NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2018 surveillance of CG184 Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (2014)

Consultation dates: 12 to 25 October 2018

Do you agree with the proposal to not to update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Department of Health and Social Care	Not answered	I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding these consultations.	Thank you for your comment.
NHS England	Not answered	No comments have been received from NHS England colleagues	Thank you for your comment.
BIOHIT HealthCare Ltd	No	BIOHIT HealthCare believes there is an opportunity to update 1) the diagnosis as part of the investigation of dyspepsia and 2) clarify referral guidance for endoscopy in the absence of alarm symptoms.	Thank you for your comment. Please see below for responses to your detailed comments.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

Royal College of Nursing	Not answered	Nurses caring for people with Gastro-oesophageal reflux disease and dyspepsia in adults have reviewed the proposal and have no comments to submit at this stage Thank you for the opportunity to participate.	Thank you for your comment.
Norgine Pharmaceuticals Limited	No	We believe there is a growing body of evidence that has evaluated treatment in patients refractory to PPIs. The efficacy of these medicines and devices have been published. For example, a randomised study with ZIVEREL has demonstrated improved symptom control in this group when added to existing therapy with PPI. This growing evidence base should be captured in the guideline and would be identified if full literature reviews were undertaken.	Thank you for your comment. Ziverel does not need a prescription and can be bought over the counter (OTC), but we note that there is limited availability of Ziverel in the UK. In addition, we were not able to identify any randomised studies of Ziverel in dyspepsia. Therefore at this time, it is not appropriate to consider Ziverel in this surveillance review of the guideline.

Are you aware of:

- **any large observational studies of PPI safety that would be missed by the searches, for example:**
  - **studies published after the search dates for the included systematic reviews**
  - **studies addressing adverse events that were not the focus of existing systematic reviews**
- **any large studies of resistance patterns of H pylori in the UK**
- **any information suggesting a need to update a section of the guideline that was not a focus of this surveillance?.**

Stakeholder	Overall response	Comments	NICE response

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

Department of Health and Social Care	Not answered	No comments provided	Thank you for your response.
NHS England	Not answered	No comments provided	Thank you for your response.
BIOHIT HealthCare Ltd	Yes	We would like to highlight information suggesting a need to update sections of the guideline that were not a focus of this surveillance. Please see the comments in the table below along with references. Comments should also be reviewed in response to the section in the Surveillance proposal consultation document entitled Long term safety of PPIs; "Other adverse effects" (pg 5): "Gastric atrophy was identified as an adverse event in one systematic review….the SPC for omeprazole notes that atrophic gastritis is associated with H pylori infection. This may be an important confounding factor to consider against the finding of increased gastric atrophy, particularly if H pylori status was unknown for the populations informing the systematic review." Current 1.4 Interventions for uninvestigated dyspepsia 1.4.1 Be aware that dyspepsia in unselected people in primary care is defined broadly to include people with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea or vomiting. Also see common elements of care. **[2004, amended 2014]** 1.4.2 Leave a 2-week washout period after proton pump inhibitor (PPI) use before testing for *Helicobacter*	Thank you for your comment. Because recommendations are written by a guideline committee on consideration of the evidence, this response is restricted to the references that you provided. The guideline recommends urea breath testing or stool antigen testing for detection of *H pylori*. Malfertheiner et al. (2017) provides support for the current diagnostic strategy. Statement 1 from the diagnosis section notes: 'Urea breath test is the most investigated and best recommended non-invasive test in the context of a 'test-and-treat strategy'. Monoclonal stool antigen tests can also be used. Serological tests can be used only after validation. Rapid ('office') serology tests using whole blood should be avoided in this regard.' This report additionally notes that gastritis, including atrophic gastritis, is usually resolved with *H pylori* treatment. Zagari et al. (2017) is a systematic review of diagnostic studies. Pepsinogen, gastrin-17 and anti-*H pylori* antibody serum assays had sensitivity of 75% and specificity of 97%. The test had negative predictive value of 91% for atrophic gastritis where the prevalence was 27%. The sensitivity of the serum assays at 75% is notably lower than the 95% found for urea breath testing when developing the guideline. Although the negative predictive value may help to rule out the

		pylori (hereafter referred to as *H pylori*) with a breath test or a stool antigen test. **[2004, amended 2014]** 1.4.3 Offer empirical full-dose PPI therapy (see table 1 in appendix A) for 4 weeks to people with dyspepsia**. [2004]** 1.4.4 Offer *H pylori* 'test and treat' to people with dyspepsia. **[2004]** 1.4.5 If symptoms return after initial care strategies, step down PPI therapy to the lowest dose needed to control symptoms. Discuss using the treatment on an 'as-needed' basis with people to manage their own symptoms. **[2004]** 1.4.6Offer H_2 receptor antagonist (H_2RA) therapy if there is an inadequate response to a PPI. **[2004, amended 2014]** Proposed Replace 1.4.2 with: Test for *Helicobacter pylori* (hereafter referred to as *H pylori*) with a combination of laboratory-based *H pylori* serology, Pepsinogen I, Pepsinogen II and Gastrin 17 (GastroPanel) blood Test to exclude *H pylori*, atrophic gastritis and hypo- or achlorhydria. 1.4.3 Offer empirical full-dose PPI therapy (see table 1 in appendix A) for 4 weeks to people with dyspepsia in whom atrophic gastritis (hypo- or achlorhydria) has been excluded**. PPI use in contra indicated in people with hypo- or achlorhydria.** 1.4.4 Offer *H pylori* 'test and treat' using GastroPanel to people with dyspepsia.	presence of atrophic gastritis, the positive predictive value is more useful to inform who does have atrophic gastritis. However, since *H pylori* eradication is expected to resolve most cases of atrophic gastritis, the added value is unclear. Therefore, this study has no impact on the current recommendations. The study by Germaná et al. (2005) is not eligible for consideration in surveillance. It was published before the search dates for this surveillance and the abstract does not contain any statistical data on diagnostic accuracy. Agréus et al. (2012) is not eligible for consideration in surveillance. It was published before the search dates for this surveillance and the abstract does not contain any statistical data on diagnostic accuracy.

		Current 1.9 Helicobacter pylori testing and eradication Testing 1.9.1 Test for *H pylori* using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology where its performance has been locally validated. [2004, amended 2014] Proposed Test for *H pylori* using laboratory-based GastroPanel to exclude *H pylori* and atrophic gastritis and diseases characterised by atrophic gastritis Current 1.11 Referral to a specialist service 1.11.1 Consider referral to a specialist service for people: • of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained[5] • with suspected GORD who are thinking about surgery • with *H pylori* that has not responded to second-line eradication therapy. **[new 2014]** **Proposed** Consider referral to a specialist service for people: **[in addition]** with evidence of Atrophic Gastritis **References**	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		Malfertheiner P, et al. Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. Gut 2017;66:6–30. Zagari RM, et al. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-Helicobacter pylori antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther. 2017;46:657–667. Germana B, et al. Clinical usefulness of serum pepsinogens I and II, gastrin-17 and anti-Helicobacter pylori antibodies in the management of dyspeptic patients in primary care. Digestive and Liver Disease 37 (2005) 501–508. Agréus L, et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand J Gastroenterol. 2012; 47: 136–147	
Royal College of Nursing	Not answered	No comments provided	Thank you for your response.
Norgine Pharmaceuticals Limited	Yes	Whilst not an observational study Savarino et al (2017) does capture clinical and safety outcomes for a cohort of patients that received PPI treatment. To our knowledge this has not been picked up in the in the guidance. In addition to this evidence on the safety of PPIs, evidence on ZIVEREL may also inform the treatment pathway as described in section 1.6, with ZIVEREL potentially offering a treatment option for those refractory to PPIs.	In the absence of a specific citation, articles meeting the description in the comment were sought. Two review articles were identified that meet these criteria (Savarino et al 2017a and Savarino et al. 2017b). Both of these articles appear to be narrative-style reviews of the treatment of gastro-oesophageal reflux disease. These do not meet criteria for inclusion in surveillance, which includes only those systematic reviews using robust methods.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Department of Health and Social Care	Not answered	No comments provided	Thank you for your response.
NHS England	Not answered	No comments provided	Thank you for your response.
BIOHIT HealthCare Ltd	No	No comments provided	Thank you for your response.
Royal College of Nursing	Not answered	No comments provided	Thank you for your response.
Norgine Pharmaceuticals Limited	No	No comments provided	Thank you for your response.

Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Department of Health and Social Care	Not answered	No comments provided	Thank you for your response.
NHS England	Not answered	No comments provided	Thank you for your response.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

BIOHIT HealthCare Ltd	No	No comments provided	Thank you for your response.
Royal College of Nursing	Not answered	No comments provided	Thank you for your response.
Norgine Pharmaceuticals Limited	No	No comments provided	Thank you for your response.