagon is not known as arrhythmogenic, and they were likely a result of the insulin induction. Both events of tachycardia were judged as mild and related to study drug; both events resolved spontaneously. The event of supraventricular extrasystoles was judged as mild and not related to study drug; it resolved spontaneously.

No serious TEAEs occurred following treatment with Ogluo in Phase 3 studies; although there was 1 SAE related to Ogluo (vasovagal reaction) in Study XSGP-202. One (0.6%) subject experienced a serious TEAE (hyperinsulinaemic hypoglycaemia) following treatment with GEK in Study XSGP-301.

Overall, there were no remarkable differences in the incidence of TEAEs between Ogluo-treated subjects and GEK-treated subjects in the Adult T1D Subjects pool. Overall, the majority of events were judged as mild or moderate, and all events were self-limiting, and resolved fully by the end of the studies. When treatments were compared on a gross level, there were no apparent and significant differences in incidence rates for TEAEs, no apparent data inconsistencies, no apparent safety signals.

In the Phase 3 Paediatric Subjects, the incidence of subjects who reported TEAEs was similar in subjects age 2 to < 6 years and those age 12 to < 18 years (71.4% and 72.7%, respectively), and higher in the 6 to < 12 years age group (92.3%). Fewer TEAEs were reported in subjects age 12 to < 18 years when they received Ogluo 0.5 mg (54.5%) compared with when these same subjects received Ogluo 1 mg (72.7%). None of the TEAEs reported were considered severe, and there were no deaths, SAEs, or TEAEs leading to discontinuation. Among the 31 Ogluo injections in paediatric subjects, 42 TEAEs occurred, for a rate of 1.35 TEAEs per injection; 83.3% (35/42) were mild, 16.7% (7/42) were moderate and 0% (0/42) severe.

Immunogenicity is a relevant aspect regarding safety and tolerability of peptides and proteins. The notion that immunogenicity of glucagon is usually low may not apply for Ogluo due to its special formulation. Taking into account that no immunogenicity-related data have been submitted, the applicant submitted a

risk-assessment.

Summary of Product Characteristics[1]

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pheochromocytoma.

Special warnings and precautions for use

- Glycogen stores and hypoglycaemia

  To prevent relapse of the hypoglycaemia, oral carbohydrates should be given to restore the liver glycogen, when the patient has responded to the treatment.

- Insulinoma

  In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose. However, glucagon administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycaemia.

- Recovery time

  Please take into account that approximately 15% of patients achieved glucose recovery after 20 minutes or more in the pivotal trial.

Undesirable effects
The most frequently reported adverse reactions are nausea (30%) and vomiting (16%).

Within each frequency group, adverse reactions are presented in order of decreasing seriousness:

System organ class	Subject incidence	Adverse drug reaction
Nervous system disorders	Common	Headache
Cardiac disorders	Common	Tachycardia
Gastrointestinal disorders	Very common Very common Common Uncommon	Vomiting Nausea Diarrhoea Abdominal pain
General disorders and administration site conditions	Common Common Uncommon Uncommon	Injection site pain Injection site oedema Injection site bruising Injection site erythema

Frequency of most common adverse reactions among paediatric populations:

	Ages 2 to under 6 years of age (0.5 mg dose) N =7	**Ages 6 to under 12 years of age (0.5 mg dose) N = 13**	**Ages 12 to under 18 (0.5 mg dose) N = 11**	**Ages 12 to under 18 (1 mg dose) N = 11**
Nausea	43%	54%	36%	36%
Vomiting	14%	23%	0%	18%
Hyperglycaemia	14%	8%	0%	0%
Headache	0%	15%	0%	0%

Strengths and limitations of the evidence:

Strengths

- Trials compared Ogluo to relevant standards of care
- Ogluo was shown to be non-inferior to the GlucaGen Hypokit in achieving a positive glucose response, but time to achieve a positive glucose response was longer with Ogluo

- Time to achieve symptomatic relief appears to be comparable amongst the preparations
- Adverse events were generally mild and self limiting

Limitations

- Data appears to be limited to the company sponsored trials
- There was low representation of elderly patients in the trials and no representation from insulin using type 2 diabetics
- The insulin infusion algorithms could potentially be interpreted differently by different investigators
- The human factor studies had very low numbers of participants

Summary of evidence on cost effectiveness:

None identified

Prescribing and risk management issues:

Method of administration.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

The Ogluo® pen solution is stable at room temperature, pre-mixed and ready to use with no visible needle, allowing it to be stored anywhere and easily carried around, with a shelf life of 24 months[6].

