H_2-receptor antagonist (H_2RA) Shortages

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BACKGROUND

Health Canada recalls[1] and manufacturer supply disruptions may be causing shortages of commonly used acid-reducing medications called histamine H2-receptor antagonists (H_2RAs). H_2RAs include cimetidine, famotidine, nizatidine and ranitidine.

There are several Health Canada–approved indications of H_2RAs[2] (see Table 1); this document addresses the most common: gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD).

TABLE 1: HEALTH CANADA–APPROVED INDICATIONS OF H_2RAs[2]

Health Canada–Approved Indications	H_2-Receptor Antagonists (H_2RAs)			
	Cimetidine	Famotidine	Nizatidine	Ranitidine
Duodenal ulcer, treatment	✓	✓	✓	✓
Duodenal ulcer, prophylaxis	—	✓	✓	✓
Benign gastric ulcer, treatment	✓	✓	✓	✓
Gastric ulcer, prophylaxis	—	—	—	✓
GERD, treatment	✓	✓	✓	✓
GERD, maintenance of remission	—	✓	—	—
Gastric hypersecretion,* treatment	✓	✓	—	✓
Self-medication of acid indigestion, treatment and prophylaxis	—	✓†	—	✓†
Acid aspiration syndrome, prophylaxis	—	—	—	✓
Hemorrhage from stress ulceration or recurrent bleeding, prophylaxis	—	—	—	✓

✓ = Health Canada–approved indication; GERD = gastroesophageal reflux disease
*For example, Zollinger-Ellison syndrome.
†Available without a prescription.

H_2RA ALTERNATIVES

There are 4 H_2RA alternatives to consider: cimetidine, famotidine, nizatidine and ranitidine.

- 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]

Formulae for extemporaneous compounding of suspensions from tablets are available in Lexicomp, should the pharmacy have some inventory 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 gastroesophageal reflux disease (GERD).

Adults

- If more details are required, refer to the following content available in RxTx (www.myRxTx.ca) and in the *Compendium of Therapeutic Choices (CTC)* and the *Compendium of Therapeutics for Minor Ailments (CTMA)*:
  - o Gastroesophageal Reflux Disease *(CTC)*
  - o Dyspepsia and Peptic Ulcer Disease *(CTC)*
  - o Dyspepsia and GERD *(CTMA)*

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[4,5]

- Take this opportunity to determine if continued treatment is necessary.
- Consider stepping down (antacids, alginates) or stepping up (proton pump inhibitors [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.
- Suggest lifestyle modification (e.g., diet modification, weight loss, smoking/alcohol cessation, elevating head of bed). — All cases.
- Over the counter (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 2 and 6 for dosing and formulary considerations.

PUD[6]

- PUD due to *Helicobacter pylori* infection:
  - PPIs should be used as the acid-suppressing agent of the *H. pylori* 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 4 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 or *Primary Prevention of Vascular Disease* in RxTx or in the *Compendium of Therapeutic Choices (CTC)* 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.
- See Tables 3 and 6 for dosing and formulary considerations.

PEDIATRICS

GERD

- Ensure pharmacological therapy is required; this is especially important in the case in infants.[7]

INFANTS (UP TO 1 YEAR)

Reassure parents/caregivers that:[7,8]

- 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:[8,9,10]

- Avoid infant exposure to secondhand smoke.
- Consider providing smaller feedings to avoid overfeeding.
- 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 or barley).
    - Note that the inconvenience of expressing breast milk 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 diet.
  - In breastfed infants, the mother removes all cow's milk proteins, beef and major sources of soy protein.

Pharmacological treatment of infant GERD:[8,9,10]

- Consider pharmacological treatment if frequent regurgitation accompanied by infant distress, feeding refusal and/or poor weight gain persist despite instituting nonpharmacological strategies.
- PPIs are considered by some as first-line treatment of infant GERD. See Table 4 for dosages.

- **PPIs have not been found to be effective in reducing symptoms of irritability or regurgitation in infants.**[11]
  - Begin with 2-week trial:
    - If symptoms do not improve, discontinue and re-evaluate.
    - If symptoms markedly improve, consider continued treatment for 3–6 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 of age.
- See Tables 4 and 6 for dosing and formulary considerations.

PUD[12]

- *H. pylori* infection-related:
  - Most common cause of PUD in children.
  - PPIs should be used as the acid-suppressing agent of the *H. pylori* eradication regimen.
- Non-*H. pylori*-related:
  - H_2RAs and PPIs.
    - It is suggested that PPIs may be more effective with quicker time to healing,[12] though this appears to be extrapolated from adult data; pediatric data are very limited.
    - See Tables 5 and 6 for dosing and formulary considerations.

