Briefing: Ranitidine Recall – Suggested actions:

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Background:

The European Medicines Agency (EMA) has started a review of ranitidine medicines after tests showed that some of these products contained N-nitrosodimethylamine (NDMA), a probable human carcinogen (on the basis of animal studies). The Agency's press release states it is present in some foods and in water supplies but is not expected to cause harm when ingested in very low levels. In the review, it will evaluate the data to assess whether patients using ranitidine are at any risk from NDMA and will provide information about this as soon as it is available.

The Medicines and Healthcare products regulatory agency (MHRA) has now issued recalls for the originator brands, Zantac, and several generic brands.

Purpose:

This memo supports prescribers on what actions to take, especially identifying special cases.

Recommendations for managing adult patients on H2Antagonists, including ranitidine, for those indications where proton pump inhibitors (PPIs) are also licensed:

The recommendations from the Supply Disruption Alert SDA/2019/005 Issued: 15 October 2019 Valid until: 15 January 2020 are:

Licensed use for gastrointestinal conditions

- Identify current patients prescribed ranitidine tablets, effervescent tablets and oral solutions, and:
- Review to establish if ongoing treatment is still required.
- If ongoing treatment is still required, then consider switching to an alternative treatment, a useful table has been published on pages 3 and 4 of the alert (Link)

- It is recommended that omeprazole is the first-choice proton pump inhibitor (PPI) where clinically appropriate, as there are currently sufficient supplies 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. Sufficient supplies will continue to be available to meet current demand.

The All-wales medicines strategy group has produced an excellent document to support the safe prescribing of proton pump inhibitors (Link), and this will support clinicians when reviewing treatment to establish if ongoing treatment is still required, see page 10 of 32, and other support materials, including a patient information information leaflet on page 30. Although this document is geared towards appropriate prescribing of PPIs, it is relevant before transferring patients from ranitidine to a PPI.

Recommendations for patients on ranitidine under special circumstances:

Chronic Urticaria and Angioedema:

The Standards of Care Committee of the British Society for Allergy and Clinical Immunology (BSACI) developed guidance for the management of patients with chronic urticaria and angioedema, a guidance given the NICE quality accreditation. This includes a statement suggesting that H2-Antihistamines have minimal benefit:—

'A recent review [90] concluded that the evidence for the use of H2-antihistamines in urticaria was weak. The combination of cimetidine with hydroxyzine results in an increased serum level of hydroxyzine confirming the rationale for its co-administration with hydroxyzine in some patients with CU unresponsive to hydroxyzine alone. There is no therapeutic rationale for co-administration of cimetidine with cetirizine in CU [91]. In CU, the combination of ranitidine with terfenadine was superior to terfenadine alone in terms of itch, but there was no significant effect on weals or swellings [92]. There is no strong evidence to support the addition of ranitidine to treatment regimes in CU '

Immunology advice suggests that there is better/ more evidence-based second/third line agents available.

Action: Where patients are on ranitidine for this indication, consider stopping ranitidine, ensuring patients are on a long acting anti-histamine with added montelukast where necessary. This is an unlicensed indication but recommended in the British Society for Allergy and Clinical Immunology (BCACI), in a NICE accredited guideline: 'BSACI guideline for the management of chronic urticaria and angioedema'.

Where there are concerns about severe exacerbations, specialist advice should be sought. Those patients may also be considered for omalizumab (NICE) by the specialist.

Adult patients with an enteral feeding tube:

Action:

- Review patient for continued need
- Should a PPI be required, Lansoprazole Fas tabs are licensed for the administration via a nasogastric tube, and are therefore the preferred PPI

Paediatric patients:

NICE Guideline 'Gastro-oesophageal reflux disease in children and young people: diagnosis and management', (GORD) should be followed.

This guideline equally recommends ranitidine and omeprazole.

For infants on ranitidine, consider whether treatment should be continued: GORD usually becomes less frequent with time (it resolves in 90% of affected infants before they are 1 year old)

Lansoprazole is less often recommended in children as there is less experience with this PPI than for omeprazole, but there is an entry for lansoprazole both in the BNFC and the Evelina London Paediatric Formulary. The enteric coated granules are smaller and therefore may be easier to administer. The BNFC has a patient information leaflet: https://www.medicinesforchildren.org.uk/lansoprazole-gastro-oesophageal-reflux-disease-gord-and-ulcers

The manufactured special should be used only when the Omeprazole MUPS® tablets or the Lansoprazole Fas Tab cannot be used, and then changed to these as soon as possible. Formulations with reduced sodium should be selected where possible.

