# Administration of Dasiglucagon

Center for Medicare & Medicaid Services

ICD-10 Coordination and Maintenance Committee Meeting

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The enclosed information has been prepared for consideration by the Center of Medicare and Medicaid Services. A New Drug Application for this dasiglucagon product is under review by the FDA with approval pending clearance of Zealand's third-party manufacturing facility. The information provided here is a combination of publicly available information and the results of Zealand's clinical trials.

# Presentation Overview

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# Unmet Need for Patients Suffering from Congenital Hyperinsulinism (CHI)

- Current treatments for CHI include medical therapy, surgical management and nutritional treatment[1]
- Medical therapy of CHI includes of approved use of diazoxide in chronic dosage[2–5]
    - Medical standard of care also consists of off-label therapies including Glucagon, somatostatin analogues (short-acting octreotide and long-acting lanreotide), mTOR inhibitors (sirolimus) and calcium channel blockers in combination with intensive nutritional support and/or chronic intravenous (IV) glucose infusion[2–8]
- Only 41-64% of CHI patients respond to diazoxide (some only partially) and use of diazoxide carries risk of serious adverse reactions such as sodium and fluid retention[1]
- IV administration of glucagon to CHI patients is used short-term in the hospital setting; however, there are currently no marketed glucagon products available for long-term use in the home setting[2,3]
- HCPs cite the lack of responsiveness or incomplete response, along with the adverse events or intolerable side-effects as the greatest treatment limitations[1,9]
- Many patients experience neurodevelopmental delays because of delayed diagnosis or comorbid conditions[10]
- These delays and CHI itself often require at least one parent (or another individual) to act as full-time caregiver[1,10]

# Current Treatments & Limitations

| Treatment | Current Usage | Clinical Limitations / Barriers |
|---|---|---|
| **Diazoxide** | • Approved for hyperinsulinism due to various underlying conditions in the U.S.[11] | • Lack of adequate response[2]<br>• FDA-issued warning on pulmonary hypertension in infants in 2015[11,12]<br>• Hypertrichosis[11]<br>• Fluid retention, acute heart failure, pulmonary hypertension[11] |
| **Glucagon** | • Used off-label in CHI[2,3] | • Requires daily reconstitution of lyophilized glucagon[3]<br>• Precipitates in the infusion tube (cannot use long-term)[2] |
| **Somatostatin analogues (octreotide)** | • Used off-label in CHI[2]<br>• Short acting: 3-4 daily subcutaneous injections/continuous infusion[2,13]<br>• Long-acting: intramuscular injection every 28 days[9] | • Hepatotoxicity[2,13]<br>• Tachyphylaxis, QT prolongation[13]<br>• Necrotizing enterocolitis (can be fatal in children with CHI) [2,13] |
| **Pancreatic Surgery** | • Total/near-total pancreatectomy in diffuse CHI if medical management fails[2] | • Patients may develop lifelong insulin dependent diabetes mellitus[9]<br>• Patients may develop lifelong severe exocrine insufficiency[9] |

# Dasiglucagon Product Overview

- Dasiglucagon (infusion) 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[14]

- Dasiglucagon (infusion) is a stable glucagon analogue that has been specifically designed for long-term infusion via pump[14]

# Dasiglucagon Product Overview: FDA Timeline

- The U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) for Part 1 of the New Drug Application (NDA) for dasiglucagon for the prevention and treatment of hypoglycemia in pediatric patients 7 days of age and older with congenital hyperinsulinism (CHI) for up to 3 weeks of dosing. The CRL is related to deficiencies identified following an inspection at a third- party contract manufacturing facility. These deficiencies are not specific to dasiglucagon. The CRL did not state any concerns about the clinical data package or safety of dasiglucagon

- Zealand expects to resubmit the NDA for dasiglucagon for CHI for up to three weeks of dosing in the first half of 2024 contingent on successful reinspection of the third-party manufacturing facility

