ANTIHISTAMINES AND DECONGESTANTS (Systemic)

Introduction

Revised: 12/18/2000

This monograph includes information on the following:1) Acrivastine and Pseudoephedrine b; 2) Azatadine and Pseudoephedrine ; 3) Brompheniramine and Phenylephrine b; 4) Brompheniramine, Phenylephrine, and Phenylpropanolamine; 5) Brompheniramine and Phenylpropanolamine; 6) Brompheniramine and Pseudoephedrine b; 7) Carbinoxamine and Pseudoephedrine b; 8) Chlorpheniramine, Phenindamine, and Phenylpropanolamine b; 9) Chlorpheniramine and Phenylephrine b; 10) Chlorpheniramine, Phenylephrine, and Phenylpropanolamine b; 11) Chlorpheniramine and Phenylpropanolamine; 12) Chlorpheniramine, Phenyltoloxamine, and Phenylephrine b; 13) Chlorpheniramine, Phenyltoloxamine, Phenylephrine, and Phenylpropanolamine b; 14) Chlorpheniramine and Pseudoephedrine; 15) Chlorpheniramine, Pyrilamine, and Phenylephrine b; 16) Chlorpheniramine, Pyrilamine, Phenylephrine, and Phenylpropanolamine b; 17) Clemastine and Phenylpropanolamine b; 18) Dexbrompheniramine and Pseudoephedrine; 19) Diphenhydramine and Pseudoephedrine; 20) Loratadine and Pseudoephedrine ; 21) Pheniramine and Phenylephrine a; 22) Pheniramine, Phenyltoloxamine, Pyrilamine, and Phenylpropanolamine b; 23) Pheniramine, Pyrilamine, and Phenylpropanolamine; 24) Promethazine and Phenylephrine b; 25) Terfenadine and Pseudoephedrine a, b; 26) Triprolidine and Pseudoephedrine .

INN:

Chlorpheniramine¾ Chlorphenamine

VA CLASSIFICATION (Primary)¾RE501

Note: Other combinations containing antihistamines and decongestants in addition to other ingredients are found in Antihistamines, Decongestants, and Analgesics (Systemic) ; Antihistamines, Decongestants, and Anticholinergics (Systemic) ; and Cough/Cold Combinations (Systemic) .

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Antihistaminic (H 1-receptor)-decongestant.

Indications

Accepted

Congestion, nasal (treatment);

Sneezing (treatment); and

Rhinorrhea (treatment)¾Antihistamine and decongestant combinations are indicated for the temporary relief of nasal and sinus congestion, sneezing, and rhinorrhea associated with the common cold and allergic rhinitis .

The therapeutic effectiveness of oral phenylephrine as a nasal decongestant has been questioned, especially at the usual oral dose. 76

Note: Products containing terfenadine and pseudoephedrine were withdrawn from the U.S. market by the Food and Drug Administration in February 1998.

Note: In November 2000, the Food and Drug Administration (FDA) issued a public health warning regarding phenylpropanolamine (PPA) due to the risk of hemorrhagic stroke. The FDA, supported by the final report of The Hemorrhagic Stroke Project (HSP) 102 , requested that manufacturers voluntarily discontinue marketing products that contain PPA and that consumers work with their healthcare providers to select alternative products. 101

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Chemical group¾Butyrophenone derivative: Terfenadine

Ethanolamine derivatives: Bromodiphenhydramine; Carbinoxamine; Clemastine; Diphenhydramine

Ethylenediamine derivatives: Pyrilamine; Tripelennamine

Piperidine derivatives: Azatadine; Loratadine

Propylamine derivatives (alkylamines): Brompheniramine; Chlorpheniramine; Dexbrompheniramine; Pheniramine; Triprolidine

Phenothiazine derivative: Promethazine

Sympathomimetic amines: Phenylephrine; Phenylpropanolamine; Pseudoephedrine

Miscellaneous: Phenindamine; Phenyltoloxamine

Molecular weight¾Brompheniramine maleate: 435.32

Chlorpheniramine maleate: 390.87

Clemastine fumarate: 459.97

Dexbrompheniramine maleate: 435.32

Diphenhydramine hydrochloride: 291.82

Loratadine: 382.89

Phenylephrine hydrochloride: 203.67

Phenylpropanolamine hydrochloride: 187.67

Promethazine hydrochloride: 320.88

Pseudoephedrine hydrochloride: 201.70

Pseudoephedrine sulfate: 428.54

Pyrilamine maleate: 401.46

Terfenadine: 471.68

Triprolidine hydrochloride: 332.87

pKa¾Brompheniramine maleate: 3.59 and 9.12

Chlorpheniramine maleate: 9.2

Diphenhydramine hydrochloride: 9

Phenylpropanolamine hydrochloride: 9

Pseudoephedrine: 9.4 76

Triprolidine hydrochloride: 3.6 and 9.3

Mechanism of action/Effect:

