Texas Vendor Drug Program

Drug Use Criteria: Oral Histamine H2-Receptor Antagonists

Publication History

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

Notes: All criteria may be applied retrospectively. 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.

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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 nonulcer indigestion/heartburn.

1.1 Adults

The maximum adult H2RA daily doses when prescribed for **acute and maintenance FDA-approved conditions are summarized in Tables 1 and 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
duodenal ulcer	nizatidine (generics)	150 mg, 300 mg capsules; 15 mg/mL oral solution	300 mg/day in single or divided doses

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Dosage
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 > 1 cm may benefit from cimetidine 1600 mg at bedtime

Table 2. Adult Maximum Daily Maintenance Dose 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	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**	**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 Table 3. 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)	**≥ 16 years of age**	1200 mg/day^
gastric ulcer		**≥ 16 years of age**	1200 mg/day
gastroesophageal reflux disease (GERD) - nonerosive		**≥ 16 years of age**	1600 mg/day
heartburn		≥ 12 years of age	400 mg/day
hypersecretory conditions		**≥ 16 years of age**	**2400 mg/day**

Treatment Indication	Drug Name	Patient Characteristics	Maximum Recommended Dosage
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		**< 3 months of age**	**suspension: 0.5 mg/kg once daily**
heartburn		**≥ 12 years of age**	40 mg/day
EE	nizatidine (generics)	**≥ 12 years of age**	300 mg/day in single or divided doses
GERD - nonerosive		**≥ 12 years of age**	300 mg/day in single or divided doses
duodenal ulcer	ranitidine (Zantac®, generics)	**≥ 1 month of age**	300 mg/day in single or divided doses
EE		**> 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		**≥1 month of age**	300 mg/day in single or divided doses
GERD - nonerosive		**> 16 years of age**	**600 mg/day in divided doses**
GERD - nonerosive		**1 month to 16 years of age**	300 mg/day in single or divided doses
heartburn		**≥ 12 years of age**	300 mg/day in single or divided doses
hypersecretory conditions		**> 16 years of age**	6 g/day **in divided doses**

^***Patients who are heavy smokers with duodenal ulcers > 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)	≥ 16 years of age	400 mg at bedtime
hypersecretory conditions		**≥ 16 years of age**	**2400 mg/day**
duodenal ulcer	ranitidine (Zantac®, generics)	**≥ 1 month of age**	**150 mg/day at bedtime**
erosive esophagitis		> 16 years of age	300 mg/day in two divided doses
hypersecretory conditions		> 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 3.

Table 5. H2RA Dosage Modifications in Renal Impairment[1-6]

Drug Name	Dosage Adjustments in Renal Impairment
cimetidine	*moderate impairment (CrCl 10-50 ml/min):* 50% of total daily dose *severe impairment (CrCl < 10 ml/min):* 300 mg orally every 12 hours; may increase to every 8 hours cautiously based on patient response
famotidine	*moderate to severe impairment (CrCl < 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 < 20 ml/min: 150 mg orally every other day *maintenance therapy:* • CrCl 20-50 ml/min: 150 mg every other day orally • CrCl < 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

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 nonulcer 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 (**Tables 2 and 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 4 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)
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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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)
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)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
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 **as 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

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