dasiglucagon

Risk Management Plan

[redacted]

EU Risk Management Plan for dasiglucagon

RMP version to be assessed as part of this application:

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QPPV name: Liliana Cristina Hansen

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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List of abbreviations and definition of terms

ADA	Anti-Drug Antibody
ADR	Adverse drug reactions
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CHI	Congenital hyperinsulinism
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GCGR	Glucagon receptor
GFR	Glomerular filtration rate
HCP	Healthcare Professional
ICH	International Council for Harmonisation
ICSR	Individual Case Safety Report
IFU	Instructions for use
IM	Intramuscular
INN	International Nonproprietary Names (common name)
IV	Intravenous
MAA	Marketing authorisation application
PD	Pharmacodynamic
PK	Pharmacokinetics
PL	Package leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible For Pharmacovigilance
QR code	Quick-response code
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
ULN	Upper limit of normal

Part I Product(s) Overview

Active substance(s) (INN or common name)	Dasiglucagon
Pharmacotherapeutic group(s) (ATC Code)	H04AA02
Marketing Authorisation Applicant	Zealand Pharma A/S.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zegalogue
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Peptide (chemically synthesised)
	Summary of mode of action: Dasiglucagon is a glucagon receptor agonist analogue, which increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.
	Important information about its composition: the product is a clear, colorless solution for injection. It is formulated using dasiglucagon as an active ingredient and the following excipients: Trometamol, Sodium chloride, Water for injections, Hydrochloric acid and Sodium hydroxide. In latex-sensitive individuals the medicinal product may cause severe allergic reactions.
Hyperlink to the Product Information	Zegalogue SmPC
Indication(s) in the EEA	Current: not applicable.
	Proposed : treatment of severe hypoglycaemia in adults, adolescents, and children aged 6 years and over with diabetes mellitus.
Dosage in the EEA	Current: not applicable.
	Proposed: Adults, adolescents and children aged 6 years and over. The recommended dose is 0.6 mg administered by subcutaneous injection.
Pharmaceutical form(s) and strengths	Current: not applicable
	Proposed: 0.6 mg solution for injection in pre-filled syringe or pre-filled pen.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II Safety specification

Module SI Epidemiology of the indication(s) and target population(s)

Indication: treatment of severe hypoglycaemia in adults, adolescents, and children aged 6 years and over with diabetes mellitus.

Incidence: In spite of advances in diabetes treatment, severe hypoglycemia remains a relatively frequent complication. Event rates are not precisely established, but a Danish-British multicenter survey of 1076 consecutive adult patients with type 1 diabetes mellitus (T1DM) who completed a detailed questionnaire on hypoglycemia and related issues determined that the overall rate of severe hypoglycemia in the preceding year was 1.3 episodes/patient-year, with episodes being reported for 37% of patients[1]. In a 6-month retrospective and 4-week prospective global study in 27,585 people from 24 countries with insulin-treated diabetes, the rate of severe hypoglycemia in patients with T1DM was 4.9 episodes/patient-year[2]. The incidence of severe hypoglycemia in T2DM patients receiving insulin has been estimated to be about a third to a half of that observed in patients with T1DM[2,3]. In children with diabetes the incidence of severe hypoglycemia (comprising hypoglycemic coma as defined by the International Society for Pediatric and Adolescent Diabetes; ISPAD) has fallen during the last decades but nonetheless remains a clinical challenge, with a current rate of 3-7 episodes/100 patient-years[4].

Prevalence: Overall hypoglycemia is less frequent in T2DM than in T1DM. However the frequency of hypoglycemia has been reported to be similar in patients with T2DM and patients with T1DM matched for duration of insulin therapy[5,6]. A reasonable generalization is that 30 to 40 % of patients with T1DM suffer one to three episodes of severe hypoglycemia each year[6].

The main existing treatment options: Glucagon is the main counter-regulatory hormone to insulin and is used for treating hypoglycemia in situations that preclude oral consumption of carbohydrates or administration of IV glucose[4,7,8]. As the only prescription treatment for severe hypoglycemia that is not limited to administration by health care professionals, the most recent American Diabetes Association treatment guidelines[9,8] recommend that glucagon be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (<3.0 mmol/L), so that it is available should it be needed[8]. Caregivers, school personnel, or family members of these individuals are furthermore advised that they should know where glucagon treatment is stored and when and how to administer it[9]. Despite these recommendations, glucagon is underutilized for the treatment of severe diabetic hypoglycemia[7,9].

This underutilization may be at least partly attributable to the complexity of administration procedures for the 'hypo kit'[10,11] products that until recently were the only commercially available glucagon treatment option. The complexity of reconstituting and administering these products increases the risk that treatment will not be used correctly or as expeditiously as is necessary during a severe hypoglycemic event[9,12]. The impact of medication errors, delayed treatment and underutilization on morbidity and mortality related to severe hypoglycemia is unknown at present.

More recently, EMA approval has been granted for ready-to-use glucagon products for subcutaneous injection (Ogluo; formulation in the organic solvent dimethyl sulfoxide, DMSO) and intranasal administration (Baqsimi, powder formulation). While providing improvements in ease of handling and administration relative to the 'hypo kit' products, both of these newer products are characterized by a prolonged time from product administration to reaching plasma glucose target when compared to reconstituted glucagon (prolonged by 3 – 4 minutes for Ogluo[13] and by 1.5 – 4 minutes for Baqsimi[14]

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Severe hypoglycemia is a well-known side-effect of insulin treatment and insulin secretogogues such as sulfonylurea. Severe hypoglycemia, characterized by severe cognitive impairment requiring assistance from another person for recovery, is feared by patients and their relatives and may discourage patients and caregivers from pursuing appropriate glycemic targets. In addition, severe hypoglycemia has been shown to be strongly associated with increased risks of several adverse, long-term clinical outcomes including cardiovascular events and death[15-17].