Antihistaminic (H 1-receptor)¾Antihistamines used in the treatment of allergy act by competing with histamine for H 1-receptor sites on effector cells. They thereby prevent, but do not reverse, responses mediated by histamine alone. The anticholinergic actions of most antihistamines (loratadine and terfenadine have no significant anticholinergic activity) provide a drying effect on the nasal and oral mucosa. 23, 25, 30

Decongestant¾Sympathomimetic amines act on alpha-adrenergic receptors in the mucosa of the respiratory tract to produce vasoconstriction, which temporarily reduces the swelling associated with inflammation of the mucous membranes lining the nasal passages. 76

Other actions/effects:

Phenylpropanolamine¾Has appetite suppressant action; causes mild central nervous system (CNS) stimulating effects; increases heart rate, force of contraction and cardiac output, and cardiac muscle excitability; may have vasopressor action in certain susceptible individuals.

Promethazine¾Has antiemetic, antivertigo, hypnotic, and sedative actions.

Pseudoephedrine¾Has an indirect vasoconstrictor effect; has relatively weaker pressor and cardiac actions than ephedrine; may also produce mild CNS stimulation, especially in patients sensitive to sympathomimetic drugs. 1, 25, 26

Absorption:

Antihistamines and sympathomimetic amines, except phenylephrine, are well absorbed from the gastrointestinal tract after oral administration. Phenylephrine has reduced bioavailability (about 38%) from gastrointestinal tract because of first pass metabolism by monoamine oxidase in the stomach and liver. 23, 76

Protein binding:

Chlorpheniramine¾High (72%).

Diphenhydramine¾Very high (98 to 99%).

Terfenadine¾Very high (97%).

Biotransformation:

Antihistamines¾ Hepatic (cytochrome P-450 system); some renal. Of the second generation antihistamines, loratadine and terfenadine are metabolized by the hepatic cytochrome P-450 system and have active metabolites. 51, 53, 54, 55, 96

Sympathomimetic amines¾ Phenylephrine: Extensive in the intestinal wall and in the liver. Sulfate conjugates are formed largely in the intestinal wall. Also, undergoes oxidative deamination by monoamine oxidase. 76

Phenylpropanolamine: Hepatic.
Pseudoephedrine: Incompletely metabolized in the liver; less than 1% by N-demethylation to the active metabolite norpseudoephedrine. 76

Half-life:

Antihistamines¾ Acrivastine:
1.5 to 3.5 hours. 79

Brompheniramine:
25 hours.

Chlorpheniramine:

21 to 27 hours.

Diphenhydramine:
1 to 4 hours.

Loratadine:
3 to 20 hours (mean, 8.4 hours). 53, 56

Terfenadine:
8.5 hours. 78

Acid metabolite of terfenadine¾Biphasic with an initial mean plasma half-life of 3.5 hours followed by a mean plasma half-life of 6 hours. 78

Triprolidine¾ 3 to 3.3 hours.

Sympathomimetic amines 76¾ Phenylephrine:
2.1 to 3.4 hours.

Phenylpropanolamine:
3 to 4 hours.

Pseudoephedrine:
4.5 to 8 hours.
In children¾Mean half-life of pseudoephedrine has been reported to be 4.6 hours.

Onset of action:

Antihistamines¾ Most first generation antihistamines: 15 to 60 minutes.
Acrivastine: 0.5 hour. 79

Loratadine: 1 hour. 78

Promethazine: 20 minutes.
Terfenadine: 1 to 2 hours (reaching maximum effect at 3 to 4 hours, and lasting over 12 hours). 78

Sympathomimetic amines¾ Phenylpropanolamine: 15 to 30 minutes.
Pseudoephedrine: 30 minutes.

Time to peak concentration:

Antihistamines¾ Acrivastine: 0.8 to 1.7 hours. 79

Brompheniramine: 2 to 5 hours.
Chlorpheniramine: 2 to 6 hours.
Diphenhydramine: 1 to 4 hours.
Triprolidine: 2 hours.

