28:08.92 Analgesics and Antipyretics, Miscellaneous

Acetaminophen

Introduction

• Acetaminophen is a synthetic nonopiate derivative of *p*-aminophenol that produces analgesia and antipyresis.

Uses

Acetaminophen is used extensively in the treatment of mild to moderate pain and fever.

• Pain

Acetaminophen is used to provide temporary analgesia in the treatment of mild to moderate pain. The drug is most effective in relieving low intensity pain of nonvisceral origin. Acetaminophen does *not* have antirheumatic effects. Unlike salicylates and prototypical nonsteroidal anti-inflammatory agents (NSAIAs), acetaminophen does not usually depress prothrombin levels. In addition, acetaminophen produces a lower incidence of gastric irritation, erosion, or bleeding than do salicylates. Acetaminophen is a desirable alternative in patients who require a mild analgesic or antipyretic but in whom salicylates are contraindicated or not tolerated.

Acetaminophen has been used in the treatment of pain in various combinations with aspirin, caffeine, opiates, and/or other agents. Acetaminophen (650-mg oral doses) in combination with oral doses of an opiate (e.g., codeine, oxycodone) produces greater analgesic effect than that produced by either acetaminophen or higher doses of the opiate alone. Although some evidence suggests that the combination of acetaminophen, aspirin, and caffeine is more effective than acetaminophen alone for the treatment of tension-type headache, combinations of acetaminophen with aspirin or caffeine generally have not been shown to have greater analgesic effect than an optimal dose of acetaminophen alone. In addition, there is little evidence that such combinations cause fewer adverse effects than higher doses of the individual agents alone. In one study, the simultaneous administration of 325- or 650-mg oral doses of acetaminophen with 650-mg oral doses of aspirin resulted in increased blood concentrations of unhydrolyzed aspirin compared with 650-mg oral doses of aspirin alone; however, the clinical importance of such an effect remains to be established.

Pain Associated with Migraine Headache

Acetaminophen in fixed combination with aspirin and caffeine (containing 250 mg of acetaminophen, 250 mg of aspirin, and 65 mg of caffeine) is used for the temporary relief of mild to moderate pain associated with migraine headache.[212, 213, 214] Some experts state that this combination also may be used for the treatment of severe migraine headache if previous attacks have responded to similar nonopiate analgesics or nonsteroidal anti-inflammatory agents (NSAIAs).[231] The efficacy of oral acetaminophen in fixed combination with aspirin and caffeine for the management of mild to moderate pain associated with migraine headache was established by 3

double-blind, randomized, parallel group, placebo-controlled (one of them a population-based study) studies in adult patients who had migraine with aura or migraine without aura as defined by criteria established by International Headache Society (IHS).[214, 215] The efficacy of therapy for management of pain associated with migraine headache in these studies was evaluated in terms of a reduction in headache severity as rated by the patient (i.e., a reduction in pain from at least moderate to mild or to absent 2 hours after dosing using a 4-point scale).[214, 215] Pooled analysis of data from the 3 studies indicate that about 59% of patients receiving 500 mg of acetaminophen in fixed combination with aspirin and caffeine attained relief of pain associated with migraine headache within 2 hours compared with about 33% of placebo recipients; at 6 hours, about 79 and 52%, respectively, of drug- and placebo-treated patients had mild or no headache pain.[214, 215] In addition, 2 hours after dosing about 21% of patients receiving the combination were pain free versus about 7% receiving placebo, and at 6 hours 51% of drug-treated patients were pain free versus 24% receiving placebo.[214, 215] It appears that the drug also relieves manifestations of migraine other than headache, including nausea, vomiting, photophobia, and phonophobia.[214, 215] Patients in whom pain associated with migraine headache is not relieved by acetaminophen in fixed combination with aspirin and caffeine should consult their clinician about possible alternatives (e.g., use of prescription drugs including ergot alkaloids or vascular serotonin type 1-like receptor agonists) based on evaluation of their medical condition.[213] Efficacy of oral acetaminophen alone for the treatment of acute migraine headache has not been established.[231] (For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses in Sumatriptan 28:32.28.)

Pain Associated with Osteoarthritis

Acetaminophen is used in the symptomatic treatment of pain associated with osteoarthritis and is considered an initial drug of choice for pain management in osteoarthritis patients.[197, 199, 200, 201] Medical management of osteoarthritis of the hip and knee includes both pharmacologic therapy to reduce pain and nonpharmacologic therapy to maintain and/or improve joint mobility and limit functional impairment (e.g., patient education, weight loss when necessary, aerobic and muscle-strengthening exercise programs, physical therapy and range-of-motion exercises, assistive devices for ambulation and activities of daily living, patellar taping, appropriate footwear or bracing).[197] Pain management is considered an adjunct to nonpharmacologic measures and is most effective when combined with nonpharmacologic strategies.[197]

A variety of drugs have been used for management of pain in patients with osteoarthritis, including oral agents (e.g., acetaminophen, NSAIAs, tramadol), intraarticular agents (e.g., glucocorticoids, sodium hyaluronate), and topical agents (e.g., capsaicin, methylsalicylate).[197] Factors to consider when making treatment decisions for the management of pain in patients with osteoarthritis include the presence of risk factors for serious adverse GI effects or renal toxicity (which may affect decisions regarding use of NSAIAs), existing comorbidities and concomitant therapy, and the adverse effects profiles and costs of specific therapies.[197] Because there is evidence that acetaminophen can be effective and because of its relative safety and low cost, the American College of Rheumatology (ACR) and other clinicians recommended use of the drug as the initial analgesic for many osteoarthritis

patients.[197, 199, 200, 201] Acetaminophen appears to be as effective as NSAIAs for relief of mild to moderate joint pain in many patients with osteoarthritis; however, the drug is not effective in all patients and may not provide adequate relief in those with moderate to severe pain or when joint inflammation is present.[197] A NSAIA can be considered an alternative initial drug of choice for patients with osteoarthritis, especially for those who have moderate to severe pain and signs of joint inflammation, and also can be considered in patients who fail to obtain adequate symptomatic relief with acetaminophen.[197] Because NSAIAs that selectively inhibit COX-2 (e.g., celecoxib) are associated with a lower incidence of serious adverse GI effects than prototypical NSAIAs and, unlike prototypical NSAIAs, do not affect platelet aggregation and bleeding time, one of these selective inhibitors of COX-2 may be preferred when a NSAIA is being considered for management of pain in osteoarthritis patients at risk for GI complications.[197] (See Uses: Osteoarthritis, in Celecoxib 28:08.04.08.) In patients with osteoarthritis of the knee who have moderate to severe pain and signs of joint inflammation, some clinicians suggest that joint aspiration accompanied by intraarticular glucocorticoid injections or use of an oral NSAIA can be considered for initial therapy.[197]

In patients with osteoarthritis of the knee who fail to respond to adequate regimens of acetaminophen or other appropriate oral analgesics given in conjunction with nonpharmacologic therapy, intraarticular sodium hyaluronate therapy may be indicated; this alternative may be especially advantageous when oral NSAIAs are contraindicated or ineffective.[197] Intraarticular glucocorticoid injections can be used as an adjunct to oral therapy with acetaminophen or other appropriate oral analgesic or as monotherapy in selected patients with osteoarthritis of the knee; these injections also are used occasionally in patients with osteoarthritis of the hip.[197] Intraarticular glucocorticoid injections are of value and may be particularly beneficial in patients with osteoarthritis of the knee who have signs of local inflammation with joint effusion.[197] Use of topical analgesics can be considered as either adjunctive treatment or monotherapy in patients with osteoarthritis of the knee who have mild to moderate pain and have failed to obtain adequate symptomatic relief with acetaminophen and cannot or prefer not to receive other systemic analgesics; topical agents have not been evaluated for pain management in patients with osteoarthritis of the hip and are of questionable value in these patients because of the depth of the hip joint.[197]

• Fever

Acetaminophen is used frequently to lower body temperature in febrile patients in whom fever may be deleterious or in whom considerable relief is obtained when fever is lowered. However, antipyretic therapy is generally nonspecific, does not influence the course of the underlying disease, and may obscure the patient's illness. Parents and caregivers of pediatric patients should be reassured that while some parental anxiety over fever is understandable, the principal reason for treating fever is for patient comfort and that complete normalization of body temperature is not necessary and may not be possible.[226] To minimize the risk of acetaminophen overdosage, alternative antipyretics should be considered for children at increased risk of developing toxicity and in those with refractory fever.[226]

If an antipyretic is considered necessary in children or teenagers with known or suspected varicella, influenza-like illness, or other viral illness, use of acetaminophen (not aspirin) is recommended because use of salicylates in these pediatric patients

may be associated with an increased risk of developing Reye's syndrome.[208] (See Cautions: Pediatric Precautions, in the Salicylates General Statement 28:08.04.24.) In the treatment of influenza in young children, control of fever with acetaminophen or other appropriate antipyretic may be important because the fever and other symptoms of influenza could exacerbate underlying chronic conditions.[208]

Acetaminophen and aspirin are equally effective as antipyretics. In one study in febrile children, the combination of oral doses of acetaminophen and aspirin was at least as effective in reducing fever as either drug alone, and the duration of fever reduction was longer with the combination than with the individual drugs. However, because of the study design, it could not be concluded that the combination had additive effects. Many clinicians use regimens of alternating doses of acetaminophen and aspirin; however, combined overdosage with both drugs has occurred with such a regimen and the efficacy and safety of these regimens remain to be established.

To minimize the risk of acetaminophen overdosage, some clinicians have used pediatric regimens of alternating doses of acetaminophen and ibuprofen; however, the efficacy and safety of these regimens remain to be established.[226] In addition, although some such clinicians have alternated acetaminophen and ibuprofen at 2-hour intervals (i.e., with each drug administered every 4 hours) in pediatric patients, there is no pharmacokinetic rationale to support such a regimen; longer alternating dosing intervals would seem more appropriate if an alternating regimen is considered, but additional study and experience are necessary.[226]

Febrile Seizures

Because febrile seizures occur only in conjunction with a fever, it has been postulated that aggressive intermittent antipyretic therapy might prevent such seizures.[217] However, there currently is no evidence to substantiate that aggressive antipyretic therapy can prevent recurrent febrile seizures.[217] In one study in a limited number of children, 25% of patients in whom antipyretic therapy was initiated when any rectal temperature exceeded 37.2°C (99°F) experienced seizure recurrence compared with 5% of those who received continuous phenobarbital prophylaxis.[217, 218] In another study comparing low-dose diazepam, acetaminophen, and placebo, there was no evidence that acetaminophen prevented recurrent febrile seizures; acetaminophen was administered in a dosage of 10 mg/kg 4 times daily.[217, 219] In children hospitalized after a simple febrile seizure, administration of aggressive antipyretic therapy with acetaminophen 15-20 mg/kg every 4 hours was no more effective than sporadic acetaminophen use in preventing a second febrile seizure during that admission; the 2 treatment groups also had a similar frequency, duration, and magnitude of temperature elevations.[217, 220]

Dosage and Administration

• Administration

Acetaminophen usually is administered orally. Extended-release acetaminophen tablets should not be crushed, chewed, or dissolved in liquid.[222] The orally disintegrating tablets containing acetaminophen (Tylenol® Meltaways) should be allowed to dissolve in the mouth or should be chewed before swallowing.[237] The rapidly disintegrating tablets containing acetaminophen in fixed combination with caffeine (Excedrin® Quicktabs®) should be placed on the tongue, where the tablets

disintegrate within a few seconds, and subsequently swallowed.[232] For best taste, the tablets containing acetaminophen in fixed combination with caffeine should not be chewed.[232]

In patients who cannot tolerate oral medication, acetaminophen may be administered rectally as suppositories; however, the rectal dose required to produce the same plasma concentrations may be higher than the oral dose and rectal absorption can be erratic.[226, 227, 228] Dividing suppositories in an attempt to administer lower dosages may not provide a predictable dose.[226]

Some experts state that rectal preparations of acetaminophen should not be used for *self-medication* in children unless such use is specifically discussed with a clinician and parents or caregivers are instructed to adhere to dosage and administration recommendations; poor or variable absorption of acetaminophen following rectal administration may be associated with inadequate therapy or may result in toxicity following frequent or excessive doses.[226, 227, 228]

Acetaminophen preparations for *self-medication* should not be used unless seals on the tamper-resistant packaging are intact.

• Dosage

Acetaminophen should not be used for *self-medication* of pain for longer than 10 days in adults or 5 days in children, unless directed by a clinician because pain of such intensity and duration may indicate a pathologic condition requiring medical evaluation and supervised treatment.

Acetaminophen should not be used in adults or children for *self-medication* of marked fever (greater than 39.5°C), fever persisting longer than 3 days, or recurrent fever, unless directed by a clinician because such fevers may indicate serious illness requiring prompt medical evaluation.

Acetaminophen should not be used in adults or children for *self-medication* of sore throat pain (pharyngitis, laryngitis, tonsillitis) for longer than 2 days.

To minimize the risk of overdosage, no more than 5 age-appropriate doses of acetaminophen should be used for *self-medication* analgesia or antipyresis in any 24-hour period, unless directed by a clinician. Because severe liver toxicity and death have occurred in children who received multiple excessive doses of acetaminophen as part of therapeutic administration,[202, 203, 204, 205, 206] parents or caregivers should be instructed to use weight-based dosing for acetaminophen, to use only the calibrated measuring device provided with the particular acetaminophen formulation for measuring dosage,[205, 207] to ensure that the correct number of tablets required for the intended dose is removed from the package, and not to exceed the recommended daily dosage because serious adverse effects could result.[204, 205, 206, 207, 235, 236] In addition, patients should be warned that the risk of overdosage and severe liver damage is increased if more than one preparation containing acetaminophen are used concomitantly.[238]

Pharmacists have an important role in preventing acetaminophen-induced hepatotoxicity by advising consumers about the risk of failing to recognize that a wide variety of over-the-counter (OTC) and prescription preparations contain

acetaminophen.[238] Failure to recognize acetaminophen as an ingredient may be particularly likely with prescription drugs because the label of the dispensed drug may not clearly state its presence.[238] Educating consumers about the risk of exceeding recommended acetaminophen dosages also is important.[238]

Adult Dosage

Pain and Fever. For analgesia or antipyresis in adults or children 12 years of age or older, the usual oral dosage of acetaminophen as an immediate-release (conventional) preparation is 650 mg every 4-6 hours or 1 g every 4-6 hours as necessary; dosage should not exceed 4 g daily.[222] An oral acetaminophen dosage of 1.3 g as extended-release tablets every 8 hours can be used for the management of pain in adults; dosage should not exceed 3.9 g daily.[222] Some experts recommend a maximum dosage of 3 g daily when the drug is used for long-term therapy (e.g., 2 or more weeks).[243] The US Food and Drug Administration (FDA) is reviewing available data to determine whether it is possible to identify subgroups of patients with increased susceptibility to acetaminophen-associated hepatotoxicity and to determine whether data support establishing a lower (i.e., less than 4 g daily) maximum daily dosage for certain patients.[245, 246] (See Cautions: Precautions and Contraindications.)

For *self-administration* for the temporary relief of minor aches and pains in adults, the recommended oral dosage of a rapidly disintegrating tablet preparation containing acetaminophen in fixed combination with caffeine is 1 g of acetaminophen with 130 mg of caffeine every 6 hours; dosage of acetaminophen should not exceeding 4 g daily.[232]

For analgesia or antipyresis in adults or children 12 years of age or older, the usual rectal dosage of acetaminophen is 325-650 mg every 4 hours as necessary; dosage should not exceed 4 g daily.[198]

Pain Associated with Migraine Headache. For *self-medication* for the temporary relief of mild to moderate pain associated with migraine headache in adults, the recommended oral dosage is 500 mg of acetaminophen (combined with 500 mg of aspirin and 130 mg of caffeine) as a single dose of an immediate-release (conventional) preparation taken with a full glass of water; no more than 500 mg of acetaminophen (in combination with 500 mg of aspirin and 130 mg of caffeine) should be taken in any 24-hour period, unless directed by a clinician.[212] Individuals younger than 18 years of age should consult their clinician before using this combination preparation.[212]

Pain Associated with Osteoarthritis. For the treatment of pain associated with osteoarthritis, many clinicians recommend acetaminophen dosages up to 1 g administered 4 times daily as an immediate-release (conventional) preparation. Alternatively, 1.3 g as extended-release tablets every 8 hours can be used.[197, 199, 200, 201] Some experts recommend a maximum dosage of 3 g daily when the drug is used for long-term therapy (e.g., 2 or more weeks).[243] FDA is reviewing available data to determine whether it is possible to identify subgroups of patients with increased susceptibility to acetaminophen-associated hepatotoxicity and to determine whether data support establishing a lower (i.e., less than 4 g daily) maximum daily dosage for certain patients.[245, 246] (See Cautions: Precautions and Contraindications.)

Pediatric Dosage

Pain and Fever. For analgesia and antipyresis in children 12 years of age or older, the usual oral dosage of acetaminophen as an immediate-release (conventional) preparation is 650 mg every 4-6 hours or 1 g every 4-6 hours as necessary; dosage should not exceed 4 g daily.[222] For analgesia and antipyresis, children may receive the following doses every 4-6 hours as necessary (up to 5 times in 24 hours) as an immediate-release (conventional) preparation: children 11 years of age (32.5-43 kg), 480 mg; children 9-10 years of age (27-32.5 kg), 400 mg; children 6-8 years of age (21.5-27 kg), 320 mg; children 4-5 years of age (16-21.5 kg), 240 mg; children 2-3 years of age (11-16 kg), 160 mg; children 12-23 months of age (8-11 kg), 120 mg; children 4-11 months of age (5-8 kg), 80 mg; and children up to 3 months of age (2.7-5 kg), 40 mg.[207]

For analgesia and antipyresis in children 12 years of age or older, the usual rectal dosage of acetaminophen is 325-650 mg every 4 hours as necessary; dosage should not exceed 4 g daily.[198] For analgesia and antipyresis, children may receive the following rectal doses of acetaminophen every 4 hours as necessary (up to 5 times in 24 hours): children 11-12 years of age, 320-480 mg; children 9-11 years of age, 320-400 mg; children 6-9 years of age, 320 mg; children 4-6 years of age, 240 mg; children 2-4 years of age, 160 mg.[198] Rectal dosages in children younger than 2 years of age must be individualized, and the possibility of erratic systemic absorption should be considered.[226, 227, 228]

Cautions

Acetaminophen is relatively nontoxic in therapeutic doses.

Many over-the-counter drug products and prescription preparations contain acetaminophen.[238] Simultaneous use of more than one preparation containing acetaminophen can result in adverse consequences (e.g., acetaminophen overdose).[238, 240] Patients should be advised not to take multiple acetaminophen-containing preparations concomitantly.[238]

When acetaminophen is used in fixed combination with other agents (e.g., antihistamines, nasal decongestants, opiate agonists), the usual cautions, precautions, and contraindications associated with these agents must be considered in addition to those associated with acetaminophen.

• Dermatologic and Sensitivity Reactions
Dermatologic reactions including pruritic maculopapular rash and urticaria have been reported and other sensitivity reactions including laryngeal edema, angioedema, and anaphylactoid reactions may occur rarely.

• Hematologic Effects
Thrombocytopenia, leukopenia, and pancytopenia have been associated with the use of *p*-aminophenol derivatives, especially with prolonged administration of large doses. Neutropenia and thrombocytopenic purpura have been reported with acetaminophen use. Rarely, agranulocytosis has been reported in patients receiving acetaminophen.

• Hepatic Effects

Hepatotoxicity can result from ingestion of a single toxic dose or multiple excessive doses of acetaminophen, and overdosage of acetaminophen is the leading cause of acute liver failure (ALF) in adults in the US; in most cases, overdosage was inadvertent rather than intentional.[222, 223] (See Acute Toxicity and also see Chronic Toxicity.)

Substantial elevations in alanine aminotransferase (ALT) occurred in healthy individuals receiving acetaminophen in a dosage of 4 g daily in one randomized study.[239] Study participants (58-59% Hispanic American, 28-31% Caucasian, 12-13% African American) were randomized to receive 4 g of acetaminophen daily (alone or in combination with an opiate) or placebo for 14 days; the study was conducted at an inpatient clinical pharmacology unit.[239] Maximum ALT values exceeding 3 times the upper limit of normal (ULN) occurred in 38 or 31-44% of individuals receiving acetaminophen or acetaminophen in combination with an opiate, respectively; substantial elevations in ALT (i.e., values exceeding 3 times the ULN) were not observed in individuals given placebo.[239]

• **Precautions and Contraindications**

Individuals with phenylketonuria (i.e., homozygous deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that Children's Tylenol® and Junior Strength Tylenol® chewable tablets contain aspartame (NutraSweet®), which is metabolized in the GI tract to phenylalanine following oral administration.

Some commercially available formulations of acetaminophen contain sulfites that may cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown but probably low; such sensitivity appears to occur more frequently in asthmatic than in nonasthmatic individuals. Acetaminophen should be discontinued if hypersensitivity reactions occur.

Although psychologic dependence on acetaminophen may occur, tolerance and physical dependence do not appear to develop even with prolonged use.

Because concomitant administration of acetaminophen (especially when administered in high dosages or for prolonged periods) with oral anticoagulants may potentiate the effects of the oral anticoagulant,[168, 176] additional monitoring of prothrombin time (PT)/international normalized ratio (INR) values has been suggested for patients receiving oral anticoagulants following initiation of, or during sustained therapy with, large doses of acetaminophen.[168, 169] (See Drug Interactions: Oral Anticoagulants.)