Important co-morbidities: Risk factors for severe hypoglycemia in people with diabetes treated with sulfonylureas or insulin are summarized in Table 1.

Table 1 Risk factors for severe hypoglycemia in patients with T1DM and T2DM treated with sulfonylureas or insulin*

Prior episode of severe hypoglycemia
Current low A1C** (<6.0%)
Hypoglycemia unawareness
Long duration of insulin therapy
Autonomic neuropathy
Chronic kidney disease
Low economic status, food insecurity
Low health literacy
Preschool-aged children unable to detect and/or treat mild hypoglycemia on their own
Adolescence
Pregnancy
Elderly
Cognitive impairment

*Table adapted from table in Yale et al. Diabetes Canada Clinical Practice Guidelines Expert Committee[18].
***A1C*, glycated hemoglobin

Module SII Non-clinical part of the safety specification

The nonclinical safety programme for dasiglucagon was designed in accordance with the ICH M3 (R2)[19] guideline to support both acute and chronic indications. Therefore, more nonclinical safety studies than needed to support a MAA for dasiglucagon as a single-dose rescue treatment have been completed. Repeat dose toxicity studies were performed with dosing for up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. A 4-week toxicity study in rats using a degraded formulation (purity 70.9%) of dasiglucagon was performed to qualify possible impurities in the drug product. In vitro and in vivo genotoxicity studies, a 26-week carcinogenicity study in transgenic mice, a male and female fertility study in rats, embryo-fetal development studies in rats and rabbits and a pre- and post- natal development study in rats were also completed.

Key safety findings from non-clinical studies and relevance to human usage:

Repeat-dose toxicity studies

In all species tested repeated administration of dasiglucagon was associated with hepatocellular glycogen vacuolation (accumulation of glycogen in the hepatocytes). Hepatocyte glycogen accumulation likely occurred in these animals because they were healthy (as opposed to diabetic). In healthy animals, dasiglucagon/glucagon administration led to hyperglycemia, stimulating insulin release, which in turn stimulated glycogen storage.[20] Overall, the glycogen accumulation seen in animals receiving dasiglucagon is considered of limited clinical relevance because this accumulation is due to a compensatory insulin response in healthy animals, a response that is not expected in diabetic patients receiving a single dose of dasiglucagon.

Loose and liquid feces was noted following administration of dasiglucagon to dogs. This effect occurred following a single dose and consistently throughout the repeat dose toxicity studies. Loose feces is also reported to occur following administration of glucagon in dogs,[21] but diarrhea was less frequently reported in humans following administration of a single SC dose of dasiglucagon, and therefore, loose feces in dogs is considered to have limited clinical relevance.

Administration of dasiglucagon and glucagon to rats was associated with clinical signs in terms of “transient episodic freezing absences”. These clinical signs were shown to be related to exposure in terms of C_{max}. The etiology behind “transient episodic freezing absences” in rats is currently unknown, but based on the slight severity, that the animals could easily come out of the freezing state, that full recovery from the condition had occurred before administration of the next dose and because the signs did not seem to affect the overall well-being of the animals, they were not considered to be adverse. Clinical signs corresponding to the freezing absences in rats have not been observed in clinical trials with dasiglucagon. In addition, clinical signs corresponding to the freezing absences in rats have not been observed in nonclinical safety studies in mice, rabbits, or dogs and were only noted in rats following repeated dosing. Similarly, clinical signs corresponding to freezing absences in rats have not been reported when Glucagon is used as a rescue treatment for insulin-induced hypoglycemia,[7] for use in a dual

hormone artificial pancreas in T1DM-[22] and CHI patients[23] or in glucagonoma patients[24] with high plasma glucagon concentration, supporting that it is a finding specific to rats.

In chronic toxicity studies, dasiglucagon caused increased kidney weights and histopathological changes in the kidneys consisting of increased incidence of nephropathy in male and female rats, absence of hyaline droplets in the kidneys of most male rats, and increased incidence of renal hyaline/granular casts in male and female dogs. All histopathological changes in the kidneys were slight in severity and either fully or partially resolved during 4-week recovery periods. Furthermore, they were not associated with any increases in clinical chemistry parameters associated with kidney function such as urea or creatinine. Thus, such renal findings were not considered adverse. Additionally, these findings are normal background findings in rats or dogs, and were also found in the control groups, or are specific to the male rat (hyaline droplets in kidneys)[25], and not relevant to humans. The increased incidence of the background lesions and the increased kidney weight noted in rats and dogs in the repeat dose toxicity studies may reflect an increased workload on the kidney caused by an increase in glomerular filtration rate (GFR), a normal physiologic response following glucagon receptor (GCGR) agonism also seen following protein ingestion in humans.[26] Considering the single use of dasiglucagon for treatment of insulin-induced hypoglycemia, this pharmacological effect on GFR is not considered a risk for the patients. No signs of adverse effects on the kidneys has been noted in the clinical trials with dasiglucagon.

Studies to evaluate any pharmacological or toxicological effects of the degradation products of the dasiglucagon drug product included a 4-week toxicity study in rats, a single dose PD study and an in vitro study to assess possible agonistic effects on the GCGR. These studies concluded that the toxicological and pharmacological profile of a degraded and non-degraded drug product are comparable, with no increased risk of anti-drug antibody (ADA) formation.

Reproductive toxicity

Dasiglucagon had no effect on mating, fertility, early embryonic development or pre- and post-natal development in rats. In addition, dasiglucagon was not teratogenic in rats.

