National Institute for Health Research

**NIHR Innovation Observatory**
**Evidence Briefing: February 2018**

# Tenapanor for irritable bowel syndrome with constipation

NIHRIO (HSRIC) ID: 6704 NICE ID: 9736

## LAY SUMMARY

Irritable bowel syndrome with constipation (IBS-C) is a common condition that affects the digestive system (the gut). Symptoms may include stomach cramps, bloating and constipation. The exact cause is unknown, and IBS-C is often a lifelong condition. While there is no cure, dietary changes and the use of medication can often help control symptoms. IBS-C has been linked to issues of digestion, stress, and a family history of the condition. IBS-C affects approximately 7-21% of the population globally and is a significant health care burden impacting health and quality of life of affected individuals. Treatment of IBS-C is particularly challenging as symptoms fluctuate over time and are often recurrent and resistant to administered drugs.

Tenapanor is an oral drug under development for the treatment of IBS-C. It acts directly in the gut to reduce absorption of sodium. Sodium increases fluid in the gut, loosening stool, and alleviating constipation. If licensed, tenapanor may offer an additional treatment option for IBS-C by increasing intestinal fluid content, accelerating gastrointestinal (GI) motility, and providing relief from symptomatic pain and discomfort. By acting directly in the gut, tenapanor also has a potential advantage of having minimal side effects.



*This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.*

## TARGET GROUP

Irritable bowel syndrome (constipation predominant)

## TECHNOLOGY

## DESCRIPTION

Tenapanor, a small molecule with minimal systemic availability, is an inhibitor of Na+/H+ exchanger 3 (NHE3) that acts locally in the apical membrane of intestinal epithelial cells. NHE3 contributes to the uptake of sodium ions and water from the intestinal lumen, with sodium/fluid and phosphate imbalances playing a key role in stool consistency in constipation-related disorders including irritable bowel syndrome (IBS).[1] Tenapanor exhibits a mechanism of action that acts by inhibiting, or blocking, the NHE3 transporter in the gastrointestinal (GI) tract to reduce the absorption of dietary sodium, leading to increased sodium within the gut. This sodium increases fluid in the gut, loosening stool, thereby alleviating constipation.[8] In animal models, tenapanor has been shown to both increase GI motility and decrease abdominal pain. This tenapanor-induced reduction in visceral pain is thought to occur through the inhibition of TRPV-1 dependent pain signaling in neurons lining the GI tract.[2]

In a phase II, double-blind study, patients with IBS-C were randomised to receive tenapanor 5 mg, 20 mg, or 50 mg twice per day or placebo twice per day for 12 weeks.[3] In phase III studies patients received 50 mg of tenapanor twice per day or placebo comparator for 12 weeks (T3MPO-1) or 26 weeks (T3MPO-2).[4,5] A long-term phase III safety study of 50 mg of tenapanor twice daily for 52-55 weeks was completed January 2018 (T3MPO-3).[8]

Tenapanor does not currently have Marketing Authorisation in the EU for any indication. Tenapanor is also in phase III clinical development in the United States for hyperphosphatemia in patients with chronic kidney disease on dialysis.[6]

## INNOVATION and/or ADVANTAGES

IBS-C therapy is particularly difficult and challenging, as symptoms fluctuate over time and are often recurrent and resistant to administered drugs. The non-systemic action of tenapanor constitutes a significant advantage by minimising possible adverse effects or drug–drug interactions. If licensed, tenapanor will offer a first-in-class additional treatment option for IBS-C patients by increasing intestinal fluid content, accelerating GI motility, and providing relief from symptomatic pain and discomfort.[7]

## DEVELOPER

Ardelyx Inc

## REGULATORY INFORMATION/MARKETING PLANS

The company anticipate submitting a New Drug Application to the US FDA for IBS-C in the second half of 2018.[8] Regulatory information/marketing plans for the EU are currently unknown.

