Ranitidine Shortage

27 Sep 2019

Background[1]

Due to the possibility of products containing the impurity n-nitrosodimethylamine (NDMA), ranitidine is currently unavailable.

Health Canada has requested that Canadian manufacturers of ranitidine products stop distribution until levels of NDMA in Canadian ranitidine supply can be determined. Several manufacturers have voluntarily recalled their ranitidine products and more could follow. As of 27 Sep 2019, the following manufacturers have recalled their ranitidine tablets:

- Apotex Inc.
- Pro Doc Limitée
- Sandoz Canada
- Sanis Health Inc.
- Sivem Pharmaceuticals ULC

Sandoz makes injectable ranitidine; while this product has not been recalled by Sandoz, distribution has been suspended as a precaution.[2] Existing inventory at wholesalers has been placed on allocation (priority to hospitals) and Sandoz does not intend to release any product at this time.

NDMA is the same impurity that has been discovered in various angiotensin receptor blockers in the past. While classified as a probable human carcinogen, low levels are of no concern. NDMA is likely unavoidable in our environment as it is found in some foods and drinking water. Health Canada is investigating to ensure the amounts found in ranitidine products do not exceed levels that could be harmful with long-term use. This is a global issue and Health Canada is working with other regulators such as the U.S Food and Drug Administration and the European Medicines Agency.[1]

There are several Health Canada-approved indications of ranitidine; this document addresses the most common, gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD).

H_2RA Alternatives

- Alternatives to ranitidine include cimetidine, famotidine and nizatidine
    - There are few significant differences among the H_2RAs therapeutically but, if possible, consider avoiding cimetidine in the elderly or those at increased risk of drug interactions.[3]
- As of 27 Sep 2019, inventory of alternative H_2RAs has also been depleted.
    - Ranitidine accounted for 90% of the H_2RA market in Canada so it is unreasonable to expect production of alternative H2RAs to meet supply demand, even if production is increased.[4]
- Ranitidine bulk powder is not available.
- Formulae for extemporaneous compounding of suspensions from tablets are available in Lexicomp for famotidine and cimetidine, should the pharmacy have some inventory of these on hand.
- Compounding pharmacies may be able to order famotidine and cimetidine powders.
    - Even if the powders are available, the pharmacies may have to order so expect delays.
    - Availability of H_2RA powders may vary from pharmacy to pharmacy.

Therapeutic Alternatives

Use this as an opportunity to re-evaluate need for acid suppression, especially for treatment of GERD.

Adults

- If more details are required, refer to RxTx GERD & Dyspepsia (CTMA), GERD (CTC) and Dyspepsia & Peptic Ulcer Disease (CTC) topics.
    - RxTx is available to all Saskatchewan health practitioners through the Saskatchewan Health Information and Resources Program (SHIRP).
        - an account is necessary but upon setting up, access is immediate
        - RxTx can be accessed from this page or go to the Pharmacists tab, then Drug Information

GERD[5,6]

- Take this opportunity to determine if continued treatment is necessary.
- Consider stepping down (antacids, alginates) or stepping up (PPIs) for patients using H_2RAs depending on symptom frequency and severity as well as response to previous treatment trials.
- Refer to medSask Minor Ailment Guidelines for GERD.
- Lifestyle modification (e.g. diet modification, weight loss, smoking/alcohol cessation, elevating head of bed) – all cases
- OTC antacids, alginates, H_2RAs – mild and infrequent symptoms
- OTC PPIs – mild and frequent or moderate symptoms
- Prescription H_2RAs – infrequent symptoms improved but not resolved by PRN OTC treatment
- Prescription PPIs – frequent and/or moderate symptoms
- See Tables 1 and 5 for dosing and formulary considerations.

PUD[7]

- See Tables 2 and 5 for dosing and formulary considerations
- PUD due to *Helicobacter pylori* infection
    - PPIs should be used as the acid-suppressing agent of the *H. pylo*ri eradication regimen; see RxTx or RxFiles (both available through SHIRP) for specific regimens.

- Prophylaxis of PUD during ASA/NSAID therapy
    - See RxTx or RxFiles (both available through SHIRP) for patients who should receive prophylaxis.
    - PPIs or misoprostol (200 mcg PO four times daily) are more effective than H_2RAs.

- Treatment of PUD
    - Stop ASA and/or NSAID if appropriate
        - Low dose ASA for cardiovascular prophylaxis should not be stopped. See RxFiles to determine appropriate cardioprotective use of ASA (e.g. use as primary prevention may not be appropriate).
    - PPIs are more effective than H_2RAs or misoprostol; treat for 8 weeks.
    - If NSAID cannot be discontinued, consider switching to COX-2 inhibitor if bleeding ulcer; continue PPI after treatment as prophylaxis.

