

Health Technology Briefing July 2023

Pylera with omeprazole for treating helicobacter pylori associated ulcers

Company/Developer

Juvisc Pharmaceuticals

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 36688

NICE TSID: N/A

UKPS ID: 670401

Licensing and Market Availability Plans

Completed Phase III trials.

Summary

Pylera in combination with omeprazole is currently in development for the treatment of adults who test positive for *Helicobacter pylori* (*H. pylori*) with upper gastrointestinal symptoms. *H. pylori* infection occurs when *H. pylori* bacteria infect the stomach, which typically happens during childhood. The bacteria are usually passed from person to person through direct contact with saliva, vomit, or stool. It can also spread through contaminated food or water. *H. pylori* infection is a common cause of stomach ulcers. *H. pylori* treatment usually involves a triple-therapy regimen comprising a proton pump inhibitor (PPI) – a type of drug that reduces acid production in the stomach and two antibiotics. Antibiotics are key components of many first-line PPI-based triple therapies, but resistance to them is constantly rising, meaning they are no longer effective at clearing the bacteria, which leads to treatment failures.

Pylera is a 3 in 1 fixed-dose combination orally administered capsule consisting of bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride. Pylera acts via multiple mechanisms of action aimed at the eradication of *H. Pylori* bacteria from the body. If licensed, quadruple therapy consisting of Pylera in combination with omeprazole will offer an additional treatment option for patients who test positive for *H pylori* given the rising prevalence of antibiotic-resistant *H. pylori*.

Proposed Indication

For the treatment of adults who test positive for *Helicobacter pylori* (*H. pylori*) with upper gastrointestinal symptoms.¹

Technology

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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Description

Pylera (OBMT) is a fixed-dose combination of a mineral (bismuth subcitrate potassium) and two antibiotics (metronidazole and tetracycline hydrochloride) used to treat stomach ulcers associated with *H. pylori* infection.² Metronidazole is an antimicrobial drug that acts against anaerobic bacteria and protozoa and inhibits nucleic acid synthesis by disrupting DNA.^{3,4} Tetracycline binds to the 30S and possibly 50S ribosomal subunits of susceptible bacteria to inhibit protein synthesis.⁴ Bismuth subcitrate has bactericidal effects against *H. pylori*. It prevents the adhesion of *H. pylori* to epithelial cells and can inhibit enzymes secreted by *H. pylori*, such as proteases, lipases, glycosidases, and phospholipases.⁵ Omeprazole is a proton pump inhibitor (PPI), a type of drug that reduces gastric acid secretion through a highly targeted mechanism of action. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.⁶

Pylera in combination with omeprazole is intended to be a quadruple therapy for the eradication of *H. pylori* in adults with confirmed positive *H. pylori* status with upper gastrointestinal symptoms. In the completed phase III clinical trial (NCT00669955), patients were given pylera, consisting of a 3 in 1 capsule, made of bismuth subcitrate potassium 120 mg, metronidazole 125 mg, and tetracycline 125 mg, administered as 3 capsules 4 times daily. Omeprazole 20 mg is administered twice daily.¹

Key Innovation

Treatment of *H. pylori* infection usually involves a triple-therapy regimen that comprises a proton pump inhibitor (PPI) such as esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole sodium, and two antibiotics.⁷ Clarithromycin, metronidazole, and other antibiotics are key components of many first-line PPI-based triple therapies, but resistance to them is constantly rising, leading to treatment failure rates in about 40% of patients (reported in 2011) which has continued to increase.^{8,9} Bismuth-containing therapy is proposed in regions with high *in vitro* resistance to clarithromycin or metronidazole because the addition of bismuth to other antibiotic regimens has been shown to improve *H. pylori* eradication.^{10,11} Conversely, the efficacy of metronidazole-containing combination therapy (with bismuth and tetracycline) is maintained in patients harbouring metronidazole-resistant *H. pylori*.^{11,12}

Finally, comparing 10 days of treatment with quadruple therapy yields *H. pylori* eradication rates superior to the standard 7 days of treatment with standard triple therapy at rates of 80% (174 of 218 participants) in the quadruple therapy group versus 55% (123 of 222) in the standard therapy group ($p < 0.0001$). Safety profiles for both treatments were similar; main adverse events were gastrointestinal and central nervous system (CNS) disorders.⁸ If licensed, quadruple therapy consisting of pylera in combination with omeprazole will offer an additional treatment option for patients who test positive.