# PATIENT GROUP

## BACKGROUND

IBS is the name given to a longstanding illness consisting of frequent abdominal discomfort and bowel symptoms that cannot be explained by any other disease. Common IBS symptoms include: stomach pain or cramps, bloating, diarrhoea, and constipation. Constipation-predominant IBS (IBS-C) is characterized by recurrent abdominal pain and prolonged gastrointestinal transit.[10] The pathophysiology of IBS is not completely understood but appears to involve genetics, the gut microbiome, immune activation, altered intestinal permeability, and brain-gut interactions.[2]

Treatment strategies for IBS may include both non-pharmacologic and pharmacologic approaches. Lifestyle modifications that aim to improve exercise, sleep, diet, and stress may be warranted. Recent data suggest that a gluten-free diet and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may benefit some patients.[2]IBS is a functional disease that significantly reduces quality of life, is associated with depression and suicidal ideation, and patients often have an increased frequency of invasive procedures and surgery.[9]

## CLINICAL NEED and BURDEN OF DISEASE

IBS is a significant health care burden, irrespective of setting or geography, affecting approximately 7-21% of the population globally. IBS-C accounts for approximately one third of all cases of IBS. There is no universal diagnostic criteria or standardised therapy for IBS and/or its subtypes, and IBS is not considered a cause of death as there is no evidence that the disease is associated with an increased mortality risk. Prevalence estimates vary both nationally and internationally, as many patients do not seek medical attention for symptoms indicative of IBS. In the UK, it is estimated 30-50% of symptomatic individuals seek primary medical care.[9]

NICE estimates IBS affects between 10-20% of the general population, occurs in young people in their twenties, and is twice as common in women as in men.[10] In 2016-17 NHS England hospital admitted patient statistics note 7,037 finished consultant episodes (2,260 male and 4,777 female) categorised under irritable bowel syndrome (ICD-10 code: K58.0) resulting in 6,154 admissions and 5,656 bed days.[11] The population likely to be eligible to receive tenapanor could not be estimated from available published sources.

# PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal. Eluxadoline for treating irritable bowel syndrome with diarrhoea (TA471). August 2017.
- NICE technology appraisal. Lubiprostone for treating chronic idiopathic constipation (TA318). July 2014
- NICE technology appraisal. Prucalopride for the treatment of chronic constipation in women (TA211). December 2010.
- NICE clinical guideline. Irritable bowel syndrome in adults: diagnosis and management (CG61). April 2017.

- NICE clinical guideline. Faecal incontinence in adults: management (CG49). June 2007
- NICE quality standard. Irritable bowel syndrome in adults (QS114). February 2016.
- NICE quality standard. Coeliac disease (QS134). October 2016
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015
- NICE quality standard. Faecal incontinence in adults (QS54). February 2014
- NICE diagnostic guidance. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). October 2013.
- NICE diagnostic guidance. SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection (DG7). November 2012.
- NICE guidelines. Coeliac disease: recognition, assessment and management (NG20). September 2015.
- NICE guidelines. Irritable bowel syndrome in adults: diagnosis and management (CG61). February 2008.
- NICE evidence summary. Bile acid malabsorption: colesevelam (ESUOM22). October 2013.
- NICE evidence summary. Irritable bowel syndrome with constipation in adults: linaclotide (ESNM16). April 2013.

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. Excellence in continence care: Practical guidance for commissioners, providers, health and social care staff and information for the public. November 2015.

## OTHER GUIDANCE

- Guideline on the Pharmacological Management of Irritable Bowel Syndrome. American Gastroenterological Association Institute. 2014[12]
- Guidelines on the irritable bowel syndrome: mechanisms and practical management. British Society of Gastroenterology. 2007[13]

## CURRENT TREATMENT OPTIONS

Treatment of constipation-predominant IBS (IBS-C) presents significant challenges, owing to the diverse and dynamic nature of symptoms that accompany a symptom-based diagnosis of diverse pathogenesis. Laxatives, dietary fibre, and stool softeners have traditionally been recommended in the treatment of IBS-C, with more recent therapies including guanylate cyclase-C receptor agonist linaclotide and selective chloride channel activator lubiprostone. Like tenapanor, linaclotide and lubiprostone are minimally absorbed and act in the gastrointestinal tract.[14] Though both have been shown to be more effective than placebo in large randomised controlled trials, fewer than half of patients with IBS-C achieved the primary end points of improvements in stool frequency and abdominal pain, meriting the need for further therapeutic options.[15,16]

