Health Technology Briefing
November 2021

Dasiglucagon for treating congenital hyperinsulinism

Company/Developer	Zealand Pharma AS

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27139	NICE ID: 10248	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Dasiglucagon is in clinical development for treating hypoglycaemia due to congenital hyperinsulinism (CHI) in children. CHI is an inherited disorder in which the body releases insulin even when it is not needed. Insulin is a hormone that helps control blood glucose (sugar) levels by driving glucose into the cells of the body. In hyperinsulinism, the increased amount of insulin causes hypoglycaemia (low blood glucose levels). The severity of CHI varies among patients and some patients develop episodes of hypoglycaemia shortly after birth. Repeated episodes of hypoglycaemia increase the risk of serious complications such as seizures (fits), mental disability, breathing difficulties and coma. CHI is a long-term debilitating condition because of the effects of long-term hypoglycaemia on the brain. There are limited effective treatments for CHI available and sometimes surgery is required if medical management does not keep a child's blood glucose levels at an acceptable level.

Dasiglucagon is a synthetic analogue of the natural hormone glucagon which counteracts the effects of insulin by raising blood glucose levels. It does this by breaking down glycogen (the form in which glucose is stored in the liver), and by stimulating the production of glucose in the liver. Dasiglucagon is administered subcutaneously (SC) as a single dose and is expected to prevent hypoglycaemic episodes and organ damage due to CHI. If licensed, dasiglucagon could provide a stable non-surgical treatment for hypoglycaemia due to congenital hyperinsulinism in children.

Proposed Indication

Congenital hyperinsulinism (CHI) in children aged 3 months to 12 years.[1]

Technology

Description

Dasiglucagon (ZP4207) is in a class of medications called glucagon receptor agonists. It works by causing the liver to release stored sugar to the blood.[2] It is a novel peptide analogue of human glucagon, and consists of 29 amino acids with 7 amino acid substitutions compared with native glucagon. Through the adjustment of sequence, dasiglucagon has showed enhanced solubility (≥20 mg/mL) and physicochemical stability relative to native hormones in aqueous formulation at physiological pH, maintaining the potency of native glucagon. Dasiglucagon rescues insulin-induced severe hypoglycaemia in patients with type 1 diabetes, as well as rapidly increasing blood glucose level with small doses under euglycaemic and hypoglycaemic conditions.[3]

In the phase III clinical trials (NCT03777176, NCT03941236), dasiglucagon SC infusion will be administered for 8 weeks starting at 10 µg/hr on top of standard of care.[1,4]

Key Innovation

Unlike other glucagon preparations, dasiglucagon has been modified to improve its stability in aqueous solution, making it more suitable for long-term use.[5] Pharmacokinetics studies have shown dasiglucagon to exhibit higher absorption and a longer plasma elimination half-life than traditional reconstituted glucagon.[3]

Dasiglucagon potentially provides an effective non-surgical approach for CHI treatment.[3]

Regulatory & Development Status

Dasiglucagon does not currently have Marketing Authorisation in the EU/UK for any indication.

Dasiglucagon is in phase II clinical trials for hypoglycaemia in Type 1 Diabetes Mellitus and hypoglycaemia in Roux-en-Y Gastric Bypass (RYGB) operated adults.[6]

Dasiglucagon was granted orphan designation in the EU in 2017 for the treatment of CHI.[5]

Patient Group

Disease Area and Clinical Need

CHI is an inherited disorder in which the body releases insulin even when it is not needed. Insulin is a hormone that helps control blood glucose levels by driving glucose into the cells of the body. In hyperinsulinism, the increased amount of insulin causes hypoglycaemia. The severity of CHI varies among patients and some patients develop episodes of hypoglycaemia shortly after birth. CHI is a long-term debilitating condition because of the effects of long-term hypoglycaemia on the brain, such as mental disability and seizures.[5] There are up to 14 known genetic causes of CHI and others where CHI is a feature of a syndrome. These can be inherited in an autosomal recessive or dominant manner. Abnormalities in the genes ABCC8 and KCNJ11 are the most common cause of severe CHI. Other rare causes are due to abnormalities in genes involved in regulating insulin secretion from the pancreas beta cells.[7] It can be difficult to identify symptoms of CHI because they are often confused with typical behaviours of infants.

