NEW DRUG APPROVAL

Brand Name	Zegalogue®
Generic Name	dasiglucagon
Drug Manufacturer	Zealand Pharma

New Drug Approval

FDA Approval Date: March 22, 2021
Review Designation: Standard
Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA): 214231
Dispensing Restriction: Open Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hypoglycemia is a frequent adverse effect of treatment of diabetes mellitus with insulin and sulphonylureas. Fear of hypoglycemia alters self-management of diabetes mellitus and prevents optimal glycaemic control. Mild (self-treated) and severe (requiring help) hypoglycemia episodes are more common in type 1 diabetes mellitus but people with insulin-treated type 2 diabetes mellitus are also exposed to frequent hypoglycemic events, many of which occur during sleep. Hypoglycemia can disrupt many everyday activities such as driving, work performance and leisure pursuits. In addition to accidents and physical injury, the morbidity of hypoglycemia involves the cardiovascular and central nervous systems. Whereas coma and seizures are well-recognized neurological sequelae of hypoglycemia, much interest is currently focused on the potential for hypoglycemia to cause dangerous and life-threatening cardiac complications, such as arrhythmias and myocardial ischaemia, and whether recurrent severe hypoglycemia can cause permanent cognitive impairment or promote cognitive decline and accelerate the onset of dementia in middle-aged and elderly people with diabetes mellitus. Prevention of hypoglycemia is an important part of diabetes mellitus management and strategies include patient education, glucose monitoring, appropriate adjustment of diet and medications in relation to everyday circumstances including physical exercise, and the application of new technologies such as real-time continuous glucose monitoring, modified insulin pumps and the artificial pancreas.

34 million people of all ages, or 10.5% of the U.S. population, have diabetes.

Efficacy

Table 1. Zegalogue Trial Design Summary (Trial A, B, and C)

Study Population	• **Trials A and B:** Adult female or male patients with type 1 diabetes mellitus (T1DM) for at least 1 year; diagnostic criteria as defined by the American Diabetes Association (ADA); receiving daily insulin • **Trial C:** Pediatric female or male patients 6–17 years of age with T1DM for at least 1 year; diagnostic criteria as defined by the ADA; receiving daily insulin
Interventions	• All 3 trials compared the glycemic response observed after induction of hypoglycemia and administration of dasiglucagon (0.6 mg) with that of placebo and that of GlucaGen (1 mg). • During this procedure, a plasma glucose concentration of <60 mg/dL was targeted in Trials A and B, whereas the target was <80 mg/dl in Trial C.
Endpoints	**Primary outcome measure (Trials A, B, and C):** Time to plasma glucose recovery (time frame: 0–45 minutes after dosing). Plasma glucose recovery is defined as the first increase in plasma glucose of ≥20 mg/dL (1.1 mmoL/L) from baseline during the hypoglycemic clamp procedure without administration of rescue intravenous (IV) glucose. **Key secondary outcome measures (Trials A, B, and C):** • Plasma glucose recovery (time frame: 0–30 minutes after dosing). Plasma glucose recovery within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection without administration of rescue IV glucose.
	• Plasma glucose changes from baseline (time frame: 0–30 minutes after dosing). Plasma glucose changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after trial product injection or at the time of rescue IV glucose.
Efficacy and Safety Results	See nested table below

	Trial A		Trial B	
	Zegalogue (n = 82)	Placebo (n = 43)	Zegalogue (n = 34)	Placebo (n = 10)
Median time to recovery [95% CI][a]	10 min [10; 10][b]	40 min [30; 40]	10 min [8; 12][b]	35 min [20; –]
Trial C				
	Zegalogue (n = 20)		Placebo (n = 11)	
Median time to recovery [95% CI][a]	10 min [8; 12][b]		30 min [20; –]	

n = number of patients who were randomized and treated.
a. Log-log confidence interval.
b. *P* <0.001 versus placebo (log-rank test stratified by injection sites).

