Texas Vendor Drug Program

Drug Use Criteria: Oral Histamine H2-Receptor Antagonists

Publication History

- Developed December 2001.
- Revised May 2019; December 2016; March 2015; June 2013; November 2011; September 2011; September 2009; June 2009; December 2005; November 2003; October 2002.

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

Prepared by:

- Drug Information Service, UT Health San Antonio.
- The College of Pharmacy, The University of Texas at Austin

1 Dosage

Histamine H2-receptor antagonists (H2RAs) are FDA-approved for use in gastric ulcer, duodenal ulcer, gastroesophageal reflux disease (GERD), esophagitis, hypersecretory conditions, and non-ulcer indigestion/heartburn.

1.1 Adults

The maximum adult H2RA daily doses when prescribed for acute and maintenance FDA-approved conditions are summarized in Table 1 and Table 2. Dosage regimens exceeding these maximum recommended values will be reviewed.

Table 1: Adult Maximum Daily Acute Doses for Histamine H2-Receptor Antagonists: Monotherapy[1-8]

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	cimetidine (generics)	200 mg, 300 mg, 400 mg, 800 mg tablets; 300 mg/5 mL oral solution	1200 mg/day^
gastric ulcer			1200 mg/day
gastroesophageal reflux disease (GERD) - nonerosive			1600 mg/day
heartburn			400 mg/day
hypersecretory conditions			2400 mg/day
duodenal ulcer	famotidine (Pepcid®, generics)	10 mg, 20 mg, 40 mg tablets; 40 mg/5 mL oral suspension	40 mg/day
erosive esophagitis (EE)			80 mg/day
gastric ulcer			40 mg/day
GERD - nonerosive			40 mg/day
heartburn			40 mg/day
hypersecretory conditions			640 mg/day

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	nizatidine (generics)	150 mg, 300 mg capsules; 15 mg/mL oral solution	300 mg/day in single or divided doses
gastric ulcer			300 mg/day in single or divided doses
GERD - nonerosive			300 mg/day in single or divided doses
duodenal ulcer	ranitidine (Zantac®, generics)	150 mg, 300 mg capsules; 75 mg, 150 mg, 300 mg tablets; 15 mg/mL oral syrup	300 mg/day in single or divided doses
EE			600 mg/day
gastric ulcer			300 mg/day in single or divided doses
GERD - nonerosive			300 mg/day in single or divided doses
heartburn			300 mg/day in single or divided doses
hypersecretory conditions			6 g/day in divided doses

- ^ = Patients who are heavy smokers with duodenal ulcers greater than 1 cm may benefit from cimetidine 1600 mg at bedtime

Table 2: Adult Maximum Daily Maintenance Dose for Histamine H2-Receptor Antagonists (Monotherapy)

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	cimetidine (generics)	200 mg, 300 mg, 400 mg, 800 mg tablets; 300 mg/5 mL oral solution	400 mg/day
hypersecretory conditions			2400 mg/day

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
duodenal ulcer	famotidine (Pepcid®, generics)	10 mg, 20 mg, 40 mg tablets; 40 mg/5 mL oral suspension	20 mg/day
hypersecretory conditions			640 mg/day
duodenal ulcer	nizatidine (generics)	150 mg, 300 mg capsules; 15 mg/mL oral solution	150 mg/day at bedtime
duodenal ulcer	ranitidine (Zantac®, generics)	150 mg, 300 mg capsules; 75 mg, 150 mg, 300 mg tablets; 15 mg/mL oral syrup	150 mg/day at bedtime
erosive esophagitis			300 mg/day in two divided doses
hypersecretory conditions			6 g/day in divided doses

Current American College of Gastroenterology guidelines no longer include H2RAs as part of *Helicobacter pylori* treatment regimens as H2RAs are associated with lower compliance and efficacy rates compared to other available proton pump inhibitor (PPI) regimens.[9]

1.2 Pediatrics

Maximum recommended pediatric H2RA daily doses for acute and maintenance therapy are summarized in **Error! Reference source not found.**. Dosages exceeding these recommendations will be reviewed.

Table 3: Pediatric Maximum Daily Acute Doses for Histamine H2-Receptor Antagonists: Monotherapy[1-6]

Treatment Indication	Drug Name	Patient Characteristics	Maximum Recommended Dosage
duodenal ulcer	cimetidine (generics)	Greater than or equal to 16 years of age	1200 mg/day^
gastric ulcer		Greater than or equal to 16 years of age	1200 mg/day
gastroesophageal reflux disease (GERD) - nonerosive		Greater than or equal to 16 years of age	1600 mg/day

