North Central London
Joint Formulary Committee

Supply disruption of oral ranitidine
Statement for NCL Trusts

A shortage of all formulations of ranitidine was declared in the UK following the identification of an impurity in samples of the ranitidine active substance. All stock manufactured for the UK using the affected substance has been quarantined as a precaution. As a result there will be very limited supplies of all H_2-receptor antagonists available in the UK (due to subsequent high demand of remaining H_2-receptor antagonists, including a very small amount of unaffected ranitidine which is eventually expected to be depleted).

NCL has taken the position that this is an opportunity to review the requirement of these prescriptions for patients and where possible to de-prescribe. As such we have outlined the following actions for clinical teams:

1) **Patients in Primary care who request ranitidine will be reactively assessed for the clinical need of gastroprotection; those patients who do not require gastroprotection will be weaned off therapy.**
2) **Patients admitted into Secondary care on ranitidine therapy and have adequate stock of their own ranitidine should be allowed to continue treatment.**
3) **Patients running out of oral ranitidine (either during admission or estimated to run out shortly after discharge) should be assessed for the clinical need of ongoing treatment.**
   a) **Those who do not warrant ongoing gastroprotection should be weaned off therapy (with an oral antacid or alginate for symptom cover).**
   b) **Those that require long-term or life-long gastroprotective treatment under one of the indications listed in Table 1 can be switched safely to a recommended proton pump inhibitor.**
   c) **Other indications not listed in this document will require further input from Specialists in North Central London; these patients should remain on ranitidine treatment (or switched to an alternative H_2-antagonist) until further advice can be provided.**
4) **For indications where intravenous ranitidine was previously used, alternative options are suggested in Table 1.**

1. Background

In September 2019, the EMA and FDA announced the detection of an impurity named NDMA in some ranitidine medicines at low levels.[1,2] It is known that NDMA is present in some foods and water supplies but is not expected to cause harm at low levels – the FDA stating that the finding from preliminary tests barely exceeded amounts found in common foods. At the time, both organisations declared that they would be evaluating the data to assess whether patients using ranitidine would be at any risk from NDMA. The disruption does not affect intravenous ranitidine.

In the subsequent weeks, manufacturers decided to recall their ranitidine products. In October 2019, the Department of Health and Social Care (DHSC) released a supply disruption alert[3], informing healthcare professionals in Primary, Secondary and Specialist care to identify patients on all oral formulations of ranitidine and review to establish if ongoing treatment is required, and if so, to switch to an alternative treatment.

At the October 2019 Joint Formulary Committee meeting, it was decided that a central response from the Committee would be beneficial in reducing variation in practice. At the end of April 2020, the EMA announced the suspension of ranitidine medicines in the EU, which has led to the cessation of manufacturing of all formulations.[4] The DHSC alert was updated to indicate that all formulations of ranitidine would be unavailable from the end of May 2020 due to ongoing regulatory investigations.[5]

2. Indications where a switch toward PPI use is recommended

Ranitidine has been used for multiple indications and often this is for long-term use (and, in some cases, life-long). The supply disruption has been an opportunity to address the appropriateness of oral ranitidine for these indications.

The indications in Table 1 are those where it has been agreed that an initiation of a proton pump inhibitor (PPI) is appropriate, or a switch from ranitidine to a PPI is suitable (as long as there is no clinical reason for the patient to avoid a PPI, such as a true allergy). Ranitidine and PPIs have different risk/benefit profiles; in the absence of available H2-antagonists, clinicians are encouraged to give careful consideration before making a decision to provide alternative measures of gastroprotection in patients where the potential risks may outweigh the benefit of using a PPI (e.g. patients with history of bone fracture or decompensated liver disease). As with initiating any medicine the risk/benefit of PPI treatment should be considered against alternative options e.g. no protection or antacid.

The impact of this recall is that there will be an increased use of PPIs which are not without clinical risk e.g. increased risk of *C. difficile*. To mitigate the risks, all new prescriptions for a PPI must state the indication and duration of treatment in the patient's medical notes and the drug chart/prescription.

In May 2020, these recommendations have been amended to reflect the suspension of all ranitidine manufacturing and expected eventual depletion of ranitidine stock in the UK. At the moment, the current supply of alternative H_2-antagonists will not meet the excess demand left in the absence of all rantidine formulations and is therefore reserved for those indications where a H_2-antagonist must be used with no alternative. This situation will be reviewed as it changes.

