Health Technology Briefing
February 2024

Linaclotide acetate for treating Chronic idiopathic constipation

Company/Developer	AbbVie

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 37475	NICE ID: Not available	UKPS ID: 671457

Licensing and Market Availability Plans

Currently in Phase III clinical development

Summary

Linaclotide acetate is currently in clinical development for the treatment of adults with chronic idiopathic constipation (CIC). Constipation is defecation that is problematic because of infrequent and/or hard stools, difficulty passing stools (often involving straining), or the sensation of incomplete emptying or anorectal blockage. Chronic is when the symptoms are present for at least three months. CIC is a health condition in which the person experiences long-time symptoms of constipation, but healthcare providers cannot identify a cause through standard tests. CIC disproportionately affects women, the elderly, and individuals of lower socioeconomic status. Other common risk factors of constipation include reduced caloric intake, sedentary lifestyle, decreased fibre intake, and usage of anti-inflammatory agents.

Linaclotide is a first-in-class and orally administered substance. It attaches to some receptors in the gut called guanylate cyclase C and works by increasing intestinal fluid secretion, which helps ease the passage of stools and relieve the symptoms of constipation. If licenced, linaclotide acetate will offer an additional treatment option for adults with CIC.

Proposed Indication

Treatment of adult patients with chronic idiopathic constipation (CIC).[1-3]

Technology

Description

Linaclotide acetate (Constella) is a first-in class minimally absorbed Guanylate Cyclase-C (GC-C) receptor agonist with visceral analgesic and secretory activities.[4,5] Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family. Both linaclotide and its active metabolite bind to the GC-C receptor, on the luminal surface of the intestinal epithelium. Through its action at GC-C, linaclotide has been shown to reduce visceral pain and increase colonic transit in humans.[5] It works by increasing intestinal fluid secretion, which helps ease the passage of stools and relieve the symptoms of constipation.[6]

Linaclotide acetate is currently in clinical development for the treatment of adults with CIC. In the phase III clinical trials (NCT00765882, NCT00730015, and NCT02291679) patients received oral capsule of linaclotide 290 microgram, 145 microgram or 72 micrograms daily for twelve weeks.[1-3]

Key Innovation

CIC has a great impact on the quality of life.[7] The reduced quality of life and increased costs associated with CIC indicate unmet therapeutic need. Hence, a need to identify effective therapeutic options. Linaclotide is a first in class GC-C receptor agonist.[4] This therapeutic peptide has negligible bioavailability following oral administration and a favourable safety profile.[8] Studies on basis of meta-analysis shows that linaclotide improves bowel function and reduces abdominal pain and overall severity of irritable-bowel syndrome with constipation (IBS-C) or chronic constipation (CC), compared with placebo.[9,10] If licenced, linaclotide acetate will offer an additional treatment option for adults with CIC.

Regulatory & Development Status

Linaclotide has Marketing Authorisation in the UK/EU for the treatment of moderate to severe irritable-bowel syndrome (IBS) with constipation in adults.[11]

Linaclotide is in the phase II/III clinical development for these indications:[12]

- Functional constipation
- Functional dyspepsia
- Colorectal cancer
- Diabetes mellitus

Patient Group

Disease Area and Clinical Need

Constipation is a heterogeneous, symptom-based disorder. Patients describe defecation that is problematic because of infrequent and/or hard stools, difficulty passing stools (often involving straining), or the sensation of incomplete emptying or anorectal blockage.[13]. CIC is a health condition in which you experience chronic symptoms of constipation, but healthcare providers cannot identify a cause through standard diagnostic tests.[14] To be diagnosed with CIC, symptoms must not meet the criteria for irritable bowel syndrome (IBS) and be present for at least three months, with onset at least six months prior to diagnosis.[14] In addition to primary chronic symptoms, patients with CIC may also report experiencing abdominal pain or discomfort, bloating and gas pain. CIC has been found to affect all individuals in the general population, it disproportionately affects women, the elderly, and individuals of lower socioeconomic status. Other common risk factors of constipation include reduced caloric intake, sedentary lifestyle, decreased fibre intake, and usage of anti-inflammatory agents.[15]

The reported prevalence rates of constipation in the UK vary widely between studies, with figures ranging from 4% to 20%.[16] In England in 2022-2023, there were 77,890 finished consultant episodes (FCE), and 61,167 hospital admissions with constipation (ICD10 codes K590), resulting in 146,008 FCE bed days and 17,481 day cases[17]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends drug treatment with oral laxatives in chronic constipation using a stepped approach. The initial treatment being with a bulk-forming laxative such as ispaghula. If stools remain hard or difficult to pass, add or switch to an osmotic laxative, such as a macrogol. If a macrogol is ineffective or not tolerated, offer treatment with lactulose second line. If stools are soft but difficult to pass or there is a sensation of inadequate emptying, add a stimulant laxative.[18] NICE also recommends prucalopride as an option for the treatment of chronic constipation only in women for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief of symptoms and invasive treatment is being considered.[19]

Clinical Trial Information

Trial	NCT00765882, A phase III, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks in patients with chronic constipation. **Phase III**- Completed **Location(s):** United States & Canada **Study completion date:** August 2009
Trial Design	Randomised, parallel assignment, quadruple blinding
Population	N=633; adult patients who meet protocol criteria for CC; reports less than 3 bowel movements per week, straining, lumpy or hard stools, and/or sensation of incomplete evacuation during greater than 25% of bowel movement (BM) and with no significant findings on colonoscopy
Intervention(s)	Oral administration of 290 micrograms of Linaclotide once daily for 12 weeks. Oral administration of 145 micrograms of Linaclotide once daily for 12 weeks
Comparator(s)	Matching placebo
Outcome(s)	Primary Outcome(s):