In rabbits, a low incidence of malformations occurred in the mid and high dose group. The types of malformations in offspring of rabbits receiving dasiglucagon were comparable to those observed in the embryo-fetal development study with GlucaGen. Experimental studies have suggested that the major teratogenic mechanism in diabetic pregnancy is hyperglycemia[27,28] and the malformations noted in the offspring of rabbits receiving dasiglucagon were therefore considered related to the pharmacological effect of dasiglucagon in terms of increases in plasma glucose. The embryo-fetal defects seen in rabbits may be relevant for human use, as they are related to the intended pharmacological effect of dasiglucagon in terms of increases in blood glucose. However, for the use as a single dose rescue treatment in association with acute severe hypoglycemia, the risk is considered minimal because of the short duration of treatment and the short duration of the blood glucose increase. In addition, the risk-benefit balance needs to be

considered, as hypoglycemia is a severe medical condition where a quick restoration of blood glucose levels is vital.

Genotoxicity

Dasiglucagon was not genotoxic in two in vitro and one in vivo genotoxicity study.

Carcinogenicity

Dasiglucagon was not carcinogenic in a 26 week carcinogencity study in transgenic mice.

Safety Pharmacology

Dasiglucagon had no effect on human cardiac ion channels in vitro. Additionally, dasiglucagon had no effect on the nervous system function as assessed in the Irwin test in rats and had no effect on respiratory parameters or body temperature in dogs. Findings of tachycardia, decreased blood pressure, and loose feces in dogs were comparable to previous findings for glucagon administered to dogs[21,29]. Glucagon increases heart rate and has the potential to increase blood pressure in humans,[30,31] however in clinical trials single doses of dasiglucagon 0.6 mg SC was not associated with any cardiac safety concerns.

Conclusion

All findings in the nonclinical safety studies with dasiglucagon are considered related to the pharmacological effects of GCGR agonism. Based on the completed nonclinical safety studies with dasiglucagon, the applicant does not consider any of the findings warranting inclusion among the summary of safety concerns; i.e. being an important identified risk or an important potential risk. In addition, the applicant does consider the nonclinical safety study package complete with no missing information.

Module SIII Clinical Trial Exposure

Summary information on clinical trial exposure from the dasiglucagon clinical development programme for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged ≥6 years has been provided.

Table 2 Number of participants exposed to dasiglucagon in completed Zealand sponsored trials - Healthy participants

Trial indication	Number of participants*
Healthy participants	108

*Healthy participants from trials: 14013 Part 1, 15007, 17144

Table 3 Number of participants exposed to dasiglucagon in completed Zealand sponsored trials – Treatment of severe hypoglycemia in T1DM

Trial indication	Number of participants*
Treatment of severe hypoglycemia in T1DM	358

*Participants from trials ZP4207-14013 Part 2, ZP4207-15126, ZP4207-16136, ZP4207-16137, ZP4207-17084, ZP4207-17086 and ZP4207-17145

Table 4 Number of participants exposed to dasiglucagon in completed Zealand sponsored trials- Treatment of hypoglycemia in T1DM - administration in bihormonal pancreas setting

Trial indication	Number of participants*
Treatment of hypoglycemia in T1DM - administration in bihormonal pancreas setting	32

*Participants from trials ZP4207-16051 and ZP4207-16098

Table 5 Total number of participants exposed to dasiglucagon in completed Zealand sponsored trials for treatment of hypoglycemia in T1DM and healthy participants

	Number of participants*
Total number of participants	498

*Participants from trials ZP4207-14013, ZP4207-15126, ZP4207-16136, ZP4207-16137, ZP4207-17084, ZP4207-17086, ZP4207-17145, ZP4207-16051 ZP4207-16098, 15007, and 17144

Table 6 Number of participants by age group and gender in completed Zealand sponsored trials - Healthy participants

Age group			
Healthy participants age groups	**Male**	**Female**	**Total***
Adults (18 to 64 years)	87	21	108
Elderly (65-74 years)	-	-	-
Elderly 75+	-	-	-
Total	87	21	108

*Healthy participants from trials: 14013 Part 1, 15007, 17144

Table 7 Number of participants by age group and gender in treatment of severe hypoglycemia in T1DM

Treatment of severe hypoglycemia in T1DM - age groups	**Male**	**Female**	**Total***
Children (6 to 11 years)	3	5	8
Adolescents (12 to 17 years)	7	5	12
Adults (18 to 64 years)	206	124	330
Elderly (65-74 years)	5	3	8
Elderly 75 +	-	-	-
Total	221	137	358

*Participants from trials ZP4207-14013 Part 2, ZP4207-15126, ZP4207-16136, ZP4207-16137, ZP4207-17084, ZP4207-17086 and ZP4207-17145

Table 8 Number of participants by age group and gender in treatment of hypoglycemia in T1DM (administration in bihormonal pancreas setting)

Treatment of hypoglycemia in T1DM - administration in bihormonal pancreas setting - age groups	Male	Female	Total*
Adolescents (12 to 17 years)	-	-	-
Adults (18 to 64 years)	17	14	31
Elderly (65-74 years)	-	-	-
Elderly 75+	1	-	1
Total	18	14	32

*Participants from trials ZP4207-16051 and ZP4207-16098

Table 9 Dose in healthy participant trials

Dose of exposure	Participants*	Number of doses/injections
Healthy participants		
<0.6 mg	54	102
0.6 mg	18	18
> 0.6 mg	36	60
Total Participants	108	180

*Healthy participants from trials: 14013 Part 1, 15007, 17144

Table 10 Dose in trials on treatment of severe hypoglycemia in T1DM

Dose of exposure	Participants*	Number of doses/injections
Treatment of severe hypoglycemia in T1DM		
<0.6 mg	22	22
0.6 mg	300	490
>0.6 mg	36	36
Total Participants	358	548

*Participants from trials ZP4207-14013 Part 2, ZP4207-15126, ZP4207-16136, ZP4207-16137, ZP4207-17084, ZP4207-17086 and ZP4207-17145

