Health Technology Briefing
June 2025

Avexitide for treating post-bariatric hypoglycaemia

Company/Developer	Amylyx Pharmaceuticals Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13235	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Avexitide is being developed as a treatment for post-bariatric hypoglycaemia (PBH), a condition that can affect adults following weight loss surgery, particularly gastric bypass procedures. PBH is caused by an overproduction of a hormone called insulin in response to meals, leading to frequent and sometimes severe drops in blood sugar levels (hypoglycaemia). These episodes can happen soon after eating and may cause symptoms such as dizziness, confusion, fainting, or even seizures. PBH occurs because, after surgery, food moves more quickly through the digestive system, triggering an exaggerated release of a hormone called glucagon like peptide 1 (GLP-1). This hormone stimulates the pancreas to release too much insulin. Repeated hypoglycaemic episodes can significantly affect quality of life and may pose long-term health risks. Currently, there are no approved treatments specifically for PBH, and management options are limited.

Avexitide is a first-in-class inhibitor of GLP-1 receptor activity that works by blocking the action of GLP-1, thereby reducing inappropriate insulin secretion (release) and helping to stabilise blood sugar levels. It is administered once daily as a subcutaneous injection (under the skin). If licensed, avexitide could offer the first targeted therapy for PBH, potentially improving outcomes and quality of life for affected patients.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.
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Proposed Indication

Treatment of adult patients with post-bariatric hypoglycaemia (PBH).[1]

Technology

Description

Avexitide (Exendin 9-39), is a first-in-class inhibitor of glucagon-like peptide-1 (GLP-1) receptor activity, is a 31-amino acid peptide with a free amino group at the N-terminus and an amidated C-terminus.[1] Avexitide is designed to bind to the GLP-1 receptor on pancreatic islet beta cells and inhibit the effect of GLP-1 to mitigate hypoglycaemia by decreasing insulin secretion and stabilising blood glucose levels. In PBH, excessive GLP-1 can lead to the hypersecretion of insulin and subsequent debilitating hypoglycaemia events.[2]
Avexitide is currently in clinical development for the treatment of patients with PBH. In the ongoing phase III clinical trial (LUCIDITY, NCT06747468), adult patients post Roux-en-Y gastric bypass (RYBH) are receiving avexitide 90 mg via subcutaneous (SC) injection, in the morning at least 60 minutes before the morning meal, through the duration of the treatment and open label extension (OLE) periods.[1]

Key Innovation

There are currently no approved pharmaceutical treatment options for PBH, so there is a need to develop safe, effective, and targeted therapies for people with PBH.[3] While medical nutrition therapy is first-line, many patients with severe PBH do not respond adequately. Off-label pharmacotherapies such as acarbose, diazoxide, and somatostatin analogues have shown limited and inconsistent efficacy, and invasive surgical options carry significant risks. This highlights a clear innovation gap in safe and targeted therapies.[2] Avexitide addresses this gap and has been shown under experimental conditions to effectively prevent postprandial hyperinsulinemia and hypoglycaemia and reduce neuroglycopenic symptoms in patients with PBH.[3]

If licensed, avexitide would be the first NICE recommended treatment option for patients with severe PBH, as there are currently no NICE approved treatment options for this condition.[4]

Regulatory & Development Status

Avexitide does not currently have Marketing Authorisation in the EU/UK for any indication.
Avexitide is not currently in phase II/III clinical development for any other indications.
Avexitide has the following regulatory designations/awards;[5-8]

- An orphan drug designation from the US FDA for the treatment of hyperinsulinemic hypoglycemia, encompassing both PBH and congenital hyperinsulinism, granted in 2016.
- An orphan drug designation from the EMA for the treatment of hyperinsulinemic hypoglycaemia, covering both PBH and CHI, granted in 2019.
- A breakthrough therapy designation by the US FDA for both PBH and CHI, as well as a rare paediatric disease designation for CHI, both granted in 2021.