Because chronic, excessive consumption of alcohol may increase the risk of acetaminophen-induced hepatotoxicity, chronic alcoholics should be cautioned to avoid regular or excessive use of acetaminophen, or alternatively, to avoid chronic ingestion of alcohol.[128, 129, 147, 222] The manufacturers currently caution that patients who generally consume 3 or more alcohol-containing drinks per day should ask their clinician whether to use acetaminophen or an alternative analgesic for *self-medication*.[167, 209, 210, 211, 212, 222] However, the US Food and Drug Administration (FDA) has proposed eliminating this statement from the labeling of OTC acetaminophen-containing preparations and adding a new warning that would

highlight the potential for severe liver damage to occur in individuals who consume 3 or more alcohol-containing drinks per day while taking acetaminophen, in those who use more than one acetaminophen-containing product concomitantly, and in those who exceed the recommended daily dosage of the drug.[245, 246] FDA also has proposed revising the labeling of OTC acetaminophen-containing preparations to include a statement that patients should consult a clinician prior to use if they have liver disease.[245, 246] FDA is reviewing available data to determine whether it is possible to identify subgroups of patients with increased susceptibility to acetaminophen-associated hepatotoxicity and to determine whether data support establishing a lower (i.e., less than 4 g daily) maximum daily dosage for certain patients (e.g., those who chronically ingest alcohol).[245, 246]

• Pediatric Precautions

Because severe liver toxicity and death have occurred in children who received multiple excessive doses of acetaminophen as part of therapeutic administration (i.e., with therapeutic intent),[202, 203, 204, 205, 206] parents or caregivers should be instructed to use weight-based dosing for acetaminophen, to use only the calibrated measuring device provided with the particular acetaminophen formulation for measuring dosage,[205, 207] to ensure that the correct number of tablets required for the intended dose is removed from the package,[235, 236] and not to exceed the recommended daily dosage because serious adverse effects could result.[204, 205, 206, 207] Parents also should be cautioned not to use other acetaminophen-containing products (e.g., some cold and cough products) concomitantly with acetaminophen in children because of the potential for overdoses.[204, 207]

Because acetaminophen therapy usually is begun without the direct advice of a clinician and carries the risk of potential overdosage, instruction regarding appropriate pain and fever therapy preferably should be incorporated into well-child visits.[226] Optimally, clinicians should provide parents and/or caregivers with written, specific advice as part of well-child visits, which should be reviewed during subsequent visits.[226] Parents and caregivers should be advised about the appropriate dose, frequency, duration of therapy, and specific strength and formulation for an individual pediatric patient.[226] They also should be advised of the danger of substituting alternative dosage forms, particularly adult for pediatric formulations.[226] Parents and caregivers should be warned not to exceed recommended acetaminophen dosages and cautioned that children should not be allowed to administer the drug themselves.[226] They also should be warned to read the labeled contents of over-the-counter (OTC) preparations, particularly those recommended for cold, cough, fever, headache, and general ache and pain because simultaneous use of more than one preparation containing acetaminophen could be dangerous.[226] In addition, they should be warned not to substitute extended-release formulations for immediate-release (conventional) ones without making appropriate changes in the dosing interval.[226] A clinician should be contacted for advice if fever and/or other signs and symptoms amenable to acetaminophen persist.[226]

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) preparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection.[247, 248] Such preparations also may contain analgesics and antipyretics (e.g.,

acetaminophen).[247] There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by the US Food and Drug Administration [FDA]) have not been established.[247] Such preparations should be used in children younger than 2 years of age with caution and only as directed by a clinician.[247, 248] Clinicians should use caution in prescribing cough and cold preparations in these children and should ask caregivers about use of nonprescription cough and cold preparations to avoid overdosage.[247] For additional information on precautions associated with the use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in Pseudoephedrine 12:12.12.

Drug Interactions

• **Alcohol**

Because there is some evidence that chronic, excessive consumption of alcohol may increase the risk of acetaminophen-induced hepatotoxicity, chronic alcoholics should be cautioned to avoid regular or excessive use of acetaminophen, or alternatively, to avoid chronic ingestion of alcohol.[128] The manufacturers currently caution that patients who generally consume 3 or more alcohol-containing drinks per day should ask their clinician whether to use acetaminophen or an alternative analgesic for *self-medication* because acetaminophen may increase the risk of hepatotoxicity.[167, 209, 210, 211, 212, 222] However, the US Food and Drug Administration (FDA) has proposed eliminating this statement from the labeling of OTC acetaminophen-containing preparations and adding a new warning that would highlight the potential for severe liver damage to occur under certain circumstances, including in individuals who consume 3 or more alcohol-containing drinks per day while taking acetaminophen.[245, 246] (See Cautions: Precautions and Contraindications.)

• **Anticonvulsants**

Anticonvulsants (including phenytoin, barbiturates, carbamazepine) that induce hepatic microsomal enzymes may increase acetaminophen-induced liver toxicity because of increased conversion of the drug to hepatotoxic metabolites.[152, 157, 160, 162, 163, 164, 165] The risk of acetaminophen-induced hepatic toxicity is substantially increased in patients ingesting larger than recommended dosages of acetaminophen while receiving anticonvulsants.[152, 157, 160, 162, 163, 164, 165] Usually, no dosage reduction is required in patients receiving concomitant administration of therapeutic dosages of acetaminophen and anticonvulsants;[162, 163, 164] however, patients should limit self-medication with acetaminophen while receiving anticonvulsants.[165]

• **Aspirin**

Limited data indicate that administration of acetaminophen (1 g daily) does not inhibit the antiplatelet effect of aspirin (81 mg daily).[144]

• **Isoniazid**

Concomitant administration of isoniazid with acetaminophen may result in an increased risk of hepatotoxicity, but the exact mechanism of this interaction has not been established.[166] The risk of hepatic toxicity is substantially increased in patients ingesting larger than recommended dosages of acetaminophen while receiving isoniazid.[158, 159, 161] Therefore, patients should limit self-medication with acetaminophen while receiving isoniazid.[166]

• **Oral Anticoagulants**

Chronic ingestion of large doses of acetaminophen has been reported to potentiate the effects of coumarin- and indandione-derivative anticoagulants, although conflicting data exist and the clinical importance of any such interaction has been questioned. The results of an observational study in patients stabilized on warfarin therapy indicate an association between ingestion of even low to moderate dosages of acetaminophen (7 or more 325-mg tablets weekly) and excessively high international normalized ratio (INR) values, and some clinicians suggest that additional monitoring of INR values may be prudent in patients receiving warfarin therapy following initiation of, and during sustained therapy with, large doses of acetaminophen.

In a case-control study, patients receiving warfarin who had an INR exceeding 6 (target INR: 2-3) were more likely to have taken acetaminophen during the week preceding the INR than patients who had actual INRs of 1.7-3.3 (i.e., controls) on warfarin therapy; this association was dose-dependent in that case patients reported ingesting greater amounts of acetaminophen in the week preceding the INR (approximately 21 acetaminophen 325-mg tablets) than did controls (approximately 9 acetaminophen 325-mg tablets). For most of these patients, the elevated INR represented a recent deterioration in control of anticoagulation. Patients who reported taking about 1.3 g of acetaminophen daily for longer than 1 week had a tenfold increase in the risk of having an INR exceeding 6 compared with those not reporting acetaminophen use. Such risk decreased with lower acetaminophen dosages (4.6 up to 9.1 g weekly) and reached baseline values at acetaminophen dosages of about 2 g weekly or less. Although the precise mechanism of the described interaction is not known, it has been suggested that acetaminophen (particularly when administered in large doses) can inhibit metabolism of warfarin probably via inhibition of the cytochrome P-450 microsomal enzyme system, resulting in increased blood concentrations of warfarin. There is controversy concerning the design of this study (e.g., presence of possibly confounding risk factors, lack of causality assessment), and some clinicians doubt the clinical importance of these findings.

Pending completion of randomized, controlled studies to assess causality and more fully determine the clinical importance of this interaction, acetaminophen generally remains preferable to nonsteroidal anti-inflammatory agents (NSAIAs) as a mild analgesic or antipyretic in patients receiving warfarin because of the potential for serious adverse effects (e.g., bleeding) associated with concomitant warfarin and NSAIA therapy. Some clinicians suggest that when long-term therapy with acetaminophen (e.g., 3-4 g daily, as may be required for pain in patients with osteoarthritis) is initiated in patients receiving warfarin, the INR or prothrombin time (PT) should be determined about 7-14 days after beginning acetaminophen therapy. As with other drugs that may interact with warfarin, when concomitant acetaminophen therapy is initiated or discontinued or acetaminophen dosage is modified, the INR or PT should be monitored more frequently and warfarin dosage adjusted if necessary until these values have stabilized.

- **Phenothiazines**

The possibility of severe hypothermia should be considered in patients receiving concomitant phenothiazine and antipyretic (e.g., acetaminophen) therapy.

Laboratory Test Interferences

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Acute Toxicity

• Pathogenesis

The toxicity of acetaminophen is closely linked to the drug's metabolism.[121, 226] With therapeutic dosing, acetaminophen is metabolized principally by sulfate and glucuronide conjugation.[121, 226] Small amounts (5-10%) usually are oxidized by cytochrome P-450 (CYP)-dependent pathways (mainly CYP2E1 and CYP3A4) to a toxic metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[226] NAPQI is detoxified by glutathione and eliminated in urine and/or bile, and any remaining toxic metabolite may bind to hepatocytes and cause cellular necrosis.[121, 226] Because of the relatively small amount of NAPQI usually formed and the adequate supply of glutathione that usually is present in the body, acetaminophen generally has an excellent safety profile.[121, 226] However, with acetaminophen overdosage and occasionally with usual dosages in susceptible individuals (e.g., those with nutritional [malnutrition] or drug interactions, those consuming alcohol chronically, those with predisposing medical conditions, those with a genetic metabolic predisposition), hepatotoxic concentrations of NAPQI may accumulate.[121, 226]

• Manifestations

Acetaminophen toxicity may result from a single toxic dose, from repeated ingestion of large doses of acetaminophen (e.g., 7.5-10 g daily for 1-2 days), or from chronic ingestion of the drug. (See Chronic Toxicity.) Dose-dependent, hepatic necrosis is the most serious acute toxic effect associated with overdosage and is potentially fatal.

Acetaminophen toxicity usually involves 4 phases: 1) anorexia, nausea, vomiting, malaise, and diaphoresis (which inappropriately may prompt administration of additional acetaminophen); 2) resolution of phase-1 manifestations and replacement with right upper quadrant pain or tenderness, liver enlargement, elevated bilirubin and hepatic enzyme concentrations, prolongation of prothrombin time, and occasionally oliguria; 3) anorexia, nausea, vomiting, and malaise recur (usually 3-5 days after initial symptom onset) and signs of hepatic failure (e.g., jaundice, hypoglycemia, coagulopathy, encephalopathy) and possibly renal failure and cardiomyopathy develop; and 4) recovery or progression to fatal complete liver failure.[121, 226]

Nausea, vomiting, and abdominal pain usually occur within 2-3 hours after ingestion of toxic doses of the drug. Unlike salicylates, acetaminophen does not usually cause acid/base changes in toxic doses. In severe poisoning, CNS stimulation, excitement, and delirium may occur initially. This may be followed by CNS depression; stupor; hypothermia; marked prostration; rapid, shallow breathing; rapid, weak, irregular pulse; low blood pressure; and circulatory failure. Vascular collapse results from the relative hypoxia and from a central depressant action that occurs only with massive doses. Shock may develop if vasodilation is marked. Fatal asphyxial seizures may occur. Coma usually precedes death, which may occur suddenly or may be delayed for several days.

Fulminant, fatal hepatic failure may occur in chronic alcoholics following overdosage of acetaminophen.[110, 134, 135, 136, 137, 138, 140, 141, 142] *p*-Aminophenol derivatives may elevate serum bilirubin concentrations, and jaundice may develop within 2-6 days

after ingestion of one of the drugs. In adults, hepatic toxicity rarely has occurred with acute overdoses of less than 10 g, although hepatotoxicity has been reported in fasting patients ingesting 4-10 g of acetaminophen.[130] (See Pharmacokinetics: Elimination.) Fatalities are rare with less than 15 g. However, the risk of severe and possibly fatal hepatic injury following acetaminophen overdosage cannot be accurately assessed based on the amount of acetaminophen ingested.[223] Although some discordance in evidence exists,[106, 108, 114, 115, 118, 119, 120, 121, 123, 125, 126] the overwhelming weight of existing evidence currently supports a relationship between chronic, excessive consumption of alcohol and an increased risk of acetaminophen-induced hepatotoxicity.[101, 102, 103, 104, 105, 107, 108, 109, 110, 111, 112, 113, 115, 116, 117, 120, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132] When an individual has ingested a toxic dose of acetaminophen, the individual should be hospitalized for several days of observation, even if there are no apparent ill effects, because maximum liver damage usually does not become apparent until 2-4 days after ingestion of the drug. Transient azotemia and renal tubular necrosis have been reported in patients with acetaminophen poisoning; renal failure is often associated with fatality. There have been reports of acute myocardial necrosis and pericarditis in individuals with acetaminophen poisoning. Maximum cardiotoxic effects of these drugs appear to be delayed in a manner similar to hepatotoxic effects. Hypoglycemia, which can progress to coma, and metabolic acidosis have been reported in patients ingesting toxic doses of acetaminophen and cerebral edema occurred in one patient.

Young children appear to be less likely to develop hepatotoxic effects than adults, apparently because of age-related differences in acetaminophen metabolism. However, cases of severe hepatotoxicity and death have been reported in children who apparently received acetaminophen dosages exceeding those recommended[202, 203, 204, 205, 206] (10-15 mg/kg per dose with a maximum of 5 doses per day) for children.[202, 204] Factors contributing to overdosage and toxicity of acetaminophen in children appear to include improper interpretation by the parent or caregiver of dosing information or failure to read such information, use of adult-strength acetaminophen preparations because of unavailability of pediatric formulations, use of excessive dosing because of the perception that desired therapeutic effects had not been achieved, and lack of knowledge about the potential toxicity of acetaminophen in excessive dosage.[203, 204, 205, 206] Current data suggest that the outcome after multiple excessive doses of acetaminophen in children under conditions of therapeutic intent may differ from the outcome observed after acute intoxications[202, 203, 204, 205] where as few as 1% of children have developed serious liver toxicity, which was successfully managed.[203, 205] Diagnosis and treatment may be made more difficult in cases of multiple overdoses because the parent or caregiver may not recognize acetaminophen overdose as a factor in the child's symptoms[206] or may not accurately recall the dosage administered.[203, 205] The mechanism of acetaminophen toxicity in pediatric patients after multiple supratherapeutic doses remains to be elucidated.[202, 203, 204] It has been suggested that certain individuals may be more susceptible to cellular injury induced by acetaminophen, and the combination of supratherapeutic doses, disease (e.g., diabetes mellitus, viral infection, febrile illness accompanied by acute malnourishment), nutritional factors (e.g., obesity, chronic undernutrition, prolonged fasting), metabolic factors (e.g., polymorphism in expression of the cytochrome P-450 enzyme system, alternate metabolic pathways under conditions of drug accumulation after multiple doses, enzyme induction),[202, 203, 204, 205] and stage of development[202, 203, 204] may result in enhanced acetaminophen toxicity in these individuals.[202, 203, 204, 205,

[226] Whether hepatic injury resulting from other underlying conditions (e.g., viral infections, metabolic diseases) is exacerbated by acetaminophen has not been established.[226]

Low prothrombin levels have been reported in patients with acetaminophen poisoning and in one patient fatal GI hemorrhage was attributed to hypoprothrombinemia. Thrombocytopenia also has been reported. Toxic doses of *p*-aminophenol derivatives may produce skin reactions of an erythematous or urticarial nature which may be accompanied by fever and oral mucosal lesions.

• **Treatment**

In all cases of suspected acetaminophen overdosage, a regional poison control center at 800-222-1212 may be contacted immediately for assistance in diagnosis and for directions in the use of acetylcysteine as an antidote.

Management of acetaminophen acute overdosage includes determination of the magnitude of the ingestion, classification of risk, and measures to reduce morbidity and mortality.[223, 225, 229] Early recognition and treatment of overdosage are essential to prevent morbidity and mortality.[223, 225, 229]

If acetaminophen has been recently ingested, activated charcoal may reduce acetaminophen absorption and should be administered as soon as possible (preferably within 1 hour of ingestion).[223, 225, 229] Other methods of gastric decontamination (i.e., syrup of ipecac) are less effective and generally are not recommended.[225, 229] Management of acetaminophen overdose also includes general physiologic supportive measures such as control of respiration and fluid and electrolyte therapy.[223, 225, 229]

Because reported or estimated quantity of acetaminophen ingestion often is inaccurate and is not a reliable guide to the therapeutic management of the overdose, the preferred method to assess the risk of toxicity after acetaminophen ingestion usually is measurement of plasma or serum acetaminophen concentrations.[222, 223, 224, 225, 226, 229] Plasma or serum acetaminophen concentrations should be determined as soon as possible, but no sooner than 4 hours after ingestion (to ensure that peak concentrations have occurred).[229] If an extended-release preparation of acetaminophen was ingested, it may be appropriate to obtain an additional sample of plasma or serum 4-6 hours after the initial sample for determination of drug concentrations.[222, 229] Plasma or serum acetaminophen concentrations are used in conjunction with a nomogram that follows to estimate the potential for hepatotoxicity and the necessity of acetylcysteine therapy.[223, 225, 229] If the initial acetaminophen concentration falls on or above the solid line in the nomogram, hepatotoxicity is probable (in the absence of acetylcysteine therapy), and if the initial concentration falls on the dashed line or between the dashed and solid lines, hepatotoxicity is possible (in the absence of acetylcysteine therapy).[223, 225, 229] (To allow error on the side of safety, the dashed line is plotted 25% below the line indicating probable toxicity). If the initial plasma or serum acetaminophen concentration is below the dashed line on the nomogram, there is minimal risk of hepatotoxicity.[223, 225, 229]

A full course of acetylcysteine therapy is indicated if initial plasma or serum acetaminophen concentrations fall on or above the dashed line on the nomogram.[222, 223, 224, 225, 226, 229] Results are optimal if acetylcysteine therapy is initiated within 8-16 hours of ingestion, but acetylcysteine is effective when given more than 24 hours after

ingestion.[229] *If plasma or serum acetaminophen concentrations cannot be obtained, it should be assumed that the overdosage is potentially toxic, and acetylcysteine therapy should be initiated.* Acetylcysteine may be withheld until acetaminophen assay results are available provided initiation of acetylcysteine is not delayed beyond 8 hours after acetaminophen ingestion.[233, 234] If more than 8 hours has elapsed since acetaminophen ingestion, acetylcysteine therapy should be started immediately.[233, 234]

When indicated (e.g., in patients in whom the initial acetaminophen concentration is toxic on the nomogram or in those in whom a toxic dose is suspected and the time of ingestion is unknown, 8 hours have elapsed since ingestion, acetaminophen concentrations cannot be obtained, or acetaminophen concentration values will not be available within 8 hours of ingestion), acetylcysteine therapy is initiated as soon as possible with an oral or IV loading dose in adults and pediatric patients.[229, 233, 234] In the event that a loading dose of acetylcysteine is administered before plasma or serum acetaminophen concentration values are available, the initial plasma or serum concentration (obtained at least 4 hours after ingestion) is used in conjunction with the nomogram to determine the necessity of completing a full course of acetylcysteine therapy.[223, 229] In such situations, administration of a full course of acetylcysteine therapy is indicated if initial plasma or serum acetaminophen concentrations fall on or above the dashed line on the nomogram; acetylcysteine therapy is discontinued if initial acetaminophen concentrations fall below the dashed line on the nomogram.[223, 229, 233]

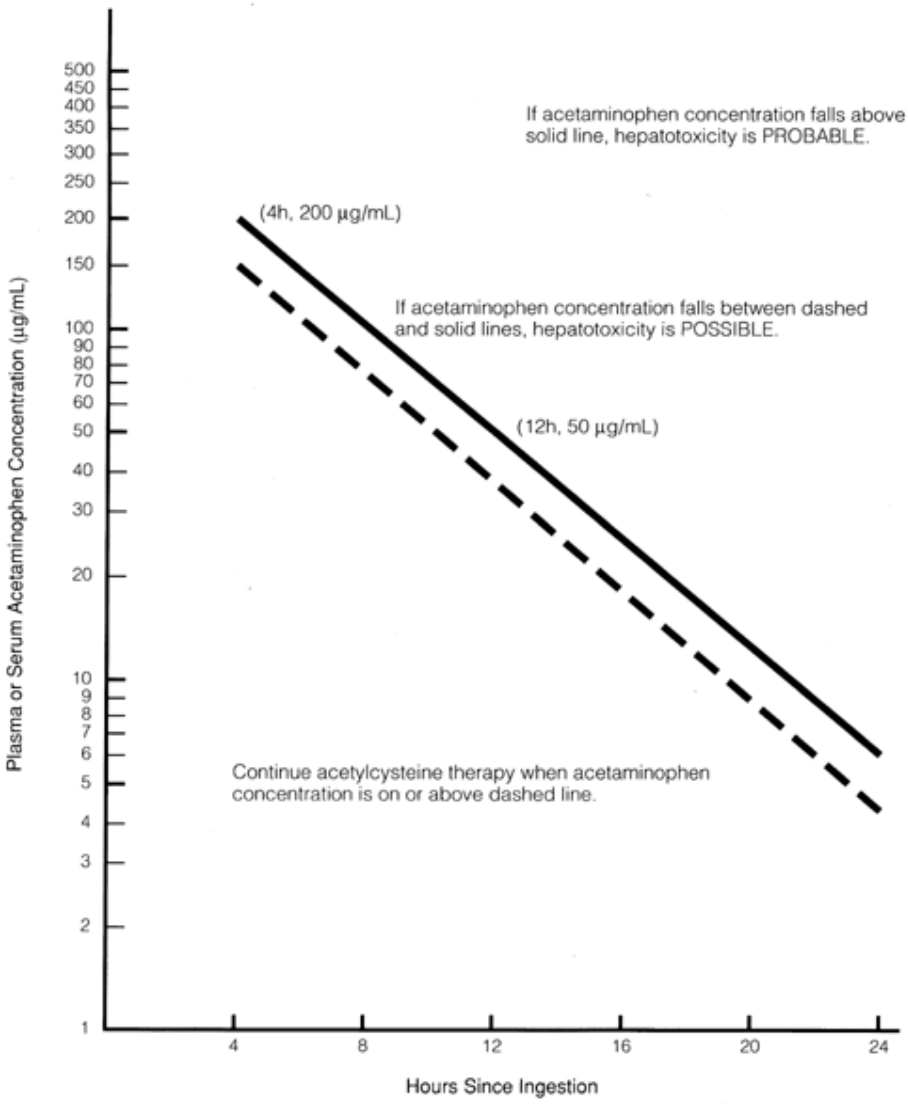
When acetylcysteine is administered orally, a loading dose of 140 mg/kg is administered; the loading dose is followed by oral maintenance doses of 70 mg/kg every 4 hours for 17 doses (full course of therapy).[229] Alternatively, when acetylcysteine is administered IV, a loading dose of 150 mg/kg is infused over 60 minutes; the loading dose is followed by an IV maintenance dose of 50 mg/kg infused over 4 hours and then 100 mg/kg infused over 16 hours (for a full course consisting of 300 mg/kg administered IV over 21 hours).[233]

