EU Risk Management Plan for Ogluo (glucagon)

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List of Abbreviations

DLP	data lock point
EPAR	European Public Assessment Report
FDA	food and drug administration
HCP	healthcare professional
HF	human factor
IL-6	interleukin-6
MEN-1	multiple endocrine neoplasia type 1
PL	package leaflet
REMS	risk evaluation and mitigation strategy
RMP	risk minimisation plan
SmPC	summary of product characteristics
US	United States

Part I: Product(s) overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Glucagon (glucagon)
Pharmacotherapeutic group(s) (ATC Code)	H04AA01 - Pancreatic hormones, Glycogenolytic hormones
Marketing Authorisation Applicant **Marketing Authorisation Holder**	Xeris Pharmaceuticals Ireland Limited Xeris Pharmaceuticals Ireland Limited
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	Ogluo
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Synthetic polypeptide hormones
	Summary of mode of action: Glucagon opposes the action of insulin; it raises the concentration of glucose in the blood by promoting glycogenolysis, and by stimulating gluconeogenesis. Additionally, glucagon inhibits the tone and motility of the smooth muscle in the gastrointestinal tract.
	Important information about its composition: Glucagon is a single chain containing 29 amino acid residues and has a molecular weight of 3483 Daltons and is identical to human glucagon. Glucagon is produced by solid phase synthesis with subsequent purification.
Hyperlink to the Product Information	1.3.1 Product, Labelling, and Package Leaflet
Indication(s) in the EEA	Current: The treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.
	Proposed: Not applicable

Dosage in the EEA	Current: Adults, adolescents and paediatric patients aged 6 years and older: 1 mg Paediatric patients aged 2 to under 6: Paediatric patients who weigh less than 25 kg: 0.5 mg Paediatric patients who weigh 25 kg or greater: 1 mg
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection Pre-filled pen 0.5 mg Pre-filled pen 1 mg Pre-filled syringe 0.5 mg Pre-filled syringe 1 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Ogluo was submitted as a hybrid application under Article 10(3) of Directive 2001/83/EC. The indication for Ogluo is for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus.

The reference product in the EU is Novo Nordisk's GlucaGen® HypoKit. However, Phase 3 clinical studies have been completed where the reference product was Lilly Glucagon for Injection (N=2) or Novo Nordisk's GlucaGen® HypoKit (N=1) as the reference product. A total of 7 Xeris clinical studies were performed in adult and paediatric patients with diabetes, or adult healthy volunteers. For information about specific clinical trial exposure refer to Part II: Module SIII.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable. Ogluo is a hybrid product.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable. This is a hybrid application.

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure

Not applicable.

Table SIII.2: Age group and gender

Age Group	Male	Female	Total
Children (2 to 11 years)	10	10	20
Adolescents (12 to 17 years)	5	6	11
Adults (18 to 64 years)	169	159	328
Elderly (65 to 74 years)	11	10	21
Total	**195**	**185**	**380**

Only subjects exposed to Ogluo are included in this table.

Table SIII.3: Dose

Of the 380 total subjects who received Ogluo, 78 of them received 2 doses in crossover studies.

Table SIII.4: Ethnic origin

Study ID	Hispanic	Non-Hispanic	Total
XSGP-304	4	123	127
XSGP-303	6	70	76
XSGP-302	0	31	31
XSGP-301	5	73	78
XSGP-202	1	6	7
XSGP-201	23	6	29
XSGP-101	13	19	32
Total	**52**	**328**	**380**

Only subjects exposed to Ogluo are included in this table.