Quick reference list

Adults

Prophylactic indications

- Stress ulcer prophylaxis (SUP)
- Prophylaxis of gastrointestinal adverse events with NSAID
- Prophylaxis of gastrointestinal adverse events with oral corticosteroids
- Prophylaxis of gastrointestinal adverse events with anti-platelets
- Prophylaxis of gastrointestinal adverse events in patients taking dual antiplatelet therapy/ combined antiplatelet and anticoagulant therapy
- Patients taking direct oral anticoagulants (DOACs)
- Prophylaxis of gastrointestinal adverse events in transplant patients/acute transplant rejection on systemic steroids
- Prophylaxis of gastrointestinal adverse events in autoimmune hepatitis or alcoholic hepatitis responsive to steroids
- Prophylaxis of gastrointestinal adverse events in adult haematology or oncology patients

Treatment indications

- Treatment of Gastro-Oesophageal Reflux Disease (GORD)
- Treatment of uninvestigated dyspepsia
- Treatment of functional dyspepsia
- Treatment of NSAID associated gastric or duodenal ulcer
- Treatment of Gastric/duodenal ulcer (not NSAID induced)
- Eradication of *Helicobacter pylori*
- Treatment of dyspepsia in pregnancy
- Hyperemesis Gravidarum
- Pre-operative acid reduction in patients at risk of aspiration, or for the prophylaxis of aspiration pneumonitis in patients undergoing a caesarean section (also known as prevention of Mendelson's syndrome)
- Symptom management of oesophageal disorders whilst taking a Multikinase inhibitor (including Tyrosine Kinase inhibitors)

Enteral tube administration in adults (all indications)

- Enteral tube administration of PPIs in adults

Paediatric indications

Prophylactic indications

- Stress ulcer prophylaxis (SUP) in neonates and children
- Prophylaxis of gastrointestinal adverse events in paediatric haematology or oncology patients
- Prophylaxis of gastrointestinal adverse events with oral corticosteroids in paediatrics

Treatment indications

- Treatment of Gastro-Oesophageal Reflux (GOR) and Gastro-Oesophageal Reflux Disease (GORD) in children and young people who can tolerate oral feeding
- Treatment of Gastro-Oesophageal Reflux (GOR), treatment of Gastro-Oesophageal Reflux Disease (GORD) or prophylaxis of gastrointestinal adverse events with oral corticosteroids in children and young people who are fed by enteral tubes.

Table 1 – Indications which has been agreed that it is appropriate to initiate or switch to a PPI

Indication	Recommendations	Choice of medication and duration of treatment
Stress ulcer prophylaxis in adults (SUP)[6,7]	• Patients should be clinically assessed for the clinical need of SUP. • Patients at low risk for a gastrointestinal bleed (e.g. patients ventilated <48 hours, few morbidities, no coagulopathy or no history of GI bleed) should be reviewed for clinical need of SUP medication on a case-by-case basis. • In patients who are established on enteral feed and absorbing (or eating and drinking) the clinical need for SUP should be reviewed. • In patients who are able to receive enteral medications and who require SUP a dispersible PPI should be prescribed. • Intravenous PPIs may be used in critically ill patients who cannot receive enteral medications; however, the patient must be reviewed for the need for stress ulcer prophylaxis throughout admission (particularly upon discharge from critical care). • Do not prescribe acid suppressive therapy for stress ulcer prophylaxis on discharge from hospital (unless there is a clear alternative clinical indication).	**If SUP is indicated and medication can be administered orally:** Lansoprazole capsules 30mg once daily **If SUP is indicated and medication can be administered via NG tube:** Lansoprazole dispersible tablets 30mg once daily (dispersed in water)‡ **If SUP is indicated and the patient is nil by mouth, has no enteral access and ranitidine IV is not available:** Intravenous omeprazole 40mg or pantoprazole 40mg once daily* **Where concerns of interaction between omeprazole and the patients other medications** Intravenous pantoprazole 40mg once daily **Duration of treatment – until the patient is eating and drinking for ≥24 hours and clinically assessed as low ongoing risk of GI bleed.** **‡ Please see the section below for more information on the administration of PPIs via enteral tubes** ***Intravenous PPI of choice may differ at some Trusts in NCL due to formulary status. Trusts should monitor the supply chain of intravenous pantoprazole throughout the ranitidine shortage and switch to IV omeprazole if concerns in availability arise; in this scenario, IV pantoprazole should be reserved for use in patients where there is concern of a possible interaction between omeprazole and the patients current medication.**

Indication	Recommendations	Choice of medication and duration of treatment
Prophylaxis of gastrointestinal adverse events with NSAIDs[8]	• Use a PPI in people at high risk of GI adverse events (which includes patients who have a history of complicated ulcer or >2 risk factors) • Consider a PPI in people at moderate risk of GI adverse events (which includes patients with 1-2 risk factors) • The risk factors for NSAID-induced gastrointestinal adverse events are: o Age over 65; o High dose of NSAID; o Prolonged requirement for NSAIDs; o Previous GI adverse reaction to NSAIDs without gastroprotection; o Concomitant use of medications known to increase the likelihood of upper GI adverse events (e.g. anticoagulants, corticosteroids or SSRIs/SNRIs); o History of gastroduodenal ulcer, GI bleeding or gastroduodenal perforation; o Serious comorbidities, such as cardiovascular disease, hepatic or renal impairment (including dehydration), diabetes or hypertension; o Heavy smoking; o Excessive alcohol consumption.	**First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **Duration of treatment – for the duration of NSAIDs**
Prophylaxis of gastrointestinal adverse events with oral corticosteroids[9]	• Consider a PPI when gastroprotection is required in patients receiving oral corticosteroids who are at high risk of gastrointestinal bleeding or dyspepsia. • The risk factors for gastrointestinal adverse effects include: o History of gastroduodenal ulcer, gastrointestinal bleeding, or gastroduodenal perforation; o Older age; o Concomitant use of drugs that are known to increase the risk of gastrointestinal bleeding, such as NSAIDs, anticoagulants or SSRIs/SNRIs; o Serious comorbidity, such as advanced cancer. o Patients taking ≥30mg prednisolone or equivalent for >7days	**First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **Duration of treatment – for the duration of oral corticosteroids**

