Department of Health & Social Care

NHS

UPDATE - Supply Disruption Alert

SDA/2019/005 (U2) Issued: 20 December 2019 Valid until: 20 March 2020

Ranitidine: all formulations – Supply Disruption Alert – second update

Summary

This supply disruption alert update supersedes the previous update (SDA/2019/005-U) issued on 27 November 2019 and advises on the following.

- Ranitidine injection is back in stock and supplies are available to order from wholesalers.
- Ranitidine tablets, effervescent tablets and oral solution will continue to be unavailable with no date for resupply until further notice.
- Clinical advice on alternatives to oral ranitidine in children has been produced by UK Medicines Information (table 2). This guidance is in addition to previous advice issued for the management of adults (table 1).
- There are short term supply issues affecting alternative H2-receptor antagonists.

Action

All healthcare professionals in primary, secondary or specialist healthcare services who prescribe or supply ranitidine should consider the following advice to manage affected patients.

Ranitidine injection

- Prescribe ranitidine injection in line with local guidance.
- Do not stockpile.

Oral ranitidine

Continue to follow the advice issued in SDA/2009/005-U, as detailed below:

Licensed use for gastrointestinal conditions

- Do not initiate treatment with oral ranitidine in new patients.
- Identify current patients prescribed ranitidine tablets, effervescent tablets and oral solution, and review to establish if ongoing treatment is still required.
- If ongoing treatment is still required, then consider switching to an alternative oral treatment (see table 1 for alternative acid suppressants in adults and table 2 for alternative acid suppressants in children).
- 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. There are currently sufficient supplies of oral omeprazole to manage an increase in demand.

Specialist / unlicensed indications

- Do not initiate treatment with oral ranitidine in new patients.
- Local specialists should be consulted for advice on alternatives for specialist / unlicensed indications and high-risk cohorts of patients.
- For clinical alternatives to oral ranitidine in paediatric patients, please see table 2.

Alternative H2 antagonists

- There are currently short-term supply issues affecting cimetidine, famotidine and nizatidine.
- 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.
- Further information and updates on these shortages will be disseminated through primary and secondary care networks.

Deadlines for actions

Actions initiated:	on receipt of this alert
Actions completed:	20 March 2020

Background

In September 2019, regulatory investigations identified a contaminant, N-nitrosodimethylamine (NDMA), a probable human carcinogen, in samples of ranitidine active substance. The Medicines and Healthcare products Regulatory Agency (MHRA), alongside European Health Authorities, has been investigating ranitidine products manufactured for the UK market. Since the previous supply disruption alert update (SDA/2019/005-U) was issued on 27 November 2019, MHRA investigations have progressed as below.

Ranitidine injection

- As regulatory investigations have progressed, MHRA have granted approval for the release of Alliance Pharmaceutical's quarantined stock of ranitidine injection on 5 December 2019.
- Alliance Pharmaceuticals have sufficient stock available to support normal UK demand.
- Ranitidine injection supplies from other manufacturers remain unavailable at this stage.
- This situation is dynamic as MHRA investigations are ongoing.

Ranitidine oral products

- There has been no change to the supply situation or regulatory position on ranitidine oral products since the last update was issued.
- Manufacturers of all affected formulations of oral ranitidine have been instructed to quarantine unreleased stock at manufacturer level. The MHRA are continually reviewing whether batches of ranitidine in quarantine can be released.
- Extremely limited supplies of oral ranitidine remaining in wholesalers and pharmacies, which have not been recalled by the MHRA, are available and can be supplied.
- Once remaining supplies of ranitidine have been exhausted, there will be no additional supply to the market until further notice.
- A message has been added to the ranitidine webpage on the NHS website and information has been shared with NHS 111 and patient groups.

MHRA class 2 recalls

To date, the MHRA have issued eight Class 2 (pharmacy, wholesaler and retailer level) recalls of ranitidine products, which are listed below.

- Class 2 Medicines recall: Zantac Injection 50mg/2ml, Zantac Syrup 150mg/10ml, Zantac Tablets 150mg, Zantac Tablets 300mg (EL (19)A 24)
- Class 2 Medicines recall: Ranitidine Effervescent Tablets 150mg, Ranitidine Effervescent Tablets 300mg (EL (19)A/27)
- Class 2 Medicines recall: Ranitidine 150mg/10ml Oral Solution (EL (19)A/29)
- Class 2 Medicines recall: Zantac 75 Relief Tablets, Zantac 75 Tablets, Gal pharm Indigestion Relief 75mg Tablets, Boots Heartburn & Indigestion Relief 75mg Tablets, Kirkland Indigestion Relief 75mg Tablets, Morrisons Indigestion & Heartburn Relief 75mg Tablets, Boots Heartburn & Indigestion Relief 75mg Tablets (EL (19)A/30)
- Class 2 Medicines Recall: Ranitidine Oral Solution 30mg/ml, PL 31862/0023, Ranitidine 150mg Tablets, PL 11311/0138 (EL(19)A/36)
- Class 2 Medicines recall: Ranitidine 75mg Tablets, (Various Liveries) (EL(19)A/37)
- Class 2 Medicines recall: Ranitidine 150mg Film-Coated Tablets, PL 20075/0063, Ranitidine 300mg Film-Coated Tablets, PL 20075/0064 (EL(19)A/40)
- Class 2 Medicines Recall: Medley Pharma Limited, Ranitidine 150mg Tablets BP, PL 43870/0026, Ranitidine 300mg Tablets BP, PL 43870/0027 (EL(19)A/41)

Alternative H2-receptor antagonists

There are currently short-term supply issues with H2-receptor antagonists; cimetidine, nizatidine and famotidine. Prescribers should work in close collaboration with pharmacy teams to understand local availability and resupply dates.

Long term supply

At present, in Europe, all suppliers of ranitidine's active ingredient have had their Certificate of Suitability (CEP) suspended. Therefore, until regulatory investigations are complete, and an uncontaminated supplier of ranitidine active ingredient has been found, no further supplies of ranitidine will be manufactured.

It is important to note that the situation is dynamic and further supplies of ranitidine in all formulations and strengths cannot be confirmed. Further details will be shared as and when they are available.

Product details

The following presentations of ranitidine are affected:

- Ranitidine 75mg, 150mg and 300mg tablets
- Ranitidine 150mg and 300mg effervescent tablets
- Ranitidine 150mg/5ml and 75mg/5ml oral solution
- Ranitidine 50mg/2ml injection

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Alternative formulations

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	Comments
Proton pump inhibitors						
Omeprazole	Capsules, tablets and dispersible tablets: 10mg, 20mg, 40mg Injection 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 Injection 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 Injection 40mg	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	UL	

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	UL	UL	
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	UL	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-*

Table 2: Alternative oral acid suppressants for gastro-oesophageal reflux disease in children [Refer to BNFC or local paediatric formulary for other indications/off label use]

Before switching to another agent, review if patients still require acid suppression or if could be stepped down to an antacid

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	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.

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Email: supplyresiliencemd@dhsc.gov.uk

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