Common symptoms include irritability, sleepiness, lethargy, excessive hunger and rapid heart rate. More severe symptoms, such as seizures and coma, can occur with a prolonged or extremely low blood sugar level. Common symptoms of low blood sugar in older children and adults include feelings of shakiness, weakness, or tiredness, confusion and rapid pulse.[8]

A recent study using data from 2007 to 2016 calculated a minimum incidence of 1 in 28,389 live births for CHI in the UK.[9] In England, in 2020-21, there were 816 finished consultant episodes in people aged <15 with a primary diagnosis of other hypoglycaemia which includes CHI (ICD-10 code: E16.1).[10] The annual cost of illness of CHI patients to the NHS has been estimated at £3,408,398.59 and average cost per patient is reported at £2124.95, with lack of response to first-line therapy and insulin-dependent diabetes mellitus development post-surgery (and associated healthcare costs) as major cost drivers.[11]

Recommended Treatment Options

Medical management of CHI aims to keep a child's blood glucose level stable at 3.5mmol/litre to 10mmol/litre. This can be managed by regular high carbohydrate feeds alongside medicines to reduce insulin secretion. Drugs used to reduce insulin secretion include: diazoxide, chlorothiazide, nifedipine (this is rarely used as it is not as effective as the other medications), glucagon and octreotide. Surgical treatment may be an option if medical management does not keep a child's blood glucose levels at an acceptable level. If a child has been diagnosed with focal CHI, usually following a PET scan, the area of the pancreas containing the defective beta cells can be removed in an operation under general anaesthetic.[7]

Clinical Trial Information

Trial	**ZP4207-17109; NCT03777176;** A Two-Period, Open-label Trial Evaluating the Efficacy and Safety of Dasiglucagon for the Treatment of Children With Congenital Hyperinsulinism **Phase III -** Completed **Location(s):** UK, USA, Germany, Israel **Study completion date:** October 2020
Trial Design	Randomised, parallel assignment, open label.
Population	N = 32; subjects with CHI; aged 3 months to 12 years old.
Intervention(s)	8 weeks of dasiglucagon treatment as SC infusion starting at 10 µg/hr on top of standard of care
Comparator(s)	4 weeks of standard of care and 4 weeks of dasiglucagon treatment as SC infusion starting at 10 µg/hr on top of standard of care
Outcome(s)	Primary outcome measure; • Hypoglycemia events [Time frame: Weeks 2-4] See trial record for full list of other outcomes.
Results (efficacy)	Dasiglucagon treatment resulted in 40-50% reductions in all measures of hypoglycemia assessed by blinded continuous glucose monitoring (CGM) (including number of events and time in hypoglycemia) compared to SOC treatment alone (all post-hoc p<0.05). These findings were seen both for hypoglycemia defined as glucose <70 mg/dL and glucose <54 mg/dL.[12]

Results (safety)	Treatment with dasiglucagon was associated with higher rates of gastrointestinal symptoms and skin changes. Overall, dasiglucagon was assessed to be safe and well tolerated.[12]

Trial	**ZP4207-17103; NCT04172441;** A Randomised Trial in 2 Parts: Double-Blind, Placebo-Controlled, Crossover Part 1 and Open-label Part 2, Evaluating the Efficacy and Safety of Dasiglucagon for the Treatment of Children With Congenital Hyperinsulinism **Phase II/III** - Recruiting **Location(s):** UK, USA, Germany, Israel **Primary completion date:** September 2021
Trial Design	Randomised, crossover assignment, quadruple-blind.
Population	N = 12; subjects with CHI; aged up to 364 days.
Intervention(s)	Dasiglucagon SC infusion and placebo See trial record for full details of dosage.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure; • Mean intravenous glucose infusion rate [Time frame: 36-48 hours after initiation of trial drug] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ZP4207-17106; NCT03941236;** An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children With Congenital Hyperinsulinism **Phase III** - Enrolling by invitation **Location(s):** UK, USA, Germany, Israel **Primary completion date:** March 2022
Trial Design	Single group assignment, open label.
Population	N = 40; subjects who completed treatment in either trial ZP4207-17103 or ZP4207-17109; aged 6 weeks to 13 years old.
Intervention(s)	Dasiglucagon treatment as SC infusion starting at 10 µg/hr on top of standard of care
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure; • Adverse Events [Time frame: Baseline through trial completion, up to 2 years] See trial record for full list of other outcomes.

Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of dasiglucagon is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Congenital Hyperinsulinism Service (Children). A17/S(HSS)/a.

Other Guidance

- Japanese Society of Pediatric Endocrinology. Clinical practice guidelines for congenital hyperinsulinism. 2017.[13]
- Pediatric Endocrine Society. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. 2015.[14]

Additional Information

Zealand Pharma AS did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. Open-label Trial Evaluating Efficacy and Safety of Dasiglucagon in Children With Congenital Hyperinsulinism. *Trial ID: NCT03777176*. 2018;Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03777176.

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5 European Medicines Agency. *Public summary of opinion on orphan designation: Synthetic glucagon analogue modified to contain 7 amino acid substitutions for the treatment of congenital hyperinsulinism* 2017. Report No.: (EU/3/17/1887). Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/17/1887-public-summary-opinion-orphan-designation-synthetic-glucagon-analogue-modified-contain-7-amino_en.pdf.

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9 Yau D, Laver TW, Dastamani A, Senniappan S, Houghton JAL, Shaikh G, et al. Using referral rates for genetic testing to determine the incidence of a rare disease: The minimal incidence of congenital hyperinsulinism in the UK is 1 in 28,389. *PLOS ONE*. 2020;15(2):e0228417. Available from: https://doi.org/10.1371/journal.pone.0228417.

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