Drug Monograph

Drug Name: Zegalogue® (dasiglucagon) solution for injection
Drug Class: Endocrine and Metabolic Agents: Agents for Hypoglycemia

Prepared For: MO HealthNet
Prepared By: Conduent

☑ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:
The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.

Dosage Forms:
Zegalogue is available in a 0.6 mg/0.6 ml single-dose autoinjector and a 0.6 mg/0.6 ml single-dose prefilled syringe.

Manufacturer:
Manufactured by: Zealand Pharma US, Inc., Boston, MA 02210.

Summary of Findings:
The efficacy of Zegalogue was established in three randomized, double-blind, placebo-controlled, multicenter, Phase 3 trials with 215 adults and 42 children age 6 to 17 years. All participants had type 1 diabetes mellitus (T1DM) for at least a year with a stable insulin regimen and hemoglobin A1C less than 10%. The primary endpoint of the median time to plasma glucose recovery showed Zegalogue acted significantly faster than placebo [10 minutes vs. 35 minutes (95% CI; p<0.001)]. The key secondary endpoints were plasma glucose recovery time and plasma glucose changes from baseline compared to placebo. All primary and key secondary endpoints were met.

Status Recommendation:
☐ Clinical Edit ☑ Open Access ☑ PA Required ☑ PDL

Type of PA Criteria:
☐ Appropriate Indications ☑ Non-Preferred ☑ Preferred ☐ No PA Required
Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

1. Hypoglycemia is defined as a lowered blood sugar level, typically below 50-70 mg/dL, that causes an altered mental status and/or symptomatic nervous system stimulation.
2. Signs and symptoms of hypoglycemia can include anxiety, irritability, sweating, confusion, and tachycardia. Hypoglycemia is considered severe when the patient requires help from someone to recover. If left untreated, it can lead to neuroglycopenia and death.
3. Hypoglycemia occurs most commonly in diabetic patients and typically results from medication usage/changes, dietary changes, infections, and metabolic changes.
   - Patients with type 1 diabetes mellitus (T1DM) report an average of up to three episodes of severe hypoglycemia per year.
   - Patients with type 2 diabetes mellitus (T2DM) have substantially less episodes of hypoglycemia than type 1 patients. However, those treated with insulin, a sulfonylurea (especially long-acting agents), or a meglitinide are generally at higher risk than those treated with diet or other medications.
4. The goal of treatment for hypoglycemia is to raise the plasma glucose concentration to normal by providing dietary or parenteral carbohydrate (specifically glucose).
   - First-line treatment of the early symptoms of hypoglycemia is administration of glucose, which can be in the form of glucose tablets, glucose gel, juice, sugar, honey, or hard candy. Treatment with glucose tablets (pure glucose) is more consistently effective and should be the treatment of choice in patients taking insulin, or an insulin secretagogue in combination with an alpha-glucosidase inhibitor, experiencing symptomatic hypoglycemia.
   - When using carbohydrates, the recommended dosage is 15 grams of carbohydrates every 15 minutes until blood sugar is stable.
   - For severe hypoglycemia, treatment options are determined by setting and IV access.
     - Patients in the hospital with parenteral access can be treated quickly by giving 25 grams of 50% dextrose IV.
     - In cases of severe hypoglycemia outside of a medical center or in patients without IV access, endogenous glucose production can be stimulated by administering glucagon either intranasally or by subcutaneous or intramuscular injection.
5. Glucagon is a hormone, produced by alpha cells of the pancreas and is released when the amount of glucose in the blood is too low. It causes the liver to engage in glycogenolysis, or conversion of glycogen into glucose. Insulin has the opposite effect on blood glucose levels by facilitating glucose uptake by insulin-dependent tissues.
• The American Diabetes Association (ADA) treatment guidelines recommend prescribing glucagon to all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose < 54 mg/dL.

**Dosage Form** *(3)*

Zegalogue is available in a 0.6 mg/0.6 ml single-dose autoinjector and a 0.6 mg/0.6 ml single-dose prefilled syringe. Zegalogue is stored in the refrigerator (20° to 25° F), kept away from the cooling agent. Additionally, the product can also be stored at room temperature (68° to 77° F) for up to 12 months. Zegalogue should be discarded at the end of the 12-month period at room temperature or the expiration date, whichever comes first.

**Manufacturer** *(3)*

Manufactured by: Zealand Pharma US, Inc., Boston, MA 02210.

**Indication(s)** *(3)*

Zegalogue is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years or older.

**Clinical Efficacy** *(3,4,5,6)* *(mechanism of action/pharmacology, comparative efficacy)*

Zegalogue works to stimulate glycogen breakdown and glucose release from the liver as an agonist of hepatic glucagon receptors. Hepatic stores of glycogen are necessary for Zegalogue to produce an antihypoglycemic effect.

