Department of Health & Social Care

NHS

UPDATE - Supply Disruption Alert

SDA/2019/005 (U) Issued: 27 November 2019 Valid until: 28 February 2020

Ranitidine: all formulations – Supply Disruption Alert – Update

Summary

- Further to the previous ranitidine supply disruption alert (SDA/2019/005) issued on 15 October 2019, this is an update on the supply status of both ranitidine oral and injectable products.
- As investigations into ranitidine have progressed, the Medicines and Healthcare products Regulatory Agency (MHRA) have instructed suppliers of both oral and injectable ranitidine in the UK to quarantine all affected, unreleased stock at manufacturer level whilst their investigations are ongoing.
- Ranitidine tablets, effervescent tablets and oral solution are expected to be out of stock with no date for resupply until further notice.
- Ranitidine injection is now also expected to be out of stock imminently with no date for resupply until further notice.
- Extremely limited supplies remaining in wholesalers and pharmacies, which have not been recalled by the MHRA, are available and can be supplied.
- No new patients should be initiated on treatment with ranitidine oral or injectable products.
- All patients should be reviewed as repeat prescriptions are requested and if ongoing treatment is required, be switched to clinical alternatives.

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.

Oral ranitidine

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). 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, including paediatrics.

Ranitidine injection

- Do not initiate treatment with ranitidine injection in new patients.
- Identify current patients prescribed ranitidine injection and review to establish if ongoing treatment is still required.
- If ongoing treatment is still required, then review to see if switching to an alternative oral treatment is appropriate *(see table 1 and additional recommendations under the Oral Ranitidine section above for advice on oral alternatives)*.
- If ongoing IV treatment is still required, then consider switching to an alternative IV treatment *(see table 2 for advice on IV alternatives).* There are currently sufficient supplies of IV omeprazole to manage an increase in demand. There are currently no licensed alternative IV H2-receptor antagonists available in the UK.

Prescribers should work in close collaboration with their pharmacists to understand which clinical alternatives are available.

Deadlines for actions

Actions initiated:	on receipt of this alerty
Actions completed:	28 February 2020

Product details

The following presentations of ranitidine are affected:

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

Background

In September 2019, an investigation by the Swiss and German regulatory agencies and the US Food and Drug Administration (FDA) 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 original supply disruption alert (SDA/2019/005) was issued on 15 October 2019, MHRA investigations have progressed. Manufacturers of all affected formulations of 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.

As a result, ranitidine tablets, effervescent tablets and oral solution continue to be expected to be out of stock. Ranitidine injection, whose supply was previously thought to be unaffected, is now also anticipated to be out of stock imminently. At this stage, there is no date for resupply of all ranitidine products until further notice.

To date, the MHRA have issued six 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)

Extremely limited supplies remaining in wholesalers and pharmacies, which have not been recalled by the MHRA, are available and can be supplied.

A message has been added to the ranitidine webpage on the NHS website and information has been shared with NHS 111 and patient groups.

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: 10,20,40mg 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® not licensed for use via enteral feeding tubes, but extensive experience of using them in this way Paediatric licence: Reflux oesophagitis treatment, symptomatic treatment of heartburn and acid regurgitation in GORD (>1yr); DU due to H Pylori (>4yrs)
Lansoprazole	Capsules and dispersible tablets: 15 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)	No paediatric licence but used off label in this population Orodispersible tablets licensed for administration down NG tube
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)	Paediatric licence above 12 years

Acid suppressant	Formulation	GU/DU treatment	GU/DU prophylaxis	GORD	NSAID associated GU/DU treatment/ prophylaxis	Comments
Proton pump inhibitors (continued)						
Esomeprazole*	Tablets, capsules 20 and 40 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* <u>Paediatric licence:</u> above 12 years for tablets, capsules (treatment of GORD) Granules: 1-11 years (GORD) >4 years (H Pylori) Granules licensed for administration down NG or gastric tube
Rabeprazole	Tablets 10 and 20mg	20mg OD	UL (10-20mg OD) ¥	20mg OD (treatment) 10-20mg long term maintenance 10mg OD symptomatic GORD	UL	No paediatric licence
H2-receptor antagonists						
Nizatidine	Capsules 150mg	150mg BD or 300mg OD	150mg OD	150-300mg bd	150 BD or 300mg OD (treatment)	No paediatric licence
Famotidine	Tablets 20 and 40mg	40mg OD	DU 20mg OD	UL	UL	No paediatric licence
Cimetidine*	Tablets 200, 400 and 800mg Liquid 200mg/5mL	400mg BD OR 800mg ON (up to 400mg QDS)	400mg ON up to BD	400mg QDS	UL	Paediatric licence >1yr **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-

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Table 2: Alternative injectable products for the main indications of ranitidine in adults:

Before switching to another IV agent, review if switching to an alternative oral treatment is appropriate *(see table 1 below for advice on oral alternatives for licensed indications)*

