

Histamine₂-Receptor Antagonist Review

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Histamine₂-Receptor Antagonist Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
cimetidine (Tagamet [®] , Tagamet HB 200)	generic	<ul style="list-style-type: none"> - Short-term treatment of active DU and benign GU up to eight weeks - Long-term prophylaxis of DU at a reduced dose after ulcer healing for up to five years - Treatment of pathological hypersecretory states (eg, Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas) - Treatment of EE and GERD for up to 12 weeks - Prevention of upper GIB in critically ill patients - Treatment and prevention of heartburn, acid indigestion or sour stomach (OTC only)
famotidine (Pepcid [®] , Pepcid AC)	generic, Merck	<ul style="list-style-type: none"> - Short-term treatment of active DU and benign GU for up to eight weeks - Maintenance therapy of DU after ulcer healing - Short-term relief of symptomatic esophagitis, GERD, and pathological hypersecretory conditions - Treatment and prevention of heartburn, acid indigestion or sour stomach (OTC only)
famotidine, calcium carbonate, magnesium hydroxide (Pepcid Complete [®])	generic, Merck	<ul style="list-style-type: none"> - Relief of heartburn associated with acid indigestion or sour stomach (OTC only)
nizatidine (Axid [®] , Axid AR)	generic, GlaxoSmithKline	<ul style="list-style-type: none"> - Treatment (up to eight weeks) and maintenance of DU at a reduced dose after ulcer healing for up to one year - Treatment of active, benign GU up to eight weeks - Treatment of EE and GERD up to 12 weeks - Treatment and prevention of heartburn, acid indigestion or sour stomach (OTC only)
ranitidine (Zantac [®] , Zantac EFFERdose)...	generic, GlaxoSmithKline	<ul style="list-style-type: none"> - Short-term treatment of active DU for up to eight weeks - Short-term treatment of active, benign GU for up to six weeks - Maintenance therapy of DU and GU at a reduced dose after ulcer healing for up to one year - Treatment of pathological hypersecretory conditions - Treatment and maintenance of EE - Treatment of GERD - Treatment and prevention of heartburn, acid indigestion or sour stomach (OTC only)

DU = duodenal ulcer

EE = erosive esophagitis

GU = gastric ulcer

GERD = gastroesophageal reflux disease

GIB = gastrointestinal bleed

Overview

Histamine₂ (H₂) antagonists or blockers have been used for many years to treat peptic ulcer disease and symptoms of gastroesophageal reflux disease (GERD). Doses are often increased to two to four times normal when treating more severe cases of GERD. For patients who fail to achieve adequate acid suppression with the H₂-antagonists, proton pump inhibitors (PPIs) with greater acid-suppressing capabilities are available.

Pharmacology^{1,2,3,4}

H₂-antagonists are reversible competitive blockers of histamine at the H₂ receptors, particularly those in the gastric parietal cells. The H₂-antagonists are highly selective, do not affect the H₁ receptors, and are not anticholinergic agents.

Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion
cimetidine (Tagamet) ⁵	60-70	2	sulfoxide	Mainly urine
famotidine (Pepcid) ⁶	40-45	2.5-3.5	S-oxide	Urine: 65-70 % Feces: 30-35 %
nizatidine (Axid) ⁷	70	1-2	N2-monodesmethyl (<7%) N2-oxide (<5%) S-oxide (<6%)	Urine: >90 % Feces: <6 %
ranitidine (Zantac) ⁸	50	2.5-3	N-oxide (<4%) S-oxide (1%) desmethyl (1%)	Mainly urine – 30% unchanged

Contraindications/Warnings^{9,10,11,12}

Do not use any of these products if any of the following are present: difficulty or pain when swallowing food, vomiting with blood, or bloody or black stools. Do not use in patients who have a known hypersensitivity to these products.

Drug Interactions^{13,14,15,16}

Drug interactions in this class occur mainly because of the inhibition of the cytochrome P450 system (CYP450). Cimetidine inhibits the CYP450 system which results in drug interactions. The most clinically significant drug interactions are with drugs that have a narrow therapeutic window. These drugs include phenytoin, theophylline, and warfarin. Clinical significance of other drug interactions is unknown. Ranitidine also inhibits the CYP450 system but to a lesser degree than cimetidine. Drug interactions with ranitidine have been reported in case reports, but it is unknown if there is a causal relationship. Both nizatidine and famotidine do not inhibit the P450 system. Thus, these two agents do not cause drug interactions with drugs that are metabolized through the cytochrome P450 system.

