ANTIHISTAMINES (Systemic)

Bromodiphenhydramine ¾Bromazine

Chlorpheniramine¾Chlorphenamine

Pyrilamine b¾Mepyramine

VA CLASSIFICATION (Primary)
Acrivastine¾AH109
Astemizole¾AH102
Azatadine¾AH109
Bromodiphenhydramine¾AH109
Brompheniramine¾AH109
Carbinoxamine¾AH109
Cetirizine¾AH109
Chlorpheniramine¾AH109
Clemastine¾AH109
Cyproheptadine¾AH109
Dexchlorpheniramine¾AH109
Dimenhydrinate¾AH109/CN550
Diphenhydramine
Oral¾AH109/; CN309; CN550 ; RE302
Parenteral¾CN204
Diphenylpyraline¾AH109
Doxylamine¾AH109/
Hydroxyzine¾AH109/
Loratadine¾AH102
Phenindamine¾AH109
Pyrilamine¾AH109
Terfenadine¾AH102
Tripelennamine¾AH109
Triprolidine¾AH109

Indications
Accepted

Rhinitis, perennial and seasonal allergic or vasomotor (prophylaxis and treatment) or

Conjunctivitis, allergic (prophylaxis and treatment)¾Antihistamines are indicated in the prophylactic and symptomatic treatment of perennial and seasonal allergic rhinitis , vasomotor rhinitis , and allergic conjunctivitis due to inhalant allergens and foods. 2, 12, 13, 48

Pruritus (treatment)

Urticaria (treatment)

Angioedema (treatment)

Dermatographism (treatment) or

Transfusion reactions, urticarial (treatment)¾ Antihistamines are indicated for the symptomatic treatment of pruritus associated with allergic reactions and of mild, uncomplicated allergic skin manifestations of urticaria and angioedema, in dermatographism, and in urticaria associated with transfusions. Cyproheptadine may be particularly useful for cold urticaria, 2, 12, 14 dermatitis including neurodermatitis and neurodermatitis circumscripta, eczema, eczematoid dermatitis, mild local allergic reactions to insect bites, angioneurotic edema, drug and serum reactions, anogenital pruritus and pruritus of chickenpox. 48 [Antihistamines are also used in the treatment of pruritus associated with pityriasis rosea.] *

Sneezing (treatment) or

Rhinorrhea (treatment)¾Antihistamines are indicated for the relief of sneezing and rhinorrhea associated with the common cold 12.

However, controlled clinical studies have not demonstrated that antihistamines are significantly more effective than placebo in relieving cold symptoms. Non-sedating (i.e., second-generation) antihistamines are unlikely to be useful in the treatment of the common cold symptoms since they do not have clinically significant anticholinergic effects (e.g., drying effects on nasal mucosa). 15

Anaphylactic or anaphylactoid reactions (treatment adjunct)¾Antihistamines are indicated as adjunctive therapy to epinephrine and other standard measures for anaphylactic reactions after the acute manifestations have been controlled, and to ameliorate the allergic reactions to blood or plasma. 2, 12, 48

Anxiety (treatment) and

Tension, psychosis-related (treatment)¾Hydroxyzine is indicated for the relief of anxiety and tension associated with psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested. The effectiveness of hydroxyzine as an antianxiety agent for long-term use (for example, more than 4 months) has not been assessed by systematic clinical studies. 12

Alcohol withdrawal (treatment)¾Parenteral hydroxyzine is indicated in the acute or chronic alcoholic with anxiety withdrawal symptoms. 12

Parkinsonism (treatment) * or

Extrapyramidal reactions, drug-induced (treatment) *¾Diphenhydramine is indicated for the symptomatic treatment of parkinsonism and drug-induced extrapyramidal reactions in elderly patients unable to tolerate more potent antidyskinetic medications, for mild cases of parkinsonism in other age groups and, in combination with centrally acting anticholinergic agents, for other cases of parkinsonism. 12

Cough (treatment)¾Diphenhydramine hydrochloride syrup is currently indicated as a non-narcotic cough suppressant for control of cough due to colds or allergy. 12