Acid suppressant	Gastric acid suppression in surgical procedures	Prophylaxis of stress ulceration	Conditions where acid suppression needed but oral route not available	Comments
Omeprazole Injection 40mg	*Not licensed* Suggest stat dose of 40mg given over 5 minutes as an IV bolus or infused over 20-30 minutes.	*Not licensed* Suggest 40mg once daily given over 5 minutes as an IV bolus or infused over 20-30 minutes	Suggest 20-40mg once daily is adequate for most conditions however for conditions such as Zollinger Ellison syndrome a higher dose of 60mg daily may be needed.	• Contra-indicated in patients with previous hypersensitivity reaction to omeprazole or the excipients contained in the injection and in patients taking nelfinavir. • For stat dose – potential for drug interactions not likely to be clinically significant. • For repeat doses - potential for adverse drug interactions should be assessed. This is especially important for patients taking concomitant clopidogrel or the antiretroviral medicines atazanavir or nelfinavir. In patients taking clopidogrel, pantoprazole may be a better choice of PPI. • Patients treated with a PPI rather than ranitidine may be more likely to develop electrolyte abnormalities such as hyponatraemia or hypomagnesaemia.
Pantoprazole Injection 40mg	*Not licensed* Suggest stat dose of 40mg given as an IV bolus over at least 2 minutes or infused over at least 15 minutes	*Not licensed* Suggest stat dose of 40mg given as an IV bolus over at least 2 minutes or infused over at least 15 minutes	Suggest 40mg once daily is adequate for most conditions however for conditions such as Zollinger Ellison syndrome a higher dose of 60mg daily may be needed.	• Contra-indicated in patients with previous hypersensitivity reaction to pantoprazole or the excipients contained in the injection. • For stat dose – potential for drug interactions not likely to be clinically significant. • For repeat doses - potential for adverse drug interactions should be assessed. This is especially important for patients taking the antiretroviral medicines atazanavir or rilpivirine. In patients taking clopidogrel, pantoprazole is probably the most appropriate choice of PPI • Patients treated with a PPI rather than ranitidine may be more likely to develop electrolyte abnormalities such as hyponatraemia or hypomagnesaemia.
Esomeprazole Injection 40mg	*Not licensed* Suggest stat dose of 40mg given as an IV bolus over at least 3 minutes or infused over 10-30 minutes	*Not licensed* Suggest stat dose of 40mg given as an IV bolus over at least 3 minutes or infused over 10-30 minutes	Suggest 40mg once daily is adequate for most conditions however for conditions such as Zollinger Ellison syndrome a higher dose of 80mg daily may be needed	• Contra-indicated in patients with previous hypersensitivity reaction to esomeprazole or the excipients contained in the injection and in patients taking nelfinavir. • For stat dose – potential for drug interactions not likely to be clinically significant. • For repeat doses - potential for adverse drug interactions should be assessed. This is especially important for patients taking concomitant clopidogrel or the antiretroviral medicines atazanavir or nelfinavir. In patients taking clopidogrel, pantoprazole may be a better choice of PPI. • Patients treated with a PPI rather than ranitidine may be more likely to develop electrolyte abnormalities such as hyponatraemia or hypomagnesaemia.

**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- , British National Formulary Issue no 78 (Sept 2019- Mar 2020) and the most recent versions of the Summary of Product Characteristics for ranitidine injection, omeprazole injection, pantoprazole injection and esomeprazole injection (all accessed via eMC website: www.medicines.org.uk)*

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Distribution

If you are responsible for cascading these alerts in your organisation, these are our suggested distribution lists.

Trusts (NHS boards in Scotland)

CAS and SABS (NI) liaison officers for onward distribution to all relevant staff including:

- A&E consultants
- A&E departments
- A&E nurses
- Cardiologists
- Cardiology departments
- Cardiology nurses
- Cardiology, directors of
- Cardiothoracic departments
- Cardiothoracic surgeons
- Cardiothoracic surgery directors
- Chief pharmacists
- Clinical governance leads
- Clinical Procurement Specialists [NEW]
- Community children's nurses
- Community hospitals
- Community midwives
- Community nurses
- Coronary care departments
- Coronary care nurses
- Day surgery units
- Dermatologists
- Dieticians
- District nurses
- Gastroenterology departments
- Gastroenterology, directors of
- Gastro-intestinal surgeons
- Haematologists
- Hospital at home units
- Hospital pharmacies
- Hospital pharmacists
- Intensive care medical staff/paediatrics
- Intensive care nursing staff (adult)
- Intensive care nursing staff (paediatric)
- Intensive care units
- Intensive care, directors of
- Maternity units
- Medical directors
- Medical oncologists
- Medical oncology, directors of
- Midwifery departments
- Midwifery staff
- Neonatal nurse specialists
- Neonatology departments
- Neonatology directors
- NHS walk-in centres
- Nutrition nurses
- Obstetricians
- Obstetrics and gynaecology departments
- Obstetrics and gynaecology directors
- Obstetrics departments
- Obstetrics nurses
- Oncology nurse specialists
- Outpatient clinics
- Paediatric intensive care units
- Paediatric medicine, directors of
- Paediatric nurse specialists
- Paediatric oncologists
- Paediatric surgeons
- Paediatric surgery, directors of
- Paediatric wards
- Paediatricians
- Paediatrics departments
- Palliative care teams
- Paramedics
- Pharmaceutical advisors
- Pharmacists
- Purchasing managers
- Risk managers
- School nurses
- Special care baby units
- Supplies managers
- Walk-in centres

NHS England Regional Offices

For onward distribution to all relevant staff including:

- Community pharmacists

General Practice

For onward distribution to all relevant staff including:

- General practitioners
- Nutritional nurse specialists
- General practice managers
- General practice nurses

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Establishments registered with the Care Quality Commission (CQC) (England only)
- Adult placement
- Care homes providing nursing care (adults)
- Care homes providing personal care (adults)
- Clinics
- Hospices
- Hospitals in the independent sector
- Independent treatment centres
- Nursing agencies
- Private medical practitioners

Enquiries

England
Send enquiries about this notice to the DHSC Supply Resilience Team, quoting reference number SDA/**2019/005 (U)**

Email: supplyresiliencemd@dhsc.gov.uk