Regulatory & Development Status

Pylera in combination with omeprazole does not currently have marketing authorisation in the UK for any indication. Pylera is licensed in select EU countries via the decentralised procedure.¹³

Omeprazole as monotherapy or in combination with appropriate antibiotics currently has a Marketing Authorisation in the UK for the eradication with *H. pylori* in peptic ulcers, among other indications such as gastro-oesophageal reflux disease, gastric ulcer, duodenal ulcer, etc.⁶ All 3 sub-components of Pylera (tetracycline, metronidazole, and bismuth) are used in *H. pylori* eradication as off-label treatments but none are licensed in the UK to treat the proposed indication.^{3,14,15}

Pylera in combination with omeprazole is not in clinical development for any other indication.¹⁶

Pylera was granted a product-specific waiver for the *H. pylori* infection on all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product is likely to be unsafe in that population.¹⁷

Patient Group

Disease Area and Clinical Need

H. pylori infection occurs when *H. pylori* bacteria infect the stomach, which typically happens during childhood. The bacteria are usually passed from person to person through direct contact with saliva, vomit, or stool. *H. pylori* may also be spread through contaminated food or water.¹⁸ A common cause of peptic ulcers is the *H. pylori* infection accounting for 95% of duodenal and 70–80% of gastric ulcers. A peptic ulcer is a sore on the lining of the stomach (gastric ulcer) or the first part of the small intestine (duodenal ulcer).^{7,18} Most people with *H. pylori* infection will never have any signs or symptoms. When there are symptoms, they are typically associated with ulcers and include stomach ache, burning pain in stomach, heartburn, indigestion, nausea, bloody/black stools, loss of appetite, etc.^{18,19} Stomach ulcers can affect anyone but are more common in people aged 60 or over. Men are more often affected than women.¹⁹

About 40% of people in the UK have *H. pylori* in their stomach; approximately 8-9 out of 10 people who have it do not have any problems. However about 15% of people with the condition get ulcers either in the stomach (gastric ulcer) or in the duodenum (duodenal ulcer).²⁰ The incidence of peptic ulcer disease is about 0.1–0.3% per year,²¹ but varies with age.^{22,23} The incidence of gastric ulcers peaks in the 5th to 7th decades, while it peaks in the 3rd to 5th decades for duodenal ulcers.²⁴ In England, 2021-22, there were a total of 35,234 finished consultant episodes (FCE) and 21,458 admissions for primary diagnoses of gastric, duodenal, and peptic ulcers-unspecified (ICD-10 code K25 – 27) which resulted in 81,731 FCE bed days and 13,930 day cases.²⁵

Recommended Treatment Options

Treatment of *H. pylori* usually involves a triple-therapy regimen that comprises a proton pump inhibitor (such as esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole sodium) and two antibiotics such as clarithromycin, metronidazole, amoxicillin, or levofloxacin depending on patient's antibiotic treatment history – to reduce risk of resistance.⁷

Clinical Trial Information

<p>Trial</p>	<p>NCT00669955; Efficacy and Safety of Quadruple Therapy by Bismuth Subcitrate Potassium, Metronidazole, and Tetracycline Given X 10 Days with Omeprazole in Eradication of Helicobacter Pylori: A Comparison to Omeprazole, Amoxicillin and Clarithromycin Given X 7 Days Phase III – Completed Location(s): United Kingdom Study completion date – August 2009</p>
<p>Trial Design</p>	<p>Randomised, parallel assignment, open label</p>
<p>Population</p>	<p>N=440 (actual); subjects with positive <i>H. pylori</i> status and presence of upper gastro-intestinal symptoms; aged 18 years and older</p>
<p>Intervention(s)</p>	<p>Quadruple therapy:</p>

	<ul style="list-style-type: none"> • pylera 3 in 1 capsule: bismuth subcitrate potassium 120 mg, metronidazole 125 mg, and tetracycline 125 mg, administered as 3 capsules 4 times daily (oral). • omeprazole 20 mg is administered twice daily (oral).
Comparator(s)	<p>Triple therapy:</p> <ul style="list-style-type: none"> • omeprazole 20 mg twice daily (oral) • amoxicillin 500 mg 2 capsules twice daily (oral) • clarithromycin 500 mg 1 tablet twice daily (oral)
Outcome(s)	<p>Primary outcome:</p> <p>Helicobacter Pylori Eradication Confirmed by Urea Breath Test [Time Frame: Week 6 and week 10 follow-up visits]</p> <p>See trial record for list of other outcomes</p>
Results (efficacy)	<p>In the intention-to-treat population (n=440), eradication rates were 80% (174 of 218 participants) in the quadruple therapy group versus 55% (123 of 222) in the standard therapy group (p<0.0001).⁸</p>
Results (safety)	<p>Safety profiles for both treatments were similar; main adverse events were gastrointestinal and CNS disorders.⁸</p>

Estimated Cost

The cost of pylera in combination with omeprazole was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (CG184). October 2019
- NICE clinical guideline. Acute upper gastrointestinal bleeding in over 16s: management (CG141). August 2016
- NICE quality standard. Dyspepsia and gastro-oesophageal reflux disease in adults (QS96). July 2015.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- British National Formulary. Helicobacter pylori infection - Treatment Summary.⁷
- P. Malfertheiner, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. 2022.²⁶
- Public Health England. Helicobacter pylori in dyspepsia: test and treat. 2007.²⁷

Additional Information

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