Motion sickness (prophylaxis and treatment) or

Vertigo (treatment)¾Dimenhydrinate and diphenhydramine are indicated for the prevention and treatment of the nausea, vomiting, dizziness, or vertigo of motion sickness. 12

Nausea or vomiting (prophylaxis and treatment)¾ Parenteral hydroxyzine is indicated for the control of nausea and vomiting, excluding nausea and vomiting of pregnancy. 12

Sedation¾Diphenhydramine and hydroxyzine are indicated for their sedative and hypnotic effects and as preoperative medications. 12

Insomnia (treatment)¾Diphenhydramine and doxylamine are indicated as nighttime sleep aids to help reduce the time to fall asleep in patients having difficulty falling asleep. 12

Analgesia adjunct, during surgery

Anesthesia, general, adjunct or

Anesthesia, local, adjunct¾Parenteral hydroxyzine is useful as pre- and postoperative, and pre- and postpartum adjunctive medication to allow reduction in narcotic dosage, and to control anxiety and emesis. 12

[Appetite, lack of (treatment)]¾Cyproheptadine is used as an appetite stimulant, in adults and children.

[Headache, vascular (treatment)]¾Cyproheptadine is used for treatment of vascular headaches, such as migraine and histamine cephalalgia. 48

[Asthma, bronchial (treatment adjunct) ] *¾Astemizole, cetirizine, loratadine, and terfenadine are used as adjunctive treatment to asthma medications to reduce symptoms and improve bronchodilation in patients with mild atopic asthma. 17, 18, 19, 20

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one of the antihistamines may be sensitive to others.

Carcinogenicity/Tumorigenicity/Mutagenicity

Long-term animal studies to evaluate carcinogenic, tumorigenic, or mutagenic potential of most antihistamines have not been performed.
Cetirizine¾In a 2-year study, cetirizine was not carcinogenic in rats given dietary doses up to 15 times the maximum recommended human daily oral dose for adults and 10 times the maximum recommended human daily oral dose for children on a mg/m2 basis 46.

In another 2-year study in male mice, cetirizine increased the incidence of benign liver tumors at a dose of 6 times the adult maximum recommended daily dose and 4 times the maximum pediatric dose on a mg/m 2 basis 46.

The clinical significance of these findings during long-term use of cetirizine is not known.
Cetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and the in vivo micronucleus test in rats 46.

Loratadine
In carcinogenicity studies, AUC data demonstrated that the exposure of mice given loratadine 40 mg/kg was 3.6 (loratadine) and 18 (active metabolite) times higher than that for a human given 10 mg/day. Exposure of rats given 25 mg/kg was 28 (loratadine) and 67 (active metabolite) times higher than that for a human given 10 mg/day. Male mice given 40 mg/kg had a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) than concurrent controls. In rats, a significantly higher incidence of hepatocellular tumors (combined adenomas and carcinomas) was observed in males given 10 mg/kg and males and females given 25 mg/kg. The clinical significance of these findings during long-term use of loratadine is not known. 3

Terfenadine
Studies in mice and rats have not shown evidence of tumorigenicity when terfenadine was given in oral doses approximately 5 and 10 times the maximum recommended human daily dose on a mg per square meter of body surface area basis, respectively. Microbial and micronucleus test assays with terfenadine have not shown evidence of mutagenesis. 8

Pregnancy/Reproduction

Pregnancy¾Animal studies have suggested that meclizine and cyclizine, chemically related to antihistamines, might have a teratogenic potential.
Astemizole
Adequate and well-controlled studies in humans have not been done. However, on the basis of 6 times the terminal half-life of astemizole, metabolites may remain in the body as long as 4 months after dosing has stopped.
Studies in rats showed embryocidal effects accompanied by maternal toxicity at doses 100 times the recommended human dose. However, at doses 50 times the recommended human dose, embryotoxicity or maternal toxicity has not been observed in rats or rabbits.

FDA Pregnancy Category C.

Azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, and loratadine
Well-controlled studies with azatadine, brompheniramine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, and loratadine in humans have not been done. Studies in animals have not shown that these medicines cause adverse effects on the fetus.
FDA Pregnancy Category B.

Cetirizine
Adequate and well-controlled studies in humans have not been done. Cetirizine was not teratogenic in mice, rats, and rabbits 1.

FDA Pregnancy Category B 1.

Diphenhydramine
Adequate and well-controlled studies in humans have not been done.
Studies in rats and rabbits at doses up to 5 times the human dose have revealed no evidence of impaired fertility or harm to the fetus.
FDA Pregnancy Category B.

Doxylamine
The Food and Drug Administration has stated that human epidemiologic data have not produced convincing evidence that the doxylamine and pyridoxine combination, a medication previously prescribed to treat nausea and vomiting during pregnancy, causes diaphragmatic hernias or other birth defects.
FDA Pregnancy Category B 21.

Hydroxyzine
Adequate and well-controlled studies in humans have not been done. However, hydroxyzine is not recommended for use in the early months of pregnancy since studies in rats have shown that it causes fetal abnormalities when given in doses substantially above the human therapeutic range.
FDA Pregnancy Category C 12.

Terfenadine
Adequate and well-controlled studies in humans have not been done.
FDA Pregnancy Category C 8.

Tripelennamine
Adequate and well-controlled studies in humans have not been done. However, there is no evidence linking the use of tripelennamine with congenital defects 21.

Limited animal reproduction studies have not shown that tripelennamine causes adverse effects in the fetus.
FDA Pregnancy Category B 21.

Triprolidine
Adequate and well-controlled studies in humans have not been done. However, there is no evidence linking the use of triprolidine with congenital defects. 21

Studies in animals have shown no evidence of adverse effects in the fetus 21.

FDA Pregnancy Category C 21.

Breast-feeding

First-generation antihistamines may inhibit lactation because of their anticholinergic actions.

Small amounts of antihistamines are distributed into breast milk; use is not recommended in nursing mothers because of the risk of adverse effects, such as unusual excitement or irritability, in infants.
Astemizole
It is not known whether astemizole is distributed into human breast milk. Astemizole is distributed into the milk of dogs. However, problems in humans have not been documented.

Cetirizine
The extent of distribution into human breast milk is unknown. Studies in dogs indicated that approximately 3% of the dose is distributed into milk 1.

Loratadine
Loratadine and its metabolite descarboethoxyloratadine are distributed into breast milk, achieving concentrations equivalent to plasma levels. In one study, approximately 0.03% of the administered dose was distributed into breast milk over 48 hours after maternal ingestion of a single oral dose of 40 mg.

Terfenadine
A small amount of terfenadine metabolite is distributed into breast milk 8.

Pediatrics

Use is not recommended in newborn or premature infants because this age group has an increased susceptibility to anticholinergic side effects, such as central nervous system (CNS) excitation, and an increased tendency toward convulsions.

A paradoxical reaction characterized by hyperexcitability may occur in children taking antihistamines.
Astemizole, cetirizine, loratadine, and terfenadine
Although adequate and well-controlled studies have not been done in the pediatric population, astemizole, loratadine, and terfenadine are not likely, and cetirizine is less likely than first-generation antihistamines, to cause anticholinergic or significant CNS effects in children.

Geriatrics

Dizziness, sedation, confusion, and hypotension may be more likely to occur in geriatric patients taking antihistamines.

A paradoxical reaction characterized by hyperexcitability may occur in geriatric patients taking antihistamines.

Geriatric patients are especially susceptible to the anticholinergic side effects, such as dryness of mouth and urinary retention (especially in males), of the antihistamines. If these side effects occur and continue or are severe, medication should probably be discontinued.
Astemizole, cetirizine, loratadine, and terfenadine
Astemizole, loratadine, and terfenadine are not likely, and cetirizine is less likely than first-generation antihistamines, to cause anticholinergic or significant CNS effects in geriatric patients 14.