The three Phase 3 trials met all primary and key secondary endpoints, with a median time to recovery of 10 minutes.

Overall, no safety concerns were raised for dasiglucagon within the trials. The side effect profile was similar to glucagon.

Sources: Zegalogue Prescribing Information; NCT03378635 (Trial A), NCT03688711 (Trial B), NCT03667053 (Trial C).

Safety

ADVERSE EVENTS

- Adverse reactions reported in adult patients treated with dasiglucagon within 12 hours of treatment and at greater incidences than with placebo in 2 placebo-controlled trials included: diarrhea (5% vs. 0%), headache (11% vs. 4%), nausea (57% vs. 4%), and vomiting (25% vs. 2%). Adverse reactions reported in pediatric patients treated with dasiglucagon within 12 hours of treatment in the 2 placebo-controlled trials include: headache (10%), nausea (65%), and vomiting (50%); these adverse reactions were not reported in the placebo group.
- Other adverse reactions in patients treated with dasiglucagon occurring within 12 hours of treatment during the 2 placebo-controlled trials included: hypertension, hypotension, bradycardia, presyncope, palpitations, and orthostatic intolerance (e.g., feeling lightheaded or dizziness on standing).
- Allergic reactions to glucagon products have been reported and may occur with dasiglucagon. Allergic reactions may include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions.
- Injection site reaction (pain) was reported in 2% of adults and 5% of children receiving dasiglucagon.
- As with all therapeutic proteins, there is a potential for immunogenicity. In clinical trials, 4 out of 498 patients (less than 1%) had treatment-emergent anti-drug antibody formation. Two patients receiving a single dose of dasiglucagon had detectable anti-drug antibodies (ADA) to dasiglucagon for at least 14 months after dosing. One ADA-positive patient receiving multiple doses of dasiglucagon had ADAs with transient neutralizing activity and with cross-reactivity against native glucagon. Although no safety or efficacy concerns were noted for these ADA-positive subjects, it is unknown whether ADAs may affect pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of the drug.

WARNINGS & PRECAUTIONS

- **Substantial Increase in Blood Pressure in Patients with Pheochromocytoma:** Zegalogue® is contraindicated in patients with pheochromocytoma because glucagon products may stimulate the release of catecholamines from the tumor. If the 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.
- **Hypoglycemia in Patients with Insulinoma:** In patients with insulinoma, administration of glucagon products may produce an initial increase in blood glucose; however, Zegalogue® administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. Zegalogue® is contraindicated in patients with insulinoma. If a patient develops symptoms of hypoglycemia after a dose of Zegalogue®, give glucose orally or intravenously.
- **Hypersensitivity and Allergic Reactions:** Allergic reactions have been reported with glucagon products; these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions.
- **Lack of Efficacy in Patients with Decreased Hepatic Glycogen:** Zegalogue® is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for Zegalogue® administration to be effective. Patients with these conditions should be treated with glucose.

CONTRAINDICATIONS

- Pheochromocytoma – This is because the drug may stimulate the release of catecholamines from the tumor. Stimulation of catecholamine release by dasiglucagon can cause a substantial increase in blood pressure. If the

patient develops a dramatic increase in blood pressure, 5 to 10 mg of phentolamine mesylate has been shown to be effective in lowering blood pressure for the short time that control would be needed.

- Insulinoma - In patients with insulinoma, glucagon products 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 the insulinoma. Any patient developing symptoms of hypoglycemia after a dose of dasiglucagon should be given glucose orally or intravenously, whichever is most appropriate.

Clinical Pharmacology

MECHANISMS OF ACTION

Dasiglucagon is a glucagon receptor agonist, 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.

Dose & Administration

ADULTS

0.6 mg administered subcutaneously.

PEDIATRICS

Children and Adolescents 6 years and older: 0.6 mg administered subcutaneously.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Zegalogue® injection is a clear, colorless solution available as:

- 0.6 mg/0.6 mL single-dose autoinjector
- 0.6 mg/0.6 mL single-dose prefilled syringe