# Dasiglucagon Clinical Trials

- Zealand Pharma has completed 2 multinational, phase 3 trials, which constitute the largest completed clinical development program conducted in CHI to date[15,16]

- The efficacy of dasiglucagon infusion to reduce or eliminate the need for IV glucose and facilitate its wean-off in the early treatment phase was shown in the double-blind, placebo-controlled, cross-over Trial 17103[15,16]
  - Part 1 of Trial: 17103: a mean reduction [95% CI] in IV GIR of 5.2 mg/kg/min [-8.3;-2.1] for dasiglucagon infusion treatment versus placebo was demonstrated, corresponding to a relative treatment difference of 55%. The reduction in IV glucose was not facilitated by an increase in other sources of carbohydrate administration[15,16]
  - Part 2 of Trial: 83% of the patients achieved 12 or more hours off IV glucose, indicating substantial improvement, as reflected by the patients becoming independent of the IV glucose and being able to be discharged to continue treatment in home settings[15,16]

# Dasiglucagon: Overall Safety Profile

- In the phase 3 program dasiglucagon was well tolerated with a safety profile as expected, confirming known class effects of glucagon. No new safety concerns were identified[17]

- The safety of dasiglucagon was evaluated in a randomized trial in 2 parts (Trial 1), comprised of a double blind, placebo controlled cross-over period (part 1), and an open-label, single-arm period (part 2). In part 1, the patients were randomly assigned in a 1:1 ratio to receive dasiglucagon or placebo for 48 hours, after which they were crossed over to the other trial treatment for an additional 48 hours. After part 1, the patients continued in the open-label single-arm part 2 to receive dasiglucagon for 21 days[14]

- The safety of dasiglucagon was evaluated in 44 patients aged 7 Days to 12 Years with Congenital Hyperinsulinism (CHI) who were treated with dasiglucagon in controlled and uncontrolled clinical trials. This includes the following[14]:
  - 31 patients who were treated for more than 6 months
  - 28 patients who were treated for more than 1 year
  - 21 patients who were treated for more than 2 years

- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of dasiglucagon cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice[6]

**Adverse Reactions Occurring in ≥2 Patients Treated with Dasiglucagon (Trial 1)**

| Adverse Reaction | Part 1 (48 hrs): Dasiglucagon N=12 n (%) | Part 1 (48 hrs): Placebo N=12 n (%) | Part 2 (21 days): Dasiglucagon N=12 n (%) |
|---|---|---|---|
| Vomiting | 1 (8.33%) | 1 (8.33%) | 2 (16.67%) |
| Constipation | - | - | 2 (16.67%) |
| Rash Papular | - | - | 3 (25%) |

- Infusion site reactions were reported sporadically throughout administration of dasiglucagon. The most frequent infusion site disorders were infusion site infection, infusion site erythema and infusion site abscess[14]
- Overall, skin reactions were reported in 7 out of 12 patients treated with dasiglucagon in Trial 1. The most frequent skin disorders were various types of rashes. In addition, necrolytic migratory erythema has been reported in CHI patients treated with dasiglucagon. Long-term treatment did not result in increased frequency or severity of skin reactions including NME. In some patients, skin reactions may require reduction of dasiglucagon infusion rate, treatment interruption or treatment discontinuation. Skin reactions may re-occur[14]

