Department of Health & Social Care

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UPDATE:

Update to communications issued 22nd May 2020.

Medicine Supply Notification

MSN/2020/025-U2

Ranitidine: All formulations update to SDA/2019/005-U2

Tier 2 – medium impact*

Date of issue: 12/06/2020

Summary:

- Ranitidine 50mg/2ml injection is anticipated to be unavailable from the end of May 2020 until further notice.
- Ranitidine film-coated tablets, effervescent tablets and oral solution continue to remain unavailable with no date for resupply.
- All formulations of ranitidine are affected due to on-going regulatory investigations into the presence of the contaminant, N-nitrosodiethylamine (NDMA), in samples of ranitidine active substance.
- Clinical advice on alternatives of oral ranitidine preparations for adults and children has been shared in the previous supply disruption alert SDA/2019/005 (U2) (see Tables 1 & 2 below).
- **UKMi have provided updated clinical advice regarding alternatives of ranitidine preparations, which can be found below (Table 2 & 3).**

Actions Required

All clinicians in primary and secondary care who prescribe ranitidine preparations should consider the following advice to manage patients;

- Ranitidine 50mg/2ml injection
  - if local supplies are insufficient, review the previous disruption alert, for advice on switching to alternative agents as appropriate (**see Table 3 below for further updated clinical guidance**)

- Oral ranitidine preparations
  - continue to follow guidance on switching, as per UKMi advice mentioned in the previous alert SDA/2019/005 (U2) **(see Table 1 & 2 below)**

*Classification of Tiers can be found at the following link: **A Guide to Managing Medicines Supply and Shortages**.

Supporting Information

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, no further supplies of ranitidine products can be manufactured. Further information can be found here.

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.

Ranitidine injection;

- There are three suppliers of IV ranitidine; Alliance Healthcare, Advanz Pharma and GSK
- Alliance Healthcare and Advanz Pharma have advised they have limited stocks available and anticipate being out of stock by the end of May 2020.
- GSK (Zantac 50mg/2ml injection) have now discontinued this product.
- All manufacturers are unable to advise on a re-supply date, due to ongoing testing required by the MHRA and EMA affecting all API supplies.
- There are currently sufficient stocks of alternative IV proton-pump inhibitors (PPI's) to support an increased demand as recommended by UKMi (**see Table 3 below**).

Ranitidine oral products;

- There has been no change to the supply situation or regulatory position on oral ranitidine products since the previous update SDA/2019/005 (U2)
- Supplies of alternatives PPIs remain readily available.
- There are currently limited stocks of some H2 receptor antagonists available, so only prescribe these products as an alternative to ranitidine in patients in whom PPI's are unsuitable. Latest supply position as below;

Drug, strength, formulation	Supplier	Stock Availability	Additional information
Famotidine 20mg tablets	Tillomed	Limited Stock	No confirmed re-supply date
	Teva	Limited Stock	Further supplies expected August 2020.
Famotidine 40mg tablets	Tillomed	Limited Stock	No confirmed re-supply date
	Teva	Limited Stock	Further stock expected June 2020
Cimetidine 200mg tablets	Ennogen	In Stock	Further supplies not due until March 2021
	Medreich	Out of Stock	No confirmed re-supply date
Cimetidine 400mg tablets	Ennogen	Limited Stocks	Further supplies not due until March 2021
	Medreich	Out of Stock	No confirmed re-supply date
Cimetidine 800mg tablets	Ennogen	In Stock	Further supplies not due until March 2021
	Medreich	Out of Stock	No confirmed re-supply date
Nizatidine 150mg tablets	Mylan	Out of Stock	Due late 2020
	Medreich	Long term out of Stock	No confirmed re-supply date
Nizatidine 300mg tablets	Mylan	Out of Stock	Due late 2020
	Medreich	Long term out of Stock	No confirmed re-supply date

- Prior to prescribing, clinicians should liaise with their pharmacists to understand local stock availability (including resupply dates) of clinical alternatives

Alternative preparations;