However, because elderly patients are more likely to have age-related renal function impairment, cetirizine and loratadine may accumulate and cause anticholinergic or CNS effects when given in such patients at the usual adult dose 1, 3.

Dental

Prolonged use of antihistamines (except astemizole, cetirizine, loratadine, or terfenadine) may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: It is not likely that astemizole, cetirizine, loratadine, or terfenadine will interact with most of the following medications because they lack significant anticholinergic and CNS actions. However, cetirizine and loratadine have been shown to cause dose-related CNS effects (e.g., sedation); and cetirizine has minimal anticholinergic effects. 1, 3, 14

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

>> Alcohol or

>> CNS depression-producing medications, other (see Appendix II )

(concurrent use may potentiate the CNS depressant effects of either these medications or antihistamines; also, concurrent use of maprotiline or tricyclic antidepressants may potentiate the anticholinergic effects of either antihistamines or these medications)

>> Anticholinergics or other medications with anticholinergic activity (see Appendix II )

(anticholinergic effects may be potentiated when these medications are used concurrently with antihistamines; patients should be advised to report occurrence of gastrointestinal problems promptly since paralytic ileus may occur with concurrent therapy)

Apomorphine

(prior administration of dimenhydrinate, diphenhydramine, doxylamine, or hydroxyzine may decrease the emetic response to apomorphine in the treatment of poisoning)

Azithromycin

>> Clarithromycin

>> Erythromycin or

>> Troleandomycin

(concurrent use of erythromycin with astemizole or terfenadine has been reported to increase the risk of cardiotoxic effects [prolongation of the QT interval, torsades de pointes, and other ventricular arrhythmias 4, 8])

(concurrent use of terfenadine with clarithromycin, erythromycin, or troleandomycin is contraindicated; pending further evaluation, concurrent use of terfenadine and azithromycin is not recommended)

(concurrent use of astemizole with clarithromycin, erythromycin, or troleandomycin is contraindicated; pending further evaluation, concurrent use of astemizole with other macrolide antibiotics, such as azithromycin, is not recommended [25])

Fluconazole

>> Itraconazole

>> Ketoconazole

Metronidazole

Miconazole or

Other potent inhibitors of the cytochrome P450 enzyme system

(concurrent use of ketoconazole or itraconazole with astemizole or terfenadine is contraindicated; concurrent use of these medications may increase plasma levels of astemizole, loratadine, and terfenadine, because of inhibition of the P450 metabolic pathways by these antifungals; increased plasma levels of astemizole and terfenadine may result in cardiotoxic effects [prolongation of the QT interval, torsades de pointes, and other ventricular arrhythmias]; there are no reports to date of serious ventricular arrhythmias associated with increased plasma levels of loratadine)

(due to the chemical similarity of fluconazole, metronidazole, and miconazole to ketoconazole, caution also is recommended with concurrent use of these other imidazole antifungals and terfenadine, and concurrent use of these other imidazole antifungals and astemizole is not recommended; also, concurrent use of other potent inhibitors of the cytochrome P450 enzyme system with astemizole is not recommended [3, 4, 8, 16, 22, 23, 24, 25])

>> Grapefruit juice

(concurrent use with astemizole or terfenadine may inhibit the metabolism of these medications, leading to increased plasma concentrations; prolonged QT intervals have been reported when grapefruit juice is administered concurrently with terfenadine; concurrent use with astemizole or terfenadine is not recommended [8, 25])

>> Human immunodeficiency virus (HIV)-protease inhibitors, such as:

Indinavir

Nelfinavir

Ritonavir

Saquinavir or

>> Serotonin reuptake inhibitors, such as:

Fluoxetine

Fluvoxamine

Nefazodone

Paroxetine

Sertraline

(fluvoxamine, nefazodone, ritonavir, and sertraline have been shown to inhibit the metabolism of terfenadine in vitro ; however, the clinical significance of these findings has not been established; pending further evaluation, concurrent use of terfenadine with HIV-protease inhibitors or serotonin reuptake inhibitors is not recommended 8 )