All H₂-antagonists create an alkaline environment in the stomach that may interfere with the

absorption of certain drugs. Cimetidine and ranitidine have been shown to inhibit renal procainamide clearance via inhibition of tubular secretion. It is unknown if this is clinically significant.

Adverse Effects

Drug	Diarrhea	Headache	Dizziness	Somnolence	Gynecomastia	Constipation
cimetidine (Tagamet) ¹⁷	1	2.1-3.5	1	nr	0.3-4	nr
famotidine (Pepcid) ¹⁸ n=2,500	1.7	4.7	1.3	Reported	nr	1.2
nizatidine (Axid) ¹⁹ n=2,694	7.2 (6.9)	16.6 (15.6)	4.6 (3.8)	1.9 (1.6)	nr	2.5 (3.8)
ranitidine (Zantac) ²⁰	Reported	Reported	Reported	Reported	nr	Reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative nor all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Gynecomastia has been reported in patients who have been treated with cimetidine for one month or longer. A four percent incidence has been reported in patients treated with cimetidine for hypersecretory conditions. Reversible impotence has also been reported in patients treated for hypersecretory conditions.²¹ Impotence has been reported with the use of famotidine, rantidine, and nizatidine but occurred at similar frequencies of those treated with placebo. Rare reports of gynecomastia have been made when using famotidine, rantidine, or nizatidine.^{22,23,24}

Reversible confusional states have been reported with all of the H₂-antagonists. Confusional states are most likely to occur in sick elderly patients with renal or hepatic impairment. In three cimetidine studies conducted in outpatients, central nervous system (CNS) reaction rates were 0.04 percent to 0.16 percent. Disturbances usually occur within two weeks of initiation of treatment and include the following reactions: confusion, disorientation, agitation, hostility, delirium, hallucinations, obtundation, somnolence, mental status changes, psychosis, or paranoia.²⁵

Special Populations^{26,27,28,29}

Pediatrics

Cimetidine and nizatidine are not approved for pediatric use. Famotidine is approved for patients younger than three months of age, while ranitidine is indicated in patients one month and older.

Pregnancy

All products in this class are rated Pregnancy Category B.

Other considerations – renal, hepatic, race, etc.

Cimetidine, famotidine, nizatidine, and ranitidine should be dose and/or interval adjusted in patients with impaired renal function. Nizatidine and ranitidine should also be used with caution in patients with hepatic impairment.

Dosages

Drug	Dosing	Availability
cimetidine (Tagamet, Tagamet HB 200)	<p>Active DU: 800 mg at bedtime OR 300 mg four times daily OR 400 mg twice daily</p> <p>Maintenance DU: 400 mg at bedtime</p> <p>Erosive esophagitis/GERD: 800 mg twice daily OR 400 mg four times daily</p> <p>Benign GU: 800 mg at bedtime OR 300 mg four times daily</p> <p>Hypersecretory conditions: Start at 300 mg four times daily up to 2,400 mg daily</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach prophylaxis for patients 12 years and older: 200 mg (OTC only) up to 30 minutes prior to meals that are known to cause symptoms once daily or twice daily.</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach treatment for patients 12 years and older: 200 mg (OTC only) once daily or twice daily</p>	<p>Prescription: 300 mg/5 mL solution; 200, 300, 400, 800 mg tablet</p> <p>OTC: 200 mg tablet ; 200 mg/5 mL solution</p>

Dosages (continued)

Drug	Dosing	Availability
famotidine (Pepcid, Pepcid AC)	<p>Active DU: 40 mg at bedtime OR 20 mg twice daily Maintenance DU: 20 mg at bedtime GERD: 20 mg twice daily Erosive esophagitis: 20 or 40 mg twice daily GU: 40 mg at bedtime Hypersecretory conditions: Start at 20 mg every six hours up to 160 mg every six hours Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach prophylaxis for patients 12 years and older: 10 mg to 20 mg (OTC only) given 15 minutes to 1 hour prior to eating a meal which is expected to cause symptoms. No more than two tablets daily. Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach treatment for patients 12 years and older: 10 mg to 20 mg (OTC only) given 1—2 times per day</p> <p><i>Pediatric</i> GERD: 0.5 mg/kg/dose once daily (patients less than 3 months of age); 0.5 mg/kg/dose twice daily (patients ages three months to one year); 1 mg/kg/day in two divided doses up to 40 mg twice daily (patients ages one to 16 years of age) Peptic ulcer: 0.5 mg/kg/day at bedtime or in two divided doses up to 40 mg daily (patients ages one to 16 years of age)</p>	<p>Prescription: 40 mg/5 mL suspension 20, 40mg tablet</p> <p>OTC: 20 mg chewable tablet; 10 mg gelcap; 10, 20 mg tablet</p>
famotidine, calcium carbonate, magnesium hydroxide (Pepcid Complete)	<p>Relief of heartburn associated with acid indigestion or sour stomach for patients 12 years and older: chew one tablet and swallow (Do not use more than two tablets in 24 hours)</p>	<p>OTC: 10 mg famotidine, 800 mg calcium carbonate, 165 mg magnesium hydroxide chewable tablet</p>