Treatment Indication	Drug Name	Patient Characteristics	Maximum Recommended Dosage
heartburn		Greater than or equal to 12 years of age	400 mg/day
hypersecretory conditions		Greater than or equal to 16 years of age	2400 mg/day
duodenal ulcer	famotidine (Pepcid®, generics)	1 to 17 years of age	40 mg/day
erosive esophagitis (EE)		1 to 17 years of age	80 mg/day
gastric ulcer		1 to 17 years of age	40 mg/day
GERD - nonerosive		1 to 16 years of age	tablet: 40 mg/day suspension: 80 mg/day
GERD – nonerosive		3 months to 1 year of age	suspension: 0.5 mg/kg twice daily
GERD - nonerosive		Less than 3 months of age	suspension: 0.5 mg/kg once daily
heartburn		Greater than or equal to 12 years of age	40 mg/day
EE	nizatidine (generics)	Greater than or equal to 12 years of age	300 mg/day in single or divided doses
GERD - nonerosive		Greater than or equal to 12 years of age	300 mg/day in single or divided doses
duodenal ulcer	ranitidine (Zantac®, generics)	Greater than or equal to 1 month of age	300 mg/day in single or divided doses
EE		Greater than or equal to 16 years of age	600 mg/day in four divided doses
EE		1 month to 16 years of age	600 mg/day in 2 divided doses
gastric ulcer		Greater than or equal to 1 month of age	300 mg/day in single or divided doses
GERD - nonerosive		Greater than or equal to 16 years of age	600 mg/day in divided doses

Treatment Indication	Drug Name	Patient Characteristics	Maximum Recommended Dosage
GERD - nonerosive		1 month to 16 years of age	300 mg/day in single or divided doses
heartburn		Greater than or equal to 12 years of age	300 mg/day in single or divided doses
hypersecretory conditions		Greater than or equal to 16 years of age	6 g/day in divided doses

- ^ = Patients who are heavy smokers with duodenal ulcers greater than 1 cm may benefit from cimetidine 1600 mg at bedtime

Table 4: Pediatric Maximum Daily Maintenance Doses for Histamine H2-Receptor Antagonists[1-6]

Treatment Indication	Drug Name	Patient Characteristics	Maximum Recommended Dosage
duodenal ulcer	cimetidine (generics)	Greater than or equal to 16 years of age	400 mg at bedtime
hypersecretory conditions		Greater than or equal to 16 years of age	2400 mg/day
duodenal ulcer	ranitidine (Zantac®, generics)	Greater than or equal to 1 month of age	150 mg/day at bedtime
erosive esophagitis		Greater than 16 years of age	300 mg/day in two divided doses
hypersecretory conditions		Greater than 16 years of age	6 g/day in divided doses

1.3 Dosage in Renal Impairment

H2RAs are primarily renally excreted. Dosage modifications for H2RA use in renal impairment are summarized in Table 5.

Table 5: H2RA Dosage Modifications in Renal Impairment

Drug Name	Dosage Adjustments in Renal Impairment
Cimetidine	• moderate impairment (CrCl 10-50 ml/min): 50% of • total daily dose • severe impairment (CrCl less than 10 ml/min): 300 mg orally every 12 hours; may increase to every 8 hours cautiously based on patient response

Drug Name	Dosage Adjustments in Renal Impairment
Famotidine	• moderate to severe impairment (CrCl less than 50 ml/min): reduce total daily dose by 50%; • alternately, dosing interval may be lengthened to 36-48 hours based on patient response and degree of renal impairment

Nizatidine	• Active treatment:
	  ▸ CrCl 20-50 ml/min: 150 mg/day orally
	  ▸ CrCl less than 20 ml/min: 150 mg orally every other day
	• Maintenance therapy:
	  ▸ CrCl 20-50 ml/min: 150 mg every other day orally
	  ▸ CrCl less than 20 ml/min: 150 mg every 3 days orally

Ranitidine	• CrCl < 50 ml/min: ▸ 150 mg/day orally; may increase to every 12 hours cautiously based on patient response

2 Duration of Therapy

2.1 Adult and Pediatric Patients

Clinical trials document a maximum treatment duration of 56 days (eight weeks) for anti-ulcer therapy in treating acute duodenal and gastric ulcers. In pediatric patients, an 8-week maximum GERD acute treatment duration is recommended[1-5]. H2RA treatment regimens at acute dosage levels lasting longer than four months will be reviewed.

When used for non-ulcer indigestion/heartburn, H2RA treatment duration should not exceed 14 days at the maximum dose, unless directed by a physician[1-5].

Maintenance therapy, at recommended daily maintenance doses (Table 2 and Table 4), may be continued indefinitely based on patient need.

H2RAs may be used in conjunction with PPIs in GERD patients experiencing nocturnal breakthrough symptoms.[10-14]