Of all subjects, 344 have been exposed to the pre-filled pen, 61 to the pre-filled syringe and 7 to investigational vial and syringe. Please note in the XSGP-101 crossover study, the 32 subjects received both pre-filled pen and pre-filled syringe.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable. Ogluo has not been launched yet on the market at the DLP of this RMP.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

To identify the safety concerns for Ogluo, safety information (SmPC) of the reference product (GlucaGen) was used as well as safety information for glucagon containing products marketed in other territories in the public domain. Furthermore, the safety clinical overview of Ogluo and the clinical safety documentation were used in analyses. These studies included: 1) the completed clinical studies (XSGP-101, XSGP-201, XSGP-202, XSGP-301, XSGP-302, XSGP-303, XSGP-304), and 2) the human factor (HF) studies (mannikins) XSGP-HF3 G-Pen (glucagon injection) Auto-Injector Summative Human Factors Validation, XSGP-HF5 G-Syringe (glucagon injection) Summative Human Factors Validation, XSGP-HF6 G-Pen Supplemental Summative Human Factors Validation – Untrained Paediatric Users, XSGP-HF7 G-Syringe Supplemental Summative Human Factors Validation – Untrained Paediatric Users). Safety information and literature on other products formulated in an auto-injector was also taken into account. There are no post marketing cases for serious adverse events for Ogluo, since the launch to the US market. Furthermore, as this is a hybrid application, requirements are based on risk proportionality principle, addressing new data generated or differences with the reference product.

SVII.1 Identification of safety concerns in the initial RMP submission

Ogluo was approved by the FDA in the US on 10 September 2019. The FDA determined that Ogluo did not require a REMS.

Important identified risks:

- None

Important potential risks:

- Drug administration error leading to loss of drug benefit

Missing information:

- None

Medical device part of Ogluo pre-filled syringe and pre-filled pen

As this hybrid application includes medical device parts as well (resp. the pen and the pre-filled syringe), these parts will be discussed here.

Regarding both the devices, the pre-filled syringe and the pre-filled pen the following conclusions were drawn:

Pre-filled syringe:

The Systems Hazards risk analysis that was performed on the pre-filled syringe according to ISO 14971, concluded the following residual risks:

1. Cross-contamination or infection through the reuse, sharing, or incorrect disposal of the used syringe. This is addressed through design features and instructions for use.

2. Storage of the product in an environment (for example high temperature or low temperature) that causes degradation of the drug product.

3. Drug administration error leading to loss of drug benefit. (important potential risk)

A summative human factors study with the Ogluo pre-filled syringe, paediatric and adult, trained and untrained users (Study XSGP-HF5 G-Syringe (glucagon injection) Summative Human Factors Validation),

demonstrated a successful (98.7%) delivery rate during a simulated severe hypoglycaemia situation. In a supplemental human factor (HF) study in untrained paediatrics using the Ogluo pre-filled syringe (XSGP-HF7), 100% of participants performed a successful rescue and injected a full dose of glucagon with the Ogluo pre-filled syringe.

These risks cannot be eliminated and are known but are accepted risks associated with syringe systems (1) and personal drug delivery systems (2).

Pre-filled pen:

The System Hazard Analysis that was performed on the pre-filled pen according to ISO 14971, led to the identification of the attributes Cross-contamination or infection, and Storage.

In reliability studies using pre-conditioned Ogluo pre-filled pen (aged, heat/cold temperatures, dropping), Ogluo pre-filled pen demonstrated 99.999% reliability for functional testing of critical attributes of failure to fire, injection time, injection volume, activation force, and exposed needle length thus validating that the Ogluo pre-filled pen design comprehensively incorporates necessary design features that ensure delivery of a full dose.

In a summative human factors study with the auto-injector, paediatric and adult, trained and untrained users (Study XSGP-HF3 G-Pen (glucagon injection) Auto-Injector Summative Human Factors Validation), Ogluo pre-filled pen demonstrated a 98.7% successful rate in delivery of a full dose of glucagon during a simulated severe hypoglycaemia situation. In a supplemental HF study in untrained paediatrics using the Ogluo pre-filled pen (XSGP-HF6), 100% of participants performed a successful rescue and injected a full dose of glucagon with both the Ogluo pre-filled pen.