If a patient receiving oral acetylcysteine vomits a loading or maintenance dose within 1 hour of administration, the dose should be repeated.[229] If the patient is persistently unable to retain orally administered acetylcysteine, the drug may be administered via a duodenal tube.[229] Antiemetic therapy also may be used for persistent vomiting.[229] The usual dosage of oral acetylcysteine is appropriate in patients given activated charcoal; higher dosages are not necessary in these patients.[223, 224, 229]

Because acetylcysteine therapy may be useful even when instituted more than 24 hours after an overdose, a full course of acetylcysteine therapy is recommended for patients presenting 24 or more hours postingestion with measurable plasma or serum acetaminophen concentrations or biochemical evidence of hepatic injury.[229] In a few patients with fulminant hepatic failure, IV administration of acetylcysteine has been associated with increased oxygen delivery and consumption resulting in beneficial effects on survival in such patients.[139, 140, 141, 142, 155, 229]

Because there is some evidence that excessive consumption of alcohol may increase the risk of acetaminophen-induced hepatotoxicity, some clinicians recommend that plasma or serum acetaminophen concentrations on the nomogram indicating the necessity for acetylcysteine therapy be lowered (by 25-70%) in chronic alcoholic patients.[129, 135, 136, 146, 152, 156] Some clinicians recommend that following overdosage

of acetaminophen, plasma or serum acetaminophen concentrations on the nomogram indicating the necessity for acetylcysteine therapy also be lowered in patients receiving drugs that may interfere with the hepatic metabolism of acetaminophen (e.g., isoniazid; anticonvulsants including phenytoin, phenobarbital, primidone, valproic acid, carbamazepine) because the risk of acetaminophen-induced hepatotoxicity also may be increased in these patients.[152, 157, 158, 159, 160, 161] It has been suggested that when acetaminophen toxicity results from repeated ingestion of large doses of acetaminophen (e.g., 7.5-10 g daily for 1 or 2 days), acetylcysteine therapy should be considered irrespective of plasma or serum acetaminophen concentrations.[152] Some experts state that early therapy with acetylcysteine should be considered when acetaminophen toxicity is a likely contributor to hepatic dysfunction.[226] In addition, some clinicians state that if an extended-release preparation of acetaminophen has been ingested, the usefulness of the current nomogram (which is based on ingestion of immediate-release preparations) may be limited.[143] Although area under the plasma concentration-time curve (AUC) may be increased following ingestion of an extended-release preparation, delayed absorption and decreased peak plasma acetaminophen concentrations may occur, which may lead to an underestimation of the need for antidotal therapy.[143] Some clinicians suggest that higher than usual doses of acetylcysteine may be necessary in patients ingesting an overdosage of acetaminophen extended-release preparations.[143] However, the manufacturer states that the standard nomogram may be used for acetaminophen extended-release tablets, but that an additional determination of plasma or serum acetaminophen concentrations from a sample obtained 4-6 hours after the initial sample also should be evaluated using the nomogram.[148, 150] In cases where it is unclear whether high doses of the drug were ingested as extended-release tablets or as conventional preparations of acetaminophen, the manufacturer suggests that overdosage of the drug be managed as if extended-release preparations were ingested.[150]



Nomogram relating plasma or serum acetaminophen concentration and probability of hepatotoxicity at varying intervals following ingestion of a single toxic dose of acetaminophen. Modified from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics.* 1975; 55:871-6. © American Academy of Pediatrics 1975.—and from Rumack BH et al. Acetaminophen overdose. *Arch Intern Med.* 1981; 141:380-5. © American Medical Association.

In addition to plasma or serum acetaminophen concentrations, baseline prothrombin time, BUN, blood glucose concentration, and serum AST (SGOT), ALT (SGPT), bilirubin, creatinine, and electrolyte concentrations should be determined. Prothrombin time, blood glucose concentration, and serum AST, ALT, bilirubin, and electrolyte concentrations should be determined at 24-hour intervals for at least 96 hours after the time of ingestion; if toxicity is evident, these parameters should continue to be monitored at least daily as necessary. Fluid and electrolyte balance should be maintained; use of diuretics and forced diuresis should be avoided. Hypoglycemia should be treated as necessary. If the prothrombin time is greater than 1.5 times the control value, phytonadione should be administered; if the prothrombin time is greater than 3 times the control value, fresh frozen plasma should be given. If

hepatic or renal impairment develops, appropriate laboratory parameters should be monitored until values return toward normal. A serum bilirubin concentration greater than 4 mg/dL and a prothrombin time greater than 2.2 times the control value may indicate impending hepatic encephalopathy. Hemodialysis or charcoal hemoperfusion generally are not useful in enhancing the elimination of acetaminophen from the body. Peritoneal dialysis is ineffective.

Chronic Toxicity

Three hundred and seven cases of liver injury associated with acetaminophen use were reported to the US Food and Drug Administration (FDA) from January 1998 to July 2001.[230] Sixty percent of these adverse events were categorized as severe life-threatening injury with liver failure (category 4); 40% of patients died.[230] Review of these case reports indicates that use of higher than recommended daily dosages of acetaminophen results in adverse hepatotoxic effects more often than use of recommended dosages.[230]

Twenty-five of these case reports involved pediatric patients 12 years of age or younger and 84% (21) of these cases involved medication errors.[230] Administration of higher than recommended dosages of acetaminophen has occurred as a result of parents or caregivers misunderstanding the directions provided on the product label or given by a clinician.[230] An added source of confusion is the different concentrations of acetaminophen available in pediatric preparations (e.g., acetaminophen drops 100 mg/mL, acetaminophen suspension 160 mg/5 mL).[230] Based on information from 10 of these reports, the dosage range of acetaminophen in these children was 106-375 mg/kg daily.[230] The maximum recommended pediatric dosage is 75 mg/kg daily.[230] Limited information indicates that the daily dosage of acetaminophen was higher in children who experienced serious hepatic injury (category 4) compared with those who experienced less severe hepatic effects.[230]

The mean and median daily dosage of acetaminophen was 6.5 and 5 g daily, respectively, in the 282 adults who experienced liver toxicity.[230] The maximum recommended adult dosage is 4 g daily.[230] Liver toxicity occurred at a lower acetaminophen dosage in adults who reported alcohol use compared with adults who did not report alcohol use.[230] Ninety-three adults experiencing liver toxicity were receiving drug therapy (74 drugs) that may have contributed to toxicity.[230] Prescription labeling for 64 of these drugs contained information on hepatotoxic events; 10 drugs had warnings or precautions concerning hepatic failure.[230]

In contrast to acute acetaminophen overdosage, guidelines for the treatment of ingestions involving multiple higher-than-recommended doses of acetaminophen currently are not available.[244] Some poison centers use plasma aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) concentrations and plasma or serum acetaminophen concentrations to estimate the potential for hepatotoxicity and necessity of acetylcysteine therapy.[233, 244] In cases of repeated supratherapeutic ingestion of acetaminophen, a regional poison center (800-222-1222) or an assistance line for acetaminophen overdosage (800-525-6115) can be contacted.[233]

Chronic ingestion of large doses of analgesics (e.g., 1 kg or more of phenacetin [no longer commercially available in the US] and/or salicylate over any period of time)

has been associated with analgesic nephropathy which is characterized by papillary necrosis and subsequent chronic interstitial nephritis, with or without pyelonephritis. Analgesic nephropathy frequently has been associated with ingestion of large amounts of combinations of aspirin, phenacetin, and caffeine (combinations containing phenacetin no longer are commercially available in the US). Because phenacetin previously was a component of many analgesic drug mixtures, this drug has been implicated as the causative agent of renal damage. Many clinicians, however, believe that nephropathy may be caused by a combination of several analgesics rather than a single drug. Cancer of the renal pelvis has been reported in patients with analgesic nephropathy and in patients following chronic ingestion of phenacetin-containing analgesic mixtures. Splenomegaly has also been associated with abuse of phenacetin-containing mixtures.

Pharmacology

Acetaminophen produces analgesia and antipyresis by a mechanism similar to that of salicylates. Unlike salicylates, however, acetaminophen does not have uricosuric activity. There is some evidence that acetaminophen has weak anti-inflammatory activity in some nonrheumatoid conditions (e.g., in patients who have had oral surgery). In equal doses, the degree of analgesia and antipyresis produced by acetaminophen is similar to that produced by aspirin.

Acetaminophen lowers body temperature in patients with fever but rarely lowers normal body temperature. The drug acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow.

The effects of acetaminophen on cyclooxygenase activity have not been fully determined.[144] Acetaminophen is a weak, reversible, isoform-nonspecific cyclooxygenase inhibitor at dosages of 1 g daily.[144] The inhibitory effect of acetaminophen on cyclooxygenase-1 is limited, and the drug does not inhibit platelet function.[144]

Therapeutic doses of acetaminophen appear to have little effect on cardiovascular and respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics

• Absorption
Acetaminophen is rapidly and almost completely absorbed from the GI tract following oral administration. In healthy men, steady-state oral bioavailability of 1.3-g doses of extended-release tablets of acetaminophen administered every 8 hours for a total of 7 doses was equal to 1-g doses of conventional tablets of acetaminophen given every 6 hours for a total of 7 doses.[148] Food may delay slightly absorption of extended-release tablets of acetaminophen.[148] Following oral administration of immediate- or extended-release acetaminophen preparations, peak plasma concentrations are attained within 10-60 or 60-120 minutes, respectively. Following oral administration of a single 500-mg conventional tablet or a single 650-mg extended-release tablet, average plasma acetaminophen concentrations of 2.1 or 1.8 mcg/mL, respectively, occur at 6 or 8 hours, respectively.[148] In addition, dissolution

of the extended-release tablets may depend slightly on the gastric or intestinal pH.[148] Dissolution appears to be slightly faster in the alkaline pH of the intestines compared with the acidic pH of the stomach; however, this is of no clinical importance.[148] Following administration of conventional preparations of acetaminophen, only small amounts of the drug are detectable in plasma after 8 hours.[149] The extended-release tablets of acetaminophen release the drug for up to 8 hours, but in vitro data indicate that at least 95% of the dose is released within 5 hours.[148, 150]

Following rectal administration of acetaminophen, there is considerable variation in peak plasma concentrations attained, and time to reach peak plasma concentrations is substantially longer than after oral administration.[226, 227, 228]

• Distribution

Acetaminophen is rapidly and uniformly distributed into most body tissues. About 25% of acetaminophen in blood is bound to plasma proteins.

• Elimination

Acetaminophen has a plasma half-life of 1.25-3 hours. Plasma half-life of acetaminophen may be prolonged following toxic doses or in patients with liver damage, although limited data indicate that following overdosage of acetaminophen the terminal plasma half-life of the drug reported with extended-release tablets is comparable to that reported with standard-release preparations.[150]

About 80-85% of the acetaminophen in the body undergoes conjugation principally with glucuronic acid and to a lesser extent with sulfuric acid. Acetaminophen also is metabolized by microsomal enzyme systems in the liver.

In vitro and animal data indicate that small quantities of acetaminophen are metabolized by a cytochrome P-450 microsomal enzyme to a reactive intermediate metabolite (*N*-acetyl-*p*-benzoquinoneimine, *N*-acetylimidoquinone, NAPQI) which is further metabolized via conjugation with glutathione and ultimately excreted in urine as a mercapturic acid. It has been suggested that this intermediate metabolite is responsible for acetaminophen-induced liver necrosis and that high doses of acetaminophen may deplete glutathione so that inactivation of this toxic metabolite is decreased. At high doses, the capacity of metabolic pathways for conjugation with glucuronic acid and sulfuric acid may be exceeded, resulting in increased metabolism of acetaminophen by alternative pathways. In addition, it also has been suggested that in fasting individuals conjugation of high doses of acetaminophen with glucuronic acid may be reduced, secondary to decreased hepatic carbohydrate reserves and microsomal oxidation may be increased, resulting in increased risk of hepatotoxicity.[130] Drugs that potentially modify these metabolic processes are used (e.g., acetylcysteine) or are being studied (e.g., cysteine, mercaptamine) as antidotes for acetaminophen-induced hepatotoxicity.[139, 140, 141, 142, 143, 151, 152, 153]

Acetaminophen is excreted in urine principally as acetaminophen glucuronide with small amounts of acetaminophen sulfate and mercaptate and unchanged drug. Approximately 85% of a dose of acetaminophen is excreted in urine as free and conjugated acetaminophen within 24 hours after ingestion. Administration of acetaminophen to patients with moderate to severe renal impairment may result in accumulation of acetaminophen conjugates.

Chemistry and Stability

• Chemistry

Acetaminophen is a synthetic nonopiate derivative of *p*-aminophenol that produces analgesia and antipyresis. Acetaminophen is a major metabolite of phenacetin. Phenacetin, another derivative of *p*-aminophenol, has been associated with analgesic nephropathy (renal papillary necrosis with subsequent chronic interstitial nephritis) and no longer is commercially available in the US. Acetaminophen occurs as a white, crystalline powder with a slightly bitter taste. Acetaminophen is soluble in boiling water and freely soluble in alcohol.

Acetaminophen oral solution has a pH of 3.8-6.1, and the oral suspension has a pH of 4-6.9. Although an official USP acetaminophen elixir that contained 6.5-10.5% alcohol was previously available under this title, USP combined the official descriptions for the elixir and solution to just acetaminophen oral solution in 1990 to simplify compendial standards for these liquid oral dosage forms. Therefore, both preparations, regardless of whether they contain alcohol, currently are titled oral solutions; those that contain alcohol are differentiated from those that do not only by specifying the alcohol content on the labeling.

Acetaminophen 650-mg extended-release core tablets (Tylenol® Arthritis Pain Extended Relief) contain the drug in an immediate-release outer shell (325 mg) and in an extended-release matrix core (325 mg) that slowly releases acetaminophen.[145, 148]

• Stability

Acetaminophen preparations should be stored at a temperature less than 40°C, preferably between 15-30°C; freezing of the oral solution or suspension should be avoided.

Preparations

In response to concerns regarding the safety and efficacy of cough and cold preparations in young children, many nonprescription cough and cold preparations specifically formulated for infants have been voluntarily withdrawn from the US market.[249] Therefore, some of the preparations described below may no longer be commercially available in the US.

* Available generically.

Acetaminophen

Routes Dosage Forms Strengths Brand Names Manufacturer Bulk Powder Oral Capsules 500 mg* Solution 160 mg/5 **Genapap® Children's** Teva mL* 167 mg/5 mL **Tylenol® Extra Strength Adult** McNeil 100 mg/mL* **Genapap® Drops Infant's** Teva **Liquiprin® Drops** (with parabens) Lee **Tylenol® Concentrated Drops Infant's** (with McNeil butylparaben and propylene glycol) Suspension 160 mg/5 mL **Tylenol® Suspension Children's** (with butylparaben McNeil and propylene glycol; cherry flavor) Tablets 325 mg* **Genapap®** Teva **Genebs®** Teva **Tylenol®** (scored) McNeil 500 mg* **Genapap® Extra Strength Caplets®** Teva **Genapap® Extra Strength Tablets** Teva **Genapap® Gel-Coat Caplets®** Teva **Genebs® Extra Strength**

Caplets® Teva **Genebs® Extra Strength Tablets** Teva **Tylenol® Extra Strength Gelcaps®** (with benzyl McNeil alcohol and parabens) **Tylenol® Extra Strength Geltabs®** (with benzyl McNeil alcohol and parabens) **Tylenol® Extra Strength Tablets** McNeil Tablets, 80 mg* **Genapap® Children's** Teva chewable **Tylenol® Children's** (with aspartame and povidone; McNeil bubble gum, fruit, or grape flavor scored) 160 mg **Tylenol® Junior Strength** (with aspartame) McNeil Tablets, 650 mg **Tylenol® Arthritis Pain Extended Relief Caplets®** McNeil extended- (with povidone) release, film- coated Tablets, film- 160 mg coated 325 mg **Tylenol®** (scored) McNeil 500 mg* **Anacin® Aspirin Free Maximum Strength Tablets®** Wyeth (with povidone and propylene glycol) **Tylenol® Extra Strength Caplets®** McNeil Tablets, orally 80 mg **Tylenol® Meltaways Children's** (with povidone; McNeil disintegrating bubble gum, grape, or watermelon flavored) 160 mg **Tylenol® Meltaways Junior Strength** (with povidone; McNeil bubble gum or grape flavored) Rectal Suppositories 80 mg **FeverAll® Infants'** Actavis 120 mg* **Acephen®** G&W **FeverAll® Children's** Actavis 125 mg 325 mg* **Acephen®** G&W **FeverAll® Junior Strength** Actavis 650 mg* **Acephen®** G&W

Acetaminophen, Aspirin, and Caffeine

Routes Dosage Strengths Brand Names Manufacturer Forms Oral For 260 mg/packet Acetaminophen, Aspirin **Goody's® Headache Powders** GlaxoSmithKline solution 520 mg/packet, and Caffeine 32.5 mg/ packet Tablets 125 mg Acetaminophen, Aspirin 240 mg, **Gelpirin®** Alra Caffeine 32 mg, and buffers 130 mg Acetaminophen, Aspirin 260 mg, **Goody's® Fast Pain Relief Tablets** GlaxoSmithKline and Caffeine 16.25 mg 130 mg Acetaminophen, Aspirin 260 mg, **Goody's® Extra Strength Tablets** GlaxoSmithKline and Caffeine 16.25 mg 160 mg Acetaminophen, Aspirin 230 mg, **Supac®** (scored) Mission Caffeine 33 mg, and buffers 250 mg Acetaminophen, Aspirin 250 mg, **Excedrin® Extra-Strength Tablets** Bristol-Myers and Caffeine 65 mg (with povidone and propylene Squibb glycol) **Excedrin® Migraine Caplets®** (with Bristol-Myers povidone and propylene glycol) Squibb **Excedrin® Migraine Geltabs** (with Bristol-Myers povidone and propylene glycol) Squibb **Excedrin® Migraine Tablets** (with Bristol-Myers povidone and propylene glycol) Squibb Tablets, 194 mg Acetaminophen, Aspirin 227 mg, **Vanquish® Caplets®** Bayer film- Caffeine 33 mg, and buffers coated 250 mg Acetaminophen, Aspirin 250 mg, **Excedrin® Extra-Strength Caplets®** Bristol-Myers and Caffeine 65 mg (with povidone and propylene Squibb glycol)

* Available generically.

Acetaminophen and Codeine Phosphate

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Solution 120 mg/5 mL Acetaminophen and Codeine **Tylenol® with Codeine Elixir** (C-V; Ortho-McNeil Phosphate 12 mg/5 mL* with alcohol 7% and propylene glycol) Suspension 120 mg/5 mL Acetaminophen and Codeine **Capital® and Codeine** (C-V) Amarin Phosphate 12 mg/5 mL* Tablets 300 mg Acetaminophen and Codeine Phosphate 15 mg* 300 mg Acetaminophen and Codeine **Tylenol® with Codeine No. 3** (C- Ortho-McNeil Phosphate 30 mg* III; with sodium metabisulfite) 300 mg Acetaminophen and

Codeine **Tylenol® with Codeine No. 4** (C- Ortho-McNeil Phosphate 60 mg* III; with sodium metabisulfite)

Acetaminophen and Diphenhydramine Citrate

Routes Dosage Strengths Brand Names Manufacturer Forms Oral Tablets, 500 mg Acetaminophen **Excedrin P.M.® Caplets®** (with parabens Bristol-Myers film- and Diphenhydramine and propylene glycol) Squibb coated Citrate 38 mg **Excedrin P.M.® Geltabs®** (with parabens, Bristol-Myers povidone, and propylene glycol) Squibb **Excedrin P.M.® Tablets** (with parabens Bristol-Myers and propylene glycol) Squibb

* Available generically.

Oxycodone and Acetaminophen

Routes Dosage Strengths Brand Names Manufacturer Forms Oral Capsules 5 mg Oxycodone Hydrochloride and **Tylox®** (C-II; with sodium Ortho-McNeil Acetaminophen 500 mg* metabisulfite) Solution 5 mg/5 mL Oxycodone
* Available generically.

Propoxyphene Hydrochloride and Acetaminophen

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Tablets 65 mg Propoxyphene Hydrochloride and Acetaminophen 650 mg* Tablets, film- 65 mg Propoxyphene Hydrochloride and **Wygesic®** (C- Leitner coated Acetaminophen 650 mg* IV; scored)

* Available generically.

Other Acetaminophen Combinations

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Capsules 325 mg with Butalbital 50 mg and Caffeine 40 mg* 325 mg with Butalbital 50 mg, **Fioricet® with Codeine** (C-III; with Novartis Caffeine 40 mg, and Codeine benzyl alcohol and parabens) Phosphate 30 mg 325 mg with Butalbital 50 mg and **Esgic®** Forest Caffeine Anhydrous 40 mg* 325 mg with Dichloralphenazone **Duradrin®** Barr, Duramed 100 mg and Isometheptene Mucate 65 mg* **I.D.A.®** Teva **Midrin®** Amarin 500 mg with Caffeine 65 mg **Excedrin® Aspirin-Free Caplets®** Bristol-Myers (with parabens, povidone, and propylene glycol) **Excedrin® Aspirin-Free Geltabs®**

Sumatriptan, Sumatriptan Succinate

Introduction

$C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$

• Sumatriptan is a selective agonist of vascular serotonin (5-hydroxytryptamine; 5-HT) type 1-like receptors.[1, 2, 3, 4, 5, 6, 7, 8, 223, 224, 268]

Uses

• Vascular Headaches

Sumatriptan is used orally, by subcutaneous injection, or intranasally for the acute management of attacks of migraine with aura (also called classic migraine) or migraine without aura (also called common migraine) and by subcutaneous injection for the acute management of cluster headache episodes.[1, 2, 3, 6, 7, 8, 9, 10, 13, 48, 49, 75, 80, 145, 148, 183, 184, 195, 214, 217, 225, 249] Sumatriptan should be used only in patients in whom a clear diagnosis of migraine or cluster headache has been established.[1, 148, 198, 236, 237] The manufacturer and some clinicians state that the drug is *not* to be used for the management of hemiplegic or basilar migraine or for *prophylaxis* of migraine or cluster headache.[1, 7, 114, 158] In patients with a history of migraine or cluster headache who present with atypical symptoms (e.g., ataxia, vertigo, tinnitus, mental status changes, visual field cuts/ blindness, paresthesia, hemiparesis), care should be taken to exclude other potentially serious neurologic conditions (e.g., cerebrovascular accident, subarachnoid hemorrhage) before initiation of sumatriptan therapy.[1, 61, 148, 236, 237] (See Cautions: Precautions and Contraindications.)

General Principles in Migraine Therapy

Drug therapy in the management of migraine headache must be individualized and adjusted based on the severity and frequency of attacks, response to therapy (single or multiple drugs), and tolerance to drug-induced adverse effects.[244, 245, 246, 247, 248, 267, 268, 269] Important considerations in the choice of drug therapy include the wide range in severity of the attacks, considerable interindividual variation in response and tolerance, toxic potentials of the drugs, presence of concomitant illness (e.g., cardiovascular disease, uncontrolled hypertension) or pregnancy, potential tolerance to the therapeutic effects of the drugs, the potential for abuse and misuse of the drugs, and cost.[244, 245, 246, 247, 248, 268, 269] Decisions regarding drug therapy in the management of migraine headache should be weighed carefully (e.g., do the headaches threaten to disrupt the patient's normal functioning), particularly when potentially toxic, habituating, and/or potent drugs are considered.[237, 244] Although the benefit of therapy may principally be pain relief, the long-term goals of therapy are to prevent or reduce the frequency and severity of attacks, reduce the disability associated with migraine headaches, improve quality of life, avoid escalation of antimigraine drug therapy, and educate and enable patients to manage their illness.[269] Management also should include appropriate nondrug therapy such as lifestyle modification, avoidance of precipitating factors, and behavioral and/or psychologic therapy.[237, 246, 247, 251, 269] Although the pathogenesis of migraine headache has not been fully elucidated (see Pharmacology), it is known that avoidance of certain triggering factors such as alcohol (e.g., red wine), certain foods or food additives (e.g., chocolate, certain cheeses, monosodium glutamate, nitrates), irregular eating habits, irregular sleep, and acute changes in stress level as well as proper management of other factors such as travel across time zones, high-altitude barometric pressure changes, and association with the menstrual cycle may be useful in the management of migraine attacks.[246, 247, 251, 267] The possible presence of other types of headaches (e.g., tension-type, cluster) should be evaluated.[237, 244, 246, 247, 267]

Although migraine headache is common (about 15-18% of women and 6% of men in the general population suffer migraine attacks), the condition is underrecognized and undertreated probably because of the lack of biologic markers to confirm the diagnosis.[237, 244, 245, 246, 251] About two-thirds of patients with migraine headache experience infrequent attacks (e.g., 1 or 2 per year), with the remainder experiencing one or more migraine attacks each month.[245, 246] Over 80% of migraine sufferers experience some degree of headache-associated disability.[244] For a diagnosis of migraine without aura (also called common migraine) or with aura (also called classic migraine), the criteria established by the International Headache Society (IHS) usually are used.[198, 236, 237, 244, 246, 251, 267] According to IHS, migraine without aura is an idiopathic, recurring headache disorder manifested by untreated or unsuccessfully treated attacks lasting 4-72 hours and characterized by unilateral, pulsating headache of moderate to severe intensity that may disrupt routine physical activity and is associated with nausea, vomiting, photophobia, and/or phonophobia and worsens with movement;[198, 236, 237, 244, 267] some experts also consider osmophobia a diagnostic criterion.[244] Migraine with aura is characterized by the same manifestations as migraine without aura, but it also is accompanied before or during the attack by neurologic manifestations (e.g., visual disturbance) indicating focal cerebral cortical and/or brain stem dysfunction.[198, 244, 246, 247]

Acute Attacks. Because patients may experience a wide spectrum of severity in migraine attacks with variable effects on functioning, multiple appropriate therapies for attacks of differing severity generally are made available to the patient.[244] The goals of acute migraine therapy are as follows: provide rapid and consistent relief of migraine attacks without recurrence; restore the patient's ability to function; minimize the use of back-up and rescue medications (i.e., drugs used at home when other therapies fail); optimize self-care and reduce subsequent use of medical resources; be cost-effective for overall management; and relieve the headache while minimizing or avoiding adverse effects of therapy.[269] To meet these goals, some experts recommend use of selective 5-HT_1 receptor agonists, dihydroergotamine, or ergotamine in patients with moderate or severe migraine or in those with mild to moderate headaches that respond poorly to nonsteroidal anti-inflammatory agents (NSAIAs) or fixed-combination analgesics such as those containing aspirin, acetaminophen, and caffeine.[269] Failure to promptly use an effective treatment may increase pain, disability, and the impact of the headache.[269] Patients should be advised, however, that excessive use of some of these drugs (e.g., ergotamine [but not dihydroergotamine], opiates, selective 5-HT_1 analgesics [including fixed combinations containing butalbital, caffeine, or isometheptene]) may cause rebound headache.[244, 248, 251, 269] Medical attention (including hospitalization) may be necessary for detoxification from drug overuse or abuse.[237, 245] Because nausea is one of the most aversive and disabling symptoms of migraine attacks, selection of nonoral routes of administration and/or use of antiemetics is recommended in patients in whom nausea and/or vomiting are prominent early symptoms of migraine attacks.[269] Antiemetics should not be restricted to patients who are vomiting or likely to vomit.[269] In some patients, concomitant therapy with an antiemetic and an oral antimigraine drug may be appropriate.[269] In addition, some experts state that IV metoclopramide may be considered as monotherapy for relief of migraine pain.[269]

Some clinicians recommend that mild migraine headache (patient's normal activities are minimally disrupted; headache usually lasts for 4-8 hours and may be

accompanied by nausea) be treated with an NSAIA (e.g., aspirin, ibuprofen, indomethacin, naproxen sodium) or combined acetaminophen, aspirin, and caffeine.[237, 244, 246, 247, 248, 267, 269] In addition to these analgesics, an antiemetic (e.g., dimenhydrinate, metoclopramide, prochlorperazine), mild vasoconstrictor (e.g., isometheptene), or sedative-hypnotic may be beneficial.[237, 244, 246, 247, 248, 267, 269]

For the management of moderate migraine headache (patient's normal activities are moderately disrupted; headache may last for more than 4 hours and up to about 24 hours and may be accompanied by nausea and vomiting), many clinicians recommend an oral NSAIA either given alone or in fixed combination with acetaminophen, an opiate analgesic (e.g., codeine), a barbiturate (e.g., butalbital), and/or caffeine.[244, 246, 247, 248, 249, 250, 257, 267] However, because of the risk of dependency and misuse or abuse, some clinicians recommend that use of opiate analgesics and barbiturates be reserved for patients with infrequent migraine headaches, for those who do not respond to other drugs, and when the sedative effects of the drugs will not put the patient at risk and the abuse potential has been addressed.[237, 269] In addition, many clinicians state that moderate migraine headache can be treated with a 5-HT_1 selective (e.g., almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [given orally, subcutaneously, or intranasally], zolmitriptan) or nonselective (e.g., dihydroergotamine [given parenterally or intranasally], or possibly ergotamine [given alone or in fixed combination with caffeine and/or a barbiturate]) receptor agonist.[244, 246, 247, 248, 249, 250, 258, 259, 262, 263, 264, 267, 269] Parenteral dihydroergotamine or 5-HT_1 selective receptor agonists are particularly useful in patients with rapid onset of migraine, and parenteral and intranasal preparations of these drugs may be particularly useful in those unable to take oral drugs because of severe nausea and/or vomiting.[236, 237, 269] Many moderate headaches may respond to an NSAIA alone; combinations of an NSAIA or acetaminophen with an opiate or barbiturate may be useful for attacks not responding to initial therapy or if vasoconstrictors are not tolerated.[244, 246, 247, 248, 249, 250, 269] Although the role of ergotamine has been questioned (e.g., because of toxicity profile [including severe nausea and vomiting], rebound effect),[244, 248, 251, 256] some patients continue to find the drug useful, particularly when combined with an antiemetic.[236, 237, 244, 267]

For the initial management of severe migraine headache (patient's normal activities are severely disrupted; headache generally lasts for longer than 12 hours and usually is accompanied by nausea, and vomiting occasionally may occur), many clinicians recommend dihydroergotamine (given parenterally or intranasally) or a 5-HT_1 selective receptor agonist, including almotriptan (given orally), frovatriptan (given orally), naratriptan (given orally), rizatriptan (given orally), zolmitriptan (given orally), or sumatriptan (given orally, subcutaneously, or intranasally).[237, 244, 248, 262, 264, 267, 269] Alternatively, a phenothiazine (e.g., chlorpromazine given IM, IV, or rectally) may be used; if pain is not relieved, a parenteral NSAIA (e.g., ketorolac given IM) or a corticosteroid (e.g., dexamethasone given IV) may be considered.[244, 247] *Self-administration* of rescue medications (e.g., butorphanol nasal solution, parenteral opiates) in a home setting also should be considered for patients with severe migraine attacks that do not respond adequately to other treatments[269] once the drugs' abuse potential has been addressed.[237, 244, 248, 258, 259, 260, 261, 269] Although rescue medications often do not completely eliminate pain and return patients to normal functioning, they permit the patient to achieve relief without the discomfort and expense of an office or emergency department visit.[269]

For the management of ultra-severe migraine attacks, including status migrainosus (patient's normal activities are severely disrupted for more than 72 hours) that are accompanied by vomiting, it is recommended that patients be rehydrated initially, which should be followed by administration of dihydroergotamine (given IV every 8 hours for 24 hours), and each dose should be preceded by a dose of metoclopramide to prevent nausea.[244, 247, 269] Some clinicians state, however, that IV dihydroergotamine should be reserved for patients who do not respond to any other drug therapy, including 5-HT_1 selective receptor agonists.[237] Alternatively, for ultra-severe migraine attacks, an IV phenothiazine (e.g., chlorpromazine, prochlorperazine) may be given alone or in combination with a parenteral corticosteroid (e.g., dexamethasone, methylprednisolone) and/or an opiate agonist (e.g., meperidine).[244, 247, 269] Parenteral opiate-agonist therapy generally is considered a last resort because of the risks of dependence, tolerance, and associated adverse effects.[237, 244, 246, 247, 248]

Prophylaxis of Chronic Attacks. Previously accepted recommendations for prophylaxis of chronic migraine attacks principally focused on patients who had 2 or more attacks per month.[268] Such recommendations have been described by some experts as being arbitrary and as failing to account for individual patient needs or other migraine characteristics.[268] Therefore, prophylactic therapy currently can be considered in patients with recurring migraine attacks when, in the opinion of the patient and despite acute therapy, the attacks substantially interfere with daily routines; in patients in whom the frequency of migraine attacks and resultant reliance on acute therapy would increase the potential for drug-induced (rebound) headache; in patients in whom acute therapy is ineffective, contraindicated, or not tolerated; in patients who prefer prophylactic therapy; and in those with uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction (to prevent neurologic damage).[268] The goals of prophylactic therapy are to decrease the frequency, severity, and duration of migraine attacks and the disability associated with such attacks; improve responsiveness of acute attacks to therapy; and improve patient functioning.[268] For prevention of migraine headache, a β-adrenergic blocking agent (e.g., atenolol, metoprolol, nadolol, propranolol, timolol), calcium-channel blocking agent (e.g., verapamil), tricyclic antidepressant (e.g., amitriptyline), anticonvulsant (e.g., valproate sodium), high-dose riboflavin (e.g., 400 mg daily), or NSAIA (e.g., naproxen sodium) may be used.[244, 245, 246, 247, 248, 251, 265, 266, 267 268] However, analysis of clinical studies in which these agents were used for prophylaxis of chronic migraine attacks has shown that efficacy and safety of individual agents, even within the same class of drugs, may exhibit substantial interpatient variation.[268]

Although most studies of drugs used for prophylaxis of migraine attacks are limited by poor study design and/or interpretation of study findings, analysis of these studies by the US Headache Consortium suggests that drugs with medium to high efficacy, good strength of evidence, and mild to moderate adverse effects include amitriptyline, divalproex sodium, propranolol, and timolol.[268] Comparative studies have demonstrated few clinically important differences in efficacy among these agents.[268] Agents with lower efficacy or limited strength of clinical evidence, and mild to moderate adverse effects include aspirin (alone), atenolol, fenoprofen, flurbiprofen, fluoxetine, gabapentin, guanfacine, ketoprofen, magnesium, mefenamic acid, metoprolol, nadolol, naproxen/naproxen sodium, nimodipine, riboflavin, and verapamil.[268] While clinical efficacy has not been established in controlled studies for

bupropion, cyproheptadine, diltiazem, doxepin, fluvoxamine, ibuprofen, imipramine, mirtazepine, nortriptyline, paroxetine, protriptyline, sertraline, tiagabine, topiramate, trazodone, or venlafaxine, experts consider these agents efficacious based on consensus and clinical experience.[268] Experts consider phenelzine to be efficacious based on consensus and clinical experience, but the drug has adverse effects that are of concern to some experts.[268] Similarly, methysergide has medium to high efficacy for prophylaxis of migraine attacks, but its usefulness is limited by reports of retroperitoneal and retropleural fibrosis associated with long-term (principally uninterrupted) therapy.[268] (See Cautions: Fibrosis and Fibrotic Complications, in Methysergide Maleate 12:16.) Evidence from clinical studies indicate that efficacy of agents such as acebutolol, carbamazepine, clomipramine, clonazepam, clonidine, indomethacin, lamotrigine, nabumetone, nicardipine, nifedipine, and pindolol is comparable to that of placebo for prophylaxis of migraine attacks in patients with chronic migraine.[268]

Experts from the US Headache Consortium currently recommend that the choice of an initial agent for prophylaxis of migraine attacks be individualized, taking into account concomitant illness (e.g., stroke, myocardial infarction, Raynaud's syndrome, seizure disorder, affective or anxiety disorders).[268] Such experts recommend use of drugs that are effective for both the concomitant illness and migraine prophylaxis whenever possible.[268]

Some clinicians recommend that drug therapy for migraine prophylaxis be initiated as monotherapy at a low dosage and then titrated upward as tolerated to a maximum effective dosage; such therapy should be given for several months and then withdrawn slowly to prevent rebound headaches.[244, 245, 246, 247, 268] If initial drug therapy is not effective, a combination of drugs may be used.[244, 268]

Selection of an agent for prophylaxis of migraine attacks in women who are or may become pregnant should take into account the teratogenic potential of such agents.[268] If drug therapy for migraine prophylaxis is absolutely necessary, some experts state that the prophylactic agent with the lowest risk of adverse effects to the fetus should be used.[268]

Use of Sumatriptan in Migraine

Sumatriptan provides rapid relief of migraine headache and generally is well tolerated when appropriate precautions regarding patient selection are employed.[1, 13, 148, 217, 225, 236, 237] (See Cautions: Precautions and Contraindications.) The drug also relieves manifestations of migraine other than headache (including nausea, vomiting, photophobia, and phonophobia), decreases the need for supplemental analgesic therapy, and improves functional ability.[1, 2, 8, 9, 13, 56, 84, 92, 93, 108, 148, 162, 171, 173, 180, 190, 225, 226] Few comparative studies evaluating the efficacy and safety of sumatriptan relative to other antimigraine therapies have been performed to date.[4, 13, 236] However, available evidence suggests that sumatriptan is at least as effective as current therapies for migraine (e.g., ergot alkaloids, oral analgesics) and generally provides more rapid headache relief and return to normal functioning than these therapies but may be associated more frequently with headache recurrence.[3, 13, 84, 124, 167, 226, 236, 237] Although cost considerations and concerns about the potential for headache recurrence may favor the use of other antimigraine agents (e.g., dihydroergotamine) over subcutaneous sumatriptan, effective self-management of migraine through patient self-administration of sumatriptan may be cost-effective if associated with a

reduced need for hospital visits.[3, 211, 212, 213] While clinical studies directly comparing subcutaneous versus oral therapy with sumatriptan in patients with migraine have not been performed,[236, 237] response to oral sumatriptan therapy occurs later and generally is somewhat less than that with subcutaneous therapy.[3, 178, 236, 237] Therefore, subcutaneous therapy with the drug may be particularly advantageous in patients with severe migraine headache in whom the most rapid onset of action is desirable and/or in those who have appreciable nausea and vomiting associated with migraine; oral sumatriptan therapy should be less costly and may be useful in patients who are unable to tolerate subcutaneous sumatriptan, unwilling or unable to self-administer the injection, or who have relatively less severe migraine symptoms.[123, 171, 178, 190, 195, 214, 236, 237]

The efficacy of sumatriptan in alleviating established migraine attacks does not appear to be influenced by type of migraine (i.e., with or without aura), duration of the attack, timing of the attack (e.g., early morning, menstruation-associated), concomitant use of non-ergot-alkaloid drugs for migraine prophylaxis (e.g., β-blockers, calcium-channel blockers, tricyclic antidepressants), or by patient gender or age.[1, 2, 8, 13, 50, 55, 58, 92, 93, 108, 124, 142, 145, 148, 158, 180, 217, 214, 225] Unlike other antimigraine drugs (e.g., ergotamine), sumatriptan has been effective even when given late in the attack.[8, 59, 176] However, subsequent doses of sumatriptan in patients not responding adequately to an initial dose generally have not provided additional benefit.[8, 145, 237]

Most controlled clinical studies of sumatriptan therapy involved patients who had migraine with aura or migraine without aura[8, 9, 10, 13, 15, 84, 92, 93, 108, 111, 123, 124, 142, 145, 162, 171, 173, 189, 190, 191, 217, 226] as defined by criteria established by the Headache Classification Committee of the International Headache Society (IHS).[198] However, while a clear diagnosis of migraine is recommended before initiation of sumatriptan therapy,[1, 148, 198, 236, 237] some evidence suggests that response to sumatriptan may be similar in patients not meeting strict IHS criteria for migraine.[181, 237] The efficacy of therapy for migraine in controlled studies generally was evaluated in terms of a reduction in headache severity as rated by the patient (i.e., a reduction in pain from severe or moderately severe to mild or absent using a 4-point scale).[1, 13, 148] In placebo-controlled clinical studies, approximately 70-88% of patients receiving a single 6-mg subcutaneous dose of sumatriptan attained relief of migraine headache within 1-2 hours compared with 18-39% of placebo recipients; at 2 hours, 48-65% of sumatriptan-treated patients were pain free.[1, 8, 9, 13, 37, 56, 93, 162, 171, 214, 225] Relief of migraine headache generally begins as early as 10 minutes following subcutaneous administration of sumatriptan and is maximal at 2 hours.[1, 13] Smaller doses (less than 6 mg) of sumatriptan also may be effective in relieving migraine, although the proportion of patients obtaining adequate relief is reduced and the time to obtain relief is greater.[1, 3, 57, 72] Subcutaneous doses exceeding 6 mg (e.g., 8 mg) do not appear to provide additional therapeutic benefit and are associated with a greater incidence of adverse effects.[1, 3, 57, 72] The efficacy of sumatriptan in patients receiving the drug subcutaneously generally is similar whether the injection is given manually or with an autoinjection device, although the incidence of local injection-site reactions appears to be lower when the autoinjection device is used.[1, 13, 93, 142, 158]

Onset of relief of migraine symptoms with oral sumatriptan therapy is slower than that with subcutaneous administration of the drug, generally occurring 0.5-3 hours

after single oral doses of 25-100 mg;[13, 92, 148, 162, 178, 191, 217] maximum pain relief is attained within 3-6 hours.[13, 148, 178, 191, 217] In clinical trials, 50-73% of patients receiving sumatriptan in single oral doses of 25-300 mg obtained relief of headache pain (defined as no pain or only mild pain) within 2 hours compared with 10-33% of patients receiving placebo; 65-78% of patients receiving sumatriptan reported relief of pain at 4 hours.[13, 108, 148, 190] The proportion of patients obtaining relief from single oral doses of sumatriptan appears to be greater with doses of 50 or 100 mg than with 25 mg; however, doses of 100 mg do not appear to provide greater benefit than doses of 50 mg.[13, 92, 108, 148, 178, 180, 190]

Since migraine is a chronic, recurrent condition, successful therapy may require long-term, intermittent use of sumatriptan.[40, 82, 178] In several controlled studies of 6-24 months' duration in patients with migraine, intermittent sumatriptan has remained effective throughout subsequent attacks.[40, 173, 181, 191] Among patients receiving oral sumatriptan during 9 migraine attacks, approximately 14% of patients responded during all 9 migraine episodes, 24% responded during 8 of 9 attacks, and 62% responded during 7 of 9 attacks.[191] Among patients in a controlled study who were treated for 4 migraine attacks (3 with subcutaneous sumatriptan and one with placebo), 73% of patients responded to therapy during all 3 sumatriptan-treated attacks, 89% responded in at least 2 of 3 such attacks, and 93% responded in at least 1 of 3 such attacks; only 7% of patients receiving sumatriptan therapy did not respond at all.[56, 236] Data from long-term (1 year) uncontrolled studies suggest that oral sumatriptan was effective in 82-86% of patients and in 55% of all attacks treated.[40] Patients who received subcutaneous or oral sumatriptan treated a median of 18 and 22 attacks per year, respectively, and used a mean of 1.4 injections or 1.9 tablets per attack.[40, 82] The mean number of doses used was similar in patients with frequent (more than 30) and infrequent (less than 10) attacks.[82]

Data from comparative trials suggest that sumatriptan is at least as effective as current antimigraine therapies (e.g., ergot alkaloids, oral analgesics) and generally provides more rapid headache relief than these therapies.[84, 124, 167, 226] In a double-blind, controlled study in patients with migraine, subcutaneous therapy with sumatriptan was associated with headache relief and improvement in functional ability in a greater proportion of patients than was dihydroergotamine at 1 hour (78 versus 57%, respectively) and 2 hours (85 versus 73%, respectively) following the dose; headache relief and functional ability at 3 and 4 hours were similar with both drugs.[167, 226] However, the rate of headache recurrence within 24 hours after treatment was approximately 2.5 times as great with sumatriptan as with dihydroergotamine (45 versus 18%, respectively).[226] In another placebo-controlled, comparative study, 66% of patients receiving oral sumatriptan (100 mg) obtained pain relief (reduction in headache intensity from severe or moderate to mild or none) at 2 hours compared with 48% of patients receiving the combination of ergotamine tartrate 2 mg and caffeine 200 mg (Cafergot®).[124] The onset of headache relief was more rapid with sumatriptan therapy, although more patients reported recurrence of migraine within 48 hours with sumatriptan; the incidence of adverse effects with both therapies was similar.[124] In another controlled study in patients who treated up to 3 migraine attacks during a 3-month period either with oral sumatriptan (100 mg) or with oral aspirin (900 mg) and metoclopramide hydrochloride (10 mg), the proportion of patients who had pain relief at 2 hours during the initial attack (the primary end point) with sumatriptan versus aspirin and metoclopramide was similar (56 versus 45%, respectively), although

sumatriptan was more effective than aspirin and metoclopramide during attack 2 (58 versus 36%, respectively, of patients with pain relief) and attack 3 (65 versus 34%, respectively, of patients with pain relief).[84] In addition, sumatriptan therapy was associated with a reduced need for supplemental analgesics and greater incidence of improvement in functional ability than aspirin and metoclopramide therapy.[84] Relief of nausea, vomiting, photophobia, and phonophobia was similar for both therapies, while the incidence of adverse effects, which usually were mild to moderate in intensity and transient, was higher with sumatriptan.[84]

Recurrence of migraine within 24 hours after successful treatment of the initial migraine attack occurs in up to about 60% or up to about 40% of patients receiving initial therapy with subcutaneous or oral sumatriptan, respectively.[2, 8, 46, 47, 50, 59, 93, 162, 173, 181, 189, 214] The high rate of recurrent migraine with sumatriptan may be related to the short half-life of sumatriptan[2, 6, 13, 16, 47, 93, 173, 181, 189, 214, 236, 237] or the reversibility of the drug's binding to 5-HT receptors;[47, 59, 189, 236, 237] however, in some cases, apparent repeat attacks of migraine may have been the result of breakthrough of the suppressed but ongoing original attack.[47, 51, 82, 91, 176, 189] Recurrent migraine has been characterized as resolution followed by return of headache within the typical 4-72 hours of a migraine attack without recurrence of aura or other premigraine symptoms.[189, 236, 237] Recurrence of migraine appears to be more common with sumatriptan therapy than with ergotamine, dihydroergotamine, combined therapy with aspirin and metoclopramide, or placebo.[3, 13, 84, 124, 167, 226, 236, 237] The median time to headache recurrence has been reported to be approximately 9-13 hours in patients receiving sumatriptan subcutaneously and 14-24 hours in patients receiving the oral drug.[8, 40, 47, 84, 173, 181, 189] Data from a limited number of controlled studies and clinical experience in patients treated for 3-12 episodes of migraine with oral or subcutaneous sumatriptan indicate that the incidence of migraine recurrence decreases as the number of successfully treated migraine attacks increases.[173, 181, 214] An additional dose of oral sumatriptan appears to be more effective than placebo in treating recurrent migraine after successful treatment of the initial attack; 65-81% of patients receiving oral sumatriptan (100 mg) for the treatment of a recurrent headache following initial use of oral or subcutaneous sumatriptan experience relief of headache pain.[162, 173, 181] However, the benefit or safety of administering a second dose of subcutaneous or oral sumatriptan in patients who have not responded to an *initial* dose has not been demonstrated conclusively in controlled studies.[1, 6, 8, 9, 93, 176, 181, 236, 237]

While most patients with migraine respond to initial subcutaneous or oral doses of sumatriptan, some patients do not experience relief; exacerbation of migraine has been reported in a few patients.[9, 56, 82, 84, 148, 154, 171, 180, 181, 190, 191] Although administration of a second subcutaneous dose of sumatriptan generally does not provide relief of ongoing migraine headache in patients not responding to an initial subcutaneous dose for that attack,[1, 9, 48, 56, 174, 181] data from several studies in which multiple doses of subcutaneous or oral sumatriptan were administered over several episodes of migraine indicate that patients who fail to respond to therapy for one episode may respond to sumatriptan during subsequent episodes; only 5-7% of patients are consistent nonresponders.[56, 143, 173]

Data from several long-term (1-2 year) studies suggest that subcutaneous or oral therapy with sumatriptan does not alter the frequency of migraine attacks.[82, 114, 191]

However, some case reports and data from uncontrolled and/or postmarketing surveillance studies indicate an increased frequency of initial or recurrent migraine attacks in some patients taking sumatriptan.[40, 154, 172, 182, 184] In some patients with a history of frequent migraines or dependence on other antimigraine drugs, such as analgesics or ergot-alkaloid-containing compounds,[113, 140, 165, 170, 172] this increased frequency of migraine attacks has been associated with inappropriate use/misuse of the drug.[63, 64, 165, 172] (See Cautions: Precautions and Contraindications.) The contribution of sumatriptan to the increased frequency of migraine headaches in such patients has not been established.[64, 114, 165, 170, 172]

Intranasal administration of sumatriptan is more effective than placebo in relieving migraine headache.[13, 123, 243, 268] In double-blind, controlled studies in patients with migraine, headache relief (defined as reduction in pain from moderate or severe to mild or none) at 2 hours following the dose occurred in approximately 55-75% of patients receiving intranasal sumatriptan (20 mg) versus about 25-36% of those receiving placebo; associated nausea, vomiting, photophobia, and functional disability also were improved in sumatriptan-treated patients.[13, 123, 243, 249, 270, 271] Smaller doses (5 or 10 mg) also may be effective, although in several studies the proportion of patients obtaining relief was reduced.[249] Although sumatriptan has been given IV[#] in patients with acute migraine attacks, this route of administration has been associated with a high incidence of adverse effects (probably because of the rapid increase in plasma drug concentrations associated with such administration);[13, 90, 239] the manufacturer and most clinicians state that the drug should *not* be given IV.[1, 13, 236, 237] (See Cautions: Precautions and Contraindications.)

The manufacturer states that sumatriptan is not to be used for prophylaxis of migraine headache[#];[1, 148] and prophylactic use of the drug following successful treatment of an initial attack has produced equivocal results.[40, 173, 189] In one study, routine addition of a second oral dose of sumatriptan (100 mg) 2 hours after successful treatment of the initial migraine episode did not influence the frequency or time to recurrence of subsequent attacks.[173] However, in another study, routine administration of a single oral dose of sumatriptan (100 mg) 4 hours after successful treatment with a subcutaneous dose of the drug (6 mg) delayed recurrence of the migraine attack.[189]

Cluster Headache

Sumatriptan also is used subcutaneously for the acute management of cluster headache episodes; *oral* therapy with sumatriptan is unlikely to be beneficial because of its slower onset of action and is *not* indicated in the management of cluster headache.[1, 2, 49, 75, 183, 184, 185, 210, 214] Cluster headache occurs principally in older men and is characterized by brief, unilateral, extremely intense headaches occurring up to 8 times daily and generally accompanied by ipsilateral manifestations of autonomic dysfunction, such as lacrimation, conjunctival injection, and rhinorrhea.[1, 2, 49, 75, 183, 184, 210] Management of cluster headaches is difficult since the onset of action of many therapies often is delayed beyond the duration of the attack.[2, 13, 49, 61, 75, 199, 200, 201, 205, 210, 217] Inhalation of 100% oxygen, rectal or sublingual ergotamine, or parenteral dihydroergotamine typically has been used effectively to treat cluster headache; intranasal administration of lidocaine, cocaine, or capsaicin also has been used with some success in treating acute attacks.[2, 13, 49, 75, 199, 200, 201, 205, 210, 217] Oral agents (e.g., ergot alkaloids, analgesics, oral sumatriptan) generally have not been effective in

treating these brief headaches, as the onset of action of these drugs is too slow.[49, 61, 75, 205, 210, 217]

While comparative studies with oxygen and/or oral analgesic therapy have not been performed, subcutaneous sumatriptan may be particularly useful in patients with cluster headache because of its ease of administration compared with oxygen and its rapid onset of action compared with oral analgesics.[40, 61, 75, 183, 205, 217] In 2 placebo-controlled studies in which patients were treated for up to 3 consecutive cluster headache attacks, headache improvement (as indicated by a reduction in headache pain to mild or no pain) occurred within 15 minutes in about 75% of patients receiving subcutaneous sumatriptan (6 mg) compared with 26-35% of patients receiving placebo.[1, 49, 75] Amelioration of autonomic manifestations associated with cluster headache, such as nasal congestion, rhinorrhea, lacrimation, miosis, ptosis, photophobia, and periorbital edema, also has been reported with subcutaneous sumatriptan therapy.[13, 49, 75, 184] In the 2 placebo-controlled studies, conjunctival injection persisted in 36-38 or 60-74% of patients 15 minutes after receiving subcutaneous sumatriptan or placebo, respectively.[49, 75] Approximately 14% of patients receiving subcutaneous sumatriptan and 38-49% of patients receiving placebo in these studies required supplemental therapy with oxygen 15 minutes after administration of the study drug.[49, 75] Use of higher subcutaneous doses of sumatriptan (12 mg) does not appear to increase the response rate in patients with cluster headache;[1, 13, 75, 214] in fact, lower subcutaneous doses (3 mg) reportedly may be effective in the management of acute cluster headache episodes.[13, 210]

Although an increased frequency of cluster headache attacks has been reported in some patients receiving sumatriptan in uncontrolled studies,[13, 184] such increases in attack frequency generally have been transient (lasting up to a few weeks) and may have been related in part to withdrawal of prophylactic antimigraine medication prior to initiation of sumatriptan therapy.[13, 214] Limited data based on long-term (e.g., up to 3 months) experience with the drug in patients with cluster headache suggest that tolerance to the effects of sumatriptan does not develop with such use; at least one patient used a total of 480 injections (6 mg each) of the drug over an 11-month period with reportedly consistent efficacy.[13, 209] Sumatriptan therapy is not associated with an increase in early recurrence of cluster headache and has little effect on the incidence of subsequent episodes (i.e., those occurring from 2-24 hours after the first cluster headache).[1, 13, 183, 209, 214, 236] In a controlled study, prophylactic[#] administration of oral sumatriptan (100 mg 3 times daily for 7 days) did not reduce the number, severity, or duration of subsequent cluster headache attacks in patients who responded successfully to a single 6-mg subcutaneous dose of the drug for the first cluster attack of a series.[13, 185] Patients with a history of more than 2 cluster headaches per day may require prophylactic therapy in addition to the use of sumatriptan for the management of acute breakthrough cluster attacks, as 12 mg (two 6-mg injections) is the maximum recommended daily subcutaneous dose of sumatriptan.[1, 185, 205]

Sumatriptan has been used with some success in a limited number of patients with chronic paroxysmal hemicrania[#], a rare, variant form of cluster headache.[13, 210, 229, 230] Sumatriptan also has been used in at least one patient with short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing (SUNCT)[#], a possible variant of cluster headache characterized by brief (30-60 seconds), recurrent episodes of intense pain.[13, 202, 231, 236] In this patient, sumatriptan therapy was associated with

relief of pain and limited relief of accompanying manifestations (e.g., conjunctival injection, Horner's syndrome, lacrimation).[202, 231]

• Other Types of Headache

Sumatriptan has been used subcutaneously or orally in a limited number of patients with chronic tension-type headache[#],[13, 80, 134] acute post-traumatic (e.g., post-dural puncture) headache[#],[13, 54, 203, 227, 228] drug-induced headache[#] (e.g., in combination with amitriptyline and dexamethasone),[232] or high-altitude headache[#].[147, 204] In a limited number of patients receiving sumatriptan subcutaneously for the treatment of postdural puncture headache[#], a complication of spinal anesthesia and unintentional dural puncture during attempted epidural anesthesia, the onset of pain relief and the potential for headache recurrence was similar to that reported in patients with migraine.[54, 203, 227] Additional study and experience are required to elucidate the safety and efficacy of sumatriptan therapy in these conditions.[13, 54, 134, 147, 203, 204, 227, 228, 229, 230]

• Other Uses

Sumatriptan has been used in a few patients with intractable cyclic vomiting[#], which appears to share some common pathogenesis to migraine,[206] and in the management of adverse events (e.g., perioperative migraine, severe anesthesia-associated vomiting) associated with general anesthesia[#] in patients with a history of migraine.[13, 233] The safety and efficacy of sumatriptan therapy in these conditions require further evaluation.[13, 206, 233]

Dosage and Administration

• Administration

Sumatriptan succinate is administered orally.[1, 12, 148] The drug also can be administered parenterally but *only* by subcutaneous injection; subcutaneous injection of sumatriptan succinate preferably should be made into the lateral aspect of the thigh or deltoid.[1, 12, 148] Sumatriptan also can be administered intranasally.[249] *Sumatriptan should not be given IV because of the potential risk of inducing coronary vasospasm.*[1] (See Cautions: Precautions and Contraindications.)

An autoinjection device is available for use with prefilled syringes labeled as containing 4 or 6 mg of sumatriptan to facilitate *self-administration* of the drug by subcutaneous injection by patients for whom these doses are deemed appropriate.[1, 273] Because the needles that accompany this device penetrate approximately 5-6 mm (1/4 inch), patients should be directed to use injection sites with adequate skin and subcutaneous thickness to accommodate the length of the needle.[1, 273] Care should be taken to avoid IM or IV administration.[1, 273] Patients should be given adequate instructions by their clinician, as well as the written instructions supplied with the autoinjection device, before they self-administer sumatriptan injection for the first time.[1, 171, 273]

The patient information provided by the manufacturer should be consulted for directions on intranasal administration of sumatriptan.[268]

Consideration should be given to administering the *initial* dose of sumatriptan under medical supervision in patients in whom unrecognized cardiovascular disease may be likely (e.g., postmenopausal women, men older than 40 years of age, smokers, and

patients with hypertension, hypercholesterolemia, obesity, diabetes mellitus, or other coronary artery disease risk factors) but who have had a satisfactory cardiovascular evaluation.[1, 29, 34, 37, 94, 148, 249] Although some clinicians differ, the manufacturer states that electrocardiographic evaluation during the interval immediately after administration of sumatriptan should be considered in patients with these risk factors since cardiac ischemia can occur in the absence of symptoms.[1, 148, 249]

Although sumatriptan generally is effective at whatever stage of a migraine attack it is administered, it is advisable to initiate therapy with the drug as soon as possible after the onset of an attack so that the patient may experience maximum relief.[50, 92, 108, 124, 148, 180, 237]

• Dosage

Dosage of sumatriptan succinate is expressed in terms of sumatriptan.[1, 148]

Subcutaneous Dosage

For the symptomatic treatment of acute attacks of migraine with aura (also called classic migraine) or migraine without aura (also called common migraine) or cluster headache, the maximum single adult subcutaneous dose of sumatriptan recommended by the manufacturer is 6 mg given as a single injection.[1, 72, 111] Smaller subcutaneous doses of the drug may also prove effective for the symptomatic treatment of migraine, although the proportion of patients obtaining adequate relief is decreased and the time to attain that relief is greater.[1, 111] In patients in whom dose-limiting adverse effects occur following a single 6-mg dose of sumatriptan, lower doses (e.g., 4 mg) of the drug may be given.[1, 273] In patients receiving doses other than 4 or 6 mg, only the single-dose vials containing 6 mg/0.5 mL should be used to provide the desired dose.[1, 273]

If the patient fails to respond to an initial 6-mg subcutaneous dose of sumatriptan for the symptomatic treatment of migraine, additional subcutaneous or oral doses are unlikely to provide benefit.[1, 2, 3, 6, 7, 8, 9, 174, 176, 181, 236, 237] However, following successful treatment with an initial subcutaneous dose, a second 6-mg subcutaneous dose or additional oral doses of sumatriptan (see following section on oral dosage) may be given if manifestations of migraine recur.[1, 148, 236] The manufacturer states that the maximum subcutaneous dosage of sumatriptan to be administered in any 24-hour period is 12 mg (i.e., two 6-mg injections); doses should be given at least 1 hour apart.[1, 184, 185]

Oral Dosage

For the management of acute migraine pain and associated symptoms, single oral sumatriptan doses of 25, 50, or 100 mg were effective in adults in clinical studies.[148] Available evidence suggests that oral doses of 50 or 100 mg may provide greater benefit than 25 mg, but doses of 100 mg do not provide substantially greater relief than doses of 50 mg.[148] Because individuals may vary in their response to oral sumatriptan, dosage selection should be individualized, weighing the possible benefit of higher doses with the potential for an increased risk of adverse effects.[148] The maximum recommended single oral dose is 100 mg.[148] If a satisfactory response has not been obtained within 2 hours following the initial dose, a second oral dose of up to 100 mg may be given.[148] If headache recurs, additional oral doses of sumatriptan may be taken at intervals of not less than 2 hours up to a maximum oral dosage of 200 mg daily.[148, 173] If headache recurs following an initial *subcutaneous* dose of

sumatriptan, additional *oral* doses may be given at intervals of not less than 2 hours (up to a maximum *oral* dosage of 100 mg daily).[148, 162, 181, 236] Oral sumatriptan dosages of up to 300 mg daily have been given, administered either as a single 300-mg dose or as 3 single doses of 100 mg each given at intervals of not less than 2 hours.[180] However, while these doses generally have been well tolerated, there is no evidence that such doses afford greater relief than the recommended dose, and these high doses are associated with an increased incidence of adverse effects.[180, 237]

Intranasal Dosage

For the management of acute migraine pain and associated symptoms, single intranasal sumatriptan doses of 5, 10, or 20 mg were effective in adults in clinical studies, although the 20-mg dose was effective in a greater proportion of patients.[249] Individuals vary in their response to intranasal sumatriptan, and the choice of dose in this range should be individualized, weighing the possible benefit of the 20-mg dose with the potential for an increased risk of adverse effects.[249] A 5- or 20-mg dose is administered into one nostril using the corresponding single-use nasal spray; if a 10-mg dose is used, it is administered by spraying a 5-mg dose into each nostril.[249] Single doses exceeding 20 mg do not provide greater benefit.[249]

If the headache returns, the dose of intranasal sumatriptan may be repeated once after 2 hours, not to exceed 40 mg daily.[249] The safety of treating an average of more than 4 headaches per 30-day period has not been established.[249]

• Dosage in Renal and Hepatic Impairment

Although the effect of renal impairment on the pharmacokinetics of sumatriptan has not been evaluated, little clinical effect would be expected since the drug is largely inactivated metabolically.[1, 13, 14, 146, 148]

The liver plays an important role in the presystemic clearance of orally administered sumatriptan.[1, 148] Accordingly, the bioavailability of sumatriptan following oral administration may be increased markedly in patients with liver disease.[1, 148] In a few patients with hepatic impairment who received a single 50-mg oral dose of sumatriptan, the area under the plasma concentration-time curve (AUC) and peak drug concentration increased by 70% and the peak concentration occurred 40 minutes earlier compared with these values in healthy individuals.[1, 13, 44, 148, 236] If *oral* sumatriptan therapy is considered in patients with hepatic impairment, the manufacturer states that the maximum single dose generally should not exceed 50 mg.[148]

Cautions

Sumatriptan generally is well tolerated when given in recommended dosage.[2, 3, 6, 13, 148, 217] Most adverse effects associated with sumatriptan are well defined, transient, and mild to moderate in intensity,[16, 75, 82, 108, 143, 158, 161, 171, 173, 174, 178, 180, 181, 183] although serious cardiac events (coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation) have been reported rarely in patients receiving the drug subcutaneously or orally.[1, 2, 13, 16, 23, 29, 31, 48, 93, 94, 143, 148, 161, 171, 178, 183, 194, 249] Adverse effects associated with the drug usually occur within 1 hour after subcutaneous or oral administration of sumatriptan and generally resolve within 10-30 minutes (subcutaneous) or 1 hour (oral).[2, 8, 9, 13, 15, 16, 56, 72, 75, 78, 82, 94, 111, 143, 162, 174, 178, 214, 236] The incidence of adverse effects

associated with sumatriptan generally remains unchanged or decreases with repeated use of the drug.[108, 173, 178, 181, 183, 189] However, the incidence of adverse effects appears to increase with higher than recommended doses of the drug.[72, 111, 180] In addition, the overall incidence of adverse effects among patients receiving sumatriptan injection for the treatment of cluster headache is lower than that in patients being treated with the drug for migraine.[1]

The most frequently reported adverse effects associated with subcutaneous sumatriptan succinate therapy are injection site reaction (e.g., minor pain, edema, tingling at the site of injection, burning, transient erythema), tingling, dizziness or vertigo, and sensations of warmth or heat.[12] Common adverse effects reported in patients receiving oral sumatriptan for the treatment of migraine or cluster headache include malaise or fatigue, nausea or vomiting, dizziness or vertigo, tingling, and nasal discomfort.[49, 148, 178, 180, 185, 191] Since some adverse effects noted with sumatriptan therapy (e.g., nausea or gastric symptoms, tingling, photophobia, visual disturbances, headache, numbness, neck pain, drowsiness/sedation, asthenia, fatigue) also are symptoms associated with migraine attacks and/or the postdromal period, it may be difficult to distinguish the effects of underlying disease processes from drug-induced effects.[51, 61, 72, 82, 84, 87, 94, 108, 110, 111, 118, 143, 178, 190, 191, 220] The most frequently reported adverse effects associated with intranasal sumatriptan include disturbances of taste, nausea or vomiting, and disease of nasal cavity or sinuses.[12] For adverse effects reported with sumatriptan therapy in the Cautions section, a causal relationship to the drug has not always been established.[1, 24, 183, 189, 191] In addition, the incidence of adverse effects reported in clinical trials may not predict precisely the likelihood of encountering these effects under usual medical practice where patient characteristics and other factors differ from those prevailing in the trials.[1, 148, 249]

- **Local Effects**

Pooled data from controlled studies[178] indicate that the most frequently reported adverse effect associated with subcutaneous sumatriptan succinate therapy is injection site reaction, consisting of minor pain, edema, induration, swelling, contusions, subcutaneous bleeding, stinging or tingling at the site of injection, burning, and/or transient erythema.[1, 2, 3, 8, 13, 49, 55, 56, 58, 72, 75, 78, 93, 94, 111, 143, 171, 189, 220] Lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) has been reported in less than 0.1% of patients receiving the drug subcutaneously.[1] Injection site reactions occurred in 58.7% of patients receiving the drug subcutaneously in controlled trials;[1, 9] this effect occurred with less frequency in patients using an autoinjector to administer the drug.[2, 58, 93, 142, 143, 171, 174]

Nasal and/or throat irritation were reported in approximately 5% of patients receiving 5-, 10-, or 20-mg doses of intranasal sumatriptan on 1 or 2 occasions in controlled clinical studies.[249] Transient irritative symptoms (e.g., burning, numbness, paresthesia, discharge, pain or soreness) were reported to be severe in about 1% of patients receiving intranasal sumatriptan; these symptoms generally resolved in less than 2 hours.[249] Limited examination of the nose and throat did not reveal clinically noticeable injury in these patients.[249] In addition, an increased incidence of local irritation has not been observed in patients receiving intranasal sumatriptan repeatedly for up to 1 year.[249] However, epithelial hyperplasia (with and without keratinization) and squamous metaplasia were observed in the larynx of rats receiving inhaled sumatriptan daily for 1 month at dosages as low as one-half the maximum daily

human exposure (based on dose per surface area of nasal cavity).[249] In addition, evidence of epithelial hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis was observed in the respiratory and nasal mucosa in dogs administered various formulations of sumatriptan by intranasal instillation daily for up to 13 weeks, at exposure rates of 2-4 times the maximum daily human exposure (based on dose per surface area of nasal cavity).[249] The changes observed in both species are not considered to be signs of preneoplastic or neoplastic transformation.[249] Local effects on nasal and respiratory tissues after chronic, repeated intranasal administration of sumatriptan have not been studied in animals or humans.[249]

• Nervous System Effects

Atypical sensations are the most commonly reported adverse nervous system effects of sumatriptan, occurring in up to 42% of patients receiving sumatriptan in controlled trials.[1, 72, 148, 158, 183, 220] Atypical sensations include dysesthesia; sensations of warmth, heat, burning, cold, tingling or numbness; paresthesia; pressure sensation or feelings of heaviness or tightness; and/or strange feeling.[1, 148, 249] The incidence of these sensations varies, ranging from less than 0.1-14% of patients receiving sumatriptan.[1, 148, 249]

Although sumatriptan distributes poorly into the CNS, adverse CNS effects have been reported in patients receiving the drug.[6, 13, 14, 67, 87, 138, 146, 176] Dizziness/vertigo[1, 8, 9, 49, 55, 58, 72, 93, 143, 148, 162, 174, 181, 183, 185, 189, 220, 249] or drowsiness/sedation[1, 8, 9, 58, 143, 48, 181, 220] has been reported in up to 12%,[1] of patients receiving subcutaneous sumatriptan in clinical trials. In addition, agitation,[16, 148, 249] anxiety,[1, 9, 58, 143, 148, 249] drowsiness/sedation,[1, 8, 9, 58, 143, 148, 181, 220, 249] headache,[1, 72, 143, 171, 174, 185, 220] and malaise/fatigue[1, 8, 9, 49, 57, 58, 72, 75, 93, 143, 148, 183] have been reported in up to 3% of patients receiving sumatriptan in controlled trials.[1] Severe rebound migraine headache, which occurred upon withdrawal of sumatriptan therapy and persisted for a few days, has been reported in several patients inappropriately taking sumatriptan on a daily basis for headache prophylaxis.[64, 170, 237] Other adverse nervous system effects occurring in up to 1% of patients receiving sumatriptan therapy include aggressiveness,[148] apathy,[148, 249] bradylogia,[148] chills,[1, 249] cluster headache,[148] confusion,[1, 148, 249] depression,[1, 148, 153, 249] detachment,[148] difficulties in concentration,[1, 148 249]disturbance of smell,[1, 148, 249] drug abuse,[148] dysarthria,[1, 148, 249] dysesthesia,[1, 148] dysphasia,[1] dysphoria,[222] dystonia,[1, 148, 156] emotional disturbance,[249] euphoria,[148, 249] facial pain,[1, 148, 249] facial paralysis,[148] globus hystericus,[1] hallucinations,[148] heat sensitivity,[148] hyperesthesia,[1, 148] hysteria,[1, 148] incoordination,[148, 249] increased alertness,[148] increased intracranial pressure,[148] intoxication,[1, 249] lacrimation, [1, 148, 249] memory disturbance,[148, 249] monoplegia/diplegia,[1, 148, 249] motor dysfunction,[148] myoclonia,[1] neuralgia,[148] neurotic disorders,[148] panic disorder,[148] paralysis,[148] personality change,[148] phobia,[148] phonophobia/photophobia,[1, 148] psychomotor disorders,[148] radiculopathy,[148] relaxation,[1] restlessness[16] rigidity,[148] seizures,[1, 148] sensations of lightness,[1, 148, 161, 249] "serotonin agonist effect",[1] shivering,[1, 148, 249] sleep disturbance,[1, 148, 190, 249] stress, [148, 249] suicide,[148] syncope,[148, 249] transient hemiplegia,[1, 148] tremor,[1, 148, 249] twitching,[148] unsteadiness,[57] speech disturbance,[148] voice disturbance,[148, 249] and yawning.[1, 148]

• Cardiovascular Effects

The most common adverse cardiovascular effect associated with subcutaneous administration of sumatriptan is flushing,[1, 8, 9, 58, 75, 143, 148, 171, 181, 185, 189, 220] which has been reported in 6.6% of patients receiving the drug by this route in placebo-controlled trials.[1] Flushing has been reported infrequently in patients receiving the drug intranasally or orally.[148, 249] Chest discomfort/pain, pressure, or tightness[1, 3, 9, 16, 17, 27, 28, 29, 46, 55, 75, 94, 143, 144, 162, 171, 174, 181, 183, 184, 185, 189, 220, 249] occurred in 4.5% of patients receiving subcutaneous sumatriptan in controlled trials;[1, 173, 180, 181, 191] these adverse effects have been reported in up to 2% of patients receiving intranasal or oral sumatriptan.[148, 249] In patients experiencing chest pain while receiving subcutaneous sumatriptan therapy, onset of pain was within 1-60 minutes after injection of the drug, and the duration of chest pain was 2 minutes to 12 hours.[16, 17, 22, 56, 75, 162, 163] In some patients, chest pain was severe and accompanied by other manifestations such as paresthesia or numbness; nausea; syncope; flushing; anxiety; diaphoresis; pain radiating into shoulders, neck, or throat; dyspnea; palpitation; bronchospasm; decreases in heart rate and blood pressure; and fatigue.[16, 17, 21, 22, 148, 173, 181, 185] Several patients receiving subcutaneous sumatriptan in controlled trials experienced chest pain/pressure[17, 21, 25, 184, 189] and paresthesia[17, 21, 174, 181, 185] that was severe enough to necessitate discontinuance of the drug; upon rechallenge, some patients developed similar reactions.[17, 21, 25, 220]

Chest, jaw, and/or neck tightness are relatively common in patients receiving subcutaneous sumatriptan and have been reported following use of oral or intranasal sumatriptan, but only rarely have these effects been associated with ischemic changes.[1, 148, 236, 249] Data from patients who participated in clinical trials with subcutaneous or oral sumatriptan indicate that 8 of more than 1900 patients receiving subcutaneous sumatriptan and 2 of 6348 patients receiving the drug orally may have developed coronary vasospasm shortly after receiving the drug.[1, 17, 18, 20, 29, 148, 163, 194] In addition, data from patients who participated in clinical trials with intranasal sumatriptan indicate that 1 of approximately 4000 patients receiving the drug experienced asymptomatic subendocardial infarction, possibly secondary to coronary vasospasm.[1, 148, 249] Coronary vasospasm may result in myocardial ischemia or infarction or Prinzmetal variant angina.[1, 17, 18, 20, 27, 28, 30, 148, 155, 163, 194, 218] Serious adverse cardiac effects reported within a few hours following administration of subcutaneous or oral sumatriptan include acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death. [1, 148, 249] Cardiac arrhythmias/ECG abnormalities associated with chest pain, coronary artery disease, or myocardial ischemia in patients receiving sumatriptan include ST-wave changes,[1, 18, 27, 28, 29, 30, 94, 155, 164, 181, 220] ventricular fibrillation or tachycardia,[16, 23, 148, 163, 164, 173, 194, 220] abnormal T waves,[27, 56, 94, 164, 181, 218] abnormal Q waves,[27, 28, 164] and sinus bradycardia or atrial fibrillation.[56, 148, 194] Some of these events occurred in patients who had no indication of coronary artery disease and may represent sequelae of coronary artery vasospasm.[1, 218] However, most patients with serious cardiac events that occurred within 1 hour of sumatriptan administration had risk factors predictive of coronary artery disease, and the use of sumatriptan may have been contraindicated in these patients.[1, 194]

Other arrhythmias or ECG abnormalities reported infrequently in patients receiving sumatriptan therapy include bradycardia,[249] tachycardia,[143, 148 249] nonspecific ST or T wave changes, [1, 148]prolongation of PR or QT_c intervals,[148, 173, 249] sinus arrhythmias, [1]abnormal P waves with nodal rhythm,[57] QRS/T-axis deviations,[173] nonsustained

ventricular premature complexes,[148, 183, 249] isolated junctional ectopic beats,[249] atrial ectopic beats,[249] and delayed activation of the right ventricle.[1, 249]

Transient increases in systolic and/or diastolic blood pressure have been observed in patients receiving sumatriptan.[1, 9, 45, 148, 174, 178, 249] Increases of 2-6 mm Hg in diastolic pressure have been noted after oral administration of the drug in some but not in other studies.[45, 148, 178] Increases or decreases in blood pressure have been reported in up to 1% of patients receiving subcutaneous sumatriptan; hypertensive episodes, including hypertensive crises, have occurred on rare occasions in patients with or without a history of hypertension who were receiving the drug.[1, 148, 189, 249]

Other adverse cardiovascular effects reported in up to 1% of patients receiving sumatriptan include edema,[1, 249] abdominal aortic aneurysm, [148, 249] abnormal pulse,[1] angina,[148] atherosclerosis,[148] cardiomyopathy,[148] cerebral ischemia,[148] cerebrovascular lesion,[148] heart block,[148] increased heart rate,[1, 174] pallor,[1, 148, 174, 249] palpitation,[1, 148, 249] peripheral cyanosis,[148] phlebitis,[249] pulmonary embolism,[148] pulsating sensations,[1, 148] Raynaud's syndrome,[1] retinal artery occlusion,[148] syncope,[1] temporal arteritis,[148] thrombosis,[148] transient myocardial ischemia,[148] and vasodilation.[1, 148]

Impairment or death attributed to stroke, cerebral hemorrhage, cerebral infarction, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan.[1, 36, 42, 53, 148, 152] In some of these patients, sumatriptan was used to treat severe, atypical headaches thought to be migraine but actually secondary to an evolving neurologic lesion (e.g., cerebrovascular accident, subarachnoid hemorrhage).[1, 36, 53, 148] Patients with migraine may be at increased risk for the development of certain cerebrovascular events (e.g., stroke, transient ischemic attack, aphasia, or hemiparesis).[1, 152]

• GI Effects

Dysgeusia/taste disturbance has occurred in approximately 14-25% of patients receiving intranasal sumatriptan compared with 1.7% of those receiving placebo in controlled trials.[249] Dysgeusia/taste disturbance[164, 180, 190] also has been reported with oral sumatriptan therapy; this adverse effect appears to be minimized with the currently available film-coated tablets.[8, 9, 15, 59, 72, 75, 82, 93, 94, 108, 143, 145, 148, 164, 178, 180] In addition, nausea[1, 75, 183, 184, 185, 190, 191] and vomiting[108, 148, 164, 173, 180, 181, 185, 190, 191] have been reported in up to 14% of patients receiving sumatriptan for the treatment of migraine.[249] The incidence of nausea and vomiting was greater among patients receiving the drug subcutaneously for cluster headache than for the treatment of migraine.[1, 158, 162, 164, 171] However, nausea and vomiting also are symptoms associated with migraine attacks and/or the postdromal period, and it may be difficult to distinguish the effects of underlying disease processes from drug-induced effects.[51, 61, 72, 82, 84, 87, 94, 108, 110, 111, 118, 143, 178, 190, 191, 220]

Other adverse GI effects reported in up to 5% of patients receiving sumatriptan include abdominal discomfort,[1, 9, 108, 148, 191, 220, 249] abdominal distention,[148] colitis or ischemic colitis,[1, 148, 249] constipation,[148, 249] dental pain,[148] diarrhea,[1, 148, 249] dyspeptic symptoms,[148] dysphagia,[148, 249] flatulence/eructation,[1, 148, 249] gallstone,[1, 148] gastric symptoms (e.g., pain, pressure),[148] gastritis,[148] gastroenteritis,[148, 249] gastroesophageal reflux,[1, 148, 249] GI hemorrhage,[148, 249] hematemesis,[148, 249] hypersalivation,[148] intestinal obstruction,[148, 249] jaw discomfort,[1, 9] melena,[148, 249] orolingual disorders[1, 9, 72, 249, 181, 249] (e.g., burning or numbness of tongue,[249] discomfort,[1, 249] swallowing disorders,[148]

dry mouth[249]), oral itching and irritation,[148] pancreatitis,[148] peptic ulcer,[1, 148, 249] rectal bleeding,[1, 249] retching,[1, 148] salivary gland swelling,[148] and xerostomia.[1, 249] Changes in esophageal motility also have been reported in patients receiving high doses (16 mg) of subcutaneous sumatriptan, and some clinicians suggest that chest pain occurring in the absence of cardiac manifestations may be related to changes in esophageal motility.[159, 220] (See Pharmacology: Other Effects.)

• Musculoskeletal Effects

Neck pain/stiffness[1, 9, 46, 72, 75, 93, 94, 181, 184, 185, 189] and weakness have been reported in up to 5% of patients receiving sumatriptan in controlled trials.[1, 8, 9, 56, 72, 94, 148, 180] Neck stiffness was severe enough in at least one patient receiving the drug to necessitate discontinuance.[148, 190, 191] Myalgia[1, 9, 148, 181, 220, 249] has been reported in up to 2% of patients receiving sumatriptan in controlled clinical trials.[1, 148, 249]

Other adverse musculoskeletal effects reported in patients receiving sumatriptan include acquired musculoskeletal deformity,[148] arthritis,[249] articular rheumatitis,[148] backache,[1, 249] swelling of the extremities,[1] intervertebral disc disorder,[249] muscle atrophy,[148] muscle cramps,[1, 148, 249] muscle stiffness,[1, 148, 249] muscle tightness,[148] the need to flex calf muscles,[1, 148] muscle tiredness/rigidity,[1, 148] muscle weakness,[148] musculoskeletal inflammation,[148] tetany,[1, 148, 249] difficulty walking,[249] and various joint disturbances (e.g., arthralgia,[148] edema, pain, stiffness).[1, 249]

• Dermatologic and Sensitivity Reactions

Hypersensitivity reactions, including allergic vasculitis, rash, urticaria, pruritus, erythema, wheal and flare at injection site, shortness of breath, angioedema, hypertension, increased heart rate, pallor, hyperventilation, diaphoresis, shock, and anaphylaxis or anaphylactoid reactions have occurred rarely in patients receiving sumatriptan.[1, 52, 75, 148, 174, 183, 184, 185, 189, 221, 249] Hypersensitivity reactions to sumatriptan can be life-threatening or fatal.[1, 148] At least one patient receiving subcutaneous sumatriptan in a controlled trial discontinued therapy as a result of moderate urticaria; this patient also had a history of intolerance to ergotamine.[174] In general, hypersensitivity reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens.[1, 148, 249]

Other adverse dermatologic or sensitivity reactions associated with sumatriptan include dry/scaly skin,[148] eczema,[148] exacerbation of sunburn,[1, 148, 249] peeling of skin,[249] photosensitivity,[1, 249] seborrheic dermatitis,[148] skin eruptions,[1, 249] nodules,[148] skin tenderness,[1, 148] tightness/wrinkling of skin,[148] sweating,[1, 148, 249] and facial swelling.[249]

• Respiratory Effects

Discomfort of the nasal cavity/sinuses or throat[1, 9, 56, 72, 148, 181, 191, 249] has been reported in up to 4% of patients receiving sumatriptan in controlled trials; several of these patients discontinued therapy after moderate to severe throat tightness/discomfort.[1, 148, 158, 174, 183, 191, 220] Dyspnea or hyperventilation has been reported in up to 1% of patients receiving sumatriptan.[1, 9, 57, 143, 144, 148, 174, 191, 220, 249] Upon rechallenge, some patients again experienced dyspnea.[220] Bronchospasm has been reported in at least 1% of patients with or without a history of asthma receiving sumatriptan;[1, 148, 249] the incidence of bronchospasm among patients with cluster headaches appears to be greater than the incidence among those with migraine receiving the drug subcutaneously.[1] Influenza,[1, 183] diseases of the upper[1, 9, 148, 249] and

lower respiratory tract,[1, 148, 249] hiccups,[1, 148] asthma,[148, 249] bronchitis,[1, 148] and cough have been reported in up to 1% of patients receiving sumatriptan.[1, 24, 148, 191]

• Renal and Genitourinary Effects

Adverse renal effects reported in up to 1% of patients receiving sumatriptan include acute renal failure,[1, 148, 249] bladder inflammation,[148] dysuria,[1, 148, 191, 249] hematuria,[148] increased urination,[1, 148, 249] micturition disorders,[148] renal calculus,[1] urethritis,[148] urinary infections,[148] and urinary frequency.[148]

Adverse genitourinary effects reported in up to 1% of patients receiving sumatriptan include abnormal menstrual cycle,[148] abortion,[148] disorders of the breast[249] (e.g., tenderness,[148] nipple discharge,[148]) dysmenorrhea,[1, 148, 249] endometriosis,[249] inflammation of fallopian tubes,[148] intermenstrual bleeding,[148] and menstruation or menstrual cycle symptoms.[148]

• Ocular Effects

Vision alteration/disturbance and ocular irritation have been reported in up to 3% of patients receiving sumatriptan in controlled trials.[1, 9, 148, 249] Accommodation disorders,[148] conjunctivitis,[148] disorders of sclera,[148] external ocular muscle disorders,[148] keratitis,[148] lacrimation,[1, 16] blindness/low vision,[148] miosis,[16] mydriasis,[148] and ocular edema, hemorrhage, itching, pain, or swelling[148] also have been reported in up to 1% of patients receiving sumatriptan in clinical studies.[1, 148, 249] In addition, ischemic optic neuropathy, [1, 148, 249] retinal artery occlusion, [1, 148, 249] retinal vein thrombosis, [1, 148, 249] and vision loss[1, 148, 249] have been reported during postmarketing surveillance. [1, 148, 249] Transient or permanent blindness and substantial partial vision loss have been reported very rarely with sumatriptan use.[273, 274, 275] (Vision disorders also may be part of a migraine attack.)[273, 274, 275]

• Otic Effects

Adverse otic effects reported in up to 1% of patients receiving sumatriptan include ear infection,[249] external otitis, [1, 249]feeling of fullness in the ears,[148] hearing disturbances (e.g., increased sensitivity to noise, hearing loss),[148] Meniere's disease,[249] otalgia,[148, 249] and tinnitus. [1, 249] In addition, deafness[1, 9, 148] has been reported during postmarketing surveillance.[1, 148, 249]

• Hepatic Effects

Elevated liver function test results have been reported during postmarketing surveillance.[1]

• Endocrine and Metabolic Effects

Adverse endocrine and metabolic effects reported in up to 1% of patients receiving sumatriptan in clinical studies include elevations in thyrotropin (TSH),[148] endocrine cysts, lumps, or masses,[148] fluid disturbances (e.g., retention),[148] galactorrhea,[148, 249] hyperglycemia,[148] hypoglycemia,[148] hypothyroidism,[148, 249] thirst,[1, 148, 249] polydipsia,[1] hunger,[1, 148, 249] increased/decreased appetite,[1, 148, 249] and weight gain/loss.[148, 249]

• Hematologic Effects

Anemia,[148] elevated platelet count[183] and lymphadenopathy,[148, 249] have been reported in up to 1% of patients receiving sumatriptan.[148] In addition, hemolytic anemia,[1, 148, 249] pancytopenia,[1, 148, 249] and thrombocytopenia have been reported during postmarketing surveillance. [1, 148, 249]

• Other Adverse Effects

Other adverse effects reported in up to 1% of patients receiving sumatriptan include dehydration,[1] diaphoresis,[9, 72, 75, 143, 181] fever,[1, 148, 185] overdose,[148] and pituitary neoplasm,[249]

• Precautions and Contraindications

Because sumatriptan rarely can cause potentially serious or life-threatening adverse effects, the manufacturer cautions that the drug should be used subcutaneously only in patients in whom a clear diagnosis of migraine or cluster headache has been established, and the drug should be used orally or intranasally only in patients with a clear diagnosis of migraine.[1, 148, 198, 236, 237, 249] Sumatriptan should be used with caution in patients not previously diagnosed with migraine attacks and in those with a history of migraine or cluster headache who present with atypical symptoms.[1, 148] Care should be taken to exclude other potentially serious neurologic conditions (e.g., cerebrovascular accident, subarachnoid hemorrhage) before initiation of sumatriptan therapy.[1, 148, 249] Patients with a history of migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).[1, 148, 249] If a patient does not respond to the first dose of sumatriptan for a given attack, the diagnosis of migraine or cluster headache should be reconfirmed before administration of subsequent doses.[1, 148, 249] Patients should be cautioned about potential misuse (e.g., for prophylaxis) of sumatriptan for vascular headache.[1, 148, 237] Patients also should be cautioned against frequent use/misuse of sumatriptan[237] since abuse of sumatriptan has resulted in rebound headache in patients with a history of analgesic or ergot alkaloid abuse.[63, 64, 114, 165, 170]

Because there have been rare reports of seizure following administration of sumatriptan, the drug should be used with caution in patients with a history of seizure disorders or conditions associated with a lowered seizure threshold.[273, 274, 275]

Because substantial increases in blood pressure, including hypertensive crises, have been reported rarely in patients with or without a history of hypertension, sumatriptan should not be used in patients with uncontrolled hypertension.[1, 148, 249] The drug should be used with caution in patients with controlled hypertension.