Indication	Recommendations	Choice of medication and duration of treatment
Prophylaxis of gastrointestinal adverse events with anti-platelets[10]	• Patients at high risk of gastrointestinal adverse effects with anti-platelets can be prescribed a PPI • The risk factors for high risk gastrointestinal adverse effects include: o High dose of aspirin (>100mg daily); o Older age (especially >70 years); o History of gastroduodenal ulcer, GI bleeding or gastroduodenal perforation; o Helicobacter pylori infection; o Concomitant use of medicines known to increase GI bleed risk (e.g. corticosteroids, NSAIDs or SSRIs/SNRIs). • For dual anti-platelet therapy or anti-platelet with anti-coagulant, see below.	**For low-dose aspirin, ticagrelor or prasugrel** Omeprazole capsules 20mg once daily OR Lansoprazole capsules 15mg once daily **For clopidogrel alone** Lansoprazole capsules 15mg once daily **(Avoid co-prescribing omeprazole or esomeprazole with clopidogrel)** **Duration of treatment – for the duration of anti-platelets**
Prophylaxis of gastrointestinal adverse events in patients taking dual antiplatelet therapy/ combined antiplatelet and anticoagulant therapy (including parenteral anticoagulant)[11,12]	• All patients requiring dual anti-platelet therapy should receive gastroprotective cover with a PPI • If it is essential for patients to remain on antiplatelet therapy whilst receiving an anticoagulant, then ensure gastroprotective cover with a PPI. • "Anticoagulant" in this section can refer to an oral OR a parenteral anticoagulant. • Gastroprotection could be considered in high risk patients requiring VTE thromboprophylaxis (although not routinely required)	**First-line** Lansoprazole capsules 30mg once daily **Duration of treatment – at least for the duration of dual antiplatelet or antiplatelet/anticoagulant therapy**