Table 11 Number of participants administered dasiglucagon in completed Zealand sponsored trials for treatment of severe hypoglycemia in T1DM by ethnic origin

Racial group	Participants*
White	342
Asian	7
Black or African American	3
American Indian or Alaska native	1
Native Hawaiian or Other Pacific Islander	-
Other	3
Multiple	2
Total	358

*Participants from trials ZP4207-14013 Part 2, ZP4207-15126, ZP4207-16136, ZP4207-16137, ZP4207-17084, ZP4207-17086 and ZP4207-17145

Table 12 Number of participants administered dasiglucagon in completed Zealand sponsored trials: healthy subjects and administration in bihormonal pancreas setting for hypoglycemia in T1DM, by ethnic origin

Racial group	Participants*
White	136
Asian	1
Black or African American	1
American Indian or Alaska native	-
Native Hawaiian or Other Pacific Islander	-
Other	1
Multiple	1
Total	140

*Participants from trials ZP4207-16051 and ZP4207-16098 and healthy participants from trials: ZP4207-14013 Part 1, ZP4207-15007, ZP4207-17144

Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria were chosen to exclude patients with clinically significant concomitant illnesses or medical histories that could increase the risk of early trial withdrawal and/or potentially confound the safety assessment. To ensure independent outcomes, all clinical trials had exclusion criteria aimed at preventing participants from participating in more than one trial with dasiglucagon.

Table 13 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be 'missing information'?	Rationale (if not included as missing information)
Pregnant or breastfeeding women	According to regulatory guidelines to protect from research-related risks. The risk associated with participating in a trial including insulin induced lowering of blood glucose to hypo-glycaemic levels is not considered acceptable for pregnant women.	No	Untreated hypoglycemia in pregnancy can cause complications and may be fatal. Dasiglucagon had no effect on mating, fertility, early embryonic development or pre- and post-natal development in rats and was not teratogenic in rats. In rabbits, a low incidence of malformations occurred in the mid and high dose group. Experimental studies have suggested that the major teratogenic mechanism in diabetic pregnancy is hyperglycemia and the malformations noted in the offspring of rabbits receiving dasiglucagon were therefore considered related to the pharmacological effect of dasiglucagon in terms of increases in plasma glucose. Dasiglucagon is a peptide

Exclusion criteria	Reason for exclusion	Is it considered to be 'missing information'?	Rationale (if not included as missing information)
			and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore unlikely to cause harm to an exposed infant.
Patients with Congestive heart failure[1], hypertension[2], bleeding disorder[3] [1] New York Heart Association Class II-IV [2] Defined as systolic ≥160 mmHg or diastolic blood pressure ≥90 mmHg) at screening, [3] Including anti-coagulant treatment	Hyperinsulinemic-hypoglycaemic glucose clamp procedure precludes inclusion for the same reason as pregnant women.	No	These patients were excluded from the pivotal studies for safety reasons due to the procedure used to induce hypoglycemia and not because of any potential safety concern from dasiglucagon administration. Dasiglucagon is predicted to ensure the same metabolic effects in these patient populations regardless of the underlying disease, thus ensuring life saving acute treatment of severe hypoglycaemia.
Known presence or history of pheochromocytoma (i.e. adrenal gland tumor) or insulinoma (i.e. insulin secreting pancreas tumor)	Pheochromocytoma: glucagon products may substantially increase blood pressure by stimulating the release of catecholamines from the tumor. Insulinoma: Administration of glucagon products may directly or indirectly (through an initial increase in blood glucose) stimulate exaggerated insulin	No	Included in the summary of product characteristics (SmPC) in the contraindication section and in the warning and precaution section as a known warning for glucagon.

Exclusion criteria	Reason for exclusion	Is it considered to be 'missing information'?	Rationale (if not included as missing information)
	release from an insulinoma and cause hypoglycemia		
Use of a daily systemic beta-blocker drug, indomethacin, warfarin	Beta-blockers: glucagon treatment results in catecholamine release from the adrenal glands, and concomitant use of beta-blockers could result in unopposed alpha-adrenergic stimulation and consequently, a greater increase in both pulse and blood pressure Indometacin: dasiglucagon when used with indomethacin may lose its ability to raise blood glucose or may even produce hypoglycaemia. Warfarin: glucagon may increase the anticoagulant effect of warfarin.	No	Included in the SmPC in drug interaction section as a known interaction for glucagon
Hepatic* or renal** impairment	The risks associated with the Hyperinsulinemic-hypogycaemic glucose clamp procedure precludes inclusion as for other populations mentioned above.	No	Dasiglucagon is cleared mainly in the blood, liver, and kidneys via normal proteolytic degradation pathways. Following glomerular filtration, peptides are degraded by the proteases present in the proximal tubule and the peptide fragments are reabsorbed. The pharmacokinetic profile is not considered to be different in the excluded

Exclusion criteria	Reason for exclusion	Is it considered to be 'missing information'?	Rationale (if not included as missing information)
			population (based on knowledge of the pharmacokinetic profile or the known mechanism of action). No dose adjustment is considered necessary for hepatic or renal impairment.
Pediatric patients aged <6 years	Population to be investigated in a pediatric trial	No	The safety profile was studied in patients aged 6 years and over deferring pediatric development for patients aged less than 6 years. A pediatric trial is currently in progress including patients from 0 to 6 years (Trial ZP4207-21052).