Dosages (continued)

Drug	Dosing	Availability
nizatidine (Axid, Axid AR)	<p>Active DU or GU: 300 mg at bedtime OR 150 mg twice daily</p> <p>Maintenance DU: 150 mg at bedtime</p> <p>GERD: 150 mg twice daily</p> <p>Erosive esophagitis: 150 mg twice daily</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach prophylaxis for patients 12 years and older: 75 mg (OTC only) twice daily immediately before eating or up to 60 minutes before consuming food and beverages that may cause heartburn.</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach treatment for patients 12 years and older: 75 mg (OTC only) once or twice daily</p>	<p>Prescription: 15 mg/mL solution 150, 300 mg pulvules</p> <p>OTC: 75 mg tablet</p>
ranitidine (Zantac, Zantac EFFERdose)	<p>Active DU: 300 mg after the evening meal or at bedtime OR 150 mg twice daily</p> <p>Maintenance DU: 150 mg at bedtime</p> <p>GERD: 150 mg twice daily</p> <p>Erosive esophagitis: 150 mg four times daily</p> <p>Maintenance erosive esophagitis: 150 mg twice daily</p> <p>GU: 150 mg twice daily</p> <p>Maintenance GU: 150 mg at bedtime</p> <p>Hypersecretory conditions: Start at 150 mg twice daily up to 6 g daily in patients with severe disease</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach prophylaxis for patients 12 years and older: 75—150 mg (OTC only) immediately before eating or up to 60 minutes before consuming food and beverages that may cause heartburn. Do not take more than two tablets daily.</p> <p>Pyrosis (heartburn), acid dyspepsia (acid indigestion), or sour stomach treatment for patients 12 years and older: 75—150 mg (OTC only) once or twice daily</p> <p><i>Pediatric (one month to 16 years)</i></p> <p>Treatment DU and GU: 2 to 4 mg/kg twice daily up to 300 mg daily</p> <p>Maintenance DU and GU: 2 to 4 mg/kg once daily up to 150 mg daily</p> <p>GERD and Erosive esophagitis: 5 to 10 mg/kg daily, given in two divided doses</p>	<p>Prescription: 15 mg/mL syrup; 150, 300 mg tablet; 150, 300 mg capsule; 25 mg Efferdose tablet</p> <p>OTC: 75, 150 mg tablet</p>

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Equal efficacy has been shown among all four H₂-antagonists when treating duodenal ulcers.^{30,31,32,33,34} When given in equipotent doses, they all suppress nocturnal acid by 85 to 96 percent.^{35,36,37,38} Clinical trials comparing each agent to placebo in duodenal ulcers have shown healing rates at six weeks of 80 to 90 percent. For all agents, single bedtime dosing or multiple daytime doses have been shown to be equally effective in producing healing of ulcers.³⁹

For the treatment of gastric ulcers, clinical trials compared the agents to placebo, and a few trials have compared one agent to another.^{40,41,42,43,44,45,46,47} From these trials, the agents are all effective in the treatment of gastric ulcers. Comparing the results from each trial, the agents appear to be equally efficacious for treatment of gastric ulcers.

According to the American Gastroenterological Association H₂-antagonists improve health outcomes in patients diagnosed with gastroesophageal reflux disease (GERD).⁴⁸ Trials evaluating gastroesophageal reflux disease (GERD) have compared each of the agents to placebo, and some agents have been compared to each other.^{49,50,51,52} Small numbers of patients have been used in these trials. Relapse rates are high with all drugs used. Healing rates for each of the agents range from 40 to 80 percent depending on the dose and frequency of the dosing for each agent. Better results are obtained with higher doses given more frequently.

Comparative data for other indications are lacking; no particular drug has been distinguished as superior in conditions such as hypersecretory diseases and maintenance therapy of ulcers.

Summary

H₂-antagonists are equally effective for the approved indications. The products are all available as generic products in some formulations as well as over-the-counter (OTC) formulations. Cimetidine (Tagamet) and ranitidine (Zantac) have significant drug interactions. Famotidine (Pepcid) and ranitidine (Zantac) have additional use in pediatrics; nizatidine (Axid) and cimetidine do not have any reliable clinical data in children.

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