Indication	Recommendations	Choice of medication and duration of treatment
Patients taking direct oral anticoagulants (DOACs)[11]	• Studies demonstrated a higher risk of GI bleeding with rivaroxaban (all doses), dabigatran 150mg or edoxaban 60mg daily compared to warfarin. • There is a higher risk of GI bleed when a patient is prescribed an anticoagulant in certain situations. Examples include: o A concomitant ulcer-causing treatment (such as NSAID, antiplatelet, corticosteroid, or SSRI/SNRIs); o A history of GI bleed or ulcer. • For patients at higher risk of GI bleeding, consider an alternative anticoagulant with a lower GI bleeding risk (e.g. warfarin, apixaban, LMWH). • A PPI may be considered in patients where there is concern of the risk of GI bleed. • When concurrent antiplatelet and anticoagulant is recommended by a Specialist, a higher dose of lansoprazole is advised.	**First-line** Omeprazole capsules 20mg once daily **Second-line** Lansoprazole capsules 15mg once daily **If concurrent antiplatelet unavoidable** Lansoprazole capsules 30mg once daily **Duration of treatment –the duration of "higher-risk" period (this is potentially long-term)**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of Gastro-Oesophageal Reflux Disease (GORD)[13,14]	• Use a "full-dose" PPI first-line for 4-8 weeks in patients with GORD. • If symptoms recur after initial treatment, offer a PPI at the lowest possible dose to control symptoms. • Use a "full-dose" PPI for 8 weeks to heal severe oesophagitis • If the initial treatment for severe oesophagitis fails, consider switching to another "full-dose" PPI or a "high-dose" or the initial or alternative PPI • Offer a "full-dose" PPI as long-term maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances. • For patients receiving long-term maintenance therapy with a H_2-receptor antagonist for severe oesophagitis and no clinical circumstances preventing the use of a PPI, switch the patients therapy to the recommended "full-dose" PPI option. • If the patient fails to respond to maintenance treatment, consider an alternative PPI at "full-dose" or "high-dose".	**"Low-dose" PPI** **First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **"Full-dose" PPI** **First-line** Omeprazole capsules 40mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 30mg once daily **"High-dose" PPI** **First-line** Omeprazole capsules 40mg twice daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 30mg twice daily **Duration of treatment – Initially 4-8 weeks, then review**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of uninvestigated dyspepsia[13,14]	• Review for medications contributing to dyspepsia and the need for ongoing treatment. • Offer the recommended "full-dose" PPI therapy for 4 weeks to patients with dyspepsia. • Offer *H pylori* testing to patients with dyspepsia. • Step-down PPI therapy to the lowest dose required to control symptoms. • For patients on long-term maintenance therapy with a H_2-receptor antagonist and no clinical circumstances preventing the use of a PPI, switch the patients therapy to the recommended "low-dose" PPI option.	**"Low-dose" PPI** **First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **"Full-dose" PPI** **First-line** Omeprazole capsules 40mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 30mg once daily **Duration of treatment – initially 4 weeks, then review**
Treatment of functional dyspepsia[13,14]	• In patients that have *H pylori* infection excluded, offer a "low-dose" PPI for 4 weeks. • If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms. • For patients on long-term maintenance therapy with a H_2-receptor antagonist and no clinical circumstances preventing the use of a PPI, switch the patients therapy to the recommended "low-dose" PPI option.	**"Low-dose" PPI** **First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **Duration of treatment – initially 4 weeks, then review**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of NSAID associated gastric or duodenal ulcer[13–15]	• Wherever possible, the NSAID should be withdrawn if an ulcer occurs. • Test the patient for *H pylori* infection. • Use a "full-dose" PPI first-line to treat active ulcer for 8 weeks. • For patients continuing to take an NSAID after peptic ulcer healing, discuss the potential harm from NSAID treatment and offer alternative arrangements (e.g. lower-dose or PRN use). Review the need for NSAID use regularly (at least every six months). • For patients who continue on an NSAID following ulcer healing, prescribe alongside a PPI. • If ulcer healing fails, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent NSAID use, other ulcer-inducing medications and rare causes (e.g. Zollinger-Ellison syndrome or Crohn's disease). • If symptoms recur after initial treatment, offer a PPI to be taken at the lowest dose possible to control symptoms.	**"Low-dose" PPI** **First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **"Full-dose" PPI** **First-line** Omeprazole capsules 40mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 30mg once daily **Duration of treatment – initially 8 weeks, then review**
Treatment of Gastric/duodenal ulcer (not NSAID induced)[13–15]	• Test the patient for *H pylori* infection. • Offer a "full-dose" PPI for 4 to 8 weeks to patients who have tested negative for *H pylori* and do not take NSAIDs. • If ulcer healing fails, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent NSAID use, other ulcer-inducing medications and rare causes (e.g. Zollinger-Ellison syndrome or Crohn's disease). • If symptoms recur after initial treatment, offer a PPI to be taken at the lowest dose possible to control symptoms.	**"Low-dose" PPI** **First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **"Full-dose" PPI** **First-line** Omeprazole capsules 40mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 30mg once daily **Duration of treatment – initially 4-8 weeks, then review**

Indication	Recommendations	Choice of medication and duration of treatment
Eradication of *Helicobacter pylori*[15–17]	• Use standard first-line combination therapy using a PPI and associated antibiotics • In patients that fail first-line eradication therapy, a salvage regimen of bismuth quadruple therapy can be considered (PPI + tetracycline + metronidazole + tripotassium dicitratopbismuthate) • Pepto Bismol® was ratified onto the NCL Joint Formulary in April 2019 by the JFC as a treatment option (as part of combination therapy) for patients with resistant *H pylori* after first-line treatment and previous exposure to levofloxacin (restricted to Secondary care only).	**For a list of *H pylori* eradication regimes, please see the page of "recommended regimens for helicobacter pylori eradication" in the BNF** **Pepto Bismol® restricted to Secondary care only.** **Duration of treatment – usually 7-14 days, then review**
Prophylaxis of gastrointestinal adverse events in transplant patients/acute transplant rejection on systemic steroids	As per "Prophylaxis of gastrointestinal adverse events with oral corticosteroids"	**First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **Duration of treatment – for the duration of oral corticosteroids**
Prophylaxis of gastrointestinal adverse events in autoimmune hepatitis or alcoholic hepatitis responsive to steroids	As per "Prophylaxis of gastrointestinal adverse events with oral corticosteroids"	**First-line** Omeprazole capsules 20mg once daily **Second-line (or if taking concomitant clopidogrel)** Lansoprazole capsules 15mg once daily **Duration of treatment – for the duration of oral corticosteroids**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of dyspepsia in pregnancy[18,19]	• The first measure for patients is recommendation of lifestyle advice. • Antacid and alginates products are recommended as first-line products (alginate products may be particularly useful if GORD symptoms are dominant). • Patients can be asked to continue ongoing antacid treatment by purchasing from their local pharmacy (unless they meet a general exception that requires the treatment to be prescribed by a GP, such as symptoms that suggest the condition is not minor). • For severe symptoms or symptoms persisting with an antacid or alginate, use a PPI.	**First-line** Peptac® or equivalent – 10-20mL four times daily (after food and before bed). **Second-line (following optimisation of first-line)** Omeprazole capsules 20mg once daily **Duration of treatment – for the duration of symptoms in pregnancy**
Hyperemesis Gravidarum[19]	• The use of a H_2-antagonist or PPI in hyperemesis gravidarum is intended to treat the associated epigastric pain. • For this reason, please refer to "Dyspepsia in pregnancy".	**First-line** Peptac® or equivalent – 10-20mL four times daily (after food and before bed). **Second-line (following optimisation of first-line)** Omeprazole capsules 20mg once daily **Duration of treatment – for the duration of symptoms in pregnancy**

