

Shortage of Ranitidine Products

LOCAL ADVICE WHICH SHOULD BE USED IN CONJUNCTION WITH THE TWO CAS ALERTS ISSUED BELOW

CAS Alert Issued 15th October 2019 available at:

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102904>

CAS Alert Issued 27th November 2019 available at:

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102934>

UPDATED 28th November 2019

Description of product affected^{1,2}

- Ranitidine is a specific, rapidly acting histamine H₂-antagonist.
- Ranitidine inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.
- Ranitidine has a relatively long duration of action and so a single 150mg dose effectively suppresses gastric acid secretion for 12 hours.
- For many conditions' ranitidine is only recommend for short-term use.
- In adults, ranitidine is licensed for:
 - Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
 - Prevention of NSAID associated duodenal ulcers.
 - Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.
 - Post-operative ulcer.
 - Oesophageal reflux disease including long term management of healed oesophagitis.
 - Symptomatic relief in gastro-oesophageal reflux disease.
 - Zollinger-Ellison syndrome.
 - Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but is not associated with the above conditions.
 - Prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.
 - Prophylaxis of recurrent haemorrhage with bleeding peptic ulcers.
 - Before general anaesthesia in patients at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

- In children, ranitidine is licensed for:
 - Short term treatment of peptic ulcer
 - Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

Background

UPDATE:

- **Further to the previous ranitidine supply disruption alert (SDA/2019/005) issued on the 15th October 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) have instructed suppliers of oral ranitidine in the UK to quarantine ALL affected, unreleased stock at manufacturer level whilst their investigations are ongoing.** The MHRA are continually reviewing whether batches of ranitidine in quarantine can be released.
- **Ranitidine tablets, effervescent tablets and oral solution are expected to be out of stock with no date for resupply until further notice.**
- Some batches of ranitidine have been found to contain a contaminant: the chemical involved is called N-nitrosodimethylamine (or NDMA) and is classified as a "probable human carcinogen" on the basis of animal studies. The European Medicines Agency (EMA) states that it is present in some foods and in water supplies but is not expected to cause harm when ingested in very low levels. The EMA are currently evaluating the data to assess whether patients who are using ranitidine are at any risk from NDMA, and they will provide information for this as soon as it is available.³
- **To date and prior to the most recent supply disruption alert (SDA/2019/005) the MHRA have issued SIX Class 2 (pharmacy, wholesaler and retailer level) recalls of ranitidine products, listed below:**
 - **Ranitidine 75mg tablets, (Various Liveries) (EL (19)A/37).**
OTC Concepts Ltd, Relconchem Ltd and Noumed Life Sciences Ltd are recalling all unexpired batches of the above products from pharmacies and retail stores.
 - **Ranitidine Oral Solution 30mg/ml, PL 31862/0023, Ranitidine 150mg Tablets, PL 11311/0138 (EL(19)A/36).**
Creo Pharma Limited and Tillomed Laboratories Limited are recalling all unexpired stock of the products listed in this alert.
 - **Zantac 75 Relief Tablets, Zantac 75 Tablets, Galpharm 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).**
Omega Pharma Limited and Galpharm International Limited are recalling unexpired stock from pharmacies and retail stores as a precautionary measure due to possible contamination with an impurity.
 - **Ranitidine 150mg/10ml Oral Solution (EL (19)A/29).**
Rosemont Pharmaceuticals Limited is recalling unexpired stock from pharmacies as a precautionary measure.
 - **Ranitidine Effervescent Tablets 150mg, Ranitidine Effervescent Tablets 300mg (EL (19)A/27).**
Teva UK limited trading as ratiopharm GmbH is recalling all unexpired stock of Ranitidine Effervescent Tablets from pharmacies.

- [Zantac Injection 50mg/2ml, Zantac Syrup 150mg/10ml, Zantac Tablets 150mg and Zantac Tablets 300mg \(EL \(19\)A 24\).](#)
GlaxoSmithKline is recalling unexpired stock of Zantac (ranitidine hydrochloride) prescription only medicines (POM) from pharmacies.
- **The MHRA have confirmed that there have been NO patient level recalls for ranitidine. Patients can continue to use their supplies of ranitidine, which have been already dispensed to them, whilst investigations are ongoing.⁴**
- **There is extremely limited stock of ranitidine currently available from wholesalers and pharmacies, which have not been recalled by the MHRA and these should be reserved for those patients in whom alternatives are not clinically appropriate.**

Alternative agents and management options

- **No new patients should be initiated on treatment with ranitidine.**
- **There is no current advice for patients to stop taking ranitidine that is already dispensed to them, as there have been NO patient level recalls.** If you receive queries about this issue from patients, advise them not to stop taking their medication as the health risk of discontinuing the medicine is higher than the potential risk presented by the contaminant.
- **Identify current patients prescribed ranitidine tablets, effervescent tablets and oral solution.**
- **All patients should be reviewed. A treatment review should take place before their next repeat prescription is requested to decide if ongoing treatment is clinically required or whether the medication can be deprescribed. If ongoing treatment is clinically required, patients should be switched to clinical alternatives.** There are extremely limited supplies of ranitidine products remaining in wholesalers and pharmacies, that have not been recalled by the MHRA, which are available and can be supplied. These should be reserved for patients where there are no clinically acceptable alternatives.
- If patients are buying ranitidine over the counter, then they should discuss alternative appropriate options with their pharmacist as part of self-care. Please note, ranitidine 75mg tablets are not recommended to be prescribed on prescription but should be considered as part of SELF-CARE.
- It is important that the prescriber takes into consideration lifestyle changes and potentially over the counter use of indigestion remedies which may be clinically appropriate for the patient i.e. a compound alginate preparation e.g. Peptac liquid (other brands can be purchased).
- However, depending on the clinical indication the patient may benefit from alternative treatment options on prescription. This decision on which therapy to prescribe will depend on the indication, past medical history, co-morbidities and concomitant administration of other medications for each individual patient. 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.
- If ongoing treatment is still required:
 - **Where clinically appropriate it is recommended to switch patients to a PPI.** Omeprazole is the first-choice proton pump inhibitor (PPI) as there are currently sufficient supplies to manage an increase in demand and it is the first line on our formulary. There are currently sufficient supplies of oral omeprazole to manage an increase in demand.