*Hepatic impairment exclusion criteria: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of the normal range (ULN), bilirubin >1.5 × ULN
**Renal impairment: exclusion criteria estimated glomerular filtration rate <30 mL/min/1.73 m2 according to the Modification of Diet in Renal Disease study definition (Levey 2006), or altered electrolyte values of clinical relevance for cardiac conduction, as judged by the Investigator

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme, designed for a single-use emergency product is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. In addition, such adverse reactions are considered less relevant, as dasiglucagon is to be used in discrete emergency situations. Therefore, Zealand Pharma considers the clinical safety of dasiglucagon sufficiently investigated.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 14 Exposure of special populations included or not in clinical trial development programme

Type of special population	Exposure
Pregnant women	

Breastfeeding women	There have been no clinical studies evaluating dasiglucagon in pregnant women or lactating women
Patients with relevant comorbidities: • Patients with hepatic impairment[1] • Patients with renal impairment[2] • Patients with cardiovascular impairment[3] • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials [1] Aspartate aminotransferase or alanine aminotransferase >2.5 × the upper limit of the normal range (ULN), bilirubin >1.5 × ULN) [2] estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 [3] Cardiovascular impairment: or altered electrolyte values of clinical relevance for cardiac conduction, as judged by the investigator	Not included in the clinical development programme
Population with relevant different ethnic origin	Not included in the clinical development programme*
Subpopulations carrying relevant genetic polymorphisms	Not relevant (no subpopulation identified)
Other Children aged <6 years	Not included in the clinical development programme. A pediatric study is ongoing in this population.

*No exclusion criteria prevented participants of different ethnic origins to participate. The population was recruited from the populations of the communities in which the investigative clinics are situated. The resulting population may therefore not be fully representative of all areas or countries considered registration of dasiglucagon.

Module SV Post-authorisation experience

SV.1 Post-authorisation exposure

FDA approval of dasiglucagon (Zegalogue®) for the treatment of severe hypoglycemia was granted on 22-March-2021. As of 21-September-2023, 1 non-serious AE (burning sensation) has been reported.

SV.1.1 Method used to calculate exposure

- Dasiglucagon is marketed in the US under the brand name of Zegalogue®. Zegalogue® is available as 1 or 2 pen packs for the autoinjector, and the pre-filled syringe is available in 1 or 2 syringe packs. Patient exposure estimates are calculated using sales data. The manner of reporting sales data changed in October 2022: From launch (March 2021) to October 22, the total number of prescriptions filed was [redacted] (prescriptions could be for 1 or 2 pre-filled syringes or autoinjectors per package). Taking the approach of assuming one prescription for each patient, this gives an estimated total number of patients of [redacted] patients.

- From October 2022 to end March 2023 the total package volume (1 or 2 autoinjectors/pre-filled syringes per package) was [redacted] packages which taking the approach of asssuming one package for each patient, gives an estimated total number of patients of [redacted] patients.

- From April 2023 to end September 2023 the total package volume (1 or 2 autoinjectors/pre-filled syringes per package) was [redacted] packages which taking the approach of asssuming one package for each patient, gives an estimated total number of patients of [redacted] patients.

SV.1.2 Exposure

Using the method to estimate patients exposed in the section above, the cumulative exposure data in US obtained from March 2021 (launch) to 31 September 2023 is estimated at [redacted] patients. The approach taken to estimate exposure, uses sales data for each package unit as representing one patient. Of note, as dasiglucagon is used in a rescue indication with a shelf life of up to 3 years if kept in refrigerated conditions, and as the packages dispensed may not yet have been used, the actual exposure is very difficult to quantify and is likely to be considerably less.

Module SVI Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the available nonclinical and clinical data, it is concluded that dasiglucagon has no potential for abuse, does not lead to dependence, and tolerance does not develop following repeated administration. In line with this conclusion, glucagon receptor agonism is not stated as being associated with a risk for abuse, dependence, or tolerance according to the Prescribing Information of currently approved glucagon products with a similar mode of action as dasiglucagon, including recently approved glucagon products.[10,32-34]

Module SVII Identified and potential risks

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

Initial RMP submission: see Table 15 below (Summary of safety concerns).

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients

Development of anti-drug antibodies (ADA) has been considered an important potential risk for all dasiglucagon development programmes. In the development programme supporting the indication of treatment of severe hypoglycaemia in diabetes mellitus, in the trials completed in healthy subjects or patients with T1DM, a total of 498 participants have been exposed to dasiglucagon. A total of four ADA positive patients were identified and none of these patients showed an observable clinical consequence from the ADA. Furthermore, there was no effect of ADA on PK, PD and safety in the few patients who had an anti-dasiglucagon antibody response. The ADA incidence is less than 1% and the potential of dasiglucagon to induce ADAs at clinically relevant doses in relation to rescue treatment of severe hypoglycemia is considered to be low. No clinical consequences of ADA formation has yet been identified in 28-day non-clinical studies or in short duration clinical studies, which indicate that the clinical immunogenicity risk is low (see 5.3.5.3 Integrated Summary of Immunogenicity Section 6). In the postmarketing setting, patients may use dasiglucagon more than once per year. The long-term immunogenicity risk of repeated dosing over years is unknown. Antibody assessment is not planned for as a routine assessment in the post-marketing setting. Monitoring of adverse events related to immunogenicity, including hypersensitivity reactions and potential lack of efficacy, will be covered by routine pharmacovigilance activities. Of note, with respect to chronic dasiglucagon administration, in the CHI indication no safety findings related to ADA have currently been identified.