Current NICE guidelines recommend laxatives and/or antispasmodics as first-line pharmacological treatment for IBS-C. Second-line treatment may include linaclotide only if optimal or maximum tolerated doses of previous laxatives have not proved beneficial, and constipation has persisted for a minimum of 12 months. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) may also be considered as second-line treatment for IBS-C if laxatives or antispasmodics have not proven beneficial.[17] Guidelines for the management of IBS by The American Gastroenterological

Association Institute recommend using laxatives, linaclotide, and lubiprostone over no drug treatment in patients with IBS-C.[12]

## EFFICACY and SAFETY

| | |
|---|---|
| **Trial** | T3MPO-3, NCT02727751; adults ≥18; tenapanor; phase III |
| **Sponsor** | Ardelyx Inc |
| **Status** | Complete but unpublished |
| **Source of Information** | Company press release[18], trial registry[19] |
| **Location** | USA |
| **Design** | Interventional, single group assignment |
| **Participants** | n=240; aged 18 to 75 years; IBS-C; completion of all 16 weeks of T3MPO-1 or all 26 weeks of T3MPO-2 |
| **Schedule** | 50 mg of tenapanor twice daily for 52-55 weeks total |
| **Follow-up** | During the treatment period of up to 39-weeks, subjects returned for study visits approximately every 13 weeks. Subjects underwent safety assessments at these visits, which may have included a physical exam, ECG, vital signs, and clinical labs. |
| **Primary Outcomes** | Incidence of Treatment - Emergent Adverse Events [Safety and Tolerability] [Time Frame: 52-55 weeks] |
| **Secondary Outcomes** | None |
| **Key Results** | Results from T3MPO-3 showed a mean tenapanor compliance rate of approximately 98 percent, and that tenapanor was well-tolerated among the 240 patients treated. |
| **Adverse effects (AEs)** | Of patients treated, 9.2 percent reported experiencing diarrhoea, with only 1.7 percent of patients discontinuing treatment due to diarrhoea. The overall discontinuation rate in the study was just 2.1 percent. |
| **Expected reporting date** | Not reported |

| | |
|---|---|
| **Trial** | T3MPO-2, NCT02686138; adults ≥18; tenapanor vs placebo; phase III |
| **Sponsor** | Ardelyx Inc |

| | |
|---|---|
| **Status** | Complete but unpublished |
| **Source of Information** | Company[20], trial registry[5] |
| **Location** | USA |
| **Design** | Randomized, double-blind, placebo-controlled |
| **Participants** | n=629; aged 18 to 75 years; IBS-C; must meet definition of IBS-C using Rome III criteria and who have active disease as determined after a two-week screening period |
| **Schedule** | Randomised to 50 mg of tenapanor twice daily for 26 week treatment period or placebo comparator (1:1) |
| **Follow-up** | Not stated |
| **Primary Outcomes** | • Percentage of Subjects with Overall Response for 6 out of 12 Weeks [Time Frame: First 12 weeks] |
| **Secondary Outcomes** | • Percentage of Subjects with Overall Complete Spontaneous Bowel Movement (CSBM) Response for 6 out of 12 Weeks [Time Frame: First 12 weeks]<br>• Percentage of Subjects with Overall Abdominal Pain Response for 6 out of 12 Weeks [Time Frame: First 12 weeks]<br>• Percentage of Subjects with Overall Response for 13 out of 26 Weeks [Time Frame: 26 weeks]<br>• Percentage of Subjects with Overall Complete Spontaneous Bowel Movement (CSBM) Response for 13 out of 26 Weeks [Time Frame: 26 weeks]<br>• Percentage of Subjects with Overall Abdominal Pain Response for 13 out of 26 Weeks [Time Frame: 26 weeks]<br>• Percentage of Subjects with Overall Response for 9 out of 12 Weeks [Time Frame: First 12 weeks ]<br>• Percentage of Subjects with Overall Complete Spontaneous Bowel Movement (CSBM) Response for 9 out of 12 Weeks [Time Frame: First 12 weeks]<br>• Percentage of Subjects with Overall Abdominal Pain Response for 9 out of 12 Weeks [Time Frame: First 12 weeks] |
| **Key Results** | The primary endpoint, the combined responder rate for six of 12 weeks, showed that a greater proportion of tenapanor-treated patients compared to placebo-treated patients (36.5% vs. 23.7%) had at least a 30% reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements in the same week for at least six of the 12 weeks of the treatment period. |
| **Adverse effects (AEs)** | Tenapanor was well-tolerated in treated patients. |

| | |
|---|---|
| **Expected reporting date** | Not reported |

| | |
|---|---|
| **Trial** | T3MPO-1, NCT02621892; adults ≥18; tenapanor vs placebo; phase III |
| **Sponsor** | Ardelyx Inc |
| **Status** | Complete but unpublished |
| **Source of Information** | Company press release[21], trial registry[4] |
| **Location** | USA |
| **Design** | Randomised, double-blind, placebo-controlled |
| **Participants** | n=629; aged 18 to 75 years; IBS-C; must meet definition of IBS-C using Rome III criteria |
| **Schedule** | Randomised to 50 mg of tenapanor twice daily for 12 week treatment period or placebo comparator followed by a 4 week randomized withdrawal period; in the withdrawal period, experimental arm randomized to either 50 mg of tenapanor twice daily or placebo twice daily (1:1) and the placebo arm assigned to receive tenapanor 50 mg twice daily |
| **Follow-up** | Not stated |
| **Primary Outcomes** | • 6 of 12 week overall responder rate [time frame: 12 weeks] |
| **Secondary Outcomes** | • 6 of 12 Week Overall Complete Spontaneous Bowel Movement (CSBM) Responder Rate [Time Frame: 12 weeks]<br>• 6 of 12 Week Overall Abdominal Pain Responder Rate [Time Frame: 12 weeks]<br>• 9 of 12 Week Overall Responder Rate [Time Frame: 12 weeks]<br>• 9 of 12 Week Overall CSBM Responder Rate [Time Frame: 12 weeks]<br>• 9 of 12 Week Overall Abdominal Pain Responder Rate [Time Frame: 12 weeks] |
| **Key Results** | T3MPO-1 trial achieved statistical significance for the primary endpoint and seven of eight secondary endpoints. The primary endpoint, the combined responder rate for six of 12 weeks, showed that a greater proportion of tenapanor-treated patients compared to placebo-treated patients (27.0% vs 18.7%, p=0.02) had at least a 30 percent reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements (CSBM) in the same week for at least six of the 12 weeks of the treatment period. Tenapanor was well-tolerated, consistent with the experience across previous clinical trials. |
| **Adverse effects (AEs)** | The only adverse events observed in more than two percent of patients treated with tenapanor, as compared with placebo, were diarrhoea (14.6% vs |

| | |
|---|---|
| | 1.7%) and nausea (2.6% vs 1.7%). Discontinuations due to diarrhoea were 5.9 percent for the tenapanor-treated patients, compared to 0.6 percent for the placebo group, based on the preliminary results. |
| **Expected reporting date** | Not reported |

# ESTIMATED COST and IMPACT

## COST

The cost of tenapanor is not yet known.

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ No impact identified

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ None identified

### IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other: uncertain unit cost compared to existing treatments

☐ None identified

### OTHER ISSUES

☒ None identified

## REFERENCES


[1] Johansson S, Rosenbaum DP, Knutsson M, Leonsson-Zachrisson M. A phase 1 study of the safety, tolerability, pharmacodynamics, and pharmacokinetics of tenapanor in healthy Japanese volunteers. *Clinical and Experimental Nephrology*. 2017;21(3): 407-416. Available from: https://doi.org/10.1007/s10157-016-1302-8

[2] Chey, WD. World Congress of Gastroenterology at ACG 2017 (Tenapanor). *The Lancet: Gastroenterology & Hepatology*. 2017;2(12): 850. Available from: https://doi.org/10.1016/S2468-1253(17)30328-X

[3] Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor Treatment of Patients With Constipation-Predominant Irritable Bowel Syndrome: A Phase 2, Randomized, Placebo-Controlled Efficacy and Safety Trial. The American Journal of Gastroenterology. 2017;112: 763-774. Available from: https://doi.org/10.1038/ajg.2017.41

[4] ClinicalTrials.gov. *A 12-Week Study With a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Tenapanor for the Treatment of IBS-C (T3MPO-1)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02621892 [Accessed 12th February 2018] Last updated: 8th February 2017