	Complete Spontaneous Bowel Movement (CSBM) Overall Responder [Time frame: change from baseline to week 12]. See trial record for full list of outcomes.
Results (efficacy)	For Trials 303 and 01, respectively, the primary end point was reached by 21.2% and 16.0% of the patients who received 145 µg of linaclotide and by 19.4% and 21.3% of the patients who received 290 µg of linaclotide, as compared with 3.3% and 6.0% of those who received placebo (P<0.01 for all comparisons of linaclotide with placebo). Improvements in all secondary end points were significantly greater in both linaclotide groups than in the placebo groups.[20]
Results (safety)	The incidence of adverse events was similar among all study groups, with the exception of diarrhoea, which led to discontinuation of treatment in 4.2% of patients in both linaclotide groups.[20]

Clinical Trial Information	
Trial	NCT00730015; A phase 3, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks followed by a 4-week randomized withdrawal period in patients with chronic constipation. **Phase III**- Completed **Location(s):** United States **Study completion date:** October 2009
Trial Design	Randomised, parallel assignment, quadruple blinding
Population	N=643; adults patients who meet protocol criteria for CC; reports less than 3 bowel movements per week, straining, lumpy or hard stools, and/or sensation of incomplete evacuation during greater than 25% of bowel movement (BM) and with no significant findings on colonoscopy.
Intervention(s)	Oral administration of 290 micrograms of Linaclotide once daily for 12 weeks. Oral administration of 145 micrograms of Linaclotide once daily for 12 weeks
Comparator(s)	Matching placebo
Outcome(s)	Primary Outcome(s): • Complete Spontaneous Bowel Movement (CSBM) Overall Responder [Time frame: change from baseline to week 12].
Results (efficacy)	For Trials 303 and 01, respectively, the primary end point was reached by 21.2% and 16.0% of the patients who received 145 µg of linaclotide and by 19.4% and 21.3% of the patients who received 290 µg of linaclotide, as compared with 3.3% and 6.0% of those who received placebo (P<0.01 for all comparisons of linaclotide with placebo). Improvements in all secondary end points were significantly greater in both linaclotide groups than in the placebo groups[20]
Results (safety)	The incidence of adverse events was similar among all study groups, with the exception of diarrhoea, which led to discontinuation of treatment in 4.2% of patients in both linaclotide groups[20]

Clinical Trial Information	
Trial	NCT02291679; A phase 3, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide (72 ug or 145 ug) administered orally for 12 weeks to patients with chronic idiopathic constipation **Phase III:** Completed **Location(s):** United States **Study completion date:** August 2015
Trial Design	Randomised, parallel assignment, quadruple blinding
Population	N=1223; adults patient who meets protocol criteria for CIC that reports less than 3 bowel movements per week, straining, lumpy or hard stools, and/or sensation of incomplete evacuation during greater than 25% of bowel movement (BM) and with no significant findings on colonoscopy.
Intervention(s)	Oral administration of 75 micrograms of Linaclotide once daily for 12 weeks. Oral administration of 145 micrograms of Linaclotide once daily for 12 weeks
Comparator(s)	Matching placebo
Outcome(s)	Primary Outcome(s): • Percentage of 12-Week CSBM Overall Responders [Time frame: Week 12] • Complete Spontaneous Bowel Movement (CSBM) Overall Responder [Time frame: Change from Baseline to Week 12]
Results (efficacy)	The primary endpoint was met by 13.4% of linaclotide 72-µg patients vs. 4.7% of placebo patients (P<0.0001, odds ratio=3.0; statistically significant controlling for multiplicity). Sustained response was achieved by 12.4% of linaclotide 72-µg patients vs. 4.2% of placebo patients (nominal P<0.0001). Linaclotide 72-µg patients met 9-of-10 secondary endpoints vs. placebo (P<0.05; abdominal discomfort, P=0.1028). Patients treated with linaclotide 145 µg also improved CIC symptoms for the primary (12.4%) and sustained responder endpoint parameters (11.4%) and for all 10 of the secondary endpoint parameters including abdominal discomfort (P<0.05).[21]
Results (safety)	Diarrhoea, the most common adverse effect was mild in most instances and resulted in discontinuation of 0, 2.4%, and 3.2% of patients in the placebo, linaclotide 72-µg, and linaclotide 145-µg groups, respectively.[21]

Estimated Cost
The NHS indicative price for a pack of 28 x290 microgram linaclotide capsule is £37.56.[22]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Prucalopride for the treatment of chronic constipation in women (TA211). December 2010

NHS England (Policy/Commissioning) Guidance

- NHS Dudley Clinical Commissioning Group. Guidance for the Prevention and Management of Constipation in Adults. 2018
- NHS Herts Valleys Clinical Commissioning Group. Guideline for the management of chronic constipation in adults. 2014

Other Guidance

- National Institute for Health and Care Excellence (NICE): Clinical Knowledge Summary (CKS): Constipation in adults. 2024.[18]
- American Gastroenterological Association: American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. 2023.[23]
- European society of neurogastroenterology and motility: Guidelines on functional constipation in adults. 2019.[24]
- Jordi Serra, Juanjo Mascort-Roca, Mercè Marzo-Castillejo et al: Clinical practice guidelines for the management of constipation in adults. Part 2: Diagnosis and treatment. 2017.[25]
- World Gastroenterology Organisation: Global guideline: Constipation–a global perspective. 2011.[26]

Additional Information

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