Sumatriptan also should be used with caution in patients with diseases that may alter the absorption, metabolism, or excretion of the drug, such as impaired renal or hepatic function.[1, 148, 249] (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because sumatriptan binds to melanin, it could accumulate in melanin-rich tissues (such as the eye) over time and cause toxicity in these tissues with extended use.[1, 148] In addition, corneal opacities were noted after 1 month of treatment in dogs receiving oral sumatriptan 2 mg/kg daily (representing about 5 or 3 times the human exposure after a 100-mg oral or a 6-mg subcutaneous dose, respectively).[1, 148] Although the manufacturer states that ophthalmologic function in clinical trials was not systematically monitored in patients receiving sumatriptan for migraine and offers no specific recommendations for ophthalmologic monitoring, clinicians should be aware of the potential for ophthalmologic effects with long-term sumatriptan therapy.[1, 148]

Cases of potentially life-threatening serotonin syndrome have been reported during concurrent therapy with 5-HT_1 receptor agonists and selective serotonin-reuptake

inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs).[272, 273, 274, 275] Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).[272, 273, 274, 275] If concurrent therapy with a 5-HT_1 receptor agonist and a SSRI or SNRI is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated.[272, 273, 274, 275] (See Drug Interactions: Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors.)

Because sumatriptan has the potential to cause vasospasm, the manufacturer warns that therapy with the drug should not be used in patients with signs or symptoms of ischemic heart disease (angina pectoris, Prinzmetal variant angina, myocardial infarction, documented silent ischemia), cerebrovascular disease (e.g., stroke of any type, transient ischemic attacks), or peripheral vascular disease (e.g., bowel ischemia) or in those with a history of such conditions.[1, 3, 11, 16, 17, 18, 23, 24, 29, 33, 35, 148, 249] Patients who experience signs or symptoms suggestive of angina following sumatriptan administration should be evaluated for the presence of coronary artery disease or a predisposition to Prinzmetal variant angina before receiving additional doses of the drug and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur.[1, 148, 249] Similarly, patients who experience symptoms or signs suggestive of decreased arterial flow (e.g., manifestations of bowel ischemia or Raynaud's syndrome), following sumatriptan administration should be evaluated for atherosclerosis or predisposition to vasospasm.[1, 148, 249] Sumatriptan should not be given to patients in whom unrecognized coronary artery disease is likely (e.g., postmenopausal women, men older than 40 years of age, patients with risk factors such as hypertension, hypercholesterolemia, obesity, diabetes, smoking, or family history of coronary artery disease) unless a prior cardiovascular evaluation provides satisfactory evidence that the patient does not have coronary artery disease, ischemic heart disease, or other clinically important underlying cardiovascular disease.[1, 34, 148, 164, 249] In particular, because most patients with cluster headaches possess at least one risk factor for coronary artery disease (i.e., are men over 40 years of age), a cardiovascular evaluation should be undertaken prior to initiation of sumatriptan therapy in such patients.[1] In addition to these recognized risk factors contributing to the development of coronary vasospasm, history of migraine also may be a possible risk factor in that migraine may be part of a generalized vasospastic disorder predisposing to the development of cardiomyopathy.[112, 115, 116]

For patients with risk factors for coronary artery disease who nevertheless have completed a satisfactory cardiovascular evaluation, the manufacturer and some clinicians strongly recommend that administration of an initial dose of sumatriptan take place under medical supervision (e.g., in the clinician's office) unless such patients have received the drug previously.[1, 148, 236, 237, 249] The manufacturer also states that because myocardial ischemia can occur in the absence of clinical symptoms,[33, 40] clinicians should consider obtaining an ECG following the initial dose of sumatriptan in patients with cardiovascular risk factors.[1, 40, 148, 249] Some other clinicians, however, doubt the value of electrocardiographic evaluation under these circumstances and differ with this recommendation.[236] Patients with risk factors for

the development of coronary artery disease should undergo periodic cardiovascular evaluation while receiving sumatriptan therapy.[1, 148, 236, 237] If symptoms of angina occur after sumatriptan administration, electrocardiographic evaluation should be used to identify possible ischemic changes associated with coronary artery disease or a predisposition to variant angina before sumatriptan therapy is continued.[1, 29, 34, 148, 220, 249] IV nitroglycerin has been shown to reverse mild coronary artery vasoconstriction that was associated with subcutaneous sumatriptan therapy in patients with suspected coronary artery disease.[150] Patients receiving sumatriptan should be instructed to report to their clinician symptoms such as pain or tightness in the throat or chest and to contact their clinician immediately if chest pain is severe or persists.[1, 148, 249]

Because the incidence of adverse effects and the risk of precipitating coronary vasospasm increases with IV administration, sumatriptan should *not* be administered IV.[1, 13, 40, 90, 236, 237]

Concomitant use of *oral* or *intranasal* sumatriptan and monoamine oxidase-A isoenzyme (MAO-A) inhibitor therapy or use of such sumatriptan preparations within 2 weeks of discontinuance of MAO-A inhibitor therapy is contraindicated because of the potential of these drugs to produce substantial increases in the bioavailability of oral or intranasal sumatriptan.[148, 236, 249] In addition, *subcutaneous* therapy with sumatriptan generally should not be used in patients receiving MAO-A inhibitors, since pretreatment with an MAO-A inhibitor decreases sumatriptan clearance.[1, 26, 37, 48, 148, 157] (See Drug Interactions: Monoamine Oxidase Inhibitors.) If such concomitant therapy is clinically warranted, however, the dosage of subcutaneous sumatriptan should be appropriately adjusted and the drug administered under careful medical supervision.[1, 237] The manufacturer states that sumatriptan should not be used within 24 hours of treatment with ergot alkaloids (e.g., ergotamine, dihydroergotamine, methysergide) or another 5-HT_1 receptor agonist.[1, 148, 237, 249] (See Drug Interactions: Ergot Alkaloids.)

Sumatriptan should not be administered to patients with hemiplegic or basilar migraine or uncontrolled hypertension.[1, 3, 11, 36, 48, 148, 249]

Sumatriptan is contraindicated in patients with severe hepatic impairment and/or known hypersensitivity to sumatriptan or any of its components.[1, 148, 249] Patients should be advised to discontinue use of sumatriptan and contact their clinician immediately if they experience symptoms suggestive of hypersensitivity to the drug, such as shortness of breath, wheezing, palpitations, swelling of the eyelids, face or lips, rash, or urticaria.[1, 148, 249] Other symptoms that warrant reporting (e.g., at the next clinician contact) include sensations of tingling, heat, flushing, heaviness or pressure, drowsiness, dizziness, or fatigue.[1, 148, 249]

• Pediatric Precautions

The manufacturer states that safety and efficacy of sumatriptan in those younger than 18 years of age have not been established.[1, 12, 148, 236, 237]

Available data from placebo-controlled clinical trials have failed to establish the efficacy of oral sumatriptan (25-100 mg) for the treatment of migraine in adolescents 12-17 years of age[#].[1, 148, 249] Adverse effects observed in adolescents who received oral sumatriptan in clinical trials were similar in nature to those reported in clinical

trials in adults; the incidence of all adverse effects in adolescents appears to be both dose and age dependent, with younger patients reporting adverse effects more commonly than older adolescents.[1, 148, 249] A limited number of serious adverse effects, including effects similar in nature to those rarely reported in adults, have been reported during postmarketing surveillance in children following use of subcutaneous and/or oral sumatriptan.[1, 148, 249] Myocardial infarction reportedly occurred in one 14-year-old boy within 1 day of receiving oral sumatriptan.[1, 148, 249] Because there are insufficient data to determine the incidence of serious adverse effects in pediatric patients receiving sumatriptan, use of the drug in patients younger than 18 years of age is not recommended by the manufacturer.[1, 148, 249]

• Geriatric Precautions

Because geriatric patients are more likely to have decreased hepatic function, are at increased risk for coronary artery disease, and increases in blood pressure may be more pronounced than in younger patients, use of the drug in geriatric patients is *not* recommended by the manufacturer.[1, 148, 249]

• Mutagenicity and Carcinogenicity

Sumatriptan did not exhibit evidence of mutagenicity in vitro in gene mutation assays (i.e., the Ames microbial mutagen test and the V-79/HGPRT assay in Chinese hamster cells) with or without metabolic activation.[1, 148] No increase in chromosomal aberrations was observed in the in vitro human lymphocyte assay or in the in vivo rat micronucleus assay.[1, 148]

No evidence of carcinogenicity was demonstrated in a 78-week study in mice given oral sumatriptan dosages representing up to 40 or 110 times, respectively, the exposure in humans receiving the maximum recommended single dose of 100 mg orally or 6 mg subcutaneously.[1, 148] In addition, no evidence of carcinogenicity was seen in rats given dosages representing 15 or 260 times, respectively, the exposure in humans receiving the maximum recommended single dose of 100 mg orally or 6 mg subcutaneously on a mg/m^2 basis for 104 weeks.[1, 148]

• Pregnancy, Fertility, and Lactation

Pregnancy

There are no adequate and well-controlled studies evaluating the use of sumatriptan in pregnant women.[1, 148, 249] Although a causal relationship to the drug has not been definitely established, agenesis of the corpus callosum has been reported in an infant whose mother received oral sumatriptan at week 4 and 6 of pregnancy.[173] Sumatriptan should be used during pregnancy only if the potential benefit justifies the risk to the fetus.[1, 148, 249] The manufacturer has established a Sumatriptan Pregnancy Registry to facilitate assessment of fetal outcomes in women who have inadvertently received oral or subcutaneous sumatriptan during pregnancy.[1, 236] Clinicians are encouraged to contact the manufacturer at 800-336-2176, to enroll such women in this registry.[1]

Sumatriptan has been associated with fetal abnormalities and embryo and fetal mortality in animals.[1, 148, 249] Embryolethality was noted in pregnant rabbits given IV sumatriptan throughout the period of organogenesis in daily doses at or close to those producing maternal toxicity, representing systemic exposures approximately equivalent to the maximum recommended single dose in humans of 6 mg (on a mg/m^2 basis).[1] The mechanism of the embryolethality is not known.[1] This effect was not seen in pregnant rats given IV sumatriptan throughout organogenesis at dosages

representing approximately 20 times the maximum subcutaneous human dose of 6 mg or in pregnant rats given subcutaneous sumatriptan prior to and throughout pregnancy.[1] In pregnant rabbits, oral sumatriptan dosages of 100 mg/kg daily (representing 18 times the maximum single human dose of 100 mg on a mg/m^2 basis) throughout the period of organogenesis produced embryolethality and maternotoxicity; these effects were not observed at oral sumatriptan dosages of 50 mg/kg daily.[148] No fetal effects were observed in rats receiving 50 mg/kg daily (representing 5 times the maximum single human dose of 100 mg on a mg/m^2 basis).[148]

Sumatriptan has been shown to be teratogenic in pregnant rats given long-term oral sumatriptan dosages of 500 mg/kg daily (representing 50 times the maximum single human oral dose of 100 mg on a mg/m^2 basis); an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) was observed in these animals.[148] Sumatriptan was associated with an increased incidence of cervicothoracic vascular defects and skeletal abnormalities in fetuses of rabbits receiving oral dosages greater than 15 mg/kg daily (representing 3 or 50 times the maximum single human oral or subcutaneous dose of 100 or 6 mg, respectively, on a mg/m^2 basis); these effects were not observed at lower dosages.[1] Blood vessel abnormalities (cervicothoracic and umbilical) occurred in offspring of pregnant rats given oral dosages of 250 mg/kg daily or greater (representing 25 times the maximum single human oral dose of 100 mg on a mg/m^2 basis); these effects were not observed at oral dosages of approximately 60 mg/kg daily or less (representing 6 times the maximum single human oral dose of 100 mg on a mg/m^2 basis).[148] The clinical importance of these abnormalities is not known.[1] In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.[1] Studies in rats and rabbits evaluating the teratogenic potential of sumatriptan administered subcutaneously only during organogenesis have not been performed.[1]

Oral sumatriptan produced a decrease in pup survival between birth and postnatal day 4 when administered to pregnant rats at dosages of 250 mg/kg daily or higher (representing 25 times the maximum single human oral dose of 100 mg on a mg/m^2 basis) during the period of organogenesis; pups were not affected when dams were given 60 mg/kg daily (representing 6 times the maximum single human dose of 100 mg on a mg/m^2 basis).[148] In rats given oral dosages of 1000 mg/kg daily (representing 100 times the maximum single human oral dose of 100 mg on a mg/m^2 basis) from gestational day 17 through postnatal day 21, decreased pup survival was found at postnatal days 2, 4, and 20; pups were not affected when dams were given 100 mg/kg of sumatriptan daily.[148]

Fertility

Reproduction studies in rats given subcutaneous sumatriptan at a dosage representing 100 times the maximum recommended single human dose of 6 mg (on a mg/m^2 basis) prior to and during the mating period have shown no evidence of impaired fertility. However, similar reproduction studies in rats given oral dosages of 50 and 500 mg/kg daily prior to and during mating revealed evidence of drug-induced decreases in mating ability; no effects on fertility were observed at oral doses representing half the maximum recommended single oral dose of 100 mg or 8 times the maximum recommended single subcutaneous dose of 6 mg in humans (on a mg/m^2 basis).[1, 148]

Whether mating impairment is related to sumatriptan in females or males has not been determined.[1, 148]

Lactation
Sumatriptan is distributed into breast milk following administration of the drug to lactating animals or nursing mothers.[1, 14, 40, 148, 242, 249] (See Pharmacokinetics: Distribution.) It has been suggested that exposure of the infant to the limited amount of drug excreted in milk following a single 6-mg subcutaneous dose could be minimized by expressing and discarding all milk for 8 hours after the dose.[242] However, the manufacturer recommends minimizing infant exposure to sumatriptan by avoiding breast-feeding for 12 hours after receiving the drug as oral tablets, subcutaneous injection, or nasal spray.[273, 274, 275]

Drug Interactions

• Monoamine Oxidase Inhibitors
Because of the important role of monoamine oxidase (MAO) in the presystemic clearance of sumatriptan, particularly the A isoenzyme (MAO-A), concomitant therapy with MAO-A inhibitors may decrease sumatriptan clearance and increase half-life and blood concentrations of the drug.[1, 37, 48, 148, 249] In healthy women receiving sumatriptan subcutaneously, pretreatment with an MAO-A inhibitor resulted in a 40% increase in the half-life of sumatriptan, a marked decrease in plasma clearance (Cl_p/F), and a twofold increase in area under the plasma concentration-time curve (AUC).[1, 148] In one small study, pretreatment with an MAO-A inhibitor resulted in an approximately sevenfold increase in systemic exposure to sumatriptan following administration of a single 25-mg oral dose of the drug.[148, 249] In contrast, pretreatment with an MAO-B inhibitor does not have an appreciable effect on the metabolism of sumatriptan.[148, 193] The manufacturer states that although studies of this interaction have not been performed with intranasal sumatriptan, the effects of an MAO-A inhibitor on intranasal sumatriptan bioavailability would be expected to be greater than those seen with subcutaneous sumatriptan but less than those seen with the oral drug, since only swallowed drug would be subject to first-pass effects.[148, 249] Therefore, concurrent use of *oral* or *intranasal* sumatriptan and MAO-A inhibitors or use of such sumatriptan preparations within 2 weeks of discontinuance of MAO-A inhibitor therapy is contraindicated.[26, 37, 148, 157, 236, 249] If clinically warranted, *subcutaneous* sumatriptan may be used concomitantly with MAO-A inhibitors with appropriate dosage adjustment and careful monitoring.[1, 237] (See Cautions: Precautions and Contraindications.)

• Ergot Alkaloids
Because ergot alkaloids (e.g., ergotamine, dihydroergotamine, methysergide) have been reported to cause prolonged vasospastic reactions and preliminary data suggest that the vasoconstrictor effects of these drugs may be additive to those of sumatriptan,[1, 26, 33, 60] the manufacturer states that ergot alkaloids and sumatriptan should not be used within 24 hours of each other.[1, 148, 249] However, in a placebo-controlled study in patients with a history of migraine who were receiving dihydroergotamine prophylaxis, no clinical evidence of a drug interaction was observed when subcutaneous sumatriptan was used to treat breakthrough migraine attacks.[142]

• **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors**

Cases of potentially life-threatening serotonin syndrome have been reported during concurrent therapy with 5-HT_1 receptor agonists and selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs).[272, 273, 274, 275] Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).[272, 273, 274, 275] If concurrent therapy with a 5-HT_1 receptor agonist and an SSRI or SNRI is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated.[272, 273, 274, 275] In addition, patients receiving such concomitant therapy should be advised of potential drug interaction symptoms (e.g., weakness, progressive agitation, tingling, incoordination, chest pain, dyspnea) and be instructed to report such symptoms to their clinician immediately.[1, 236, 237, 272]

Oral or subcutaneous sumatriptan and serotonin reuptake inhibitors were used concomitantly in some clinical studies without unusual adverse effects.[192, 193, 234] However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.[151]

• **Protein-bound Drugs**

The effect of sumatriptan on the protein binding of other drugs has not been evaluated[1] but would be expected to be minor because of the low-level protein binding of sumatriptan.[148, 249]

• **Acetaminophen**

In patients with migraine, pretreatment with oral sumatriptan followed by administration of oral acetaminophen delayed the absorption of acetaminophen, although the extent of acetaminophen absorption over 8 hours was not affected.[187] Since IV sumatriptan has been shown to delay gastric emptying time in healthy individuals, it has been suggested that delayed absorption of acetaminophen following pretreatment with oral sumatriptan may be the result of a delay in gastric emptying time.[76, 187]

• **Alcohol**

In a limited number of healthy individuals, administration of alcohol (0.8 mg/kg) 30 minutes prior to oral sumatriptan (200 mg) did not affect the pharmacokinetics (e.g., peak plasma concentration, time to peak plasma concentration, area under the plasma concentration-time curve, half-life) of the drug.[44, 45, 148, 236]

• **Topical Vasoconstrictors**

Topical application of xylometazoline to the nasal mucosa 15 minutes prior to an intranasal sumatriptan dose of 20 mg reportedly did not affect the pharmacokinetics of sumatriptan.[249]

• **Other Drugs**

Retrospective evaluation of phase III clinical trials in which certain drugs used for migraine prophylaxis, such as verapamil, amitriptyline, or propranolol, were used concomitantly with sumatriptan did not indicate any effect of such concomitant therapy on the efficacy of sumatriptan. [1, 40, 62] Pretreatment with propranolol (80 mg twice daily for 7 days) did not alter the pharmacokinetics (e.g., plasma concentrations, time to peak plasma concentration, half-life) or pharmacodynamics (as determined by changes in heart rate and blood pressure) of oral sumatriptan given as a single 300-mg dose.[62]

Laboratory Test Interferences

Sumatriptan is not known to interfere with commonly employed clinical laboratory tests.[1, 148]

Acute Toxicity

Limited information is available on the acute toxicity of sumatriptan; no gross overdoses in clinical practice have been reported.[1] Single oral, subcutaneous, or intranasal doses of 140-300, 8-12, or up to 40 mg, respectively, have been administered to patients with migraine, and single oral, subcutaneous, or intranasal doses of 140-400, up to 16, or up to 40 mg, respectively, have been administered to healthy individuals, without clinically important adverse effects.[1, 148, 249] However, coronary vasospasm has been observed after IV administration of usual doses of sumatriptan.[1] (See Cautions: Precautions and Contraindications.) Based on studies in animals given high doses of sumatriptan (0.1 g/kg in dogs and 2 g/kg in rats), overdosage with the drug may be expected to cause seizures, tremor, inactivity, ptosis, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, salivation, lacrimation, injection site reactions (desquamation, hair loss, scab formation), and paralysis.[1, 148, 249] Since the elimination half-life of sumatriptan is about 2-2.5 hours, monitoring of patients after overdosage should continue while symptoms persist or for at least 10-12 hours.[1, 148, 249]

The effect of hemodialysis or peritoneal dialysis on serum concentrations of sumatriptan is not known.[1, 148, 249]

Chronic Toxicity

The manufacturer states that the abuse potential of sumatriptan cannot be fully delineated prior to extensive postmarketing experience.[1] Currently available data from long-term and/or postmarketing surveillance studies suggest that subcutaneous or oral sumatriptan use is not associated with dose escalation or withdrawal symptoms in patients using the drug as recommended for acute treatment of migraine or cluster headache attacks.[1, 114, 148, 170, 236, 237] However, misuse of sumatriptan (e.g., daily use as prophylaxis) has been reported in a few patients receiving the drug orally or subcutaneously for migraine headache, most of whom had a history of analgesic or ergot alkaloid abuse.[63, 64, 114, 165, 170, 172] Some clinicians state that frequent (e.g., daily) use of sumatriptan may be associated with rebound headache;[237] overuse of sumatriptan has been reported to sustain ergotamine-induced headache, with the addition of superimposed migraine-like episodes, in at least one patient.[172] Patients should be cautioned against frequent use/misuse of sumatriptan for headache prophylaxis.[1, 148, 237]