After all mitigations are applied, the most significant residual risks are those relating to:

1. Cross-contamination or infection through the reuse, sharing or incorrect disposal of the used syringe. The devices are intended for single use only, and this is clearly described in the labelling. This is addressed through design features and instructions for use that are currently accepted as state of the art. This risk cannot be eliminated and is a known and accepted risk associated with syringe systems.

2. Storage of the product in an environment (for example high temperature) that causes degradation of the drug product. This is addressed through design features and instructions for use that are currently accepted as state of the art. This risk cannot be eliminated and is a known and accepted risk associated with personal drug delivery systems.

3. Drug administration error leading to loss of drug benefit. (important potential risk)

Conclusion on medical device part of the products:

The SmPC and the PL include instructions for use of the pre-filled syringe and the pre-filled pen. Human factors testing has validated that the instructions for use are adequate.

- To address the potential risk for drug administration error leading to loss of drug benefit, additional risk minimisations have been provided.
- The benefits of use of Ogluo outweigh each individual residual risk, as well as the combined overall residual risk of the product as a whole; therefore residual risk is deemed to be acceptable.
- There are no identified important risks to be included in the risk management plan.
- The important potential risk of drug administration error leading to loss of drug benefit, will be included in the risk management plan.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Although nausea, vomiting, headache, and injection site reactions are the events with the highest incidence in the clinical trials, and with other glucagon products, they will not be included as important safety concerns in this RMP. The indication of Ogluo is for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus. Severe hypoglycaemia is a serious condition that without prompt medical intervention may lead to seizures, loss of consciousness, and even death. Most adverse reactions are outweighed by the dire clinical impact of severe hypoglycaemia. As glucagon has been used as anti-hypoglycaemic drug since the 1960's, the adverse drug reactions associated with glucagon are also well-known to the prescribers and users. These safety concerns do not require further characterisation and are followed up via routine pharmacovigilance, and the risk minimisation messages in the product information are adhered to by prescribers. They are not regarded as important risks for the inclusion in this RMP.

In the presence of phaeochromocytoma, glucagon may stimulate the release of catecholamines from the tumour. If the patient develops a dramatic increase in blood pressure, use of non-selective α-adrenergic blockade has been shown to be effective in lowering blood pressure. Ogluo is contraindicated in patients with phaeochromocytoma. 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. A patient developing symptoms of hypoglycaemia after a dose of glucagon should be given glucose orally or intravenously. Allergic reactions, which have been reported with injectable glucagon, may occur and include generalised rash, and in some cases anaphylactic shock with breathing difficulties, and hypotension. If the patient experiences difficulty breathing call for immediate medical assistance. These described safety concerns do not require further characterisation and are followed up via routine pharmacovigilance, and the risk minimisation messages in the product information are adhered to by prescribers. They are not regarded as important risks for the inclusion in this RMP.

The device related risks are low to moderate, rare, and are addressed in the SmPC and PL.

Use during lactation is not included as important missing information because since the 1960's no harm to the baby has been identified or reported when this incidental use occurred during the lactation period. Clinical studies have not been performed for lactating patients. However, in the context of severe hypoglycaemia the benefits for use of glucagon during a severe hypoglycaemia emergency outweigh the risks. Glucagon is cleared from the bloodstream quickly (mainly by the liver) ($t_{1/2}$= 3–6 min.); thus the amount excreted in the milk of nursing mothers following treatment of severe hypoglycaemic reactions is expected to be extremely small. As glucagon is degraded in the digestive tract and cannot be absorbed in its intact form, it will not exert any metabolic effect in the child.

In the studies across 349 adult subjects who received at least 1 dose of G-Pen, 21 subjects were ≥ 65 years of age. The incidence of treatment emergent adverse events was generally similar between age groups and there were no apparent age-related trends (ISS Table 9.2.1). In the context of severe hypoglycaemia emergencies, the benefits for use of glucagon during an emergency outweigh the risks.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Drug administration error leading to loss of drug benefit. In an emergency setting, the first-time user who is not familiar with the device or its instructions for use may fail to administer the medication correctly to the patient. Risk groups for inappropriate use of the device are likely to be first-time users who are unfamiliar with the device and the instructions for use.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The important potential risk of drug administration error leading to loss of drug benefit, has been included in the risk management plan.