Known risks that require no further characterisation

Hemodynamic events. Based on literature, glucagon exerts positive inotropic and chronotropic effects on the heart and may, therefore, cause tachycardia and hypertension[35,30]). Additionally, hypotension has been reported up to 2 hours after administration in patients receiving GlucaGen® as premedication for upper gastrointestinal endoscopy procedures[10,32-34]. Dasiglucagon is a selective agonist for the glucagon receptor. In the dasiglucagon phase 3 clinical trials supporting the indication of treatment of severe hypoglycaemia in diabetes mellitus, hemodynamic changes, defined as post-dose clinical signs or measured vital signs indicating a clinically significant drop in blood pressure (including signs of orthostatic hypotension, vasovagal responses or bradycardia) or post-dose change in pulse or blood

pressure, were considered adverse events of special interest (AESIs). Across the clinical trials with dasiglucagon conducted in the severe hypoglycemia programme, hemodynamic events occurred at a low frequency in the dasiglucagon and GlucaGen® groups in adults. The events in the dasiglucagon group occurred in patients dosed with dasiglucagon at the intended therapeutic dose of 0.6 mg or above. Most events in adults had an onset 1.5−3 hours after administration of active treatment, and most events were related to a decrease in blood pressure. In healthy subjects, all hemodynamic events occurred in participants who had received dasiglucagon or GlucaGen® doses of 1 mg or above. No hemodynamic events in the active treatment groups were reported in the pediatric patients. In line with data in the literature for glucagon[36], the hemodynamic effects of dasiglucagon appear to be transient; in most cases, vital sign values normalized within 2 hours. None of the events were serious or severe. In all treatment groups (dasiglucagon, GlucaGen® and placebo), small or no increases in pulse were observed. In some trials, small changes in blood pressure, notably a decrease in diastolic blood pressure, were seen with dasiglucagon and GlucaGen®, but this pattern was not consistently observed across trials. At follow-up, the mean vital sign values had returned to the pre-dose or screening level.

Known risks that do not impact the risk benefit-profile

The most common adverse reactions seen in the development programme were nausea, vomiting, headache, dizziness and diarrhoea. Of note, these ADRs are labelled for other approved glucagon products (with the exception of dizziness and diarrhoea). The ADR identified of nausea, vomiting, headache, dizziness and diarrhoea were non-serious and resolved without sequelae. These appear to be temporary tolerability issues, and it is considered that inclusion in the ADR table of the SmPC is adequate to inform of these adverse reactions. In the development programme injection site reactions also appear to occur more frequently with dasiglucagon than with placebo or GlucaGen®, although numbers of events are small, limiting conclusions. The ADRs observed were non-serious and self-limiting and it is considered that their inclusion in the ADR table of the SmPC is adequate to inform of these adverse reactions.

The drug interactions included in the SmPC (with concomitant beta blocker, warfarin or indomethacin administration) are class effects and these are monitored by routine pharmacovigilance activities with no additional risk minimisation measures or additional pharmacovigilance activities deemed necessary.

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

An important potential risk has been identified of ‘Drug administration leading to loss of benefit’. No important identified risks have been identified.

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

Not applicable, as the RMP has been prepared as part of new marketing authorisation application.

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

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

An important potential risk has been identified of 'Drug administration error leading to loss of drug benefit'. No important identified risks have been identified (see Table 15).

Table 15 Presentation of the important potential risk of '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 subject. A failure to administer the medication correctly may result in a failure to deliver the full dose of dasiglucagon required to restore normal blood glucose levels and thus not recover as rapidly from the severe hypoglycaemia episode.
Evidence source(s) and strength of evidence	With the auto-injector, the five failures (5/61) where drug administration error was noted were observed with untrained user of which four were injection naïve. Four failures were attributed to perceptual errors resulting in prematurely lifting the auto-injector during injection, and one failure due to the urgency of the situation resulting in performing the injection through clothing. In all cases, a partial dose was delivered. The users demonstrated understanding of the instructions and successfully administered a full dose on second attempt. With the pre-filled syringe, the three failures (3/60) where drug administration error was noted were attributed to a first responder who primed the syringe based on professional experience, an untrained user who applied pressure to the plunger rod, and an untrained user who removed the plunger rod when attempting to remove the needle cap. As a result, all expelled portions of the drug prior to injection and a partial dose was delivered. The users successfully administered a full dose on second attempt.
Characterisation of the risk	Failure to dose or administration of an inadequate dose during a severe hypoglycaemia episode may lead to worsening of the the severe hypoglycaemia episode and clinical sequelae such as seizure or coma. Human factors testing demonstrates that 91.8% (56/61) of users of the auto-injector and 95.0% (57/60) of users of the pre-filled syringe can

Important Potential risk	Drug administration error leading to loss of drug benefit
	successfully and promptly administer a full dose of dasiglucagon during simulated emergency settings. These results were obtained by users using the product for the first time, without any training. User groups in the human factors testing include first responders, experienced and naïve lay caregivers, and adolescent lay caregivers.
Risk factors and risk groups	Risk groups for inappropriate use of the device are likely to be first time users, subjects or their caregivers who are untrained or unfamiliar with the device and the instructions for use.
Preventability	Initial and recurrent instructions and education by the health care provider that includes training for the proper use of the dasiglucagon 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 undertreated or untreated severe hypoglycaemia may lead to seizure, coma and death. However the risk of inadequate administration is anticipated to be small because human factor testing has demonstrated that 91.8% and 95.0% of users for the auto-injector and pre-filled syringe, respectively, can successfully and promptly administer a full dose of dasiglucagon during simulated emergency settings. Of note it is included in the product information that a second dose can be given if there is no response within 15 minutes. Therefore the impact of this potential risk upon the total benefit: risk balance is considered to be small.
Public health impact	Reduction of drug administration error leading to loss of benefit will support successful use of dasiglucagon in the individual treatment of severe hypoglycaemia, especially in the setting outside of hospital. If compared with handling of the first generation glucagon rescue treatments (GlucaGen Hypokit), the risk may be lower with dasiglucagon. In this case, replacing first generation glucagons with dasiglucagon may impact public health positively because of more doses correctly administered resulting in fewer patients needing subsequent hospital care.

SVII.3.2 Presentation of the missing information

Not applicable.