Pediatrics

GERD

- Ensure pharmacological therapy is required; this is especially the case in infants[8].

Infants (up to 1 year)

Reassure parents/care givers that[8,9]:

- reflux/regurgitation is common in infants (40-70%)
- use of agents that reduce gastric acidity and/or motility agents do not improve infants' crying or spitting up
- symptoms usually improve without intervention

Non-pharmacological strategies for infant reflux/regurgitation[9-11]

- avoid infant exposure to second-hand smoke
- consider providing smaller feedings to avoid over-feeding
- consider a 2 week trial of thickened feeds
  - formula and/or food may be thickened with cereal (if using rice cereal, ensure low/no arsenic; preferably use other cereals such as oat, wheat, barley)
    - note that the inconvenience of expressing breastmilk in order to thicken may preclude trial of thickening in breastfed infants
  - thickening feeds may reduce vomiting and regurgitation
- consider a 2 week trial of removing cow's milk/soy protein from the diet
  - in breastfed infants, the mother removes all cow's milk proteins, beef and major sources of soy protein

Pharmacological treatment of infant GERD[9-11]

- Consider pharmacological treatment if frequent regurgitation accompanied by infant distress, feeding refusal and/or poor weight gain persist despite instituting non-pharmacological strategies.
- PPIs are considered by some first line treatment of infant GERD. See Tables 3 and 5 for doses and formulary considerations.
- **PPIs have not been found to be effective in reducing symptoms of irritability or regurgitation in infants**.[12]
  - begin with trial of 2 weeks
    - if symptoms do not improve, discontinue and re-evaluate
    - if symptoms markedly improve, consider continued treatment for 3 to 6 months then re-evaluate
- H_2RAs generally are considered if PPIs cannot be used.
- H_2RAs and PPIs may increase the risk of respiratory and gastrointestinal infections.
- Antacids should be avoided in infants because of concerns of aluminum toxicity and milk-alkali syndrome (calcium-containing products).
- Motility agents (e.g. domperidone, metoclopramide) are not recommended for infant GERD because of potentially serious dystonic (metoclopramide) and cardiovascular (domperidone) adverse effects.

Older children and adolescents

- Refer to adults above.
- Pharmacists cannot prescribe for GERD in patients < 18 years.
- See Tables 3 and 5 for doses and formulary considerations.

PUD[13]

- *Helicobacter pylori* Infection-Related
  - most common cause of PUD in children
  - PPIs should be used as the acid-suppressing agent of the *H. pylor*i eradication regimen
- Non-*H. pylori*- Related
  - H_2RAs and PPIs
    - It is suggested PPIs may be more effective with quicker time to healing[13] though this appears to be extrapolated from adult data, as pediatric data are very limited.
    - See Tables 4 and 5 for doses and formulary considerations

Tables

Table 1: ORAL Adult Doses of H_2RAs and PPIs for GERD[3,14]

Agent	Dose*		Notes
	Treatment	Maintenance	
H_2RAs			
Cimetidine	800 mg BID or 300-400 mg QID and at bedtime		8-12 weeks
Famotidine	20 mg BID 40 mg BID if esophageal erosions	20 mg BID	
Nizatidine	150 mg BID		
Ranitidine	Reflux esophagitis 300 mg at bedtime or 150 mg BID	150 mg BID	**Treatment**: up to 8 weeks
PPIs			
Dexlansoprazole	60 mg daily	30 mg daily	**Treatment**: 4-8 weeks
Esomeprazole	40 mg daily	20 mg daily	**Treatment**: 4-8 weeks
Lansoprazole	30 mg daily	15 mg daily	**Treatment**: 4-8 weeks
Omeprazole	20 mg daily	10 mg daily	**Treatment**: 2-8 weeks
Pantoprazole	40 mg daily	20 mg daily	**Treatment**: 2-8 weeks
Rabeprazole	20 mg daily	10 mg daily	**Treatment**: 4-8 weeks

Table 2: ORAL Adult Doses of H_2RAs and PPIs for PUD[3,14]