- UKMi have produced a summary of suitable clinical alternatives;
    - Alternative oral acid suppressants for the main indications of oral ranitidine in adults (see Table 1 below)
    - Alternative oral acid suppressants for gastro-oesophageal reflux disease in children (see Table 2 below)
    - Alternative parenteral acid suppressants covering main indications of intravenous ranitidine in adults (Table 3 below)

Enquiries

If you have any queries, please contact DHSCmedicinesupplyteam@dhsc.gov.uk

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Table 1 Alternative oral acid suppressants for the main indications of oral 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	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, however there is extensive experience of using via this route in practice.
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)	Orodispersible tablets 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)	

*Classification of Tiers can be found at the following link: A Guide to Managing Medicines Supply and Shortages.

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	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 10 and 20mg	20mg OD	UL (10-20mg OD) ¥	20mg OD (treatment) 10-20mg long term maintenance 10mg OD symptomatic GORD	UL	
H2-receptor antagonists						
Nizatidine	Capsules 150mg	150mg BD or 300mg OD	150mg OD	150mg-300mg bd	150mg BD or 300mg OD (treatment)	
Famotidine	Tablets 20mg and 40mg	40mg OD	DU 20mg OD	20mg BD (but for erosion/ulcer linked to reflux 40mg BD for 6-8 weeks)	UL	
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	400mg BD (treatment)- see SPC for other dose regimens	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-

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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 Oral suspension 2mg/ml and 4mg/ml *In the absence of the licensed liquid being available, consider using an unlicensed liquid (manufactured special). However, there is only limited evidence of efficacy.*	> 1 year and ≥ 10 kg	<2.5kg 0.7mg-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® not licensed for use via enteral feeding tubes, however there is extensive experience of using this route in practice (NB: granules ~ 0.5mm diameter and have tendency to block fine-bore feeding tubes [<8Fr]) • Esomeprazole granules are licensed for administration down tubes ≥6Fr, • *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, 20 and 40mg	≥12 years	20-40mg OD	Granules licensed for administration via enteral 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 20 and 40mg	≥12 years	20 mg OD	
Lansoprazole	Capsules and dispersible tablets: 15 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	Dispersible tablets • Excipients include aspartame. • Dose should be rounded up or down to nearest solid dosage form i.e. half or quarter of tablet.

*Classification of Tiers can be found at the following link: A Guide to Managing Medicines Supply and Shortages.

			10 - 30kg 15mg OD >30kg 30mg OD	• 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 down 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.
Acid suppressant	**Formulation**	**Licensed age group**	**Dose**	**Comments**
Proton pump inhibitors (cont'd)				
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
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 water, in 2-5 minutes. This process can be quickened by crushing and mixing tablets with water 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.

Table 3: Alternative parenteral acid suppressants covering main indications of intravenous ranitidine in adults

The need for a parenteral treatment should be assessed and if considered necessary the following injectable proton pump inhibitors may be considered to offer a suitable clinical alternative to intravenous ranitidine

Acid suppressant	Gastric acid suppression in surgical procedures	Prophylaxis of stress ulceration	Conditions where acid suppression needed but oral route not available	Comments
Omeprazole 40 mg Powder for Solution for Infusion	***Not licensed*** Suggest stat dose of 40mg given as an IV infusion over 20-30 minutes.	***Not licensed*** Suggest 40mg once daily given as an IV infusion 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. However, when repeat doses are needed the 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 proton pump inhibitor rather than ranitidine may be more likely to develop electrolyte abnormalities such as hyponatraemia or hypomagnesaemia.
Pantoprazole 40 mg powder for solution for injection	***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 40mg once daily 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. However when repeat doses are needed the 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 may be a better choice of PPI. Patients treated with a proton pump inhibitor rather than ranitidine may be more likely to develop electrolyte abnormalities such as hyponatraemia or hypomagnesaemia.

Esomeprazole 40 mg powder for solution for injection/infusion	***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 40mg once daily 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. However, when repeat doses are needed the 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 proton pump inhibitor 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)