Sympathomimetic amines 76¾ Phenylephrine: 0.75 to 2 hours (to achieve peak levels ranging from 0.9 to 298 ng/mL, respectively).
Phenylpropanolamine: 1.5 hours (average).
Pseudoephedrine: 1.97 hours (to achieve a concentration of 422 ng/mL).

Time to peak effect:

Antihistamines¾ Brompheniramine: 3 to 9 hours.
Chlorpheniramine: 6 hours.
Triprolidine: 2 to 3 hours.

Duration of action:

Antihistamines 1, 31¾ Ethanolamine derivatives:
6 to 8 hours.

Ethylenediamine derivatives:
Pyrilamine¾8 hours.

Piperidine derivatives:
Loratadine¾At least 24 hours. 78

Terfenadine¾Over 12 hours. 78

Propylamine derivatives:
4 to 8 hours.
Acrivastine: 6 to 8 hours. 79

Sympathomimetic amines¾ Phenylpropanolamine:
3 hours.

Pseudoephedrine:
3 to 4 hours.

Promethazine and pseudoephedrine combination¾ 4 to 6 hours.

Elimination:

Antihistamines¾ Renal (primarily fecal with terfenadine). Most of the antihistamines studied are excreted as metabolites within 24 hours.
Promethazine: Renal; slow; mainly as inactive metabolites.

Sympathomimetic amines¾ Renal.
Phenylephrine: 2.6% of the administered oral dose is excreted unchanged. Eighty to 86% of unchanged phenylephrine and metabolites are recovered in 48 hours after oral administration. 76

Phenylpropanolamine: Eighty to 96% of administered dose is excreted unchanged in urine within 24 hours. 76

Pseudoephedrine: Forty-three to 96% is excreted unchanged in urine within 24 hours. Clearance of pseudoephedrine is more rapid in children than in adults. 76

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to other antihistamines or other sympathomimetics (for example, amphetamines, ephedrine, epinephrine, isoproterenol, metaproterenol, norepinephrine, terbutaline) may be sensitive to these medications also.

Carcinogenicity/Mutagenicity

Long-term animal studies to evaluate carcinogenic or mutagenic potential have not been performed.

Loratadine¾In 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 a human given 10 mg/day. Exposure of rats given 25 mg/kg was 28 (loratadine) and 67 (active metabolite) times higher than 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. 78

Terfenadine¾Studies in mice and rats have not shown evidence of tumorigenicity when terfenadine was given in oral doses 63 times the recommended human daily dose. Microbial and micronucleus test assays with terfenadine have not shown evidence of mutagenesis. 40

Pregnancy/Reproduction

Pregnancy¾Although the occasional use at the recommended doses of antihistamine and decongestant combinations during pregnancy is not likely to result in adverse effects on the fetus or newborn infant, the following information should be considered in the event of high-dose and/or long-term usage.

Azatadine and pseudoephedrine¾ Studies in humans have not been done.

Some studies in animals have shown that azatadine and pseudoephedrine combination administered to pregnant rabbits at multiples of the human dose caused retarded fetal development, hyoid wings in the offspring, and increased incidence of resorption. When administered to rats at multiples of the human dose, the fetal survival rate was decreased.

FDA Pregnancy Category C.

Carbinoxamine and pseudoephedrine;

Chlorpheniramine and pseudoephedrine;

Chlorpheniramine, phenyltoloxamine, phenylephrine, and phenylpropanolamine;

Chlorpheniramine, pyrilamine, and phenylephrine; and

Pheniramine, pyrilamine, and phenylpropanolamine: Studies have not been done in humans.

Studies have not been done in animals.

FDA Pregnancy Category C.

Clemastine and phenylpropanolamine; and

Triprolidine and pseudoephedrine: Studies in humans have not been done.

Studies in rats and rabbits at doses up to 933 and 560 times the human dose, respectively, of clemastine alone, and doses up to 70 times the human dose of triprolidine and pseudoephedrine have not shown that these combinations cause adverse effects on the fetus.

FDA Pregnancy Category B.

Phenothiazines: Phenothiazines have been reported to cause jaundice and extrapyramidal symptoms in infants whose mothers received these medications during pregnancy. Adequate and well-controlled studies in humans have not been done with promethazine. However, promethazine taken within 2 weeks prior to delivery may inhibit platelet aggregation in the newborn.

