CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214231Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214231
PDUFA Goal Date	March 27, 2021
OSE RCM #	2020-610
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	January 11, 2021
Subject	Evaluation of Need for a REMS
Established Name	Dasiglucagon
Trade Name	Zegalogue
Name of Applicant	Zealand Pharma.
Therapeutic Class	An antihypoglycemic agent
Formulation(s)	0.6 mg/0.6 ml syringe to give subcutaneously
Dosing Regimen	0.6 mg one dose

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity dasiglucagon is necessary to ensure the benefits outweigh its risks. Zealand Pharma A/S submitted a New Drug Application (NDA) 214231 for dasiglucagon with the proposed indication for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above. The risks associated with dasiglucagon include substantial increase in blood pressure in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, and lack of efficacy in patients with decreased hepatic glycogen. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO) agree that a REMS is not needed to ensure the benefits of dasiglucagon outweigh its risks. Severe hypoglycemia is a serious and potentially life-threatening complication of diabetes therapy. Dasiglucagon demonstrated the ability to effectively raise blood glucose in adults and pediatrics ages 6 and above. It is available in a pre-filled syringe that can be stored at room temperature and offers additional benefits of ease of administration.

This reviewer recommends that, if dasiglucagon is approved, a REMS is not necessary to ensure its benefits outweigh its risks. The risks of substantial increase in blood pressure in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, and lack efficacy in patients with decreased hepatic glycogen will be adequately described in the labeling. All glucagon products carry the same risks and none of these risks warrants a boxed warning.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] dasiglucagon is necessary to ensure the benefits outweigh its risks. Zealand Pharma A/S submitted a New Drug Application (NDA) 214231 for dasiglucagon with the proposed indication for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above. This application is under review in the Division of Diabetes, Lipid Disorders, and Obesity (DDLO). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Dasiglucagon is a glucagon analog and an antihypoglycemic agent. Dasiglucagon is comprised of 29 amino acids, with 7 amino acid substitutions compared to glucagon to improve physical and chemical stability, thereby enabling an aqueous formulation. Dasiglucagon increases blood glucose concentration by activating hepatic glucagon receptors, resulting in a breakdown of glycogen and release of glucose from the liver.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Dasiglucagon will be supplied as 0.6 mg/0.6 ml [redacted] (b) (4) HypoPal and 0.6 mg/0.6 ml [redacted] (b) (4) pre-filled safety syringe. The recommended dose of dasiglucagon is 0.6 mg one dose subcutaneously. Dasiglucagon is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214231 relevant to this review:

- 01/23/2017: Investigation New Drug (IND) 127866 was submitted.
- 06/29/2017: End of phase 2 meeting.
- 11/19/2019: pre-NDA meeting.
- 03/27/2020: Complete NDA submitted.
- 09/14/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for dasiglucagon.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Severe hypoglycemia is a serious and potentially life-threatening complication of diabetes therapy that, if left untreated, can lead to seizures, coma, or death.[b] The mortality rate from severe hypoglycemia in type 1 diabetes (T1D) ranges from 4-10%.[1] The American Diabetes Association (ADA) and Endocrine Society define severe hypoglycemia as an episode of hypoglycemia that causes neurological impairment and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions for recovery.[2] Severe hypoglycemia is a relatively frequent complication of diabetes therapies, ranging from 115 to 320 events per 100 patient-years in patients with T1D and 35 to 70 per 100 patient-years in patients with type 2 diabetes (T2D),[c] respectively.[2]

Severe hypoglycemia is a significant barrier to obtaining optimal glycemic control and has been associated with increased morbidity and mortality in patients with diabetes. Additionally, fear of hypoglycemia has been shown to influence a patient's adherence to therapy and lead to suboptimal glycemic control.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Currently, treatment for severe hypoglycemia are intravenous dextrose and exogenous glucagon. Intravenous dextrose requires it to be administered by trained personnel within a medical setting. Exogenous glucagon is the main option in outpatient settings as it can be administered by a caregiver.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

The goal of glucagon therapy is to increase blood glucose levels rapidly to the point where the patient with severe hypoglycemia regains sufficient cognitive function to safely consume oral carbohydrates.

Table below shows five approved glucagon products. Of the five products, Baqsimi is administered intranasally and all other therapies are administered via injection. Gvoke is the only glucagon for injection available in a pre-filled syringe; all other products for injection require reconstitution prior to use.

Table 1: Approved Glucagon Products for the Treatment of Hypoglycemia

Name	Indication	Route & Dosing	Warnings & Precautions	Boxed warning
Glucagon powder (Baqsimi)[3] NDA 210134 approved 2019	Diabetic patients (pts) ≥4 years	Intranasally, 3mg	Catecholamine release in pts with pheochromocytoma, lack of efficacy in pts with insulinoma, hypersensitivity & allergic reactions, lack of efficacy in pts with decreased hepatic glycogen	none
Glucagon injection (Gvoke)[4] NDA 212097 approved 2019	Diabetic pts ≥4 years	Subcutaneously pt ≥12 yrs - 1mg pt 2-12 yrs, 1 mg for ≥ 45 kg, 0.5 mg for < 45 kg	Same as Baqsimi, plus necrolytic migratory erythema, and hypoglycemia in pts with glucagonoma	none
GlucaGen[5] NDA 020918 Novo Nordisk	No age limit	Reconstitute before administration Subcutaneous/intravenous/ intramuscular 1mg ≥ 6 years, 0.5 mg < 6 years	Same as Gvoke	none
Glucagon[6] NDA 201849 Fresenius Kabi	No age limit	Same as GlucaGen	Same as Gvoke	none
Glucagon[7] NDA 020928 Lilly	No age limit	Same as GlucaGen	Same as Gvoke	none