Indication	Recommendations	Choice of medication and duration of treatment
Pre-operative acid reduction in patients at high risk of aspiration/ prophylaxis of aspiration pneumonitis (including patients undergoing a caesarean section) – also known as prevention of Mendelson's syndrome[20–23]	• There are several treatment options to prevent aspiration; these are similar between pregnant and non-pregnant populations. • The aim of treatment is to increase the gastric pH >2.5 and/or reduce gastric volume. • There are suggestions of alternative treatment options in text for caesarean section patients. However, the studies used to determine the possible treatment options were generally of poor quality. • Oral ranitidine was formerly supplied to patients via a PGD. The production of a new PGD to suit the needs of the local population should be considered. • Trusts in NCL should have further discussions locally and come to a decision as to the treatment protocol to adopt in their respective patient cohorts. • There is some evidence to suggest there is no difference in the risk reduction of acid aspiration between intravenous PPI and intravenous H_2-receptor antagonist. • Evidence for the use of an intravenous PPI prior to caesarean section utilised omeprazole in studies; therefore, omeprazole is the preferred option in these cohorts.	**Alternative options in the absence of oral ranitidine formulations:** • A non-particulate antacid (e.g. **30mL sodium citrate**) administered immediately prior to surgery. • **Oral metoclopramide 10mg administered for two doses** (e.g. the night before and morning of surgery) • **Acid suppressive medication in the absence of intravenous ranitidine** o **Intravenous omeprazole 40mg** is the preferred option prior to elective caesarean section o **Intravenous omeprazole 40mg or intravenous pantoprazole 40mg** can be administered prior to induction for emergency surgery in other adult populations† **OR** o Consider **oral omeprazole 20-40mg** for two doses administered orally for elective surgery (e.g. the night before and morning of surgery) • **A combination of these medications can be considered for acid suppression and gastric volume reduction.** **†Intravenous PPI of choice may differ at some Trusts in NCL due to formulary status. Trusts should monitor the supply chain of intravenous pantoprazole throughout the ranitidine shortage and switch to IV omeprazole if concerns in availability arise; in this scenario, IV pantoprazole should be reserved for use in patients where there is concern of a possible interaction between omeprazole and the patients current medication.**

Indication	Recommendations	Choice of medication and duration of treatment
Prophylaxis of gastrointestinal adverse events in adult haematology or oncology patients	• Each patient should be assessed for their risk of developing gastrointestinal adverse events prior to initiating chemotherapy. • Risk factors include: o History of gastroduodenal ulcer, gastrointestinal bleeding, or gastroduodenal perforation; o Older age o Concomitant use of drugs that are known to increase the risk of gastrointestinal bleeding (e.g. anticoagulants, NSAIDs, corticosteroids etc). o Low platelet levels (<50 x 10^9/L) • Patients who require gastroprotection should be offered a PPI in the first instance. • Trusts should consider whether each chemotherapy protocol used locally require an amendment, or whether a local arrangement can be made to substitute H_2-antagonists with recommended PPIs	**First-line** Lansoprazole capsules 15-30mg once daily **<u>Duration of treatment – for the duration of chemotherapy</u>**

Indication	Recommendations	Choice of medication and duration of treatment
Symptom management of oesophageal disorders whilst taking a Multikinase inhibitor (including Tyrosine Kinase inhibitors)	• There is a risk of reduced absorption of certain multikinase inhibitors when given with acid suppressive agent, and should be avoided if possible. • If acid suppression is absolutely necessary due to adverse effects, the multikinase inhibitor needs to be given at a separate time from the acid suppressive agent. • Antacids are short-acting acid suppressive agents and are hence preferred for symptom management. • Antacids should be taken at least 4 hours before or 2 hours after a multikinase inhibitor. • Patients who remain symptomatic despite having trialled antacids titrated up to the maximum daily dose should be assessed prior to offering another line of therapy. This would consider: o The risk of reduced absorption of the respective multikinase inhibitor by the acid suppressive therapy; o The risk of interaction with other regular medication (& the possibility of these causing an increase in gastric acid production); o The severity of the symptoms; o Counselling on lifestyle measures to reduce gastric acid production; o The current availability of any unaffected batches of H_2-antagonists	**First-line** Peptac® or equivalent – 10-20mL four times daily (after food and before bed). **The dose of antacid must be taken either 2 hours before or 4 hours after the multikinase inhibitor.** **Second-line** **The patient must be reviewed to determine the need for further acid suppressive therapy;** **if further treatment is needed, the choice of agent must be made based on availability, safety, risk of interaction with the multikinase inhibitor and other regular medication.**