TABLE 2: ORAL ADULT DOSES OF H_2RAs AND PPIs FOR GERD[3,13]

Agent	Dose*		
	Treatment	**Maintenance**	**Notes**
H_2RAs			
Cimetidine	800 mg BID *or* 300–400 mg QID and at bedtime		8–12 wk
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 wk
PPIs			
Dexlansoprazole	60 mg daily	30 mg daily	**Treatment:** 4–8 wk
Esomeprazole	40 mg daily	20 mg daily	**Treatment:** 4–8 wk
Lansoprazole	30 mg daily	15 mg daily	**Treatment:** 4–8 wk
Omeprazole	20 mg daily	10 mg daily	**Treatment:** 2–8 wk
Pantoprazole	40 mg daily	20 mg daily	**Treatment:** 2–8 wk
Rabeprazole	20 mg daily	10 mg daily	**Treatment:** 4–8 wk

*When not specified whether treatment or maintenance, columns are merged.
H_2RAs = histamine H_2-receptor antagonists; PPIs = proton pump inhibitors; wk = weeks

TABLE 3: ORAL ADULT DOSES OF H_2RAs AND PPIs FOR PUD[3,13]

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 *or* 300 mg QID *or* 600 mg BID	**Treatment:** Duodenal: 6–8 wk **Benign:** 4–8 wk **Maintenance:** 4–6 months **Maximum:** 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 wk **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 wk **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 wk
PPIs			
Dexlansoprazole	N/A	N/A	
Esomeprazole	N/A	**NSAID:** 20 mg daily	4–8 wk
Lansoprazole	15 mg daily **NSAID:** 30 mg daily	15 mg daily **NSAID:** 30 mg daily	**DU:** 4 wk **GU:** 4–8 wk **NSAID:** ≤8 wk
Omeprazole	20 mg daily	20 mg daily	**DU:** 4 wk **GU:** 4–8 wk **NSAID:** 4–8 wk
Pantoprazole	40 mg daily	40 mg daily	**DU:** 4 wk **GU:** 4–8 wk
Rabeprazole	20 mg daily	20 mg daily	**DU:** 4 wk **GU:** 6 wk

DU = duodenal ulcer; GU = gastric ulcer; H_2RAs = histamine H_2-receptor antagonists; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; PPIs = proton pump inhibitors; wk = weeks

TABLE 4: ORAL PEDIATRIC DOSES OF H_2RAs AND PPIs FOR GERD[3,13]

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

*When not specified whether treatment or maintenance, columns are merged.
a Formulae for extemporaneous compounding from tablets available in Lexicomp.
b Formulae for extemporaneous compounding from tablets available from SickKids at www.sickkids.ca/pharmacy/compounding-service.
H_2RAs = histamine H_2-receptor antagonists; PPIs = proton pump inhibitors; wk = weeks; y = years

TABLE 5: ORAL PEDIATRIC DOSES OF H_2RAs AND PPIS FOR PUD[3,13]

Agent	Age	Dose*		Notes
		Duodenal Ulcer	Gastric Ulcer	
H_2RAs				
Cimetidine[a]	3 to <5 y	15–20 mg/kg/day		
	5 to <16 y	**Treatment:** 20–40 mg/kg/day **Maintenance:** 5–8 mg/kg/dose at bedtime		**Treatment:** 4–8 wk
	≥16 y	300 mg QID or 800 mg at bedtime or 400 mg BID		Up to 8 wk for both
Famotidine[a,b]	1–16 y	0.5 mg/kg/day at bedtime or divided BID		Max 40 mg/day
Nizatidine	N/A			
Ranitidine	Infant–16 y	**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:				
	Weight	**Dose**		
Esomeprazole, omeprazole[a,b,14]	15–24 kg: 25–34 kg: >35 kg:	20 mg BID 30 mg BID 40 mg BID		
Omeprazole,[a,b] lansoprazole[a,12]	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.
a Formulae for extemporaneous compounding from tablets available in Lexicomp.
b Formulae for extemporaneous compounding from tablets available from SickKids at www.sickkids.ca/pharmacy/compounding-service.
H_2RAs = histamine H_2-receptor antagonists; N/A = not applicable; PPIs = proton pump inhibitors; PUD = peptic ulcer disease; wk = weeks; y = years

TABLE 6: FORMULARY DETAILS OF H_2RAs AND PPIs[15,16]

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 For children ≤12 y 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 copayment and deductible). Patients can pay the difference or switch to a product within the limit. As of Sept 2019, pantoprazole sodium 20 mg, pantoprazole magnesium 40 mg and rabeprazole (both strengths) are products with unit prices ≤$0.20.
EDS = exception drug status; GERD = gastroesophageal reflux disease; H_2RAs = histamine H_2-receptor antagonists; LUB = limited use benefit; MAC = maximum allowable cost; NHB = non-insured health benefits; ODT = orally disintegrating tablet; PPIs = proton pump inhibitors; PUD = peptic ulcer disease; SDP = Saskatchewan Drug Plan; y = years

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