Patient Group

Disease Area and Clinical Need

Common surgical treatments for patients living with obesity include RYGBP and sleeve gastrectomy. [9] However, RYGBP, SG, and other types of bariatric surgery can cause complications and risks such as PBH

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(also known as late dumping syndrome).[10] It is characterised by hyperglycaemia (when the level of glucose in the blood is too high) followed by hyperinsulinemia (when the blood as abnormally high levels of insulin) and hypoglycaemia.[9] Characteristically, PBH appears between 1 and 3 years after surgery and 2–4 h after eating.[10] Repeated hypoglycaemic episodes can significantly affect quality of life and may pose long-term health risks.[11] The symptoms, usually linked to a high intake of carbohydrates, are often non-specific, such as dizziness, fatigue, and palpitations but can be due to severe hypoglycaemia which may also cause syncope and seizures. Some patients also experience abdominal pain.[9]

In patients who have undergone gastric surgery, an estimated 20% to 50% of patients have symptoms of dumping syndrome. Patients develop severe symptoms approximately at a rate of 1 to 5%. Early dumping syndrome appears to have a higher incidence compared to LDS.[12] In England, approximately 10,000 bariatric surgeries are performed each year (around 4,500 within the NHS and an additional 5,000–6,000 privately). Based on prevalence estimates, 2,000 to 5,000 patients each year may experience dumping syndrome symptoms, with 100 to 500 developing more severe hypoglycaemic episodes associated with late dumping syndrome.[13]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) does not provide specific guidelines exclusively for PBH.

However, NICE recommends that individuals who have undergone bariatric surgery should receive a structured follow-up care package within the bariatric surgery service for a minimum of 2 years.[14] In general, NICE recommends adults with symptoms of hypoglycaemia who have a blood-glucose concentration greater than 4 mmol/litre, should be treated with a small carbohydrate snack such as a slice of bread or a normal meal, if due. In an emergency, if the patient has a decreased level of consciousness caused by hypoglycaemia, intramuscular glucagon can be given by a family member or friend who has been shown how to use it. If glucagon is not effective after 10 minutes, glucose 10% intravenous infusion should be given.[15]

Clinical Trial Information

Trial	**PREVENT, NCT03373435;** A phase 2, multicentre, randomized, single-blind, placebo-controlled cross-over study to assess the efficacy and safety of exendin 9-39 in patients with post bariatric hypoglycaemia **Phase II** – Completed **Location(s):** USA **Study Completion date:** March 2019
Trial Design	Randomised, crossover assignment, single blind
Population	N=18; aged 18 years to 65 years; patients with RYGB surgery performed ≥12 months prior and with the diagnosis of PBH
Intervention(s)	Patients received two dose regimens of avexitide and one placebo
Comparator(s)	Placebo
Outcome(s)	Primary outcome measure: • Postprandial Glucose Nadir [Time frame: 3 hours following a liquid meal]

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	○ Plasma glucose nadir occurring within 3 hours of mixed-meal tolerance testing See trial record for full list of other outcomes.
Results (efficacy)	Compared with placebo, avexitide 30 mg twice daily and 60 mg once daily raised the glucose nadir by 21% (P = 0.001) and 26% (P = 0.0002) and lowered the insulin peak by 23% (P = 0.029) and 21% (P = 0.042), respectively. These changes corresponded to a 50% and 75% reduction in the number of participants requiring rescue intervention during the mixed-meal tolerance test. Significant reductions in the rates of Level 1 to Level 3 hypoglycaemia were observed. Level 1 hypoglycaemia was defined as self-monitored blood glucose (SMBG) below 70 mg/dL, Level 2 as SMBG below 54 mg/dL, and Level 3 as a severe event characterised by altered mental and/or physical function requiring assistance. Continuous glucose monitoring demonstrated reductions in hypoglycaemia without inducing clinically relevant hyperglycaemia.[16]
Results (safety)	Avexitide was well tolerated, with no increase in adverse events compared with placebo.[16]
Clinical Trial Information	
Trial	NCT04652479; A phase 2, open-label, cross-over study to assess the safety and efficacy of avexitide in acquired hyperinsulinemic hypoglycaemia **Phase II –** Completed **Location(s):** USA **Study Completion date:** June 2022
Trial Design	Randomised, crossover assignment, open label
Population	N=17; aged 18 years and older; patients with history of recurrent hypoglycaemia occurring after bariatric or upper-gastrointestinal surgery (RYGB, vertical sleeve gastrectomy, gastrectomy, esophagectomy, or Nissen fundoplication) at least 12 months prior to the start of Screening
Intervention(s)	Avexitide 45 mg twice daily then avexitide 90 mg once daily or avexitide 90 mg once daily then avexitide 45 mg twice daily.
Comparator(s)	-
Outcome(s)	Primary outcome measure: • Diurnal level 2 hypoglycaemia events (ada, <54 mg/dl) as measured by CGM in patients with severe HH [time frame: run-in period (14 days), treatment period 1 (14 days), and treatment period 2 (14 days)] See trial record for full list of other outcomes.
Results (efficacy)	Interim analysis at approximately 50% completion (n=8) demonstrated statistically significant improvements across all primary and secondary endpoints. Compared with medical nutrition therapy alone, avexitide reduced the rate of Level 1 hypoglycaemia (self-monitored blood glucose <70 mg/dL) by 66%