Indication	Recommendations	Choice of medication and duration of treatment
Use as a histamine blocking agent in pre-medication schedules prior to chemotherapy	• There are several systemic anti-cancer therapies that may require a schedule of pre-medications to prevent infusion reactions. • H_2-antagonists may form part of this schedule of medications due to its histamine blockade properties (one of the few indications where a switch to a PPI would be unsuitable). • It may also form part of a pre-medication regime during re-challenge or part of a desensitisation regime in patients that have previously reacted to systemic anti-cancer therapy. • The British Oncology Pharmacists Association (BOPA) have advised that on the routine use of H_2-antagonists in these areas. Click here for the full statement. • With regard to patients receiving weekly paclitaxel, it is established practice at some cancer centres to stop all pre-medications (including the H_2-antagonist) if no hypersensitivity reactions are observed after the first two doses; there is some evidence to support this. • Cabazitaxel and other regimens of paclitaxel also require pre-medication with H_2-antagonists within their licence. However, the same evidence or established practice does not exist as with weekly paclitaxel. • Consideration should be given to using alternative H_2-antagonists; this will depend on multiple factors and availability. See Table 1 in the BOPA statement for more information on alternative agents. • If no suitable alternative is available, a clinical decision must be made between proceeding with treatment without an H_2-antagonist prior to treatment or switching to an alternative therapy that does not require pre-medication with a H_2-antagonist. • Trusts are encouraged to take part in the National audit of paclitaxel infusion reactions co-ordinated by BOPA.	**Pre-medication for patients receiving weekly paclitaxel** If no hypersensitivity reactions are observed after the first two doses, consider removal of pre-medication with dexamethasone, chlorphenamine and H2-antagonists from dose three onwards (off-label). **Paediatric population** Alternative agents to ranitidine are limited in paediatrics. Cimetidine is available as a liquid and may, in the absence of drug interactions, be given to children aged 1 or over. **Pre-medication for patients receiving cabazitaxel or paclitaxel less often than weekly** Reserve any remaining ranitidine for these patients **Pre-medication protocols in other systemic anti-cancer therapies** Routine use of H_2-antagonists as pre-medication for other systemic anti-cancer therapies may not be warranted; this should be reviewed and rationalised for each. The evidence appraised for the ESMO clinical practice guideline does not have H_2-antagonists documented for many of the agents.

Indication	Recommendations	Choice of medication and duration of treatment
Enteral tube administration of PPIs in adults[24–26]	**Lansoprazole dispersible tablets** can be used for enteral tubes 8Fr or larger. • The dispersible tablet is placed into a barrel of an enteral syringe. • Draw 10mL into the syringe. • Invert the syringe and draw an additional 1mL of air into it. • Shake the syringe gently for 10-20 seconds until the tablet has dispersed. • After the tablet has dispersed, administer via enteral tube. • Refill the syringe with approximately 5mL water, shake gently, and flush the enteral tube. **Lansoprazole capsules** can be used for enteral tubes of all sizes. • Open the contents of a capsule into a medicine pot. • Add 15mL sodium bicarbonate 8.4%. • Stir to dissolve the granules. • Draw the resulting solution into a syringe and administer via the enteral tube. • Add a further 15mL water into the medicine pot; stir to ensure any remaining drug remaining in the pot is mixed with water. • Draw up this dispersion and flush down the tube to ensure the whole dose is given. • Flush the tube with water. If the tube becomes blocked, lock the tube using sodium bicarbonate 8.4% to dissolve any enteric coated granules lodged in the tube. For fine-bore feeding tubes <8 Fr, a PPI suspension formulation should be used. All liquid PPIs are generally not cost-effective and have short expiries, and most are unlicensed. It can be administered without further dilution via an enteral tube. After administration, draw up an equal volume of water into the syringe used for the PPI and flush via the enteral tube to ensure the whole dose is given.	**First-line** Lansoprazole dispersible tablets (dispersed in water) **OR** (if fine bore tube <8Fr) Lansoprazole capsules (opened and dispersed in sodium bicarbonate 8.4%) **Second-line** PPI suspension [Δ] **[Δ] PPI suspensions have a very short expiry, are not cost-effective and most are unlicensed; they should be reserved for those patients who require gastroprotection via enteral tube post-discharge and there are compliance issues with the preparation & administration of a lansoprazole dispersible tablet or capsule or if their tube becomes blocked when using lansoprazole dispersible tablets.**