# Dasiglucagon Dosing & Administration

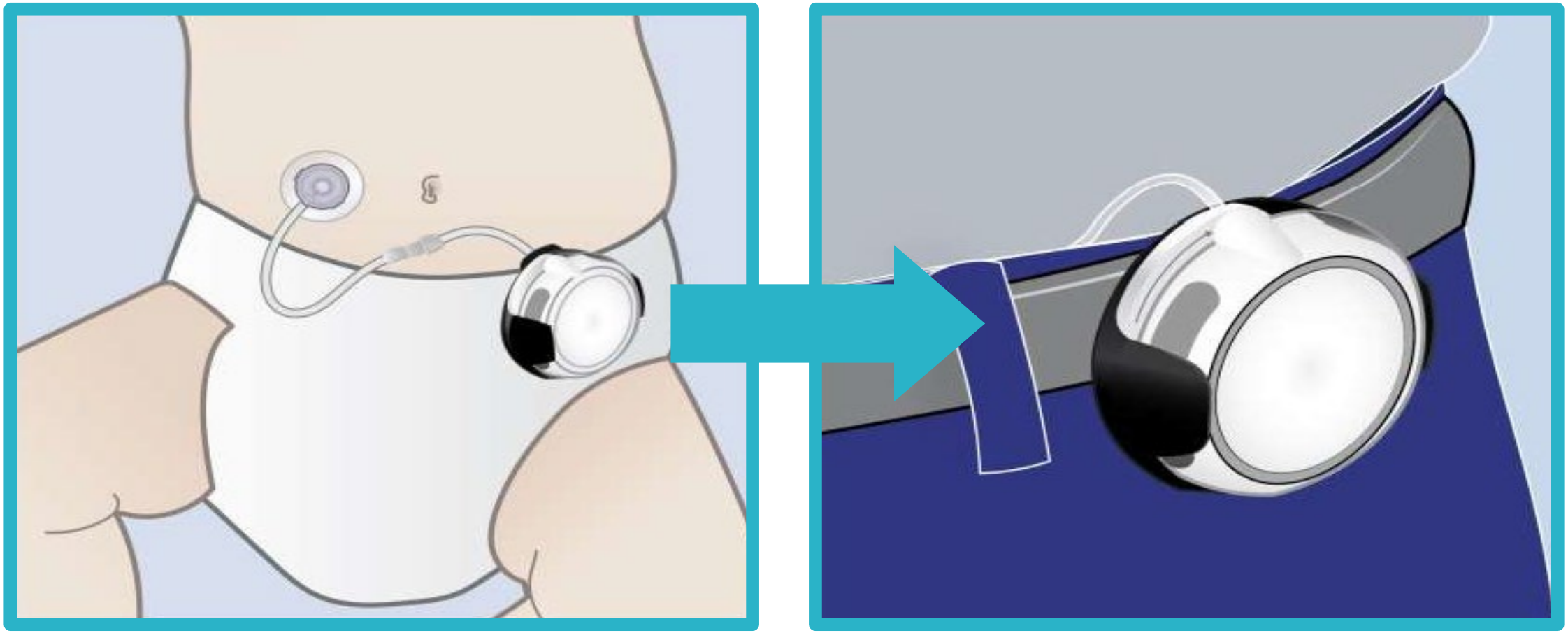
- Dasiglucagon is administered in an inpatient setting and documented in the progress notes

- The dose of dasiglucagon infusion should be individually determined and adjusted based on the patient's pharmacodynamic response (evaluated as plasma glucose/glycemic control, glucose needs (IV and/or gastric) and tolerability)[14]

- The recommended starting dose of dasiglucagon is 10 µg/h. Every 2 hours, the dose can be adjusted by 10 µg/h (2.5 µL/h). The 2-hour dose-adjustment interval will allow drug plasma levels to approach steady-state before dose adjustments[14]

# Dasiglucagon Infusion Overview

Dasiglucagon infusion is administered by continuous infusion via a subcutaneous catheter utilizing an infusion pump suitable for use with dasiglucagon[14]



DEKA R&D Corporation. DEKA Pump. User Manual.

# Summary

- Medical therapy of CHI consists of approved use of diazoxide in chronic dosage and off-label use of several other therapies[2–5]
- Only 41-64% of CHI patients respond to diazoxide (some only partially) and use of diazoxide carries risk of serious adverse reactions such as sodium and fluid retention[1]
- It is expected that dasiglucagon infusion will be indicated for prevention and treatment of hypoglycemia in pediatric patients 7 days of age and older with Congenital Hyperinsulinism (CHI)
- Dasiglucagon infusion 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[14]
- Hepatic stores of glycogen are necessary for Dasiglucagon infusion to produce an antihypoglycemic effect[14]

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