Studies in rats given doses 2.1 to 4.2 times the maximum recommended human daily dose have not shown that promethazine causes adverse effects on fetal development.

Promethazine and pseudoephedrine¾Studies have not been done with this combination in humans.

Studies have not been done in animals.

FDA Pregnancy Category C.

Terfenadine and pseudoephedrine¾Studies in humans have not been done.

Studies in rats and rabbits given doses 42 times the human dose of the combination of terfenadine and pseudoephedrine (in a ratio of 1:2 by weight) have shown that this combination reduced fetal weight, and in doses 63 times the human daily dose it delayed ossification with wavy ribs in a few fetuses.

FDA Pregnancy Category C. 40

Postpartum¾Phenylpropanolamine: Postpartum women may be at greater risk than the rest of the population of developing psychiatric disorders with the use of phenylpropanolamine at recommended doses and with overdose. 7

Breast-feeding

Antihistamines¾ Small amounts of antihistamines are distributed into breast milk; use is not recommended in nursing mothers because of the risk of antihistamines causing excitement or irritability in infants. Antihistamines (except loratadine and terfenadine) may inhibit lactation because of their anticholinergic action. 15

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. 53

Promethazine: Use is not recommended in nursing mothers since promethazine may be distributed into the breast milk. Some studies have indicated that the use of promethazine in children up to 2 years of age may be associated with the sudden infant death syndrome (SIDS) and an increase in sleep apnea, thus possibly increasing the risk to the nursing infant. However, more studies are needed to confirm these findings. 15, 59, 60, 61

Terfenadine: It is not known whether terfenadine is distributed into breast milk. However, problems in humans have not been documented.

Sympathomimetic amines¾ Small amounts of sympathomimetic amines are distributed into breast milk; use is not recommended in nursing mothers because of the high risk for infants from sympathomimetic amines. 27

Pseudoephedrine: Approximately 0.5% of an oral dose is distributed into breast milk over 24 hours. 76

Pediatrics

Antihistamines¾ Use of antihistamines is not recommended in newborn or premature infants. This age group may be at a higher risk than other age groups because of an increased susceptibility to anticholinergic effects, such as CNS excitation, and an increased tendency toward convulsions. 28

In children taking antihistamines, a paradoxical reaction characterized by hyperexcitability may occur.

Promethazine: Some studies have associated the use of promethazine with sudden infant death syndrome (SIDS) and with an increase in infant sleep apnea. Until more studies have been performed to confirm this potential risk, promethazine should not be used in children up to 2 years of age. 15

Terfenadine: Although adequate and well-controlled studies have not been done in the pediatric population, terfenadine is not likely to cause anticholinergic or significant CNS effects in children. 40

Sympathomimetic amines¾ Very young children may be more sensitive to the effects, especially the vasopressor effects, of sympathomimetic amines. Also, children under 6 years of age may be at greater risk than the rest of the population of developing psychiatric disorders with the use of phenylpropanolamine at recommended doses and with overdose. 7

Geriatrics

Antihistamines¾ Confusion, dizziness, sedation, hypotension, hyperexcitability, and anticholinergic side effects, such as dryness of mouth and urinary retention (especially in males), may be more likely to occur in geriatric patients taking antihistamines. If the anticholinergic side effects occur and continue or are severe, medication should probably be discontinued.

Terfenadine: Although adequate and well-controlled studies have not been done in the geriatric population, terfenadine is not likely to cause anticholinergic or significant CNS effects in geriatric patients. 40

Sympathomimetic amines¾ Confusion, hallucinations, seizures, and CNS depression may be more likely to occur in geriatric patients taking sympathomimetics. 29 Geriatric patients may also be more sensitive to the effects, especially to the vasopressor effects, of sympathomimetic amines.

Dental

Prolonged use of antihistamines (except loratadine and terfenadine) may decrease or inhibit salivary flow, especially in middle-aged or elderly patients, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort.

