RANITIDINE GUIDANCE

SUMMARY

- All oral formulations of ranitidine are anticipated to be out of stock, with no date for resupply until further notice.
- An investigation by the Swiss and German regulatory agencies and the US Food and Drug Administration (FDA), has identified a contaminant, N-nitrosodimethylamine (NDMA), in samples of ranitidine active substance.
- All stock manufactured for the UK using the affected ranitidine active substance has been quarantined, whilst Medicines and Healthcare products Regulatory Agency (MHRA) investigations are ongoing.
- Although all oral formulations are expected to be out of stock, very limited supplies of unaffected oral ranitidine products may remain available and should be reserved for those patients in whom alternatives are not clinically appropriate.
- Although some IV products are affected, there is sufficient unaffected IV stock available to meet current UK demand. This situation is currently under review and may change.
- Do not initiate treatment with oral ranitidine in new patients.

ACTION

All patients should be reviewed and if ongoing treatment is required, discuss with patient and look to switch to clinically appropriate alternatives.

Management for Adults

1. Review to establish if ongoing treatment is still required.
2. Can ranitidine be stopped or stepped down to an antacid/alginate?
3. If ongoing treatment is still required, then consider switching to an alternative oral treatment such as PPI if no contra-indications
4. **Consider starting at the higher dose and titrate according to symptoms** (see table 1 for indication and dose regime). Follow up should be arranged to review to reduce dose to the minimum dose required
5. **The first line formulary choice is omeprazole. Other formulary choices include lansoprazole.** There are currently sufficient supplies of oral omeprazole to manage an increase in demand.
6. Patients who have previously tried a PPI can they be considered for an alternative PPI?
7. If patient already taking PPI and not on maximum dose- increase PPI dose to control symptoms. If already taking maximum dose of PPI consider referral for specialist advice
8. Patients who clinically should remain on ranitidine see below
9. **It is recommended that, where possible, patients are NOT switched to an alternative H2-receptor antagonist in the first instance as this may exacerbate a shortage of these products.**
10. The decision on which therapy to prescribe will depend on the indication, past medical history, co-morbidities, concomitant administration of other medications for each individual patient and also stock availability.
11. It is important to counsel the patient about any CHANGE to their medication BEFORE the change is made. Especially where there is an alternative dosing regimen
12. Specialist indications / unlicensed indications - Local specialists should be consulted for advice on alternatives for specialist / unlicensed indications

Patients who clinically should remain on ranitidine but has now been withdrawn:

- On dual treatment of ranitidine and PPI and unsuitable for step-down - Consider maximising dose of PPI and trial without ranitidine if required.
- On ranitidine for pre-chemotherapy prevention, this will be reviewed in secondary care.
- On ranitidine due to C.difficile risk with PPI current or recent episode of C.diff, or previously had C.diff and currently on antibiotics and are at high risk. See recommendations below
- Allergic or intolerant to PPI or PPI contraindicated (e.g. due to interstitial nephritis, acute kidney injury, previous hyponatraemia with PPI etc). See recommendations below

Alternative H2 antagonists Recommendations:

- If a PPI is not suitable and acid suppression is required, the most cost effective alternative H2 - receptor antagonist is Nizatidine, where stocks are available locally.
- Please note that supplies of alternative H2 – receptor antagonists are extremely limited; therefore, supplies should be reserved for patients where a PPI is not clinically appropriate. (see Table 1)
- Cimetidine is considered to have many potential interactions and side effects, which may limit its suitability as an alternative.
- Famotidine is significantly more expensive.
- Only prescribe these products as an alternative to ranitidine in patients in whom proton pump inhibitors (PPIs) are unsuitable.
- Prior to prescribing, prescribers should liaise with their pharmacists to understand local stock availability (including resupply dates) of clinical alternatives.

Table 1: Alternative oral products for the main indications of ranitidine in ADULTS

Before switching to another agent, review if patients still require treatment or could be stepped down to an antacid or alginate.

Acid suppressant Formulation GU/DU treatment GU/DU prophylaxis GORD NSAID associated GU/DU treatment/ prophylaxis