SVII.3 Details of important identified risks, important potential risks, and missing information

This RMP is based on the agreed safety information of the reference drug GlucaGen and other glucagon products with the same indication and/or application forms, and safety information in the public domain. Furthermore, as this is a hybrid application, requirements are based on risk proportionality principle, addressing new data generated or differences with the reference product.

SVII.3.1. Presentation of important identified risks and important potential risks

No important identified risks have been identified.

One important potential risk has been identified:

- Drug administration error leading to loss of drug benefit.

Important Potential risk	***Drug administration error leading to loss of drug benefit***
Potential mechanisms	In an emergency setting, the first-time user who is not familiar with the device or its instructions for use may fail to administer the medication correctly to the patient. A failure to administer the medication correctly may result in a failure to deliver the full dose of glucagon drug required to restore normal blood glucose levels, thus prolonging the severe hypoglycaemia episode.
Evidence source(s) and strength of evidence:	With the auto-injector, the single failure (1/75) observed where drug administration error was noted was attributed to an untrained user who did not read the instructions and, as a result, prematurely lifted the auto-injector from the injection site during injection and a partial dose was administered. With the prefilled syringe, the single failure (1/75) observed where drug administration error was noted was attributed to an untrained user who did not read the instructions and, as a result, expelled the drug prior to injection and no dose was administered.
Characterisation of the risk:	Failure to dose or inadequate dose of glucagon during a severe hypoglycaemia episode may lead to worsening severe hypoglycaemia and clinical sequelae such as seizure or coma. Human factors testing demonstrates that 98.7% (74/75) of users for both the prefilled syringe and auto-injector formats can successfully and promptly administer a full dose of glucagon during simulated emergency settings. User groups in the human factors testing include health care emergency responders, adolescent and adult caregivers, trained and untrained caregivers.
Risk factors and risk groups:	Risk groups for inappropriate use of the device are likely to be first-time users, patients or their caregivers, who are untrained and unfamiliar with the device and the instructions for use.
Preventability:	Initial and recurrent instructions and education per the health care provider that includes training for the proper use of the glucagon devices (considered standard of care), will provide knowledge to reduce the risk of drug administration error that leads to loss of benefit (see also Part V section V.2).
Impact on the risk-benefit balance of the product:	The complications associated with drug administration error (inadequate dose, failure to dose) are severe because under treated or untreated severe hypoglycaemia may lead to seizure, coma, and death. However, the risk for drug administration error is anticipated to be small because human factors testing has demonstrated that 98.7% of users for both the prefilled syringe and auto-injector devices can successfully and promptly administer a full dose of glucagon during simulated emergency settings. Thus, the impact of this potential risk upon the total risk-benefit balance of the product is small.

Important Potential risk	*Drug administration error leading to loss of drug benefit*
Public health impact:	Reduction of drug administration error leading to loss of drug benefit, will support successful use of glucagon in the individual treatment of severe hypoglycaemia, especially in prehospital settings. No impact on public health is expected

SVII.3.2. Presentation of the missing information

None.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Drug administration error leading to loss of drug benefit
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaires:

A targeted follow-up questionnaire will be recorded at adverse event intake in order to characterise the potential risk of "drug administration error leading to loss of drug benefit."

Other forms of routine pharmacovigilance activities:

Not applicable. No other forms of pharmacovigilance activities are planned.