Children without an enteral feeding tube:

Children and young people with GORD on ranitidine should be switched to omeprazole. There is an entry for omeprazole both in the BNFC and the Evelina London Paediatric Formulary

Omeprazole MUPS® TABLETS are preferable to the oral liquid and these should therefore be used for doses greater than 5mg. The BNFC has a patient information leaflet: https://www.medicinesforchildren.org.uk/omeprazole-gastro-oesophageal-reflux-disease-gord

Lansoprazole Fas Tabs® can be dissolved and given with a small amount of water in an oral syringe and should be used where the administration of the Omeprazole MUPs® is problematic

Children with an enteral feeding tube:

The omeprazole MUPS® tablets enteric coated granules are larger than lansoprazole Fas Tabs granules.

The BNFC does not recommend that the omeprazole MUPS® tablets are administered through enteral feeding tubes, and does not give advice regarding lansoprazole Fas Tabs

The Evelina London Children's Formulary indicates that omeprazole MUPS® tablets may be administered via gastrostomy, and that, 'when using feeding tubes of Gauge under 8F in those patients over 2.5kg, lansoprazole dispersible tablets are generally easier to use than omeprazole'. Medicines information for Zoton Fas Tab® (Pfizer) indicates that:

8FR: 7.5mg/ml are given easily through the paediatric feeding tube

6FR: 7.5mg/ml partially clog the feeding tube but 0.9% NaCl flush clears the microgranules stuck to the tube

5FR: 7.5mg/ml completely clogs the feeding tube even with 0.9% NaCl flushes.

If any other special circumstances arise, please contact the initiating specialist or author by e-mail

References:

- Class 2 Medicines recall: Zantac Injection 50mg/2ml, Zantac Syrup 150mg/10ml, Zantac Tablets 150mg, Zantac Tablets 300mg (EL (19)A 24), (Link)
- Class 2 Medicines recall: Ranitidine Effervescent Tablets 150mg, Ranitidine Effervescent Tablets 300mg (EL (19)A/27), (TEVA) (Link)
- Class 2 Medicines recall: 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) (Perrigo) (Link)
- SMPC Omeprazole (LOSEC) MUPS® tablets , accessed November 4, 2019, (Link)
- SMPC Lansoprazole (Zoton) Fas Tabs, accessed November 4, 2019, (Link)
- BNFC: Omeprazole and lansoprazole monographs, accessed November 4, 2019, (Link)
- NICE: Gastro-oesophageal reflux disease in children and young people: diagnosis and management, accessed November 4, 2019, (Link)
- BSACI guideline for the management of chronic urticaria and angioedema, 2015, accessed via evidence.nhs.uk, November 4, 2019, (Link)
- Evelina London Paediatric Formulary, Monographs for Omeprazole and Lansoprazole, accessed November 4, 2019, (Link)

Appendix 1: Why are Omeprazole MUPS® tablets preferable to the oral liquid?

Why are Omeprazole MUPs preferable to the oral liquid?

Omeprazole and omeprazole magnesium are acid labile and therefore, unless protected by enteric coating, these are destroyed in the stomach.

Omeprazole MUPs have enteric coated granules which protect the omeprazole from the stomach acid, and therefore remain useful for absorption further down the gastrointestinal tract.

Omeprazole MUPs 10mg dispersible tablets can be halved to give a 5mg dose.

In order to produce an oral liquid, the omeprazole is mixed with sodium bicarbonate to both dissolve the enteric coating and to tray and reduce the acidity in the stomach to reduce the destruction of the omeprazole, this has the detrimental effect of:

- Giving a significant sodium* and bicarbonate doses (* some specials manufacturers have developed formulations with half the sodium content, but this cannot be specified in primary care)
- Creating a larger rebound effect after bicarbonate administration
- Uncertainty over dose actually available for absorption.

The Evelina London Paediatric Formulary states that: ‘A liquid is available as a manufactured special. However there is only limited evidence of their efficacy and MUPS® should be used where possible’