Financial implications of the intervention:

Ogluo = £73 per pen (single dose device)

It is recommended that patients are prescribed two Ogluo devices = £146 /prescription

Frequency of use variable. Shelf life of product 2 years.

Glucagon 1mg powder and solvent for solution for injection vials (GlucaGen Hypokit) = £11.52 per kit

If 2 kits are prescribed = £23.04 /prescription

Dextrose oral gel 40% (Glucogel) £7.16 /pack (3x25mg tubes)

Primary care prescribing of injectable glucagon in L&SC for 12 months up to Nov 2022:

Product	Items
GlucaGen Hypokit 1mg inj	1406
Glucagon 1mg inj vials	696
Glucagon 1mg/0.2ml inj pre-filled disposable devices	20
Glucagon 500micrograms/0.1ml inj pf disposable devices	13
Ogluo 1mg/0.2ml solution for injection pre-filled pens	6
Ogluo 500micrograms/0.1ml inj pre-filled pens	3
Grand Total	**2144**

GlucaGen Hypokit's = 1406 items x £11.52 = approx. £16 197 annually

If 100% of these prescriptions changed to Ogluo devices, this would be an annual spend of (1406 x £73)

£102 638.

This would be an increase in cost annually of **£86 441**.

If 50% of GlucaGen Hypokit prescriptions changed to Ogluo, this would be an increase in cost annually of **£43 220**.

Prices as per drug tariff Jan 2023

Service Impact Issues Identified:

None identified

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** recommends glucagon injection (powder for reconstitution) for hypoglycaemia, but does not refer to glucagon SC (Ogluo).

The **Greater Manchester Medicines Management Group** (GMMMG) met in November 2022 and concluded the following:

> "A formulary assessment tool prepared by the RDTC was discussed and CRG agreed that there may be benefits associated with the use of pre-filled pens rather than the reconstitution process required with GlucaGen Hypokit. To replace the existing product would add around £383k per year to the prescribing budget for GM with little evidence to support the product being safer or more effective for any patient, however CRG members found it was very difficult to define which groups are most likely to benefit from the product.
>
> It was proposed that due to licensing and the availability of a 0.5mg pre-filled injection, that patients aged 2-6 years old who have a weight of less than 25kg could be considered eligible to reduce the potential for dosing errors with GlucaGen. It was recognised that a clear GM-wide position is required to enable use in the groups which stand to benefit the most and to ensure fair access. For this reason, it was agreed that a proposal is required on which GM ICS can be consulted. JS suggested he can obtain specialist consensus through the MFT insulin safety group and PB agreed to liaise with specialist services in Salford. DN will approach the SCN for advice on a GM position. **Decision:** Members as above to seek specialist input to enable CRG to propose a GM-wide position prior to consultation. This is planned to return to CRG in January 2023."

Legal Issues Identified:

None identified

Media/ Public Interest:

Requests have been made locally for this device.

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

References

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[3] NHS, “Hypoglycaemia (hypos)”, 2021. Available: https://www.nhs.uk/conditions/type-1-diabetes/managing-blood-glucose-levels/hypoglycaemia-hypos/

[4] European Medicines Agency, “Ogluo”, 2021. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/ogluo

[5] Valentine et al, “Human Factors Usability and Validation Studiesof a Glucagon Autoinjector in a Simulated SevereHypoglycemia Rescue Situation”, *Diabetes Technology and Therapeutics*, vol. 21 (9), 2019

[6] Tetris Pharma Ltd, “WHY USE OGLUO®?”. Available: https://tetrispharma.com/hcp/products/ogluo/