[5] ClinicalTrials.gov. *A 26-Week Study to Evaluate the Efficacy and Safety of Tenapanor in IBS-C (T3MPO-2)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02686138 [Accessed 12th February 2018] Last updated: 8th February 2017

[6] Ardelyx. *Ardelyx announces successful phase 3 trial of tenapanor for hyperphosphatemia in patients with end-stage renal disease*. Available from: http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-announces-successful-phase-3-trial-tenapanor [Accessed 12th February 2018] Last updated: 15th February 2017

[7] Zielinska M, Wasilewski A, Fichna J. Tenapanor hydrochloride for the treatment of constipation-predominant irritable bowel syndrome. *Expert Opinion on Investigational Drugs*. 2015;8: 1093-1099. Available from: https://doi.org/10.1517/13543784.2015.1054480

[8] Ardelyx. *Ardelyx's Pivotal Phase 3 Study of Tenapanor for IBS-C Hits Primary and All Secondary Endpoints to Support NDA Submission in 2018*. Available from: http://ir.ardelyx.com/news-releases/news-release-details/ardelyxs-pivotal-phase-3-study-tenapanor-ibs-c-hits-primary-and [Accessed 12th February 2018]

[9] Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clinical Epidemiology. 2014;6: 71-80. Available from: https://dx.doi.org/10.2147/CLEP.S40245

[10] NICE. *Clinical guideline [CG61]: Irritable bowel syndrome in adults: diagnosis and management.* Available from: https://www.nice.org.uk/guidance/cg61/ifp/chapter/What-is-irritable-bowel-syndrome [Accessed 12th February 2018] Last updated: April 2017

[11] NHS England. *Hospital Admitted Patient care Activity, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 12th February 2018] Last updated: 3rd October 2017

[12] American Gastroenterological Association Institute. *Guideline on the Pharmacological Management of Irritable Bowel Syndrome*. Available from: http://www.gastro.org/guidelines/pharmacological-management-of-ibs [Accessed 12th February 2018]

[13] Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut*. 2007;56(12): 1770-1798. Available from: https://doi.org/10.1136/gut.2007.119446

[14] Lacy BE, Chey WD, Lembo AJ. New and emerging treatment options for irritable bowel syndrome. *Gastroenterology & Hepatology*. 2015;11(4): 1-19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26491416 [Accessed 12th February 2018]

[15] Chey WD, Lembo AJ, Lavins BJ et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *American Journal of Gastroenterology*. 2012;107: 1702–1712. Available from: https://doi.org/10.1038/ajg.2012.254

[16] Drossman DA, Chey WD, Johanson JF et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome-results of two randomized, placebo-controlled studies. *Alimentary Pharmacology & Therapeutics*. 2009;29: 329–341. Available from: https://doi.org/10.1111/j.1365-2036.2008.03881.x

[17] NICE. *Managing irritable bowel syndrome*. Available from: https://pathways.nice.org.uk/pathways/irritable-bowel-syndrome-in-adults#path=view%3A/pathways/irritable-bowel-syndrome-in-adults/managing-irritable-bowel-syndrome.xml&content=view-node%3Anodes-give-information [Accessed 12th February 2018]

[18] Ardelyx. *Ardelyx successfully completes T3MPO-3 Safety Extension Study of Tenapanor for IBS-C*. Available from: http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-successfully-completes-t3mpo-3-safety-extension-study [Accessed 12th February 2018] Last updated: 3rd January 2018

[19] ClinicalTrials.gov. A Long-Term Safety Study of Tenapanor for the Treatment of IBS-C (T3MPO-3). Available from: https://clinicaltrials.gov/ct2/show/NCT02727751 [Accessed 12th February 2018] Last updated: 15th April 2016

[20] Ardelyx. *Ardelyx reports positive T3MPO-2 phase 3 trial results in IBS-C*. Available from: https://seekingalpha.com/article/4113195-ardelyx-ardx-reports-positive-t3mpominus-2-phase-3-trial-results-ibs-c-slideshow [Accessed 12th February 2018] Last updated: 11th October 2017

[21] Ardelyx. Ardelyx reports successful Phase 3 T3MPO-1 trial of tenapanor in patients with IBS-C. Available from: http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-reports-successful-phase-3-t3mpo-1-trial-tenapanor [Accessed 12th February 2018] Last updated: 12th May 2017