Acid suppressant	Formulation	GU/DU treatment	GU/DU prophylaxis	GORD	NSAID associated GU/DU treatment/ prophylaxis	Comments
PROTON PUMP INHIBITORS						
Omeprazole	Capsules, tablets and dispersible tablets: 10mg, 20mg, 40mg	20-40mg OD	10-40mg OD (DU) 20-40mg OD (GU)	20-40mg OD (treatment) 10-40mg OD (long term management after healed reflux oesophagitis) 10-20mg OD symptomatic GORD	20mg OD (prevention and treatment)	*Not to be prescribed with clopidogrel due to risk of reducing its antiplatelet efficacy.* Losec MUPS® is not licensed for use via enteral feeding tubes, however there is extensive experience of using via this route in practice.
Lansoprazole	Capsules and dispersible tablets: 15mg and 30mg	30mg OD	UL (15-30mg OD) *	30mg OD (treatment) 15-30mg (prevention) 15-30mg OD (symptomatic GORD)	30mg OD (treatment) 15-30mg (prevention)	Orodispersible tablets are licensed for administration via nasogastric (NG) tubes.
Pantoprazole	Tablets 20 and 40mg	40-80mg OD	UL (20-40mg OD) *	20mg OD symptomatic GORD 20-40mg OD long term management and prevention of relapse	20mg OD (prevention)	
Esomeprazole	Tablets, capsules 20mg, 40mg Granules 10mg	UL (20-40mg OD) *	UL (20-40mg OD) *	40mg OD (treatment) 20mg OD (prevention and symptomatic treatment)	20mg OD (prevention and treatment)	*Not to be prescribed with clopidogrel due to risk of reducing its antiplatelet efficacy.* Granules are licensed for administration via NG or gastric tubes.
Rabeprazole	Tablets 10mg, 20mg	20mg OD	UL (10-20mg OD) *	20mg OD (treatment) 10-20mg long term maintenance 10mg OD symptomatic GORD	**UNLICENSED**	

*Key:,GU: gastric ulcer, DU: duodenal ulcer; PU: peptic ulcer; GORD: gastroesophageal reflux disease, UL: unlicensed *Based on PPI dose equivalence table for severe oesophagitis in NICE guideline (CG184) update (2014): https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-*

Acid suppressant	Formulation	GU/DU treatment	GU/DU prophylaxis	GORD	NSAID associated GU/DU treatment/ prophylaxis	Comments
H2-receptor antagonists						
Nizatidine	Capsules 150mg	150mg BD or 300mg OD	150mg OD	150-300mg bd	150 BD or 300mg OD (treatment)	
Famotidine	Tablets 20mg, 40mg	40mg OD	DU 20mg OD	**UNLICENSED**	**UNLICENSED**	
Cimetidine*	Tablets 200mg, 400mg and 800mg Liquid 200mg/5mL	400mg BD or 800mg ON (up to 400mg QDS)	400mg ON up to BD	400mg QDS	**UNLICENSED**	No data on crushing tablets **caution as CYP P450 inhibitor; care with drug interactions- consult SPC*

Key:,GU: gastric ulcer, DU: duodenal ulcer; PU: peptic ulcer; GORD: gastroesophageal reflux disease, UL: unlicensed *******Based on PPI dose equivalence table for severe oesophagitis in NICE guideline (CG184) update (2014): https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-*

Management for Children

1 Patients on Ranitidine only

a) Stable, asymptomatic patients should be considered for stopping ranitidine.
Either half the dose keeping the same frequency and stop after two or more weeks OR keep the same dose and reduce the frequency to once daily then stop over the same time frame.
b) Depending on age, consider the use of Gaviscon Infant® or Peptac®, either "as required" or regularly to ease the cessation of ranitidine if symptoms are uncontrolled.
c) If concerned that a straight withdrawal will not be possible, introduce omeprazole first then withdraw the ranitidine as above.
d) Omeprazole capsules or dispersible tablets are the preparation of choice. (see table 2 for indication)

2 Patients on Ranitidine and a PPI (including those with nasogastric/gastrostomy tubes)

a) Try stopping the ranitidine as in 1a) above.
b) If not possible to stop ranitidine, review whether the omeprazole dose been maximised or stepped up to the next highest practical dose. This may allow a gradual withdrawal of ranitidine, after which assess if the omeprazole may be reduced over the next weeks to months to keep symptoms under control.

3. Specialist indications / unlicensed indications

Local specialists should be consulted for advice on alternatives for specialist / unlicensed indications

4. If an H2 antagonist is required

a) For children (over 1 year), consider switching to **cimetidine** as a last resort. This must be carefully considered in each individual patient.
b) **Cimetidine** is a cytochrome P450 inhibitor and interacts with many drugs. Check for Drug Interactions
c) **Cimetidine oral solution** is licensed in children over 1 year old (see table 2)

Table 2: Alternative oral products for the main indications of RANITIDINE in CHILDREN (Refer to BNFC or local paediatric formulary for other indications/off label use)