Module SVIII Summary of the safety concerns

Table 16 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

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary. The Applicant has a structured plan for the identification of any new safety concerns. The Applicant maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports (ICSR), periodic safety update reports (PSUR), etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The Applicant maintains a Pharmacovigilance System Master File (PSMF), which contains details of these systems and standard practices. The routine pharmacovigilance activities described above with the targeted follow-up questionnaire noted below are deemed adequate and appropriate for the ongoing evaluation of the safety profile of dasiglucagon in the indication of severe hypoglycemia in the post-authorization setting.

Specific adverse reaction follow-up questionnaire:

A targeted follow-up questionnaire will be recorded at adverse event intake in order to characterise the risk of “Drug administration error leading to loss of drug benefit”(See Annex 4).

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are deemed necessary.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV Plans for post-authorisation efficacy studies

Not applicable.

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

V.1 Routine Risk Minimisation Measures

Table 17 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risk of 'Drug administration error leading to loss of drug benefit.	Routine risk communication: Information with precautions concerning the handling and use of the product to avoid inappropriate use are described in the SmPC section 4.2 (Posology and method of administration) and section 6.6 (Special precautions for disposal and other handling), in the Package leaflet (PL) Section 2 (What you need to know before you are given Zegalogue) and Section 3 (How to give Zegalogue) and in the Instructions for use (IFU). Instructions for users to call for medical help right away after administering dasiglucagon are in the SmPC section 4.2 and the IFU and on the protective case label. Legal status: Zegalogue is a prescription drug, requiring HCP to instruct subjects on proper use of the product before use. Instructions include the Product Information.
Important identified risk	None
Missing information	None

V.2 Additional Risk Minimisation Measures

Additional risk minimisation measure

1. An administration leaflet

2. Instructional video that is concise, focused and suitable for the use without delay in emergency situation to immediately help the patient

Objectives:

The administrative leaflet and the instructional video are aimed at minimising the potential risk of 'Drug administration error leading to loss of drug benefit'. The correct administration of Zegalogue is required in order to successfully treat episodes of severe hypoglycaemia.

Rationale for the additional risk minimisation activity:

In order to succesfuly treat the emergency medical condition of severe hypoglycaemia, it is essential to ensure the correct administration of a medicinal product by patients, their family members, caregivers. The administration leaflet and the audio-visual training materials support the appropriate use of Zegalogue.

Target audience and planned distribution path:

Access to the instructional video will be given via a QR code inserted in the administration leaflet and on the protective case label.The target audience will be HCPs who are expected to prescribe, supply, and/or train patients/caregivers upon initial Zegalogue 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:

An adverse event form intended for this risk is proposed with the RMP. The outcome of these specific follow-up questions will indicate the effectiveness of these additional risk minimisation measures.

V.3 Summary of risk minimisation measures

Table 18 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk of 'Drug administration error leading to loss of drug benefit'.	Routine risk minimisation measures (see V.1) Instructions for users to call for medical help right away after administering dasiglucagon is in the SmPC section 4.2, and in the IFU and protective case label. Additional risk minimisation measures (see V.2): An administration leaflet which links to an instructional video to guide patients and caregivers how to use the device correctly to administer the full Zegalogue dose.The instructional video	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: ADR follow-up form for adverse reactions relevant to characterise the risk of "Drug administration error leading to loss of drug benefit (see III.1 and Annex 4)

	should be concise, focused and suitable for the use without delay in emergency situation to immediately help the patient.	

Part VI Summary of the risk management plan

I. Summary of risk management plan for Zegalogue (dasiglucagon)

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

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

This summary of the RMP for Zegalogue 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 Zegalogue's RMP.

II. The medicine and what it is used for

Zegalogue is authorised for the treatment of severe hypoglycaemia in adults, adolescents, and children aged 6 years and over with diabetes mellitus (see SmPC for the full indication). It contains dasiglucagon as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Zegalogue's benefits can be found in dasiglucagon'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>.

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

Important risks of Zegalogue, together with measures to minimise such risks and the proposed studies for learning more about Zegalogues 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 Zegalogue, 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.

III.A List of important risks and missing information

Important risks of Zegalogue 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 Zegalogue. 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

III.B Summary of important risks

Important potential risk of Drug administration error leading to loss of drug benefit	
Evidence for linking the risk to the medicine	With the auto-injector, the five failures (5/61) where drug administration error was noted were observed with untrained user of which four were injection naïve. Four failures were attributed to perceptual errors resulting in prematurely lifting the auto-injector during injection, and one failure to the urgency of the situation resulting in performing the injection through clothing. In all cases, a partial dose was delivered. The users demonstrated understanding of the instructions and successfully administered a full dose on second attempt. With the pre-filled syringe, the three failures (3/60) where drug administration error was noted were attributed to a first responder who primed the syringe based on professional experience, an untrained user who applied pressure to the plunger rod, and an untrained user who removed the plunger rod when attempting to remove the needle cap. As a result, all expelled portions of the drug prior to injection and a partial dose was delivered. The users successfully administered a full dose on second attempt.
Risk factors and risk groups	Risk groups for a drug administration error leading to loss of drug benefit are likely to be first time users, subjects or their caregivers who are untrained or unfamiliar with the device and the instructions for use.
Risk minimisation measures	Routine risk minimisation measures: Instructions for proper use of Zegalogue: SmPC section 4.2 and 6.6, Patient Leaflet sections 2 and 3 Instructions for users to call for medical help right away after administering dasiglucagon is in the SmPC section 4.2, and in the IFU and protective case label.

Important potential risk of Drug administration error leading to loss of drug benefit	
	Additional risk minimisation measures: an administration leaflet and instructional video. The instructional video should be concise, focused and suitable for the use without delay in emergency situation to immediately help the patient and should guide patients and caregivers how to use the device correctly to administer the full Zegalogue dose. None
Additional pharmacovigilance activities	

III.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of dasiglucagon.