III.2 Additional pharmacovigilance activities

Not applicable. No additional pharmacovigilance activities are planned.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

N/A

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	
Important potential Risks	
Drug administration error leading to loss of drug benefit	Routine risk communication: Precautions on the handling and use of the product that describe the "potential risk of drug administration error leading to loss of drug benefit" has been provided within sections 4.2 (Posology and method of administration) & 6.6 (Special precautions for disposal and other handling of the SmPC and section 2 (What you need to know before you use Ogluo) & 3 (How to use Ogluo) of the Package Leaflet. Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How to use Ogluo, Assist step) The legal status of the product is a prescription drug, which requires HCPs to instruct patients on proper use of the product prior to use; instructions include the Product Information, administration leaflet, and an instructional video.
Missing information	
None	

V.2. Additional Risk Minimisation Measures

Additional risk minimisation measures

1. An administration leaflet.
2. Instructional video.

Objectives:

The correct administration of Ogluo is required in order to successfully treat episodes of severe hypoglycaemia. The objective of additional risk minimisation measures is to address and minimize the potential risk of drug administration error leading to loss of benefit.

Rationale for the additional risk minimisation activities:

Methods to reduce the potential risk for drug administration error may include further instruction on the correct use of Ogluo. This rationale supports the development and access to complementary administration leaflet and audio-visual training materials for the Ogluo instructions for use.

Target audience and planned distribution path:

The target audience will be HCPs who are expected to prescribe, supply, and/or train patients/caregivers upon initial Ogluo prescription. The planned distribution path of the risk minimisation materials will be agreed upon by each individual member state.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The outcomes of the routine PV questionnaires on these adverse events specific to medication error leading to loss of benefit, will be used to evaluate the effectiveness of these materials.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Drug administration error leading to loss of drug benefit	Routine risk minimisation measures: • SmPC sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal and other handling) • PLs section 2 (What you need to know before you use Ogluo) and 3 (How to use Ogluo) • Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Routine PV questionnaire for reported adverse events specific to medication error leading to loss of benefit.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(How to use Ogluo, Assist step) • Prescription drug requiring patient training by HCP Additional risk minimisation measures: • Administration leaflet • Audio Visual training materials	

Part VI: Summary of the risk management plan

Summary of risk management plan for Ogluo (glucagon)

This is a summary of the risk management plan (RMP) for Ogluo. The RMP details important risks of Ogluo, how these risks can be minimised, and how more information will be obtained about Ogluo's risks and uncertainties (missing information).

Ogluo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ogluo should be used.

This summary of the RMP for Ogluo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ogluo's RMP.

I. The medicine and what it is used for

Ogluo is authorised for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 2 years and over with diabetes mellitus. It contains glucagon as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Ogluo’s benefits can be found in Ogluo’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ogluo, together with measures to minimise such risks and the proposed studies for learning more about Ogluo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Ogluo, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ogluo is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Ogluo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ogluo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Drug administration error leading to loss of drug benefit
Missing information	None

II.B Summary of important risks

Important potential risk	
Evidence for linking the risk to the medicine	With the auto-injector, the single failure (1/75) observed where drug administration error was noted was attributed to an untrained user who did not read the instructions and, as a result, prematurely lifted the auto-injector from the injection site during injection and a partial dose was administered. With the prefilled syringe, the single failure (1/75) observed where drug administration error was noted was attributed to an untrained user who did not read the instructions and, as a result, expelled the drug prior to injection and no dose was administered.
Risk factors and risk groups	Risk groups for inappropriate use of the device are likely to be first-time users, patients or their care-givers, who are unfamiliar with the device and the instructions for use.

Important potential risk	
Risk minimisation measures	Routine risk minimisation measures: Instructions for proper use of glucagon: • SmPC Sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal and other handling) • PLs section 2 (What you need to know before you use Ogluo) and 3 (How to use Ogluo) • Instructions for users to call for medical help right away after administering glucagon—SmPC Section 4.2 (Posology and method of administration), PL Section 3 (How to use Ogluo, Assist step) • Prescription drug requiring patient training by HCP Additional risk minimisation measures: • Administration leaflet • Audio Visual training materials

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions for marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

N/A

Annex 4 - Specific adverse drug reaction follow-up forms

As part of routine pharmacovigilance, a targeted follow-up questionnaire during the adverse event intake will be implemented. The questionnaire will be used to evaluate the potential risk for drug administration error leading to loss of drug benefit.