- **It is recommended that patients are not switched to alternative H2-receptor antagonists in the first instance as this may exacerbate a shortage of these products.**
- **Ranitidine should be reserved for those patients in whom there are no clinically appropriate alternatives.**

Please note:

Due to differences in wholesaler stock availability, secondary care are unable to obtain any ranitidine formulations currently. Where a patient requires continued treatment with a H2 – receptor antagonist secondary care will be prescribing nizatidine 1st line. Please issue any further supplies of alternative H2- receptor antagonists in primary care as an acute prescription until stock shortage issues resolve.

Prescribing Information

There is no specific guidance for switching patients to alternative treatments, but appropriate prescribing options may be:

- **A proton pump inhibitor (PPI)⁵.**
 - A PPI may be used if clinically indicated and patient has no contra-indications to use.
 - The first line formulary choice is omeprazole. Other formulary choices include lansoprazole or pantoprazole. These are available to order from the 3 major wholesalers: AAH, Alliance HC and Phoenix.
 - For patients requiring an oro-dispersible PPI formulation, LANSOPRAZOLE orodispersible tablet is the orodispersible PPI first line choice.
 - Where a PPI is clinically required for a child the following should be considered:
 - LANSOPRAZOLE orodispersible tablets are not licensed for use in children but the [cBNF](#) does provide indication specific dosage information based on weight of the child.
 - OMEPRAZOLE dispersible gastro resistant tablets are licensed for use in children from 1 year. Please see the [cBNF](#) for indication specific dosage information (dosages available from neonate).
 - PPIs have a broader product license, and where a formulary choice is prescribed, they are more cost-effective than other H2 - receptor antagonists, where clinically appropriate.
 - Doses in line with the clinical indication may be found in the BNF or BNFc as appropriate.
 - Where a specialist has recommended an alternative medicine or an unlicensed formulation, based on the clinical needs of the patient, please contact the Medicines Optimisation Team via our Prescribing Partnership email CAPCCG.prescribingpartnership@nhs.net for further advice on the most cost effective formulation including prescribing of unlicensed specials.

- **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 an PPI is not clinically appropriate.
 - Cimetidine is considered to have many potential interactions and side effects, which may limit its suitability as an alternative.
 - Famotidine is significantly more expensive.
 - Doses in line with the clinical indication may be found in the [BNF](#) as appropriate.
 - Please see table 1 below for further information regarding alternatives.

Patients who have any questions about their current treatment should speak to their pharmacist or doctor. Where the above suggestions are not clinically suitable and prescribers require urgent support for individual patients within Primary Care, please contact the Medicines Optimisation Team via our Prescribing Partnership email CAPCCG.prescribingpartnership@nhs.net.

Table 1 – Information regarding H2 - receptor antagonists:

It is recommended that, where possible, patients are not switched to alternative H2-receptor antagonist treatment, in the first instance, as this will exacerbate a shortage of these products.

<i>H2 - receptor antagonist:</i>	<i>Available as:</i>	<i>Licensed for -see SPC</i>	<i>Availability at wholesalers:</i>	<i>Cost:</i>
Nizatidine	150mg capsules	Nizatidine 150mg capsules - SPC	Unavailable.	£4.38 (30 capsules)
	300mg capsules	Nizatidine 300mg capsules - SPC	DE.	£15.43 (30 capsules)
Cimetidine	200mg tablets	Cimetidine 200mg tablets - SPC	AAH, Sigma	£18.60 (60 tablets)
	400mg tablets	Cimetidine 400mg tablets - SPC	AAH, Alliance HC, DE, Ennogen and Phoenix.	£15.92 (60 tablets)
	800mg tablets	Cimetidine 800mg tablets - SPC	Alliance HC, Ennogen.	£15.47 (30 tablets)
	200mg/5ml oral solution	Cimetidine 200mg/5ml oral solution - SPC	Rosemont.	£14.25 (300ml)
Famotidine	20mg tablets	Famotidine 20mg tablets - SPC	Phoenix and Tillomed.	£21.99 (28 tablets)
	40mg tablets	Famotidine 40mg tablets - SPC	Alliance HC, Phoenix Teva and Tillomed.	£38.99 (28 tablets)

References

1. Accord Healthcare Limited. Ranitidine 150mg tablets. SPC, date of revision of the text, April 2017: <https://www.medicines.org.uk/emc/product/6040/smpc>
2. Advanz Pharma. Ranitidine 150mg/10ml oral solution. SPC, date of revision of the text, February 2017: <https://www.medicines.org.uk/emc/product/3371/smpc>
3. EMA to review ranitidine medicines following detection of NDMA. Published 13/09/2019. Available at: <https://www.ema.europa.eu/en/news/ema-review-ranitidine-medicines-following-detection-ndma>
4. Personal communication via telephone – MHRA, 27th November 2019.
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6. British National Formulary. Updated 30 September 2019. Available at: <https://bnf.nice.org.uk/>
7. British National Formulary for Children. Updated 30 September 2019. Available at: <https://bnfc.nice.org.uk/>
8. 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>

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