PDL DRUG REVIEW

Proprietary Name: Zegalogue®
Common Name: dasiglucagon injection
PDL Category: Diabetic - Other

Comparable Products	Preferred Drug List Status
Glucagen	Preferred

Summary

Pharmacology/Usage: Dasiglucagon, the active ingredient of Zegalogue®, is a glucagon analog and an antihypoglycemic agent. It is a glucagon receptor agonist, which increases blood glucose concentration by activating hepatic glucagon receptors, thus stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.

Indication: For the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data with use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Untreated hypoglycemia in pregnancy can cause complications and may be fatal. The safety and efficacy of use in the pediatric population younger than 6 years of age have not been established.

Dosage Form: A clear, colorless solution for subcutaneous injection:

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

Recommended Dosage: For subcutaneous injection only. Patients and caregivers must be instructed on signs and symptoms of severe hypoglycemia. Administer Zegalogue® as soon as possible when severe hypoglycemia is recognized. Do not attempt to reuse Zegalogue®, as each device contains a single dose of dasiglucagon and cannot be reused.

Administer Zegalogue® per the printed instructions on the protective case label and the Instructions For Use. Administer the injection in the lower abdomen, buttocks, thigh, or outer upper arm. Call for emergency assistance immediately after administering the dose. If there has been no response after 15 minutes, an additional Zegalogue® dose may be administered while waiting for emergency assistance. When the patient has responded to treatment, give oral carbohydrates to restore liver glycogen and prevent recurrence of hypoglycemia.

The recommended dose in adults and pediatric patients aged 6 years and older is 0.6mg administered by SC injection into the lower abdomen, buttocks, thigh, or outer upper arm. If there has been no response after 15 minutes, an additional 0.6mg dose from a new device may be administered.

Drug Interactions: In patients taking beta-blockers, they may have a transient increase in pulse and blood pressure when given Zegalogue®.

In patients taking indomethacin, Zegalogue® may lose its ability to raise blood glucose or may even produce hypoglycemia.

Zegalogue® may increase the anticoagulant effect of warfarin.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (dasiglucagon®) minus reported % incidence for placebo in adults within 12 hours of treatment. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nausea (53%), vomiting (23%), headache (7%), diarrhea (5%), and injection site pain (2%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (dasiglucagon®) minus reported % incidence for placebo in pediatric patients within 12 hours of treatment. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included nausea (65%), vomiting (50%), headache (10%), and injection site pain (5%).

Other adverse reactions in patients treated with dasiglucagon occurring within 12 hours of treatment included hypertension, hypotension, bradycardia, presyncope, palpitations, and orthostatic intolerance.

Zegalogue® is contraindicated in patients with pheochromocytoma. If the patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10mg of phentolamine mesylate, administered IV, has been shown to be effective in lowering blood pressure.

In patients with insulinoma, administration of glucagon products may produce an initial increase in blood glucose; however, Zegalogue® administration may directly or indirectly 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.

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: In patients with:

- Pheochromocytoma, because of the risk of substantial increase in blood pressure
- Insulinoma, because of the risk of hypoglycemia

Manufacturer: Zealand Pharma A/S

Analysis: The safety and efficacy of Zegalogue® were assessed in 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients with type 1 DM. Two trials (Trial A and Trial B) included adult patients, while Trial C included pediatric patients aged 6 to 17 years of age. In all 3 studies, patients were randomized to Zegalogue®, placebo, or (in Trials A and C) glucagon for injection 1.0mg. Zegalogue® and the comparators were administered as single SC injections following a controlled induction of hypoglycemia using IV administration of insulin. During this procedure, a plasma glucose concentration of <60mg/dL was targeted in Trials A and B, whereas the target was <80mg/dL in Trial C.

The primary endpoint for all 3 trials was the time to plasma glucose recovery (treatment success), defined as an increase in blood glucose of ≥20mg/dL from time of administration, without additional intervention within 45 minutes. In Trials A and B, plasma glucose values were collected and assessed pre-dose and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 45, 50, 60, 75, 90 minutes after treatment. Trial C assessed plasma glucose at the same timepoints as did Trials A and B with the exception of the 25, 40, 50, 75, and 90-minute post-treatment timepoints. The primary hypothesis test was superiority of Zegalogue® versus placebo. There was no formal hypothesis test of Zegalogue® versus glucagon for injection.

The mean age of patients in Trial A was 39.1 years, while 63% were male and 92% were White. The mean duration of diabetes was 20 years and the mean baseline plasma glucose was 58.8mg/dL. Results of this trial indicated that the median time to plasma glucose recovery was statistically significantly shorter for Zegalogue® (10 minutes) versus placebo (40 minutes). The median time to plasma glucose recovery was numerically similar between Zegalogue® (10 minutes) and glucagon for injection (12 minutes).

The mean age of patients in Trial B was 41.0 years, while 57% were male and 93% were White. The mean duration of diabetes was 22.5 years and the mean baseline plasma glucose was 55.0mg/dL. Results suggested that the median time to plasma glucose recovery was statistically significantly shorter for Zegalogue® (10 minutes) versus placebo (35 minutes). Results can be seen in the table below, which was adapted from the prescribing information.

	Trial A		Trial B	
	Zegalogue® N=82	Placebo N=43	Zegalogue® N=34	Placebo N=10
Median time to recovery	10 minutes (p<0.001 vs placebo)	40 minutes	10 minutes (p<0.001 vs placebo)	35 minutes

Trial C included pediatric patients aged 6 to 17 years of age and weighing ≥20kg who were randomized to Zegalogue®, placebo, and glucagon for injection. The mean age of included patients was 12.5 years, while 56% were male and 95% were white. The mean duration of diabetes was 5.9 years, and the mean baseline plasma glucose was 72.0mg/dL. Results suggested that the median time to plasma glucose recovery was statistically significantly shorter for Zegalogue® (10 minutes) as compared with placebo (30 minutes). The median time to plasma glucose recovery was numerically similar between Zegalogue® (10 minutes) and glucagon for injection (10 minutes). Results can be seen in the table below, which was adapted from the prescribing information.

	Trial C	
	Zegalogue® N=20	Placebo N=10
Median time to recovery	10 minutes (p<0.001 vs placebo)	30 minutes

Place in Therapy: Zegalogue®, a glucagon receptor agonist, is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above. It is for subcutaneous injection only, and emergency assistance should be called immediately after administering a dose. Its efficacy was assessed in 3 randomized, double-blind, placebo-controlled trials that also included patients randomized to glucagon for injection in 2 of the trials. The time to plasma glucose recovery (treatment success) was the primary endpoint for all 3 studies, and the median time to plasma glucose recovery was statistically significantly shorter for Zegalogue® as compared with placebo in all 3 trials. The median time to plasma glucose recovery was 10 minutes for Zegalogue® in all 3 studies. In one adult trial and one pediatric trial, some patients were randomized to glucagon for injection. In both studies, the median time to plasma glucose recovery was numerically similar between Zegalogue® and glucagon for injection.

Zegalogue® is a safe, effective and relatively cost-effective medication. It is therefore recommended that Zegalogue® be added to the PDL as preferred after a step through a preferred reconstitution product.

PDL Placement: ☒ **Preferred**
☐ **Non-Preferred**

References

[1] Zegalogue [package insert]. Soborg, Denmark: Zealand Pharma A/S; 2021.