Promethazine: Involuntary orofacial muscle movement may result from extrapyramidal effects. These involuntary movements may result in occlusal adjustments and bite registrations being less reliable. In addition, treatment for bruxism may be less effective. 50

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 the combinations containing loratadine or terfenadine will interact with the medications that exacerbate anticholinergic or CNS depressant effects since loratadine and terfenadine lack significant anticholinergic and CNS actions. 40

Combination products 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 1)

Anesthetics, hydrocarbon inhalation, such as:

Chloroform

Cyclopropane

Enflurane

Halothane

Isoflurane

Methoxyflurane

Trichloroethylene or

Digitalis glycosides

(cardiac arrhythmias may occur when phenylephrine, phenylpropanolamine, and pseudoephedrine are used prior to anesthesia or concurrently with digitalis glycosides, since these medications may sensitize the myocardium to the effects of the sympathomimetics 32)

>> 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)

>> Antidepressants, tricyclic or

>> Maprotiline

(concurrent use with antihistamines may potentiate the anticholinergic and/or CNS depressant effects of either these medications or the antihistamine contained in these combinations)

(tricyclic antidepressants may potentiate the response to sympathomimetic amines by blocking the reuptake of biogenic amines by nerve terminals 19, 32, 35)

Antihypertensives or

Diuretics used as antihypertensives

(antihypertensive effects may be reduced when these medications are used concurrently with sympathomimetic amines; the patient should be carefully monitored to confirm that the desired effect is being obtained 1, 32, 33, 35)

Azithromycin or

>> Clarithromycin or

>> Erythromycin or

>> Troleandomycin

(concurrent use of erythromycin with terfenadine has been reported to increase the risk of cardiotoxic effects [prolongation of the QT interval, torsades de pointes , and other ventricular arrhythmias]; concurrent use of terfenadine with erythromycin, clarithromycin, or troleandomycin is contraindicated; pending further evaluation, concurrent use of terfenadine and azithromycin is not recommended 63, 64, 65, 66, 67, 68, 69, 78)

>> Beta-adrenergic blocking agents

(concurrent use with sympathomimetic amines may result in significant hypertension and excessive bradycardia with possible heart block; concurrent use requires careful monitoring 19, 22, 32, 33)

>> Cisapride or

>> Sparfloxacin

(concurrent use with terfenadine may increase the risk of adverse cardiovascular events, including QT interval prolongation; concurrent use with terfenadine-containing combination is not recommended 97)

>> CNS stimulation-producing medications, other (See Appendix II)

(concurrent use with phenylpropanolamine and pseudoephedrine may result in additive CNS stimulation to excessive levels, which may cause unwanted effects, such as nervousness, irritability, insomnia, or possibly convulsions or cardiac arrhythmias 21)

Doxapram

(concurrent use may increase the pressor effects of either doxapram or the sympathomimetic amine)

Fluconazole or

>> Itraconazole or

>> Ketoconazole or

Metronidazole or

Miconazole

(concurrent use with ketoconazole or itraconazole may increase plasma levels of loratadine and terfenadine because of inhibition of the P450 metabolic pathways by these antifungals; increased plasma levels of 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 is also recommended with concurrent use of these other imidazole antifungals and terfenadine 51, 54, 63, 64, 65, 68, 72, 73, 74, 78 ; however, concurrent use of itraconazole and ketoconazole with the terfenadine-containing combination is contraindicated 97)

>> Grapefruit juice

(concurrent use with terfenadine may inhibit the metabolism of terfenadine, leading to increased plasma concentrations; prolonged QT intervals have been reported when grapefruit juice is administered concurrently with terfenadine; concurrent use with the terfenadine-containing combination is not recommended 97)

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

Indinavir

Nelfinavir

Ritonavir

Saquinavir or

>> Serotonin reuptake inhibitors, such as:

Fluvoxamine

Nefazodone

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 the terfenadine-containing combination with HIV protease inhibitors or serotonin reuptake inhibitors is not recommended 97)

>> Mibefradil

(concurrent use with terfenadine has been reported to cause an increase in the plasma concentrations of terfenadine and to prolong the QT interval; concurrent use with the terfenadine-containing combination is contraindicated 97)

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

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

(concurrent use with sympathomimetic amines may prolong and intensify cardiac stimulant and vasopressor effects [including headache, cardiac arrhythmias, vomiting, sudden and severe hypertensive and hyperpyretic crises] of phenylephrine, phenylpropanolamine, and pseudoephedrine because of release of catecholamines, which accumulate in intraneuronal storage sites during MAO inhibitor therapy; these medications should not be administered during or within 14 days following the administration of a MAO inhibitor 1, 32, 35, 37, 76)

Ototoxic medications (See Appendix II)

(concurrent use with antihistamines may mask the symptoms of ototoxicity such as tinnitus, dizziness, or vertigo 30)