Stress ulcer prophylaxis (SUP) in neonates and children[27,28]	• Patients at low risk for a gastrointestinal bleed (e.g. patients ventilated <48 hours, few morbidities, no coagulopathy, no major surgery or trauma, no high dose steroids and no acute lung injury) should be reviewed for clinical need of SUP medication on a case-by-case basis. • Patients in intensive care with shock, sepsis, coagulopathy, or who have respiratory, hepatic or renal failure will usually require stress ulcer prophylaxis. • SUP should be stopped when risk factors no longer exist. • In patients who are able to receive enteral medications and who require SUP a dispersible PPI should be prescribed. • Intravenous PPIs may be used in critically ill patients who cannot receive enteral medications; however, the patient must be reviewed for the need for stress ulcer prophylaxis throughout admission (particularly upon discharge from critical care). • Do not prescribe acid suppressive therapy for stress ulcer prophylaxis on discharge from hospital (unless there is a clear alternative clinical indication).	**If SUP is indicated and medication can be administered orally:** Lansoprazole dispersible tablets* For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **If SUP is indicated and medication can be administered via NG tube:** Lansoprazole capsules† For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **If SUP is indicated and the patient is nil by mouth, has no enteral access and ranitidine IV is not available:** **Intravenous omeprazole** <1 month: 0.5mg/kg OD (over 5 mins) 1 month to 11 years: 0.5mg/kg OD (max 20mg OD); increased if necessary to 2mg/kg OD (max 40mg OD) 12 years to 17 years: 40mg once daily **Or Intravenous esomeprazole** 0-1 month: 0.5mg/kg OD 1-11 months: 1mg/kg OD 1 **year** – 11 **years**: If <20kg = 10mg OD; If ≥20kg = 10-20mg OD 12 **years** – 17 **years**: 40mg OD **Where concerns of interaction between** **Duration of treatment – until there are no longer risk factors for stress ulcers.** ***Please note that the SPC for lansoprazole dispersible tablets cannot recommend the use of the medication in**

Indication	Recommendations	Choice of medication and duration of treatment
		children due to limited data; however, it is a recommended treatment option used by Specialist teams at Great Ormond Street Hospital. **†Granules can be emptied from capsules and mixed with 10mL of 8.4% sodium bicarbonate prior to administration; this has shown to be effective when administered nasogastrically and has a shelf-life of 14 days when stored in the fridge (though Specialist teams at GOSH advocate each reconstitution to be single-use only).**
Prophylaxis of gastrointestinal adverse events in paediatric haematology or oncology patients[29]	• Each patient should be assessed for their risk of developing gastrointestinal adverse events prior to initiating chemotherapy. • The risk of developing dyspepsia or epigastric pain is compounded by several factors, such as concomitant corticosteroids, stress, chemotherapy, low platelets, nausea and vomiting. • Patients who require gastroprotection should be offered a PPI in the first instance. • Trusts should consider whether each chemotherapy protocol used locally require an amendment, or whether a local arrangement can be made to substitute H_2-antagonists with recommended PPIs	Lansoprazole dispersible tablets* For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **Duration of treatment – for the duration of chemotherapy** ***Please note that the SPC for lansoprazole dispersible tablets cannot recommend the use of the medication in children due to limited data[24]; however, it is a recommended treatment due to the lower risk of interactions with chemotherapy compared to omeprazole.**

Indication	Recommendations	Choice of medication and duration of treatment
Prophylaxis of gastrointestinal adverse events with oral corticosteroids in paediatrics[9]	• Consider a PPI when gastroprotection is required in patients receiving oral corticosteroids who are at high risk of gastrointestinal bleeding or dyspepsia. • The risk factors for gastrointestinal adverse effects include: o History of gastroduodenal ulcer, gastrointestinal bleeding, or gastroduodenal perforation; o Concomitant use of drugs that are known to increase the risk of gastrointestinal bleeding, such as NSAIDs and anticoagulants; o Serious comorbidity, such as advanced cancer.	Lansoprazole dispersible tablets*† For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **Duration of treatment – for the duration of corticosteroid treatment** ***Please note that the SPC for lansoprazole dispersible tablets cannot recommend the use of the medication in children due to limited data; however, it is a recommended treatment option used by Specialist teams at Great Ormond Street Hospital.** **†If dispersing the tablet in water, consider dose rounding to the nearest quarter tablet into water and using the whole of the resultant solution.**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of Gastro-Oesophageal Reflux (GOR) and Gastro-Oesophageal Reflux Disease (GORD) in children and young people who can tolerate oral feeding.[30]	• In breast fed infants with frequent regurgitation associated with marked distress despite a breastfeeding assessment and advice, consider alginate therapy for a trial period of 1-2 weeks. • In formula-fed infants, if the stepped approach of feeding is unsuccessful as per Section 1.2.3 of NICE Guidance, stop the thickened formula and offer alginate therapy for a trial period of 1-2 weeks. • Alginate therapy can be continued if successful, but try stopping at intervals to see if the infant has recovered. • Acid-suppressing drugs should not be offered to treat over regurgitation in infants and children occurring as an isolated symptom. • Consider a 4-week trial of a PPI for those who are unable to tell you about their symptoms who have overt regurgitation and one or more of the following: o Unexplained feeding difficulties (e.g. refusing feeds, gagging or choking). o Distressed behaviour o Faltering growth • Consider a 4-week trial of a PPI for children and young people with persistent heartburn, retrosternal or epigastric pain. • Assess the response to the 4-week trial and refer to specialist if symptoms do not resolve or recur after stopping treatment. • Offer PPI treatment to infants, children and young people with endoscopy-proven reflux oesophagitis, and consider repeat endoscopic examinations as necessary to guide subsequent treatment. • Please note that some Specialists may recommend higher doses in the most severe cases of GORD (on Consultant approval only).	**Alginate therapy** Gaviscon infant® powder sachets Neonate (body weight up to 4.5kg) 1 dose as required; maximum 6 doses per day Neonate (body weight 4.5kg or above) 2 doses as required; maximum 12 doses per day Child aged 1-23 months (body weight up to 4.5kg) 1 dose as required; maximum 6 doses per day Child aged 1-23 months (body weight 4.5kg or above) 2 doses as required; maximum 12 doses per day **PPI therapy** Lansoprazole dispersible tablets*† For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **Duration of treatment – 4 weeks, then review** ***Please note that the SPC for lansoprazole dispersible tablets cannot recommend the use of the medication in children due to limited data; however, it is a recommended treatment option used by Specialist teams at Great Ormond Street Hospital.** **†If dispersing the tablet in water, consider dose rounding to the nearest quarter tablet into water and using the whole of the resultant solution.**