4 Benefit Assessment

Three randomized, double-blind, placebo controlled, multicenter trials were conducted in patients with T1D. Trial A (NCT03378635) and Trial B (NCT03688711) were conducted in adult patients and Trial C (NCT03667053) was conducted in pediatric patients aged 6 to 17 years.[8] In all three trials, patients were randomized to dasiglucagon or placebo following insulin induced hypoglycemia. For Trial A and C, patients could be randomized to a third therapy arm with glucagon for injection. The primary efficacy endpoint for all three trials was time to plasma glucose recovery, defined as an increase in blood glucose of ≥ 20 mg/dL from time of administration, without additional intervention within 45 minutes. The median age was 39 years and 41 years in Trial A and Trial B, respectively. Table 2 below demonstrates the efficacy in Trial A and Trial B.

Table 2 Trial A and Trial B: Plasma glucose recovery in adult patients[8]

	Trial A			Trial B	
	Dasiglucagon n=82	Placebo n=43	Glucagon injection n=43	Dasiglucagon n=34	Placebo n=10
Medium time to recovery	10 min	40 min	12 min	10 min	35 min
Number (proportions) of patients with plasma glucose increase of ≥10 mg/dL within 15 min	81 (99%)	1 (2%)	41 (95%)	30 (88%)	0 (0%)

The mean age of the patients in Trial C was 12.5 years and mean duration of diabetes was 5.9 years. Table 3 below demonstrates the efficacy in Trial C.

Table 3 Trial C: Plasma glucose recovery in pediatric patients

	Dasiglucagon n=20	Placebo n=11	Glucagon injection n=10
Median time to recovery	10 min	30 min	10 min
Plasma glucose increase of ≥10 mg/dL within 15 min	19 (95%)	0 (0%)	10 (100%)

5 Risk Assessment & Safe-Use Conditions

The safety of dasiglucagon was evaluated in 116 adult patients in Trial A and Trial B and 20 pediatric patients in Trial C. Among pediatric patients, eight patients were 6 to 11 years old and 12 were 12 to 17 years old. [8]

All risks[d] associated with dasiglucagon listed below are currently included in the draft labeling[8] Section 5, Warnings and Precautions.

5.1 SUBSTANTIAL INCREASE IN BLOOD PRESSURE IN PATIENTS WITH PHEOCHROMOCYTOMA

Glucagon may stimulate the release of catecholamines from the tumor (b) (4), (b) (4) dasiglucagon is contraindicated in patients with pheochromocytoma.

If approved, the labeling will describe that if a patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure.

5.2 HYPOGLYCEMIA IN PATIENTS WITH INSULINOMA

In patients with insulinoma, administration of dasiglucagon may directly or indirectly stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia after a dose of dasiglucagon, give glucose orally or intravenously.

5.3 HYPERSENSITIVITY AND ALLERGIC REACTIONS

Allergic reactions have (b) (4) with glucagon, (b) (4) generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. Labeling recommends to advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions.

5.4 LACK OF EFFICACY IN PATIENTS WITH DECREASED HEPATIC GLYCOGEN

Dasiglucagon is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. (b) (4) patients in state of starvation, with adrenal insufficiency or chronic hypoglycemia. Patients with these conditions should be treated with glucose.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6 Expected Postmarket Use

If approved, it is expected that primary care providers, such as family physicians, internists, and nurse practitioners will be the likely health care providers to prescribe dasiglucagon for patients or their care givers to use in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for dasiglucagon beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of dasiglucagon on the basis of the efficacy and safety information currently available. Severe hypoglycemia is a serious and potentially life-threatening complication of diabetes therapy that, if left untreated, can lead to seizures, coma, or death. Dasiglucagon is intended to treat a medically serious and potentially life-threatening condition. Dasiglucagon demonstrated the ability to effectively raise blood glucose in adults and pediatrics ages 6 and above. It is available in a pre-filled syringe that can be stored at room temperature and offers additional benefits of ease of administration.

This reviewer recommends that, if dasiglucagon is approved, a REMS is not necessary to ensure its benefits outweigh its risks. The risks of substantial increase in blood pressure in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, and lack efficacy in patients with decreased hepatic glycogen will be adequately described in the labeling and none of these risks warrants a boxed warning.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, DRM and DDLO agree that a REMS is not necessary for dasiglucagon to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Cryer, P. E. Severe hypoglycemia predicts mortality in diabetes. *Diabetes Care* **35**, 1814-1816, doi:10.2337/dc12-0749 (2012).

[2] Seaquist, E. R. et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 36, 1384-1395, doi:10.2337/dc12-2480 (2013).

[3] Basqimi prescribing information, basqimi.com, accessed 11/06/2020

[4] Gvoke prescribing information, gvokeglucagon.com, accessed 11/06/2020

[5] GlucaGen prescribing information, www.glucagenhypokit.com, accessed 11/06/2020

[6] Glucagon for injection, NDA 201849, prescribing information, drugs@fda, accessed 11/06/2020

[7] Glucagon for injection, NDA 020928, prescribing information, drugs@fda, accessed 11/06/2020

[8] Dasiglucagon draft prescribing information, accessed 11/03/2020

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/s/

MEI-YEAN T CHEN
01/11/2021 09:27:04 AM

NAOMI S BOSTON
01/11/2021 03:05:43 PM

DORIS A AUTH
01/11/2021 03:09:06 PM