The adverse event intake questionnaire is provided below:

Adverse Event Intake Questionnaire

1. Dose (circle one): Ogluo 0.5 mg (pediatric) Ogluo 1 mg (adult)
2. Type of device (circle one): pre-filled pen pre-filled syringe
3. Marketing Authorisation Number: _____
4. Where and how was the item stored (e.g., in home, in backpack, in car, item refrigerated, room temperature, heated environment, etc.)?: _____
5. At time of use, was the item in its intact original package (circle one)? Yes/No
6. Event(s) description, onset date:

   Description: _____

   _____

   _____ Onset Date: _____

7. Was a full dose of drug delivered (circle one)? Yes/No

   If no, then explain (e.g., source of failure): _____

8. Information about drug administration

   a. The anatomical site of administration (circle one): Arm Thigh Abdomen
   b. Location and details of person who deployed the device:
      i. Location of patient at time of administration: _____
      ii. Person who deployed device
         - Self-administered: ____
         - Health Care Provider: ____
         - Caregiver: ____ Trained ___ Untrained ___
   c. Did the person review the instructions regarding administration prior to deploying the device (check all that apply)?
   d. Package Leaflet: Yes___ No___
   e. Outer foil pouch: Yes___ No___
   f. Administration leaflet: Yes___ No___
   g. Instructional video: Yes___ No___
   h. Was emergency medical help called after the injection: Yes___ No___

9. Blood sugar level prior to administration: _____ Time Taken (if known): _____
10. Blood sugar level following administration: _____ Time Taken (if known): _____
11. Result of medical evaluation:

    Diagnosis: _____ Date(s) of Evaluation _____

12. Pertinent tests/labs:

    Pertinent Tests Performed: _____

Date of Test(s): _____
Results and Test Measurement Unit(s): _____

13. Treatment for event (describe any medical interventions that occurred after product administered):

_____

_____

14. Medical history and patient information prior to initial product use (dates):

    a. Type of Diabetes (circle one): Type I Type II
    b. Concomitant meds, supplements (dose, frequency, dates):

_____

_____

    c. Patient's weight: _____
    d. Patient's height: _____
    e. Patient's race: _____

15. Event(s) outcome (circle one): recovered not recovered unknown

    a. for each event recovered - please delineate the resolution date: _____
    b. for each event not recovered, please describe as ongoing and worsened, or ongoing and improved: _____

16. Was the patient hospitalized or was a hospitalization prolonged due to the event(s)? Yes/No

    a. If hospitalized, dates and name/location of hospital: _____

_____

    b. If seen in an emergency department, dates and name/location of the emergency department:

_____

17. May we contact the health professional(s) who is most familiar with the event(s)? Yes/No

18. Name/address and phone number for the health professional(s): _____

    a. _____

19. Explanation for Incomplete Fields [No further information known by reporter/Customer declined to participate/Reporter lack of time]: _____

_____

_____

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

1. Development of an administration leaflet will contain the following key elements:
   - Patients should receive the administration leaflet from their healthcare professionals upon initial Ogluo prescription and after training.
   - It is important not to test the single-dose device in advance, not to remove the single-dose device from the foil pouch in advance and to ensure that the patient understands that each Ogluo single-dose device can only be used once.
   - The PL should be referenced for more detailed information regarding administration and handling of Ogluo.
   - Patients can use the leaflet to teach those around them how to correctly handle and administer Ogluo.
   - 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 medical assistance.
   - The leaflet should contain a URL and QR code to a website where patients can access the instructional video.
2. Development of an instructional video which will contain the following key elements:
   - To reinforce the correct Ogluo handling and administration, step-by-step instructions on the appropriate use of Ogluo should be provided.
   - 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 medical assistance.