Dasiglucagon (ZEGALOGUE)
National Drug Monograph
September 2021
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action
- Glucagon analog

Indication(s) Under Review in This Document
- Indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above

Dosage Form(s) Under Review
- 0.6mg/0.6mL single-dose autoinjector
- 0.6mg/0.6mL single-dose prefilled syringe
- For subcutaneous (SC) administration only

Clinical Evidence Summary

Efficacy Considerations
- Two randomized double-blind, placebo-controlled trials conducted in adults with type 1 diabetes. There is also a pediatric study which is not discussed in this monograph.
- Hypoglycemia was induced in a controlled setting using intravenous insulin to a target plasma glucose less than 60mg/dL. Mean baseline plasma glucose was 58.8mg/dL (study 1) and 55mg/dL (study 2)
- The primary endpoint (treatment success) was defined as an increase in blood glucose of greater than or equal to 20mg/dL from time of glucagon administration without additional intervention within 45 minutes.
- Efficacy data are summarized in Table 1. Time to glucose recovery was significantly faster and more patients recovered from hypoglycemia within 15 minutes with dasiglucagon than placebo. Time to glucose recovery and percent of patients who recovered within 15 minutes was comparable to glucagon.

Table 1: Efficacy results from clinical trials

Study	Design	Results
Pieber 2021	Dasiglucagon 0.6mg SC (n=82) Placebo (n=43) Glucagon 1mg SC (n=45)	**Results for dasiglucagon/placebo/glucagon respectively** • Median time to glucose recovery: 10min/40min/12min • Subj recovering from hypoglycemia within 15min: 99%/2%/95%
Bailey 2021	Dasiglucagon 0.6mg SC (n=34) Placebo (n=10)	**Results for dasiglucagon/placebo respectively** • Median time to glucose recovery 10min/35min • Subj recovering from hypoglycemia within 15min: 88%/0

Plasma glucose recovery is defined as first increase in plasma glucose of ≥20 mg/dL from baseline during the hypoglycemic clamp procedure without administration of rescue IV glucose.

Safety Considerations

Safety Results from Clinical Trials:

- The pooled results for adverse reactions occurring in 2% or more patients and more frequently than with placebo in adults within 12 hours of treatment are shown in Table 2. In Pieber et al., adverse events in the glucagon 1mg control arm were similar to dasiglucagon.

Table 2: Safety results

	Pieber et al.			Bailey et al.	
	Dasiglucagon (%)	**Placebo (%)**	**Glucagon (%)**	**Dasiglucagon (%)**	**Placebo (%)**
N	82	43	43	34	10
Nausea	55	2	53	62	10
Vomiting	23	2	21	29	0
Headache	10	2	9	12	0
Diarrhea	-	-	-	6	0
Injection site pain or erythema	1	5	5	6	0

- **Boxed warnings:** None
- **Contraindications: All glucagon products have the following contraindications**
  - Pheochromocytoma because of the risk of substantial increase in blood pressure
  - Insulinoma because of the risk of hypoglycemia
- **Adverse reactions**

  Adverse reactions similar to those seen with other glucagon products including, nausea, vomiting, headache, diarrhea, injection site reactions, etc.

  Immunogenicity

  In clinical trials, 4 out of 498 patients receiving dasiglucagon developed treatment-emergent anti-drug antibodies (ADAs). Two patients had detectable ADAs for at least 14 months after receiving a single dose of dasiglucagon. One ADA positive patient who had received multiple doses of dasiglucagon had transient neutralizing activity with cross-reactivity against native glucagon.

  There is a dedicated immunogenicity trial (n=111) of patients randomized to dasiglucagon or GlucaGen Administered once weekly for 3 weeks and followed for 15 weeks. No patients developed ADAs. There was no treatment-induced or treatment-boosted ADA response identified for any patient at any time point after dosing.

Other Considerations

- Storage: Refrigerate (36-46°F). Can be kept at room temperature (68-77°F) for up to 12 months. Keep in red protective case until ready to use. Do not return to refrigerator after storing at room temperature. Discard if kept at room temperature for more than 12 months.
- There is a potential risk for administration errors with the prefilled syringe/auto-injector products because they can only be administered by the subcutaneous route whereas the traditional products that require mixing can be administered subcutaneously, intramuscularly, or intravenously.

- VA purchasing data show very low demand for prefilled syringes and auto-injectors. For example, less than 1% of all glucagon product purchases over a 1-year period were for GVOKE prefilled syringes and auto-injectors.
- Areas of research: In phase 2 trials for use in dual hormone artificial pancreas pump system and in phase 3 trials as a subcutaneous infusion for treating congenital hyperinsulinemia

Other Therapeutic Options

A brief comparison of glucagon products to treat hypoglycemia is shown in table 3.

Table 3 Glucagon Products to Treat Hypoglycemia

	Dasiglucagon	Glucagon SOLN (GVOKE)	Glucagon nasal powder (BAQSIMI)	Glucagon*
Formulary	TBD	Nonformulary	Nonformulary	Formulary
Administration	SC	SC	intranasal	SC, IM, IV
Available as	PFS, auto-injector	PFS, auto-injector	Intranasal device	Kit
Reconstitution needed	No	No	No	Yes
Storage	Store in refrigerator (36-46°F) in protective case for up to 3 years until expiration date. Once removed from refrigerator can be kept at 68-77°F for up to 12 months or expiration date whichever comes first. Do not return to refrigerator after storing at room temperature	Store in original foil pouch at 68-77°F; excursions between 59-86°F permitted. Shelf-life <= 24 months from date of manufacture	Store at temperatures up to 86°F in shrink wrapped tube. Shelf-life 24 months from date of manufacture	Unmixed: Room temperature (68-77°F) in original packaging for up to 24 months. Once mixed, use immediately
Blood glucose response **•Tx success within 30min** **•Mean time to tx success**	BG increased by >= 20mg/dL •97%-100% vs 100% (SC GLU) •10 min vs 12 min (SC GLU)	BG > than 70mg/dL or increased by >= 20mg/dL •99% vs 100% (SC GLU) •13.8 min vs 10 min (SC GLU)	BG > than 70mg/dL or increased by >= 20mg/dL •96%-100% vs 99%-100% (IM GLU) • 12-16 min vs 10-12min (IM GLU)	BG rises within 10min of SC injection. Time of maximal glucose concentration is 30-45min (SC); 5-20min (IV); 30min (IM)
Other		Hypoglycemia simulation studies showed GVOKE was administered more quickly and correctly than standard glucagon	Hypoglycemia simulation studies showed BAQSIMI was administered more quickly and correctly than standard glucagon AEs unique to BAQSIMI include nasal and ocular AEs (e.g. congestion, runny nose, sneezing, itching, watery eyes, eye redness)	

*Marketed products requiring reconstitution: Two recombinant DNA products (GlucaGen Hypo Kit- NovoNordisk; Glucagon Emergency kit for low blood sugar-Eli Lilly) and two solid phase peptide synthesis products (Glucagon Emergency Kit for Low Blood Sugar-Fresenius; Glucagon for Injection-Amphastar Pharm)

Projected Place in Therapy

Based on VA purchasing data, there is low demand prefilled syringe/auto-injector products. Dasiglucagon may be an alternative for patients/care givers who prefer an injectable product, but have difficulty using standard glucagon formulations.

REFERENCES

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