>> Rauwolfia alkaloids

(concurrent use of rauwolfia alkaloids may inhibit the indirect-acting sympathomimetic action of phenylpropanolamine and pseudoephedrine by depleting catecholamine stores, and may theoretically prolong the action of direct-acting sympathomimetics, such as phenylephrine, by preventing uptake into storage granules)

>> Zileuton

(although concurrent use with terfenadine has been reported to increase the plasma concentrations of terfenadine, this increase was not associated with a significant prolongation of the QT interval; pending further evaluation, concurrent use with the terfenadine-containing combination is not recommended 97)

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

(may inhibit the cutaneous histamine response thus producing false-negative results; it is recommended that antihistamine-containing medication be discontinued at least 72 hours before testing begins [at least 1 week with loratadine and terfenadine])

For promethazine

Glucose tolerance test

(an increase in glucose tolerance has been reported)

Immunologic urine pregnancy tests

(may produce false-positive or false-negative results, depending on the test used)

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 problem exists

>> Hepatic function impairment

(increased plasma concentrations of terfenadine may result, increasing the risk of cardiac arrhythmias or QT prolongation 43, 46)

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

>> Bladder neck obstruction or

>> Urinary retention, predisposition to

(anticholinergic effects of antihistamines, and sympathomimetic amines stimulation of alpha-adrenergic receptors on the trigone and sphincter muscles of the bladder, may precipitate or aggravate urinary retention 1, 77)

>> Cardiovascular disease

(pressor effects and increase in heart rate may be exacerbated due to sympathomimetic amine-induced cardiovascular effects 35)

>> Diabetes mellitus

(sympathomimetic amines may increase risk of developing cardiovascular disease 1)

Glaucoma, angle-closure, or predisposition to

(increased intraocular pressure may precipitate an acute attack of angle-closure glaucoma 1)

Glaucoma, open angle

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

>> Hepatic function impairment 100

(reduced clearance of loratadine; avoidance of loratadine is recommended by the manufacturer)

Hypertension

(vasoconstrictive properties of sympathomimetic amines may exacerbate condition 1)

>> Hypertension, severe

(pressor effect of sympathomimetic amines may precipitate a hypertensive crisis 1)

>> Hyperthyroidism

(characterized by tachycardia, which may be increased due to cardiac stimulant properties of sympathomimetic amines 1)

>> Prostatic hypertrophy, symptomatic

(reduction in tone of urinary bladder may lead to complete urinary retention 1)

Psychosis or other psychiatric disorders, history of

(phenylpropanolamine may precipitate psychiatric reactions 7)

>> Renal function impairment 100

(reduced clearance elimination of loratadine; dosage reduction is recommended by the manufacturer)

Sensitivity to the antihistamine or decongestant in the combination used

Caution is recommended when promethazine is used, since signs of intestinal obstruction, brain tumor, or overdosage of toxic drugs may be obscured by its antiemetic action.

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:

Those indicating need for medical attention

Incidence rare¾more frequent with high dosesBlood dyscrasias (fever; sore throat; unusual bleeding or bruising; unusual tiredness or weakness); cardiac arrhythmias (fast or irregular heartbeat); mood or mental changes (psychotic episodes, usually associated with previous history of psychiatric illness); tightness in chest

Note: Prolonged QT intervals and ventricular arrhythmias (torsades de pointes or fibrillation), accompanied by syncope and cardiac arrest, have been reported in association with high doses and/or overdose of terfenadine. Severe ventricular arrhythmias have been reported with ingestion of 360 mg or more of terfenadine. Small increases in QT interval have occurred at doses of 60 mg twice a day; greater prolongations (mean increase of 46 msec) have occurred at higher doses (e.g., 300 mg twice a day). 47, 48, 49, 68, 75

Symptoms of overdose

Anticholinergic effects (clumsiness or unsteadiness; severe dryness of mouth, nose, or throat; flushing or redness of face; shortness of breath or troubled breathing); cardiac arrhythmias (fast or irregular heartbeat); CNS stimulation (hallucinations; seizures; trouble in sleeping); drowsiness, severe; extrapyramidal effects (muscle spasms, especially of neck and back; restlessness; shuffling walk; tic-like [jerky] movements of head and face; trembling and shaking of hands)¾for promethazine only; hypertension (headache, continuing; slow or fast heartbeat)

Note: Anticholinergic and CNS depressant effects are not clinically significant with loratadine or terfenadine. 40, 41