Agent	Dose*		Notes
	Duodenal Ulcer	Gastric Ulcer	
H_2RAs			
Cimetidine	**Treatment:** 800 mg at bedtime or 300 mg QID or 400-600 mg BID or 200 mg TID & 400 mg at bedtime **Maintenance:** 300 mg BID or 400 mg at bedtime	**Benign, treatment:** 800 mg at bedtime 300 mg QID or 600 mg BID	**Treatment**: Duodenal: 6-8 weeks **Benign**: 4-8 weeks **Maintenance**: 4-6 months **Max** 2400 mg/day
Famotidine	**Treatment**: 40 mg at bedtime **Maintenance**: 20 mg at bedtime	**Treatment**: 40 mg at bedtime **Maintenance**: 20 mg at bedtime	**Treatment**: 4-8 weeks **Maintenance**: 6-12 months
Nizatidine	**Treatment**: 300 mg at bedtime or 150 mg BID **Maintenance**: 150 mg at bedtime	**Treatment**: 150 mg at bedtime	**Treatment**: 4-8 weeks **Maintenance**: 6-12 months
Ranitidine	**Treatment**: 300 mg at bedtime or 150 mg BID **Maintenance**: 150 mg at bedtime	**Treatment**: 300 mg at bedtime or 150 mg BID **Maintenance**: 150 mg at bedtime	**Treatment**: 4-12 weeks
PPIs			
Dexlansoprazole	N/A	N/A	
Esomeprazole	N/A	**NSAID**: 20 mg daily	4-8 weeks
Lansoprazole	15 mg daily **NSAID**: 30 mg daily	15 mg daily **NSAID**: 30 mg daily	**DU**: 4 weeks **GU**: 4-8 weeks **NSAID**: ≤8 weeks
Omeprazole	20 mg daily	20 mg daily	**DU**: 4 weeks **GU**: 4-8 weeks **NSAID**: 4-8 weeks
Pantoprazole	40 mg daily	40 mg daily	**DU**: 4 weeks **GU**: 4-8 weeks
Rabeprazole	20 mg daily	20 mg daily	**DU**: 4 weeks **GU**: 6 weeks

Table 3: ORAL Pediatric Doses of H_2RAs and PPIs for GERD [3,14]

Agent	Age	Dose*		Notes
		Treatment	Maintenance	
H_2RAs				
Cimetidine^	Infant to 16 yrs	20-40 mg/kg/day		3-4 divided doses; max 400 mg/dose
Famotidine^	< 3 mos	0.5 mg/kg/dose daily ; if inadequate effect after 2 weeks, ↑ to 1 mg/kg/dose		Up to 8 weeks;
	≥ 3 mos to 16 yrs	0.5 mg/kg/dose BID or ≥40 kg: 20 mg BID		Up to 8-12 weeks; max 40 mg per dose
Nizatidine	Infant to < 12 yrs	5-10 mg/kg day		Divided BID, max 300 mg / day
	≥ 12 yrs	150mg BID		Max 300 mg / day
Ranitidine	Infant to ≤ 16 yrs	5-10 mg/kg/day	5-10 mg/kg/day	Divided BID, max 150 mg/dose
PPIs				
Dexlansoprazole	≥ 12 yrs	60 mg daily	30 mg daily	**Tx**: up to 8 weeks **Maint**: 16 weeks
Esomeprazole	Infant to 1 yr	3-5 kg: 2.5 mg daily >5-7 kg: 5 mg daily >7.5 kg: 10 mg daily		Up to 6 weeks
	1 to 11 yrs	< 20 kg: 10 mg daily ≥ 20 kg: 10-20 mg daily		x 8 weeks
	≥ 12 yrs	20 -40 mg daily		x 4- 8 weeks
Lansoprazole^	1 to 11 yrs	< 30 kg: 15 mg daily ≥ 30 kg: 30 mg daily		Up to 12 weeks
	≥ 12 yrs	30 mg daily		Up to 8 weeks
Omeprazole^ Weight based: 0.7-4 mg/kg/day; 1 mg/kg/day most common; max 40 mg per day	Infants	3 to<5kg: 2.5 mg daily 5 to <10 kg: 5 mg daily 10 to <20 kg: 10 mg daily		Up to 6 weeks
	1 to 16 yrs	3 to<5kg: 2.5 mg daily 5 to <10 kg: 5 mg daily 10 to <20 kg: 10 mg daily ≥ 20 kg: 20 mg daily	5 to <10 kg: 5 mg daily 10 to <20 kg: 10 mg daily ≥ 20 kg: 20 mg daily	**Tx**: up to 4-8 weeks **Maint**: continue an additional 4 weeks if needed.
Pantoprazole^	≥ 5 yrs	≥ 15 to <40 kg: 20 mg daily ≥ 40 kg: 40 mg daily		Up to 8 weeks
Rabeprazole	Infant to 11 yrs	<15 kg: 5 mg daily, ↑ to 10 mg if inadequate response ≥ 15 kg: 10 mg daily		x 4-8 weeks. If response, try to wean; if no response, re-evaluate diagnosis.

*When not specified whether treatment or maintenance, columns are merged.

^ Formulae for extemporaneous compounding from tablets available in Lexicomp (access through SHIRP) or call medSask for details.

Table 4: ORAL Pediatric Doses of H_2RAs and PPIs for PUD[3,14]

Agent	Age	Dose*		Notes
		Duodenal Ulcer	Gastric Ulcer	
H_2RAs				
Cimetidine^	3 to < 5 yrs	15-20 mg/kg/day		
	5 to < 16 yrs	**Treatment**: 20-40 mg/kg/day **Maintenance**: 5-8 mg/kg/dose at bedtime		**Treatment**: 4-8 weeks
	≥ 16 yrs	300 mg QID or 800 mg at bedtime or 400 mg BID	300 mg QID or 800 mg at bedtime	Up to 8 weeks for both
Famotidine^	1 to 16 yrs	0.5 mg/kg/day at bedtime or divided BID		Max 40 mg/day
Nizatidine	N/A			
Ranitidine	Infant to 16 yrs	**Treatment**: 4-8 mg/kg/day divided BID **Maintenance**: 2-4 mg/kg/day	**Treatment:** 4-8 mg/kg/day divided BID **Maintenance**: 2-4 mg/kg/day	**Treatment**: Max 300 mg/day **Maintenance**: Max 150 mg/day
PPIs				
Because PUD is uncommon in children, pediatric dosing of PPIs for this indication is not readily available and mostly pertains to regimens for *H. pylori* eradication (the most common cause of PUD in children). Dosing as part of *H. pylori* eradication regimens:				
Esomeprazole, omeprazole[15]	15-24 kg: 25-34 kg: >35 kg:	20 mg BID 30 mg BID 40 mg BID		
Omeprazole, lansoprazole[13]	1-2 mg/kg/day			
Dosing for ***H.pylori*-negative PUD** is very limited though it is reasonable to extrapolate treatment doses for GERD.				

*when location of ulcer not specified, columns are merged

^ Formulae for extemporaneous compounding from tablets available in Lexicomp (access through SHIRP) or call medSask for details

Table 5: Formulary Details of H_2RAs and PPIs[16,17]

Agent	NIHB	SDP MAC pricing in effect‡
All H_2RAs	Full formulary	Full formulary
Dexlansoprazole	No coverage	No coverage
Esomeprazole 20 mg, 40 mg	No coverage	EDS: including treatment of GERD and PUD
Lansoprazole 15 mg, 30 mg	LUB – quantity restriction	Full formulary
Lansoprazole ODT 15 mg, 30 mg	LUB – quantity restriction and For children ≤ 12 years unable to swallow capsules or patients with dysphagia or a feeding tube who cannot use capsule formulation	EDS: patients who cannot swallow or have an enteral feeding tube
Omeprazole 10 mg	No Coverage	EDS: pediatric patients in whom full formulary listings are not appropriate
Omeprazole 20 mg	LUB – quantity restriction	Full Formulary
Pantoprazole sodium 20 mg, 40 mg magnesium 40 mg	LUB – quantity restriction	Full Formulary
Rabeprazole 10 mg, 20 mg	LUB – quantity restriction	Full Formulary
LUB= Limited Use Benefit; prior approval is not required but patients are limited to 400 tablets/capsules of PPI every 180 days. ‡MAC pricing = Maximum Allowable Cost – SDP will pay up to $0.20 per unit for all listed PPIs (subject to patient's usual co-payment and deductible). Patients can pay the difference or switch to a product within the limit. As of Sep 2019, pantoprazole sodium 20 mg,pantoprazole magnesium 40 mg and rabeprazole (both strengths) are products with unit prices ≤$0.20.		

BID = twice daily, DU= duodenal ulcer; GU= gastric ulcer; H_2RAs = histamine H2-receptor antagonists; maint=maintenance; max = maximum; mos= months; N/A = not applicable; NIHB = Non-Insured Health Benefits; NSAID=non-steroidal anti-inflammatory drug; ODT=orally disintegrating tablet; PPIs= proton pump inhibitors; PUD =peptic ulcer disease; QID=four times daily; SDP = Saskatchewan Drug Plan; tx=treatment; yrs = years

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