(concurrent use of astemizole with HIV-protease inhibitors or serotonin reuptake inhibitors is not recommended 25 )

>> Medications causing QT interval prolongation, such as:

Antidepressants, tricyclic

Calcium channel blocking agents, especially bepridil

Cisapride

Disopyramide

Maprotiline

Phenothiazines

Pimozide

Procainamide

Quinidine

Sparfloxacin

(concurrent use of these medications with astemizole or terfenadine may increase risk of cardiac arrhythmias, which are seen on electrocardiogram [ECG] as prolongation of the QT interval 8 )

>> Mibefradil

(concurrent use with astemizole or terfenadine has been reported to cause an increase in the plasma concentrations of astemizole or terfenadine and to prolong the QT interval; concurrent use is contraindicated 8, 25 )

>> Monoamine oxidase (MAO) inhibitors, including furazolidone and procarbazine

(concurrent use of MAO inhibitors with antihistamines may prolong and intensify the anticholinergic and CNS depressant effects of antihistamines; concurrent use is not recommended) 48

Ototoxic medications (see Appendix II )

(concurrent use with antihistamines may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo)

Photosensitizing medications, other

(concurrent use of these medications with antihistamines may cause additive photosensitizing effects)

>> Quinine

(concurrent use of a single 430-mg dose of quinine with astemizole has been reported to increase plasma concentrations of astemizole and its metabolite, desmethylastemizole, resulting in prolongation of the electrocardiographic QT interval; concurrent use is contraindicated 4, 25 )

>> Zileuton

(although concurrent use with terfenadine has been reported to increase plasma concentrations of terfenadine, this increase was not associated with a significant prolongation of the QT interval; pending further evaluation, concurrent use is not recommended 8 )

(concurrent use with astemizole is not recommended 25 )

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With diagnostic test results

For all antihistamines

Skin tests using allergen extracts

(antihistamines may inhibit the cutaneous histamine response, thus producing false-negative results; it is recommended that antihistamines be discontinued at least 72 hours before testing begins [at least 4 weeks with astemizole and 1 week with loratadine and terfenadine] 5, 6, 7, 9, 11 )

For hydroxyzine (in addition to those listed for all antihistamines)

Urine 17-hydroxycorticosteroid determinations

(false increases have been reported with concurrent use of hydroxyzine)

With physiology/laboratory test values

For cyproheptadine

Amylase and

Prolactin

(serum concentrations may be increased when cyproheptadine is administered with thyrotropin-releasing hormone)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist

>> Hepatic function impairment

(increased plasma concentrations of astemizole or terfenadine may result, increasing the risk of cardiac arrhythmias or QT prolongation 4, 8 )

>> QT interval prolongation, history of

(increased risk of astemizole- or terfenadine-induced arrhythmias)

Risk-benefit should be considered when the following medical problems exist

>> Bladder neck obstruction 48 or

>> Prostatic hypertrophy, symptomatic 48 or

>> Urinary retention, predisposition to 48

(anticholinergic effects may precipitate or aggravate urinary retention )

>> Glaucoma, angle-closure, 2, 48 or predisposition to

(anticholinergic mydriatic effect resulting in increased intraocular pressure may precipitate an attack of angle-closure glaucoma)

Glaucoma, open-angle

(anticholinergic mydriatic effect may cause a slight increase in intraocular pressure; glaucoma therapy may need to be adjusted)

>> Hypokalemia

(potassium deficiency, especially from use of diuretics, should be corrected before initiation of therapy with astemizole or terfenadine because of risk of ventricular arrhythmias)

Sensitivity to the antihistamine used

Caution is recommended when dimenhydrinate, diphenhydramine, or hydroxyzine is used, since their antiemetic action may impede diagnosis of such conditions as appendicitis and obscure signs of toxicity from overdosage of other drugs.

For cyproheptadine

>> Peptic ulcer, stenosing 2

>> Pyloroduodenal obstruction 2, 48

(anticholinergic effects of cyproheptadine may exacerbate these conditions )

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive: