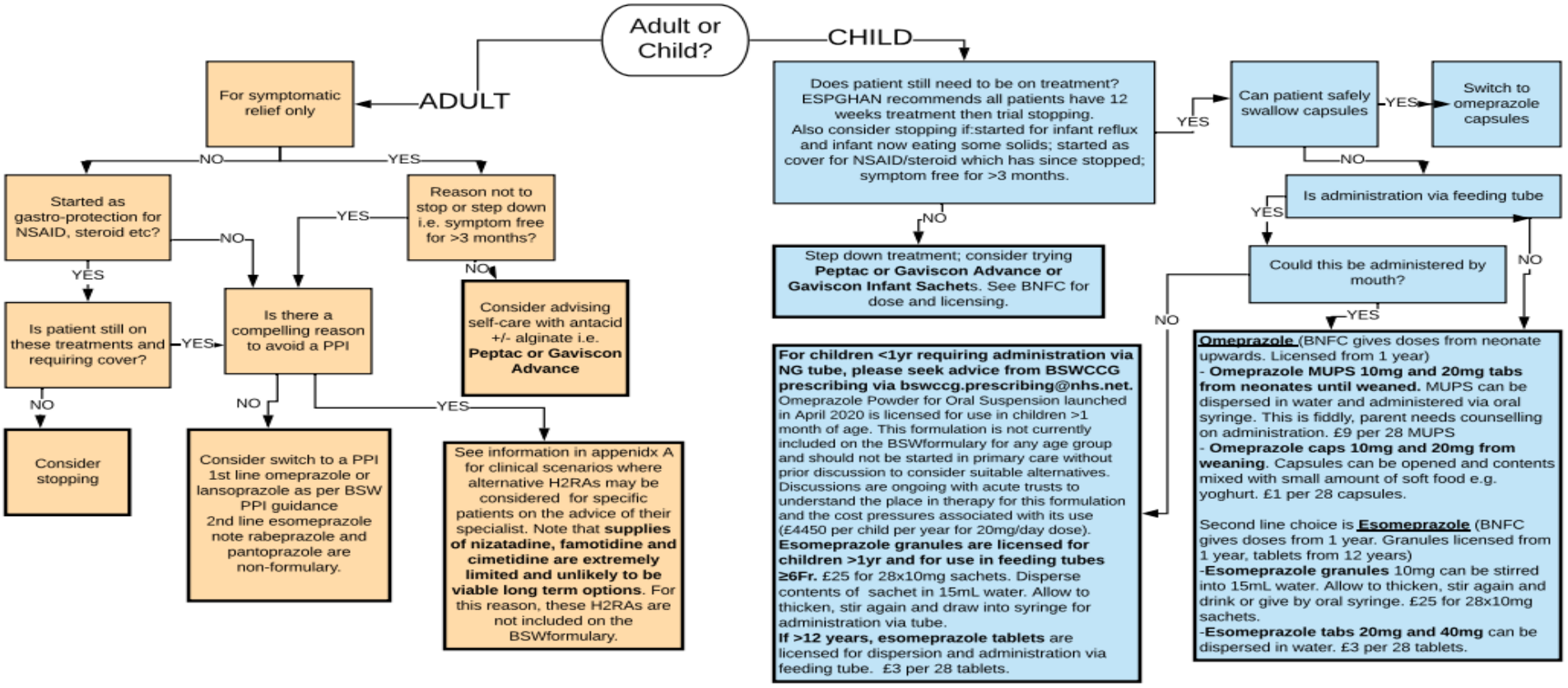
NHS BSW CCG: Ranitidine Supply Disruption. This document will be updated periodically with details of availability of products – DO NOT PRINT [CURRENT VERSION 1.0 ISSUED AUG 2020]

NHS
Bath and North East Somerset, Swindon and Wiltshire
Clinical Commissioning Group

The Department of Health and Social Care have updated the Supply Disruption Alert for ranitidine HERE.

- This BSWdocument aims to provide local advice to help manage patients currently on ranitidine. This advice does not replace the national clinical advice given in the supply disruption alert (link above) but adds extra information drawing on UK medicines information resources and local clinical expertise.
- All formulations of ranitidine are anticipated to be out of stock from the end of May 2020 due to on-going regulatory investigations into the presence of the contaminant, N-nitrosodimethylamine (NDMA), in samples of ranitidine active substance.
- Limited stocks of nizatidine, cimetidine and famotidine may be available but supplies are likely to be unreliable. For this reason these drugs have NOT been added to the BSWformulary although this document suggests small cohorts of patients where use of these H2RAs may be considered after all other options have been explored and where clinicians can liaise with pharmacists to understand local stock availability. PSNC have supply information HERE
- Review all patients as repeat prescriptions are requested, using flowchart below. See also BSW PPI guidance for adults.



Written by BSW Medicines Management Team July 2020 Approved by BSW formulary groups July/Aug 2020

Appendix A - Supporting information for specific situations where a switch to a PPI may not be straightforward.

Patients taking ranitidine for urticaria

There is no strong evidence to support the addition of ranitidine to treatment regimes in chronic urticaria and angioedema (1,2). British Society for Allergy and Clinical Immunology guidelines suggest combination H1 antihistamines and montelukast if dose escalation of H1 antihistamine has been ineffective (2). Alternatively, cimetidine (but consider interactions) or famotidine could be used as alternatives where available. Specialists should be contacted in all instances when switching for advice on dosing and /or review of supply arrangements in primary care for any of these unlicensed uses.

Patients who have had hyponatraemia with PPIs

Hyponatraemia has been reported as a rare side effect with all PPIs although causality may be difficult to establish as the cause of hyponatraemia is often multifactorial (3). A lack of evidence compares risks of hyponatraemia between the PPIs. One recent study concluded that all PPIs are associated with hospitalisation secondary to hyponatraemia in patients newly initiated on a PPI, with the exception of lansoprazole (4). Ongoing PPI use beyond 12 weeks was not associated with an increased risk (4). In patients with a history of hyponatremia or susceptible to hyponatremia, lansoprazole may be considered if benefits of treatment outweigh risks. If switching from ranitidine to lansoprazole, patient counselling and monitoring (particularly when initiating and for the first 3 months of treatment) would seem sensible. Further information on hyponatraemia can be found in the CKS topic on hyponatraemia.

Patients taking concomitant clopidogrel

The MHRA discourage the use of omeprazole and esomeprazole in patients taking clopidogrel although the evidence for a clinically meaningful interaction is controversial (5). Current available data does not support nor completely exclude an interaction between clopidogrel and other PPIs. The potential risk of a reduction in efficacy of clopidogrel should be weighed against the potential benefit of the PPI. Lansoprazole would be BSWformulary preferred choice of PPI in this instance.

Renal patients and concerns over PPI use being associated with interstitial nephritis

Large proportions of renal patients are prescribed ranitidine prophylactically over concerns of long term PPI use being associated with interstitial nephritis. Local specialist renal teams suggest all renal patients should be clinically reviewed, deprescribing any H2 antagonist where possible and managing symptomatically with alginates. Patients requiring prophylactic treatment should be offered a PPI considering interactions +/- additional therapeutic drug monitoring. Where neither of these is an option patients should be referred back to their individual named consultant to consider whether a rechallenge with PPI is the most appropriate action. Famotidine should be reserved for a very small group of renal patients who would otherwise become dialysis dependant. Full details HERE.

Use in pregnancy

Alginates/ antacids are compatible with pregnancy and should always be considered first line. Omeprazole is licensed for use in pregnancy in the UK. Although the data for all PPIs are overall reassuring, women taking PPIs other than omeprazole in pregnancy should be made aware of the lack of specific data for these drugs (6). If a PPI is not clinically appropriate, there is no evidence of an overall increase in the risk of congenital malformation for H2-antagonists although less pregnancy data is available for cimetidine and famotidine than was available for ranitidine (7). UKTIS can be contacted on 0344 892 0909 for individual patient advice and the following information leaflets from UKTIS may be useful https://www.medicinesinpregnancy.org/Medicine--pregnancy/Omeprazole / https://www.medicinesinpregnancy.org/Medicine--pregnancy/H2-receptor-antagonists/

Use in breastfeeding

Alginates/ antacids are compatible with breastfeeding and should always be considered first line. Omeprazole and pantoprazole are the PPIs of choice in lactation, although evidence is limited. There are currently no data to support the use of other PPIs, even though they are probably also safe to use (8). If a PPI is not clinically appropriate, ranitidine has been first choice due to greatest experience of use during lactation and experience in neonates where therapeutic doses given are likely to be larger than the amounts received via breast milk. Famotidine is present in breastmilk although this is not known to be harmful. Cimetidine, in general, is not widely used due to drug interactions. Further information summarising study data of H2RAs in lactation can be found on the Specialist Pharmacy Services website here

Use in palliative care settings in continuous subcutaneous infusions (CSCI)

There is currently no national advice on giving omeprazole by CSCI or on the compatibility of injectable omeprazole with other drugs. A Canadian report to determine the evidence to support subcutaneous or other non-oral routes of administration for PPIs in palliative care patients describes three cases where omeprazole was administered via CSCI (9). Further case reports note omeprazole 40mg in 100ml sodium chloride 0.9% as a CSCI over 3 – 4 hours has been given (10). Further information is expected through the palliative care network as experience grows.