Acid suppressant	Formulation	Licensed age group	Dose	Comments
PROTON PUMP INHIBITORS				
OMEPRAZOLE	Capsules, tablets and dispersible tablets: 10mg, 20mg, 40mg *An unlicensed liquid is available as a manufactured special. However, there is only limited evidence of efficacy.*	> 1 year and ≥ 10 kg	<2.5kg 0.7-1.4mg/kg to 3mg/kg/day 2.5 – 7kg 5mg to 3mg/kg/day (max10mg) 7 - 15kg 10mg to 20mg OD >15kg 20mg to 40mg OD	Losec MUPS® tablets may be dispersed in water (do not crush tablet) for oral liquid administration. Halve 10mg tablet before dispersing for 5mg dose. • Losec MUPS® is not licensed for use via enteral feeding tubes, however there is extensive experience of using via this route in practice (NB: granules are approx. 0.5mm in diameter and tend to block fine-bore feeding tubes [<8Fr]) • Esomeprazole granules are licensed for administration down tubes ≥6 Fr. • *Unlicensed liquid may be required in age<1 year with nasogastric (NG) or gastric tubes < 8 Fr, or in patients intolerant/allergic to excipients in esomeprazole granules.* *Not to be prescribed with clopidogrel due to risk of reducing its antiplatelet efficacy*
ESOMEPRAZOLE	Tablets, capsules, 20mg and 40mg	≥12 years	20-40mg OD	Granules licensed for administration via enteral feeding tube ≥*6 Fr* *Not to be prescribed with clopidogrel due to risk of reducing its antiplatelet efficacy*
	10 mg gastro-resistant granules for oral suspension	1-11 years	10 mg gastro-resistant granules for oral suspension Weight 3.5 – <20 kg 10mg OD Weight ≥20 kg: 10-20mg OD	1-11 years Weight 10 - <20 kg:10mg OD Weight ≥20 kg: 10-20mg OD
				Weight 10 - <20 kg:10mg OD Weight ≥20 kg: 10-20mg OD
PANTOPRAZOLE	Tablets 20mg and 40mg	≥12 years	20 mg OD	
LANSOPRAZOLE	Capsules and dispersible tablets: 15mg and 30mg	No paediatric licence but used off label in this population	Off label use: Infant 2.5kg – 5kg 3.75mg (1/4 of a 15mg tablet) OD 5 – 10kg 7.5mg (1/2 a 15mg tablet) OD 10 - 30kg 15mg OD >30kg 30mg OD	Dispersible tablets • • Excipients include aspartame. • • Dose should be rounded to the nearest solid dosage form i.e. half or quarter of tablet. • • Halve or quarter tablet before dispersing in water for oral liquid administration. Stir thoroughly before administration. • • Licensed for administration via NG tube (can be dispersed in 10mL water and flushed through tube > 8Fr). • • For fine-bore tubes <8Fr, dissolve contents of capsule in 8.4% sodium bicarbonate before administration). • • Lansoprazole dispersible tablets are generally easier to use than omeprazole. When using feeding tubes of gauge under 8Fr in patients over 2.5kg.
RABEPRAZOLE	Tablets 10mg and 20mg	No paediatric licence	Off label use 1-11 years; <15kg: 5mg OD ≥15kg: 10mg OD ≥12 years: 20mg OD	Crushing is not recommended. Not suitable for enteral tube administration

Acid suppressant	Formulation	Licensed age group	Dose	Comments
H2-receptor antagonists				
Cimetidine	Tablets 200mg, 400mg and 800mg Liquid 200mg/5mL	>1year	>1 year 25-30mg/kg per day in divided doses Use in age< 1 year not fully evaluated; 20mg/kg/day in divided doses has been used	No data on crushing tablets. *Caution as CYP P450 inhibitor; care with drug interactions - consult SPC*
Nizatidine	Capsules 150mg	No paediatric licence	Off label use 6 months to 11 years 5-10mg/kg/day in 2 divided doses ≥12 years 150mg BD	Not suitable to be used via enteral feeding tubes, as whilst drug dissolves in water, excipients do not and may coat and block tube.
Famotidine	Tablets 20mg and 40mg	No paediatric licence	Off label use: 1 to ≤3 months 0.5mg/kg/dose OD ≥3 months to <1 year 0.5mg/kg/dose BD 1 to 16 years 0.5mg/kg/dose BD (maximum 40mg dose)	Without crushing, tablets will disperse in 2 to 5 minutes. This process can be quickened by crushing and mixing tablets with water to for administration. No information available on giving resulting suspension via enteral feeding tubes

***References**: SPCs, Handbook of Drug Administration via Enteral Feeding Tubes, The NEWT Guidelines for administration of medication to patients with enteral feeding tubes or swallowing difficulties, Evelina London Paediatric Formulary, BNFC, Paediatric & Neonatal Dosage Handbook, 23rd ed*

Please note: Any decision to prescribe off-label must take into account the relevant GMC guidance and NHS Trust governance procedures for unlicensed medicines. Prescribers are advised to pay particular attention to the risks associated with using unlicensed medicines or using a licensed medicine off-label.

References

https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103017

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NICE Guidance (CG184) – Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Updated November 2014. Available at: https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-Dosage-information-on-proton-pump-inhibitors