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Drowsiness¾more pronounced with antihistamine ethanolamine derivatives; less pronounced with the propylamine (alkylamine) derivatives, loratadine, and terfenadine; thickening of bronchial secretions

Incidence less frequent¾more frequent with high dosesBlurred vision; confusion; difficult or painful urination; dizziness; dryness of mouth, nose, or throat; headache; loss of appetite; paradoxical reaction (nightmares; unusual excitement, nervousness, restlessness, or irritability); pounding heartbeat; ringing or buzzing in ears; skin rash; stomach upset or pain¾more frequent with antihistamine ethylenediamine derivatives

Overdose

Treatment of overdose

Since there is no specific antidote for overdose with antihistamine and decongestant combinations, treatment is symptomatic and supportive with possible utilization of the following:

· Induction of emesis (syrup of ipecac recommended); however, precaution against aspiration necessary, especially in infants and children.
· Gastric lavage (isotonic or 0.45% sodium chloride solution) if patient unable to vomit within three hours of ingestion.
· Saline cathartics (milk of magnesia) are sometimes used.
· Vasopressors to treat hypotension; however, epinephrine should not be used since it may further lower blood pressure.
· Oxygen and intravenous fluids.
· Precaution against use of stimulants (analeptic agents) because they may cause seizures.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Antihistamines and Decongestants (Systemic) .

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Sensitivity to any of the antihistamines or sympathomimetic amines

Pregnancy¾Concern for the fetus and/or newborn infant only with high doses and long-term therapy; psychiatric disorders more likely with use of phenylpropanolamine in postpartum women

Breast-feeding¾Antihistamines may cause excitement or irritability in nursing infants; high risk for infants from sympathomimetic amines

Use in children¾Increased susceptibility to anticholinergic effects of antihistamines and to vasopressor effects of sympathomimetic amines; psychiatric disorders more likely with use of phenylpropanolamine in children under 6 years of age; hyperexcitability (paradoxical reaction) may occur

Use in the elderly¾Anticholinergic and CNS stimulant effects more likely to occurContraindicated medications (with the terfenadine-containing combination only)¾Erythromycin and other macrolide antibiotics, itraconazole, ketoconazole, and mibefradil

Other medications, especially anticholinergics; CNS depressants or stimulants; cisapride (with the terfenadine-containing combination only); HIV protease inhibitors (with the terfenadine-containing combination only); medicine for high blood pressure or depression; serotonin reuptake inhibitors (with

the terfenadine-containing combination only); sparfloxacin (with the terfenadine-containing combination only); or zileuton (with the terfenadine-containing combination only)

Other medical problems, especially cardiovascular disease, diabetes, hepatic function impairment, hypertension, hyperthyroidism, prostatic hypertrophy, or renal function impairment

Proper use of this medication

>> Importance of not taking more medication than the amount recommended

Taking with food, water, or milk to minimize gastric irritation

Swallowing extended-release dosage form whole

>> Proper dosing

Missed dose: If on scheduled dosing regimen¾Taking as soon as possible; not taking if almost time for next dose; not doubling doses

>> Proper storage

Precautions while using this medication

Caution if skin tests using allergens required; possible interference with test results

May mask ototoxic effects of large doses of salicylates

>> Not taking erythromycin or other macrolide antibiotics, itraconazole, ketoconazole, or mibefradil while taking the terfenadine-containing combination

>> Avoiding use of alcohol or other CNS depressants

>> Caution if drowsiness or dizziness occurs

>> Caution if taking phenylpropanolamine-containing appetite suppressants

>> Possible insomnia; taking the medication a few hours before bedtime

Possible dryness of mouth; using sugarless gum or candy, ice, or saliva substitute for relief; checking with dentist if dry mouth continues for more than 2 weeks.

>> Not taking terfenadine-containing combination with grapefruit juice

For promethazine

Possible interference with diagnosis of intestinal obstruction, brain tumor, or overdosage of toxic drugs; need to inform physician of use

Side/adverse effects

Signs of potential side effects, especially blood dyscrasias, cardiac arrhythmias, psychotic episodes, and tightness in chest

General Dosing Information

Diet/Nutrition

This medication may be taken with food, water, or milk to lessen gastric irritation. However, gastric irritation occurs rarely with the extended-release capsules.

The terfenadine-containing combination should not be taken with grapefruit juice.

ANTIHISTAMINES AND DECONGESTANTS

Oral Dosage Forms

See Table 1.

Strength(s) usually available

U.S.¾