NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Shortage of Ranitidine Products

LOCAL ADVICE WHICH SHOULD BE USED IN CONJUNCTION WITH THE TWO CAS ALERTS ISSUED BELOW AND THE MEDICINE SUPPLY NOTIFICATION

CAS Alert Issued 15th October 2019. Available at: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102904

CAS Alert Issued 20th December 2019 which supersedes the previous update (SDA/2019/005-U) issued on the 27th November. Available at: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103377

Medicine Supply Notification Issued 12th June 2020. Available at: https://www.cambridgeshireandpeterboroughccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=20849

UPDATED: 15th December 2020

Description of product affected[1,2]

- Ranitidine is a specific, rapidly acting histamine H_2-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: There has been no change to the supply situation or regulatory position on oral ranitidine products. 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.

- **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 50mg/2ml injection:
  - Out of stock from Alliance Pharmaceuticals.
  - Advanz Pharma currently have limited stocks remaining.

- **Ranitidine tablets, effervescent tablets and oral solution will continue to be unavailable with no date for resupply until further notice due to global regulatory investigations. To date the MHRA have issued NINE Class 2 (pharmacy, wholesaler, and retailer level) recalls of ranitidine products.**

- 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]

- There are current short-term supply issues affecting alternative H2-receptor antagonists.

- **The MHRA have confirmed that there have been NO patient level recalls for ranitidine.[4]**

Alternative agents and management options

- **No new patients should be initiated on treatment with ranitidine.**

- **All patients prescribed ranitidine formulations, 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.**

- 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 as supplies of PPIs remain readily available.** 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.

    - There are currently short-term supply issues affecting cimetidine, famotidine and nizatadine. **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. These products should only be prescribed as an alternative to ranitidine in patients in whom proton pump inhibitors are unsuitable.**

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).

    - See CAS alert SDA/2019/005 (U2) for further information regarding clinical alternatives in paediatric patients.

- 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. *Currently both Mylan and Medreich are experiencing manufacturing issues with nizatadine in both strengths of the tablet formulation*.** 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:
There are short term supply issues affecting alternative 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. Prescribers should work closely with pharmacies and dispensaries to establish levels of H2-receptor antagonists held locally.

Product	Supplier	Current Stock Position	Anticipated resupply date	Suggested management plan
Famotidine 20mg tablets	Tillomed	Limited supplies	End December 2020	Unlicensed supplies have been sourced
	Teva	Out of stock	To be confirmed	
Famotidine 40mg tablets	Tillomed	In stock	n/a	
	Teva	Limited supplies	To be confirmed	
Cimetidine 200mg tablets	Ennogen	Out of stock	June 2021	
	Medreich	Out of stock	To be confirmed	
Cimetidine 400mg tablets	Ennogen	Out of stock	June 2021	
	Medreich	Out of stock	To be confirmed	
Cimetidine 800mg tablets	Ennogen	Out of stock	June 2021	
	Medreich	Out of stock	To be confirmed	
Cimetidine 200mg/5ml oral solution	Rosemont	Out of stock	n/a	n/a
Nizatidine 150mg capsules	Mylan	Out of stock	End January 2021	Unlicensed supplies have been sourced
	Medreich	Out of stock	To be confirmed	
	Relonchem	Limited supplies	End December 2020	
Nizatidine 300mg capsules	Mylan	Out of stock	End January 2021	Unlicensed supplies have been sourced
	Medreich	Out of stock	To be confirmed	
	Relonchem	Out of stock	End December 2020	

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.

5. Personal communication via telephone and email – Clinical and Medicines Information Pharmacist, Friday 11th October.
East Suffolk and North Essex NHS Foundation Trust
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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Cambridgeshire and Peterborough Clinical Commission Group, Medicines Optimisation Team. Published 25th November 2019, updated 24th December 2019, 16th December 7th February 2020, 16th March 2020, 12th of May, 17th June 2020, 10th July 2020, 23rd September 2020, 17th November 2020 and 15th December 2020 Email: CAPCCG.prescribingpartnership@nhs.net.

Disclaimer: *This memo can be adapted for local use. The content does not reflect national guidance. Some of this memo is based on* ***clinical opinion*** *from practitioners. Users should bear this in mind in deciding whether to base their policy on this document. Individual trusts should ensure that procedures for unlicensed medicines are followed where a foreign import drug is required in the interim. 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. Unlicensed medicines: In line with GMC guidance you should usually prescribe licensed medicines in accordance with the terms of their license. However, you may prescribe unlicensed medicines, where, on the basis of assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient. Prescribing unlicensed medicines may be necessary where there is no suitably licensed medicine that will meet the patient's needs. For example, where a suitably licensed medicine that would meet the patient's need is not available. This may arise where, for example, there is a temporary shortage in supply. As with all prescribing, the prescriber is medically and legally responsible for the prescriptions they sign and for their decisions and actions when they supply and administer medicines or authorise or instruct others to do so.*