3 Duplicative Therapy

The combination of two or more H2RAs is not supported by the current literature. Therefore, concurrent use of this combination will be reviewed as there is no clinical evidence to suggest that adjunctive administration improves outcome.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Table 6 summarizes major drug-drug interactions considered clinically relevant for H2RAs. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 6: Major H2RA Drug-Drug Interactions[1-6]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
cimetidine	clopidogrel (Plavix®)	co-administration may result in decreased clopidogrel active metabolite levels, platelet inhibition, and clopidogrel efficacy; clopidogrel requires metabolism through CYP2C19 to active metabolite and cimetidine is CYP2C19 inhibitor	cimetidine-clopidogrel combination should be avoided; H2RA alternatives (e.g., famotidine, ranitidine) that are not CYP2C19 inhibitors can be substituted for cimetidine	major (DrugReax) 2-major (CP)
cimetidine	dofetilide (Tikosyn®)	concurrent use may potentially increase dofetilide serum levels/ enhance pharmacologic effects (e.g., torsades de pointes) as dofetilide metabolized by CYP3A4, eliminated through renal and hepatic mechanisms; cimetidine inhibits dofetilide clearance through interference with active tubular secretion and moderate CYP3A4 inhibition	dofetilide manufacturer states that concurrent administration of dofetilide and cimetidine is contraindicated; medications without effect on dofetilide pharmacokinetics (e.g., omeprazole, ranitidine, antacids) are potential alternatives to cimetidine	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
cimetidine	theophylline	adjunctive use may cause theophylline toxicity as cimetidine inhibits theophylline hepatic metabolism	adjunctive use possible if proper monitoring and/or dosage adjustments are made; order in which therapy initiated important - adding theophylline to existing cimetidine drug regimen can be safe as theophylline dosage titrated to acceptable serum concentrations, but adding cimetidine to existing theophylline regimen may enhance theophylline pharmacologic/ adverse effects; other available H2RAs do not significantly interact with theophylline and may be appropriate alternatives for cimetidine	major (DrugReax) 2-major (CP)
cimetidine	warfarin	combined use may result in increased INR and moderate to severe bleeding in some patients as cimetidine stereoselectively inhibits hepatic metabolism of warfarin R-isomer	adjunctive use possible if proper monitoring and/or dosage adjustments are made; order in which therapy is initiated is important - adding warfarin to existing cimetidine drug regimen can be safe as warfarin dosage titrated to acceptable monitoring parameter (e.g., INR), but adding cimetidine to existing warfarin regimen may enhance warfarin-induced hypoprothrombinemic response; other H2RAs do not significantly interact with warfarin - may be appropriate alternatives for cimetidine	moderate (DrugReax) 2-major (CP)
H2RAs	atazanavir (Reyataz®)	concurrent use may cause reduced atazanavir efficacy and increased resistance, as increased gastric pH with H2RAs causes decreased atazanavir solubility/ absorption/plasma levels	administer atazanavir either with and/or at least 10 hours after H2RA dose and monitor for decreased efficacy/increased resistance	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
H2RAs	select azole antifungals (itraconazole (Sporanox®), ketoconazole, posaconazole (Noxafil®)	combined use may result in reduced azole antifungal bioavailability, decreased maximum azole antifungal serum levels, and attenuated azole antifungal pharmacologic effects, as H2RAs increase gastric pH and azole antifungal oral absorption is dependent on acidic environment	posaconazole manufacturer recommends avoiding the posaconazole-cimetidine drug combination unless benefits outweigh risks; if H2RA-azole antifungal combination necessary, monitor patients carefully for reduced antifungal activity	major, moderate (DrugReax) 2-major (CP)
H2RAs	drugs pH-dependent for solubility (e.g., dasatinib-Sprycel®; erlotinib – Tarceva®)	adjunctive administration for extended duration may result in reduced exposure and serum levels in select medications dependent on acidic gastric pH for solubility and absorption	combined use not recommended; alternative acid suppressives (e.g., antacids) should be administered 2 hours before or 2 hours after pH-dependent medication for optimal efficacy	major (DrugReax) 2-major (CP)
H2RAs	delavirdine (Rescriptor®)	combined use for extended treatment duration may result in reduced delavirdine absorption, decreased delavirdine serum levels, and attenuated delavirdine efficacy as delavirdine is dependent on an acidic gastric pH for absorption; separating drug doses may not improve delavirdine absorption as H2RAs affect gastric pH for prolonged time	concomitant use not recommended; antacids may be alternative acid suppressive therapy, with antacid and delavirdine doses separated by at least one hour	major (DrugReax) 2-major (CP)

- *CP = Clinical Pharmacology
- H2RAs = histamine (H2) receptor antagonists
- INR = International Normalized Ratio

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at micromedexsolutions.com.libproxy.uthscsa.edu/ (cited: May 29, 2019).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed May 29, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; May 29, 2019.

4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at: online-statref-com.libproxy.uthscsa.edu/. Accessed May 29, 2019.
5. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; May 29, 2019.
6. Nizatidine capsule package insert. Actavis Pharma Inc., March 2016.
7. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet. 2009;374(9699):1449-61.
8. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet. 2006;367(9528):2086-100.
9. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017; 112:212-38.
10. Anonymous. Drugs for GERD and peptic ulcer disease. Med Lett Drugs Ther. 2018; 60(1538):9-16.
11. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: A controlled study in normal subjects. Gastroenterology. 1998; 115:1335-9.
12. Xue S, Katz PO, Banerjee P, Tutuian R, Castell DO. Bedtime H2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. Aliment Pharmacol Ther. 2001; 15:1351-6.
13. Cross LB, Justice LN. Combination drug therapy for gastroesophageal reflux disease. Ann Pharmacother. 2002; 36:912-6.
14. Robinson M, Rodriguez-Stanley S, Ciociola AA, et al. Control of nocturnal gastric acidity: a role for low dose bedtime ranitidine to supplement daily omeprazole. Dig Dis Sci. 2002; 47:265-73.