Use in oncology as a pre-med for paclitaxel pre-med regimes – *secondary care only*

H2RAs have been used off-label in in the prevention and management of infusion reactions with systemic anti-cancer therapy. The British Oncology Pharmacy Association has produced guidance for situations where H2RAs are in short supply or unavailable (11). Full guidance HERE.

IV ranitidine for stress ulcer prophylaxis (SUP) in ICU – *secondary care only*

A 2018 Cochrane Review looked at interventions for preventing upper gastrointestinal bleeding in people admitted to ICU (12). Additionally, a recently published clinical trial that looked at the comparative effect on in-hospital mortality of using PPIs vs H2As for SUP in ICU may influence clinical practice (13). Suggested action is to choose PPI according to individual Trust policy and patient's ability to swallow or need for administration via NG tube.

References

1. Fedorowicz Z, van Zuuren EJ, et al. Histamine H2-receptor antagonists for urticaria. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD008596. https://www.ncbi.nlm.nih.gov/pubmed/22419335
2. R. J. Powell, S. C. Leech,S. et al. Clinical & Experimental Allergy, 2015 (45) 547–565. https://onlinelibrary.wiley.com/doi/epdf/10.1111/cea.12494
3. NICE CKS Hyponatraemia. Last revised in March 2015. https://cks.nice.org.uk/hyp onatraemia
4. Falhammar H, Lindh JD et al. Associations of proton pump inhibitors and hospitalization due to hyponatremia: A population-based case-control study. Eur J Intern Med. 2019 Jan;59:65-69. https://www.ncbi.nlm.nih.gov/pubmed/30154038
5. Meadows, T. Do proton pump inhibitors reduce the clinical efficacy of clopidogrel? July 2019 Prepared by UK Medicines Information. https://www.sps.nhs.uk/articles/do-proton-pump-inhibitors-reduce-the-clinical-efficacy-of-clopidogrel-2/
6. UK Teratology Information Service https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-PROTON-PUMP-INHIBITORS-PPIs-IN-PREGNANCY/ Date of issue: August 2015
7. UK Teratology Information Service https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-H2-RECEPTOR-ANTAGONISTS-IN-PREGNANCY/ Date of issue: August 2019
8. Specialist Pharmacy Services Q&A https://www.sps.nhs.uk/articles/proton-pump-inhibitors-for-treatment-of-reflux-in-a-breastfeeding-mother-which-is-preferred/ Last revised: May 2016
9. Canadian Agency for Drugs and Technologies in Health. Subcutaneous Administration of Proton Pump Inhibitors in Palliative Care Patients: A Review of Clinical Effectiveness and Guidelines. March 2009 http://www.cadth.ca/media/pdf/htis/L0082%20Subcutaneous%20Administration%20of%20Proton%20Pump%20Inhibitors%20in%20Palliative%20Care%20Patients%20final.pdf
10. Agar M, Webster R, Lacey J, Donovan B, Walker A. The use of subcutaneous omeprazole in the treatment of dyspepsia in palliative care patients. J Pain Symptom Manage 2004;28(6):529-31. https://www.jpsmjournal.com/article/S0885-3924(04)00404-X/fulltext
11. British Oncology Pharmacists Association. Guidance on the use of H2 antagonists for the prevention and management of hypersensitivity V1.0 June 2020 https://www.bopa.org.uk/resources/guidance-on-the-use-of-h2-antagonists-for-the-prevention-and-management-of-hypersensitivity/
12. Toews I, George AT et al. Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD008687.https://www.ncbi.nlm.nih.gov/pubmed/29862492
13. The PEPTIC Randomized Clinical Trial. JAMA. Published online January 17, 2020. doi:10.1001/jama.2019.22190 https://www.ncbi.nlm.nih.gov/pubmed/31950977