Pharmacokinetics:

<table>
<thead>
<tr>
<th>Absorption</th>
<th>C(_{\text{max}})=5110 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Proteolytic degradation pathways in blood, liver, and kidney</td>
</tr>
<tr>
<td>Excretion</td>
<td>NA</td>
</tr>
<tr>
<td>Half-life</td>
<td>(t_{1/2}=30) minutes</td>
</tr>
</tbody>
</table>

**Clinical Trials Experience**

<table>
<thead>
<tr>
<th>STUDY DESIGN (Trial A NCT03378635, Trial B NCT03688711, Trial C NCT03667053)</th>
<th>Three randomized, double-blind, placebo-controlled, multicenter Phase 3 trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCLUSION CRITERIA</strong></td>
<td></td>
</tr>
<tr>
<td>• Females or males with T1DM for at least 1 year*</td>
<td></td>
</tr>
<tr>
<td>• Receiving daily insulin with stable dosing**</td>
<td></td>
</tr>
<tr>
<td>• Hemoglobin A1c &lt;10%</td>
<td></td>
</tr>
<tr>
<td>• Not pregnant or breast-feeding and using appropriate method of contraception</td>
<td></td>
</tr>
<tr>
<td>Trial C only:</td>
<td></td>
</tr>
<tr>
<td>• Pediatric patients 6 to 17 years old</td>
<td></td>
</tr>
<tr>
<td>• Body weight ≥20 kg</td>
<td></td>
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</tbody>
</table>

*Diagnostic criteria as defined by the American Diabetes Association (ADA)  
**Defined as no more than a 10-unit daily variation in total daily insulin dose
EXCLUSION CRITERIA
- Previously treated with dasiglucagon
- Known or suspected allergy to trial product
- History of severe hypoglycemia in the last month prior to screening
- Current bleeding disorder, including anticoagulant treatment
- Presence or history of pheochromocytoma
- Use of a daily systemic beta-blocker drug, indomethacin, warfarin or anticholinergic drugs in the previous 28 days
- Donation of blood or surgery with significant blood loss in the last 12 weeks

Trial A and C:
- Active malignancy within the last 5 years
- History of hypoglycemic events associated with seizures

Trial C only:
- Use of prescription or non-prescription medications known to cause QT prolongation

TREATMENT REGIMEN

<table>
<thead>
<tr>
<th></th>
<th>Trial A (N=170)</th>
<th>Trial B (N=45)</th>
<th>Trial C (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized 2:1:1 to Zegalogue 0.6 mg, placebo or glucagon 1 mg for injection</td>
<td>Randomized 3:1 to Zegalogue 0.6 mg or placebo</td>
<td>Randomized 2:1:1 to Zegalogue 0.6 mg, placebo or glucagon 1 mg for injection</td>
</tr>
</tbody>
</table>

RESULTS
- The primary endpoint was the median time to plasma glucose recovery, defined as an increase in blood glucose ≥20 mg/dL from time of administration (95% CI; p<0.001).
- The primary hypothesis test was the superiority of Zegalogue versus placebo. There was no formal hypothesis test of Zegalogue versus glucagon for injection.

<table>
<thead>
<tr>
<th></th>
<th>Trial A (n=82)</th>
<th>Trial B (n=34)</th>
<th>Trial C (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose recovery within 30 minutes</td>
<td>10 minutes</td>
<td>10 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Plasma glucose recovery within 20 minutes</td>
<td>10 minutes</td>
<td>35 minutes</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Plasma glucose recovery within 15 minutes</td>
<td>10 minutes</td>
<td>30 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Plasma glucose recovery within 10 minutes</td>
<td>40 minutes</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

Key secondary endpoints included:
- 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

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

SAFETY
Discussed in the Adverse Effects section below.

Contraindications (3)
- Patients with pheochromocytoma- due to the risk of a substantial increase in blood pressure
- Patients with insulinoma- due to the risk of hypoglycemia
Warnings and Precautions (3)

- Hypersensitivity and allergic reactions
- Lack of efficacy in patients with decreased hepatic glycogen

Adverse Effects (3)

<table>
<thead>
<tr>
<th>Most common, ≥ 2%</th>
<th>Zegalogue (N=116)</th>
<th>Placebo (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea (not noted in children)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug Interactions (3)

- Beta-blockers- may experience a transient increase in pulse and blood pressure
- Indomethacin- may lose its ability to raise blood glucose or may produce hypoglycemia
- Warfarin- may increase the anticoagulant effect

Dosage and Administration (3)

- The recommended dose for patients aged 6 years or older is 0.6 mg administered by subcutaneous injection into the lower abdomen, buttocks, thigh, or outer upper arm. A second injection of 0.6 mg dose from a new device may be administered if there is no response after 15 minutes, while waiting for emergency assistance.
  - Patients and caregivers should be familiar with the signs and symptoms of hypoglycemia.
  - Zegalogue should be administered as soon as possible when severe hypoglycemia is recognized.
  - Emergency assistance should be called immediately after administering the first dose.
- When the patient has responded to treatment and able to safely consume food or drink, give oral carbohydrates. Give a fast-acting source of sugar (such as fruit juice) and a long-acting source of sugar (such as crackers with cheese or peanut butter).
**Conclusion**

Zegalogue, a glucagon analogue with seven amino acid substitutions different than glucagon and is sold as both an autoinjector and a prefilled syringe. Zegalogue is the third product in the last two years to offer a new easy-to-use glucagon delivery option. It is the second injectable product available that comes in a prefilled syringe and an autoinjector. The efficacy of Zegalogue was established in three randomized, double-blind, placebo-controlled, multicenter Phase 3 trials. The three Phase 3 trials met all primary and key secondary endpoints, with a median time to recovery of 10 minutes. Common adverse reactions (incidence ≥ 2%) in adults include nausea, vomiting, headache, diarrhea, and injection site pain. In pediatric patients the most common adverse reactions (incidence ≥ 2%) include nausea, vomiting, headache, and injection site pain. Zegalogue does not distinguish itself from its competitors based on ease-of-use, time to clinical effect or side effect profile. Until other useful data are available, the high cost of this product will discourage its use.

**Recommendation**

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

**References**