Indication	Recommendations	Choice of medication and duration of treatment
Treatment of Gastro-Oesophageal Reflux (GOR), treatment of Gastro-Oesophageal Reflux Disease (GORD) or prophylaxis of gastrointestinal adverse events with oral corticosteroids in children and young people **who are fed by enteral tubes**.[26,30]	• As per "Treatment of Gastro-Oesophageal Reflux (GOR) and Gastro-Oesophageal Reflux Disease (GORD) in children and young people who can tolerate oral feeding" or "Prophylaxis of gastrointestinal adverse events with oral corticosteroids in paediatrics" sections. • Please note that some Specialists may recommend higher doses of PPI in the most severe cases of GORD (on Consultant approval only).	**First-line** Lansoprazole capsules*† For children up to 30kg: 0.5-1mg/kg (max 15mg) every morning For children 30kg and over: 15mg every morning **Second-line (and for discharge after using lansoprazole capsules via enteral tube)** PPI suspension[Δ] ***Granules can be emptied from capsules and mixed with 10mL of 8.4% sodium bicarbonate prior to administration; this has shown to be effective when administered nasogastrically and has a shelf-life of 14 days when stored in the fridge (though Specialist teams at GOSH advocate each reconstitution to be single-use only).** **[Δ] PPI suspensions have a very short expiry, are not cost-effective and most are unlicensed; they should be reserved for those patients who require gastroprotection via enteral tube post-discharge and there are compliance issues with the preparation & administration of a lansoprazole dispersible tablet or capsule or if their tube becomes blocked when using lansoprazole dispersible tablets**

3. H_2-antagonist availability

For other indications not listed in this document, it has not yet been agreed between the Joint Formulary Committee and Specialists the most appropriate treatment protocol to be used in the absence of ranitidine. Patients should be reviewed for the need for an H_2-antagonist, and an appropriate alternative should be chosen based on risk versus benefit (including the severity of symptoms, clinical interactions with current medicines, formulary status and optimisation of current treatments). There may be very small amounts of nizatidine, famotidine or cimetidine available, though their routine and continued supply throughout the ranitidine supply disruption cannot be guaranteed. Prescribers should liaise with their pharmacists to understand local stock availability of clinical alternatives.

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Groups which were consulted and have given approval:	NCL Consultants, Specialist Pharmacists and Formulary Pharmacists
File name:	Supply disruption of oral ranitidine – Trust communication
Version number:	V3.0
Available on:	https://www.ncl-mon.nhs.uk/
Disseminated to:	All Trusts and CCGs in NCL
Equality impact assessment:	No impact identified
NCL Joint Formulary Committee Approval date:	15/06/2020
Review date:	01/01/2021

Document control

Date	Version	Amendments
31/10/2019	V1.0	First version
01/11/2019	V1.1	Minor amendment to enteral feeding tubes (fine-bore defined as <8 Fr) Additional sentence added to encourage clinicians to evaluate risk versus benefit of using PPIs in certain patient populations
01/11/2019	V1.2	Additional line for consideration in thromboprophylaxis
19/11/2019	V1.3	'Review date' updated
11/12/2019	V2.0	Indications for acid suppressions with multikinase inhibitors added DOAC monograph updated Section 3 updated
15/06/2020	V3.0	Updated document following disruption to intravenous ranitidine supply and suspension of manufacturing for all ranitidine formulations