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

There are no studies required for dasiglucagon.

Annex 4 - Specific adverse drug reaction follow-up forms

Adverse Event follow-up Questionnaire

A. Patient Information:

- **Name:** _____
- **Date of Birth:** _____
- **Patient's Weight:** _____
- **Patient's Height:** _____
- **Patient's Gender**
- **Patient's Race:** _____

B. Product Information:

- **Product Name:**
- **Dose (tick one (✓) inside the box):**

  ☐ 0.6 mg

  ☐ any additional dose if Yes, please specify _____
- **Type of Device (tick one (✓) inside the box):**

  ☐ Pre-filled pen

  ☐ Pre-filled syringe
- **Marketing Authorization Number:** _____

C. Storage and Packaging:

- **Storage Location (e.g., in home, in backpack, in car, etc.)?**
  _____
- **Storage Conditions (e.g., refrigerated, room temperature, heated environment, etc.)?**
  _____
- **At time of use, was the item in its intact original package (tick one (✓) inside the box):**

  ☐ Yes

  ☐ No

D. Event Information:

- **Event Description:** _____
- **Onset Date:** _____
- **Was a full dose of drug delivered (tick one (✓) inside the box):**

  ☐ Yes

  ☐ No **If No, reason of Failure:** _____

- **Treatment for event after product administered (describe any medical any medical interventions that occur after product administered):**

  ☐ Yes

  ☐ No

  Details of the treatment if Yes: _____

- **Outcome:**
  - ☐ Recovered
  - ☐ Not Recovered
  - ☐ Unknown

  Resolution Date (if recovered): _____

  Description (if not recovered): _____

E. Administration Details (tick one (✓) inside the box):

- **Anatomical Site of Administration:**

  ☐ Arm

  ☐ Thigh

  ☐ Abdomen

- **Location at Time of Administration:** _____
- **Person Who Deployed Device:**

  ☐ Self-administered

  ☐ Health Care Provider

  ☐ Caregiver (Trained / Untrained)

- **Reviewed Instructions Prior to Administration:**

  ☐ Package Leaflet

  ☐ Administration Leaflet

  ☐ Instructional Video

- **Was emergency medical help called after the injection?**

  ☐ Yes

  ☐ No

F. Blood Sugar Levels, along with time if known:

- **Prior to Administration:** _____**Time taken (if known)**_____
- **Following Administration:** _____**Time taken (if known)**_____

G. Medical Evaluation:

- **Diagnosis:** _____
- **Date(s) of Evaluation:** _____

H. If any, Tests and Labs were done:

- **Tests Performed:** _____
- **Date of Test(s):** _____
- **Results and Measurement Units:** _____

I. Medical History and patient information prior to initial product use (dates):

- **Type of Diabetes (tick one (✓) inside the box):**

  ☐ Type I

  ☐ Type II

- **Concomitant Medications and Supplements if any (dose, frequency, dates):**
  _____

  _____

  _____

J. Event Outcome:

- **Outcome (tick one (✓) inside the box):**

  ☐ Recovered

  ☐ Not Recovered

  ☐ Unknown

- **Resolution Date (if recovered):** _____
- **Describe as on going and worsened, or going and improved (if not recovered):**
  _____

K. Hospitalization Details:

- **Hospitalized Due to Event(s) (tick one (✓) inside the box):**

  ☐ Yes

  ☐ No

- **Hospital Name/Location:** _____
- **Emergency Department Name/Location:** _____

L. Health Professional Contact:

- **Permission to Contact Health Professional Contact, who is most familiar with the event (tick one (✓) inside the box):**

☐ Yes

☐ No

- **If Yes, Name/Address/Phone Number:** _____

M. Incomplete Fields Explanation (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)

The administration leaflet will contain the following key elements:

- Patients should receive the administration leaflet from their healthcare professionals upon initial prescription of Zegalogue and after training.

- Patients and family members or caregivers should be informed on how to recognize the signs and symptoms of severe hypoglycaemia and the risks of prolonged hypoglycaemia. Early symptoms of hypoglycaemia should be described.

- The importance not to test the single-dose device in advance, not to remove the single-dose device from the protective case in advance (the single-dose device should be all the time kept in the protective case) and to ensure that the patient understands that each single-dose pre-filled syringe/pen can only be used once.

- The importance to call for emergency medical help or a healthcare provider right away after Zegalogue is injected. Even if the subcutaneous injection of Zegalogue
helps the person to wake up, it should be advised to still call for emergency medical help right away.

- If the patient does not respond within 15 minutes, an additional dose of Zegalogue from a new device may be administered while waiting for emergency assistance.

- After the injection is given, the unconscious person should be rolled on to their side to prevent choking.

- The importance of correct storage of the medicinal product should be emphasized.

- The PL and the IFU at the end of the PL should be referenced for more detailed information regarding administration and handling of Zegalogue.

- Patients can use the leaflet to teach those around them how to correctly handle and administer Zegalogue.

- The administration leaflet should contain a URL and QR code to a website where patients can access the instructional video.

The instructional video will contain the following key elements:

- To reinforce the correct handling and administration, step-by-step instructions on the appropriate use of dasiglucagon should be provided.

- The instructional video should be concise, focused and suitable for the use without delay in

emergency situation to immediately help the patient.

- The importance to call for emergency medical help or a healthcare provider right away after Zegalogue is injected. Even if the injection of Zegalogue helps the person to wake up, it should be advised to still call for emergency medical help right away

- If the patient does not respond within 15 minutes, an additional dose of Zegalogue from a new device may be administered while waiting for emergency assistance.

- After the injection is given, the unconscious person should be rolled on to their side to prevent choking.

Annex 7 - Other supporting data (including referenced material)

Literature references in the RMP that are not already included in other modules of the dossier (included with other references in the List of references in Module 5.4).

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