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	(p=0.022) and 74% (p=0.010); Level 2 hypoglycaemia (<54 mg/dL) by 70% (p=0.003) and 93% (p=0.001); and Level 3 hypoglycaemia (defined as a severe event characterised by altered mental and/or physical function requiring assistance) by 77% (p=0.002) and 93% (p=0.001), respectively.
Results (safety)	Avexitide was well tolerated across both dosing regimens, with no increase in adverse events reported. The favourable safety and tolerability profile observed in earlier studies was maintained, supporting further investigation of higher doses for enhanced therapeutic benefit.
Clinical Trial Information	
Trial	**LUCIDITY,** NCT06747468**,** A phase 3 multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of avexitide in participants with post-bariatric hypoglycaemia **Phase III** – Active, recruiting **Location(s):** USA **Primary completion date:** March 2026
Trial Design	Randomised, parallel assignment, double blind
Population	N=75; aged 18 years and older; patients with clinical diagnosis of PBH-defined as history of recurrent hypoglycaemia with onset after surgery and having ruled out other causes of hypoglycaemia as per investigator judgment
Intervention(s)	Avexitide (90 mg via SC injection) will be taken once per day, in the morning at least 60 minutes before the morning meal, through the duration of the treatment and open-label extension periods.
Comparator(s)	Placebo will be taken once per day, via SC injection, in the morning at least 60 minutes before the morning meal, through the duration of the treatment period.
Outcome(s)	Primary outcome measure: • Composite rate of Level 2 and Level 3 hypoglycaemic events [Time frame: During the double-blind treatment period (approximately 16 weeks)] • Safety and tolerability of avexitide [Time frame: During the double-blind treatment period (approximately 16 weeks)] • Incidence of anti-drug antibodies[Time frame: During the double-blind treatment period (approximately 16 weeks)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost
The cost of avexitide is not yet known

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Relevant Guidance

NICE Guidance

- NICE clinical guideline. Overweight and obesity management (NG246). January 2025.
- NICE clinical guideline. Type 1 diabetes in adults: diagnosis and management (NG17). August 2015. Last updated August 2022.
- NICE clinical guideline. Type 2 diabetes in adults: management (NG28). December 2015. Last updated June 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2023/24 Commissioning recommendations following the national assessment of blood glucose and ketone meters, testing strips and lancets.

Other Guidance

- Society for Endocrinology. Guidelines for the diagnosis and management of post-bariatric hypoglycaemia. 2024.[10]
- Southeast London Integrated Medicines Committee (SEL IMOC). Guidelines for medicines optimisation in bariatric and metabolic surgery. 2024.[17]
- Fried M, Yumuk V, Oppert JM, et Al. European Association for the Study of Obesity; International Federation for the Surgery of Obesity - European Chapter. Interdisciplinary European Guidelines on metabolic and bariatric surgery. 2013.[18]

Additional Information

Amylyx Pharmaceuticals, Inc. 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.

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