Pharmacology

Sumatriptan is a selective agonist of vascular serotonin (5-hydroxytryptamine; 5-HT) type 1-like receptors, probably the 5-HT_{1D} and 5-HT_{1B} subtypes.[1, 2, 3, 4, 5, 6, 7, 8, 223, 224] The mechanisms involved in the pathogenesis of migraine and cluster headache are not clearly understood; consequently, the precise mechanism of action of sumatriptan in the management of these disorders has not been established.[4, 6, 9, 13, 77, 87] However, current data suggest that sumatriptan may ameliorate migraine and cluster headache through selective constriction of certain large cranial blood vessels and/or inhibition of neurogenic inflammatory processes in the CNS.[1, 2, 3, 6, 7, 9, 10, 13, 47, 66, 73, 77, 88, 110, 119, 131, 177, 184, 186, 217, 236, 237] While some features of migraine clearly reflect effects on cerebral blood vessels, neurogenic mechanisms involving activation of the trigeminovascular system also have been implicated; current evidence suggests that both mechanisms may be involved.[3, 6, 13, 77, 87, 95, 117, 195, 197, 217]

No single pathogenic mechanism has been identified to explain the various manifestations of cluster headache, although several pathophysiologic abnormalities that appear to involve direct or indirect activation of the trigeminovascular and cranial parasympathetic nervous systems have been identified in patients with this disorder.[103, 184, 186, 188, 196, 217] It has been suggested that the neuroendocrinologic abnormalities associated with cluster headache may indicate dysfunction of the "biologic clock" in the hypothalamus.[217]

Although sumatriptan therapy has been associated with adverse CNS effects such as drowsiness, sedation, fatigue, dizziness, and vertigo, available evidence from animal studies indicates that the drug penetrates the blood-brain barrier poorly; therefore, it has been suggested that disruption of the blood-brain barrier may occur during migraine attacks.[6, 13, 14, 41, 47, 48, 49, 67, 87, 136, 138, 141, 146, 176, 217] However, since sumatriptan also decreases migraine-associated nausea and vomiting,[1, 8, 9, 55, 56, 58, 76, 93, 108, 118, 162, 171, 173, 180] a more likely hypothesis is that sumatriptan acts on areas of the brain not protected by the blood-brain barrier (e.g., the circumventricular organs, the chemoreceptor trigger zone).[4, 6, 38, 47, 76, 118, 126, 127, 128, 129, 236, 237]

Indirect evidence suggests that serotonin is involved in the pathogenesis of migraine because of observed correlations between the physiologic effects of serotonin, which include vasoconstriction, and the clinical features of migraine.[2, 3, 6, 13, 26, 57, 73, 77, 87, 88, 119, 131, 215, 216, 217] Serotonin levels in platelets within the vascular system have been shown to increase before, and decrease rapidly during, a migraine attack.[2, 13, 57, 59, 87, 127, 131, 215] In addition, increases in the urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin, have been found in patients with migraine, suggesting rapid degradation of serotonin during migraine attacks.[13, 87] Both spontaneous migraine and that induced by reserpine, a drug that depletes serotonin stores, are ameliorated by IV administration of serotonin.[13, 87] However, clinical use of serotonin is precluded by adverse effects such as nausea, syncope, hyperpnea, peripheral vasoconstriction, and paresthesia.[59, 87, 141, 215, 216]

Sumatriptan and other currently available drugs that are effective for acute migraine, including dihydroergotamine and ergotamine, have binding affinity for serotonin type 1 (5-HT_1) receptors, particularly the 5-HT_{1D} (also called 5-$HT_{1D\alpha}$) and 5-HT_{1B} (also called 5-$HT_{1D\beta}$) subtypes located on trigeminal sensory neurons innervating dural blood vessels.[4, 13, 38, 60, 66, 73, 74, 95, 100, 101, 105, 106, 110, 120, 126, 130, 132, 135, 138, 139, 177, 195,

[223, 224] The 5-HT_{1B} and 5-HT_{1D} receptors function as autoreceptors, activation of which leads to inhibition of firing of serotonin neurons and a reduction in the synthesis and release of serotonin.[223] Upon binding to these 5-HT_1 receptor subtypes, sumatriptan inhibits adenylate cyclase activity via regulatory G proteins, increases intracellular calcium, and affects other intracellular events that lead to vasoconstriction and inhibition of sensory nociceptive (trigeminal) nerve firing and vasoactive neuropeptide release.[2, 3, 4, 6, 38, 74, 86, 109, 121, 128, 130, 132, 137, 177, 217]
Sumatriptan has the highest affinity for the 5-HT_{1D} receptor, the most common serotonin receptor subtype in the brain,[2, 13, 98] and a 2- to 17-fold lower affinity for 5-HT_{1A} receptors; agonist activity at 5-HT_{1A} and other serotonin receptors may be responsible for some of the adverse effects noted with administration of serotonin or serotonergic antimigraine drugs (e.g., ergotamine, dihydroergotamine).[2, 4, 6, 77, 83, 98, 101, 128, 131] Sumatriptan has essentially no affinity for (based on standard radioligand binding assays) nor pharmacologic activity at other serotonin receptors (e.g., 5-HT_2, 5-HT_3) or at receptors of the dopamine$_1$, dopamine$_2$, muscarinic,[2, 4, 6, 22, 83, 98] histamine,[66] benzodiazepine,[2, 4, 83, 98] or α_1-, α_2-, or β-adrenergic type.[1, 2, 4, 39, 40, 66, 73, 77, 98, 101, 132, 137, 148, 177]

- **Cerebrovascular Effects**

Some evidence suggests that migraine may be caused by initial vasoconstriction of cerebral vessels, opening of arteriovenous anastomoses, and diversion of blood from capillary beds;[4, 6, 47, 65, 98, 110, 118] these vascular changes may result in ischemia and hypoxia, vasodilation of intracranial and scalp vessels, and extravasation of plasma proteins into the dura mater.[4, 6, 10, 47, 65, 98, 110, 118, 133, 158, 169] Sumatriptan and ergot alkaloids appear to exert their therapeutic effects in migraine by reducing blood flow to anastomoses and redirecting flow to capillary beds.[65, 68, 70, 77, 110, 118, 119]
Sumatriptan selectively constricts certain large cranial blood vessels (e.g., as indicated by a selective increase in blood flow velocity in the internal carotid and middle cerebral arteries) and arteriovenous anastomoses in the carotid circulation that become inflamed and dilated during a migraine attack.[1, 2, 3, 6, 7, 9, 10, 11, 13, 43, 66, 73, 77, 88, 107, 110, 131, 177] These vasoconstrictor effects occur apparently without compromising blood flow in the cerebral or extracerebral circulation.[43, 70, 77, 119, 138, 169, 176] It has been suggested that the vasoconstriction observed following administration of sumatriptan may be related in part to a direct action on vascular smooth muscle.[66, 103, 184, 186]

Sumatriptan inhibits activation of the trigeminovascular system and associated release of vasoactive neuropeptides (i.e., substance P, neurokinin A, calcitonin gene-related peptide [CGRP]) from trigeminal nerve terminals, thereby preventing subsequent vasodilation, inflammation, and plasma extravasation from dural blood vessels.[2, 3, 6, 13, 38, 47, 67, 71, 74, 75, 87, 95, 106, 117, 118, 125, 133, 176] Sumatriptan also has been shown to reduce the ultrastructural changes resulting from trigeminal sensory nerve stimulation in the dura mater, such as vesiculation, vacuolation, microvillus projections within the endothelium of postcapillary venules, platelet aggregation and adhesion, and mast cell degranulation.[95, 121, 125]

In cluster headache, activation of trigeminal nerves and the parasympathetic nervous system leads to frontotemporal vasodilation, neuroinflammation, and venous stasis; these effects may be manifested as nasal congestion, rhinorrhea, lacrimation, abnormal sweating, and/or periorbital edema.[103, 184, 186, 188, 217] Limited data currently suggest that sumatriptan, like oxygen, may alleviate cluster headache attacks through

normalization of elevated CGRP concentrations in cranial venous blood; such normalization of CGRP levels reflects termination of activity in the trigeminovascular system.[103, 196, 217] In addition, vasoconstriction following administration of sumatriptan may be related in part to a return of firing of sympathetic nerve fibers following a decrease in neuroinflammation.[66, 103, 184, 186]

Although sumatriptan does not appear to have a direct analgesic effect, the drug inhibits firing of sensory nociceptive nerves in the trigeminovascular system that may be involved in central pain modulatory mechanisms (as indicated by inhibition of *c-fos* protein expression, an indicator of neuronal activation).[13, 38, 47, 49, 67, 71, 74, 77, 95, 217]

• Cardiovascular Effects

Sumatriptan has shown modest vasoconstrictor effects on the coronary, pulmonary, and systemic circulation in in vitro studies in animals and in most studies in humans, but these effects are much less potent than those of ergot alkaloids.[100, 118, 119, 124, 141] In vitro studies of human diseased and normal coronary artery rings and angiographic evidence in patients undergoing coronary arteriography indicate that sumatriptan causes relatively weak contractions of coronary arteries compared with the effects of serotonin or ergotamine.[5, 28, 32, 69, 102, 130] Although coronary vasospasm and myocardial ischemia or infarction have been reported in a few patients receiving sumatriptan,[1, 17, 18, 23, 27, 29, 30, 148, 194] most of these patients had risk factors predictive of coronary artery disease, and use of the drug may have been contraindicated in some of these cases.[1, 20, 29, 35, 130, 148, 194] (See Cautions: Precautions and Contraindications.) It has been suggested that the presence of atherosclerosis and/or associated changes in the function of vasoactive factors (e.g., substance P, nitric oxide, thromboxane A) in damaged coronary artery endothelium may result in enhanced sensitivity of the coronary vessels to the vasoconstrictor effects of sumatriptan in patients with coronary artery disease.[31, 34, 69, 85, 102, 130, 164]

Sumatriptan selectively reduces carotid arterial blood flow and/or constricts carotid arteriovenous anastomoses in anesthetized animals without appreciable effects on arterial blood pressure or total peripheral resistance.[1, 45, 100, 148, 178] The drug produces contraction of vascular smooth muscle in vitro in saphenous veins in dogs and humans, but such contractions are weaker than those produced by serotonin or ergot alkaloids (e.g., methysergide).[105, 120] Administration of sumatriptan in healthy individuals did not appreciably increase arterial resistance (as measured by decreases in mean toe-arm systolic blood pressure gradients) in small peripheral arteries of the leg.[1, 60, 236, 238] Increases in systolic and diastolic blood pressure noted in patients receiving oral or subcutaneous therapy with sumatriptan in clinical studies generally have been small and transient and have not been accompanied by appreciable changes in heart rate;[1, 5, 45, 100, 148, 178] however, clinically important increases in blood pressure, including hypertensive crisis, have been reported rarely with sumatriptan therapy in patients with or without a history of hypertension.[1, 5] (See Cautions: Cardiovascular Effects.)

• Hormonal and Metabolic Effects

Limited data in healthy individuals indicate that subcutaneous administration of sumatriptan may increase plasma somatotropin (growth hormone), corticotropin (ACTH), and β-endorphin concentrations through stimulation of serotonin (possibly 5-HT_{1D}) receptors on the pituitary gland, which is not protected by the blood-brain

barrier.[47, 97, 122] The effect of sumatriptan on the hypothalamic-pituitary-adrenal (HPA) axis has not been studied in patients with migraine.[47] Limited data in healthy individuals suggest that stimulation of corticotropin secretion by sumatriptan may be accompanied by increased secretion of cortisol;[97] however, increased cortisol concentrations have not been consistently demonstrated with single-dose subcutaneous or oral administration of sumatriptan.[122, 161] Secretion of other pituitary hormones, such as prolactin, luteinizing hormone (LH), or follicle-stimulating hormone (FSH, follitropin), does not appear to be affected in healthy individuals receiving subcutaneous sumatriptan (6 mg); however, increases in thyrotropin (TSH) have been reported rarely in patients receiving the drug.[122, 148]

• Other Effects

Sumatriptan has been shown to prolong GI transit time following IV administration in healthy individuals.[76] In addition, large subcutaneous doses of sumatriptan (16 mg) increase esophageal motility (as measured by increases in the frequency, strength, and duration of repetitive peristaltic contractions upon swallowing).[76, 159] It has been suggested that some instances of chest pain reported in patients receiving sumatriptan in clinical trials may have been attributable to increased esophageal motility, which may itself be associated with chest pain, rather than to cardiac problems.[5, 159, 160, 163] (See Cautions: Cardiovascular Effects.)

Clinical experience with sumatriptan in patients with migraine suggests that the drug has no appreciable effect on respiratory rate.[1, 144] Bronchospasm has been reported with sumatriptan therapy, but a causal relationship between asthmatic symptoms and sumatriptan or an increase in adverse effects in asthmatic patients receiving the drug has not been established.[1, 13, 24, 148, 236, 237] (See Cautions: Respiratory Effects.)

Pharmacokinetics

In all studies described in the Pharmacokinetics section, sumatriptan was administered as the base (nasal spray) or as the succinate salt (oral tablets or injection); dosages and concentrations of the drug are expressed in terms of sumatriptan. Most of the early pharmacokinetic studies of oral sumatriptan used a dispersible formulation of the drug rather than the currently marketed film-coated tablet; the dispersible tablet is bioequivalent to the film-coated tablet.[3, 13, 44, 168]

The pharmacokinetics of sumatriptan do not appear to be altered by patient age or gender.[1, 3, 45, 146, 148] Limited data suggest that the systemic clearance and peak plasma concentrations of sumatriptan are similar in black and white healthy individuals.[1, 236]

• Absorption

Sumatriptan is rapidly absorbed following subcutaneous or oral administration; oral absorption appears to occur in the small intestine.[1, 45, 61, 89, 166, 168] The drug also is absorbed rapidly following intranasal administration.[2, 13, 123] The bioavailability of sumatriptan given subcutaneously is almost complete, averaging about 97% of that obtained with IV administration of the drug.[1, 44] The bioavailability of sumatriptan following oral or intranasal administration averages only about 15 or 17%, respectively, principally because of presystemic metabolism of the drug and in part because of incomplete absorption.[2, 13, 14, 44, 45, 61, 89, 146, 148, 166, 168, 249] The area under the plasma concentration-time curve (AUC) and peak serum concentration of sumatriptan increase linearly with single subcutaneous doses of 1-16 mg.[2, 72, 78] The

extent of sumatriptan absorption (AUC) also is dose-proportional following single oral doses of 25-200 mg; however, peak plasma concentrations after a 100-mg oral dose of sumatriptan are approximately 25% less than those predicted from a 25-mg oral dose.[148, 168, 236] Interindividual variability in the absorption of sumatriptan after oral administration results in multiple peaks in plasma concentration, possibly because of differences in the rates of gastric emptying, small-bowel transit, and/or presystemic metabolism; however, 75-80% of the final peak plasma concentration is reached within 45 minutes after dosing.[2, 13, 89, 90, 146, 168] Administration of higher than recommended single oral doses of sumatriptan (i.e., 200-400 mg) is associated with a decrease in the rate of absorption.[146, 168]

Food does not appreciably affect the oral bioavailability of sumatriptan but prolongs the time to peak concentration.[2, 13, 44, 148] Oral absorption of the drug does not appear to be affected appreciably by gastric stasis that may occur during a migraine attack;[3, 13, 45, 146] however, the time to peak concentration is prolonged by about 30 minutes.[3, 13, 45, 96, 146, 148] The pharmacokinetics of sumatriptan following subcutaneous injection reportedly are similar during migraine attacks and pain-free periods.[1] Absorption of subcutaneous sumatriptan is not affected by race or gender.[1, 13, 15, 45, 146]

Peak plasma sumatriptan concentrations averaged about 75 ng/mL and median time to peak concentration was 12 minutes in healthy men receiving a single 6-mg subcutaneous dose of the drug by manual injection in the deltoid area.[1, 148, 236] Following subcutaneous injection of a single 6-mg dose into the thigh in these individuals, peak plasma sumatriptan concentrations averaged 61 ng/mL with manual injection of the drug and 52 ng/mL when an autoinjection device was used.[1] In this study, the time to peak plasma concentration and the amount of drug absorbed were not affected by injection site or technique.[1] Peak plasma sumatriptan concentrations after administration of a single 6-mg subcutaneous dose of the drug in healthy individuals reportedly have ranged from 55-108 ng/mL at 5-20 minutes after the dose; peak plasma concentrations of 27-137 ng/mL have been reported 0.5-5 hours after administration of a single 100-mg oral dose in healthy individuals and patients with migraine.[3, 13, 45, 78, 79, 89, 96, 146, 148, 168] After a single 25- or 50-mg oral dose, peak plasma sumatriptan concentrations averaged 18 or 31 ng/mL, respectively, at 0.5-3 hours,[166, 168] while a single 100-mg oral dose of sumatriptan produced peak plasma drug concentrations averaging 51 ng/mL approximately 2-2.5 hours after drug administration.[148] In a randomized, controlled study in patients with migraine receiving sumatriptan 10, 20, or 40 mg intranasally in one or both nostrils, peak plasma sumatriptan concentrations averaged 7.7-8.7, 11.8-12.4, or 20.1-21.7 ng/mL at 0.8, 1, or 1.8 hours, respectively, following the dose.[123] The possible contribution of oral absorption of the drug to sumatriptan plasma concentrations as a result of swallowing the intranasal dose has not been determined.[2, 123, 243]

The onset of action of sumatriptan in patients with migraine or cluster headaches correlates well with peak plasma drug concentrations.[1, 9, 10, 13, 40, 49, 75, 184] Plasma sumatriptan concentrations associated with therapeutic effects in patients with migraine have ranged from 8-66 ng/mL with subcutaneous therapy and from 18-60 ng/mL with oral sumatriptan.[2, 91, 175] In controlled clinical studies in patients with moderate to severe migraine headache pain, onset of pain relief following subcutaneous injection of sumatriptan usually occurred within 10-34 minutes, maximum relief was achieved within 1-2 hours, and pain relief persisted for 9-24

hours in some patients.[1, 8, 9, 13, 47, 56, 162, 176, 181] In patients with cluster headache, the onset to pain relief following subcutaneous injection of sumatriptan generally occurs within 4-7 minutes, with resolution of the headache shortly thereafter.[40, 49, 75, 184] Onset of relief of migraine symptoms with oral sumatriptan therapy generally occurs 1-3 hours after single oral doses of 25-100 mg,[92, 148, 162, 178, 191] with maximum pain relief attained within 3-6 hours.[148, 178, 191] Although the delayed onset of action of oral versus subcutaneous sumatriptan may result from slower absorption, a small decrease in oral bioavailability of the drug also has been reported during migraine attacks.[96, 168] Compared with subcutaneous sumatriptan, the prolonged absorption observed with oral administration may lead to sustained plasma drug concentrations that delay recurrences of headache.[3, 173, 189] (See Uses: Vascular Headaches.) However, administration of a second oral dose of sumatriptan 2 hours after the first dose during a migraine attack does not influence the development of recurrences, and factors other than pharmacokinetic alterations may contribute to the development of recurrent migraine attacks.[173]

In patients with migraine who received sumatriptan 10, 20, or 40 mg intranasally, the onset of headache relief occurred within 30 minutes following the dose.[123, 243]

• Distribution

After subcutaneous administration, sumatriptan is rapidly and widely distributed into body tissues, with an apparent volume of distribution of 2.4 L/kg.[1, 14, 146, 148, 168] Following IV administration of radiolabeled sumatriptan in rats, the drug was detected in the liver, small intestine, and kidney within 10 minutes.[14] Sumatriptan is approximately 14-21% bound to plasma proteins over a concentration range of 10-1000 ng/mL.[1, 14, 45, 148]

Sumatriptan, like exogenously administered serotonin, does not cross the blood-brain barrier in appreciable amounts in animals; however, the occurrence of adverse effects such as transient drowsiness, sedation, dizziness, vertigo, and fatigue with sumatriptan therapy in humans suggests that the drug may have access to the CNS.[6, 13, 14, 67, 87, 138, 146, 176]

In vitro studies in isolated, perfused human placenta suggest that only small amounts of sumatriptan cross the placenta by passive transport.[235]

Sumatriptan is distributed into milk in humans and animals; in animals, sumatriptan concentrations are eightfold higher than concurrent maternal plasma concentrations.[1, 13, 14, 242] In a limited number of healthy lactating women, the total recovery of sumatriptan in breast milk averaged 0.24% of a single 6-mg subcutaneous dose, corresponding to an average infant exposure of 3.5% of the maternal dose on a weight-adjusted basis.[242]

Results of studies in rats given a single oral (2 mg/kg) or subcutaneous (0.5 mg/kg) dose of radiolabeled sumatriptan suggest that sumatriptan and its metabolites bind to melanin in the eye (as indicated by an ocular elimination half-life of 15-23 days); the clinical importance of this binding is unknown.[1, 148]

• Elimination

Following single subcutaneous (6 mg) or oral (50-100 mg) doses of sumatriptan in healthy individuals, the terminal elimination half-life of the drug is 1.5-2.6 hours.[1, 6,

[44, 45, 78, 79, 89, 91, 148, 166, 168] Following single-dose oral administration of large doses of sumatriptan (300-400 mg) or repeated administration of smaller doses (100 mg), a second terminal elimination phase has been observed but not characterized.[3, 6, 15, 45, 62, 79, 146, 168, 236] The prolonged elimination half-life with multiple dosing or administration of large single doses may indicate enterohepatic recycling or prolonged oral absorption and does not appear to affect substantially the disposition of the drug.[6, 15, 146, 168] Most of a dose of sumatriptan is excreted within 10-24 hours.[14, 236] Following intranasal administration of sumatriptan, the elimination half-life reportedly is about 2 hours.[249]

Metabolism is the principal clearance process for sumatriptan.[1, 3, 13, 14, 45, 148, 166] Sumatriptan is metabolized in the liver and possibly in the GI tract and is eliminated in urine and feces.[1, 3, 13, 14, 148, 166] In vitro studies suggest that sumatriptan is metabolized by monoamine oxidase (MAO), principally the A isoenzyme (MAO-A); inhibitors of this enzyme may increase systemic exposure to sumatriptan.[1, 37, 48, 148] (See Drug Interactions: Monoamine Oxidase Inhibitors.)

The principal metabolite of sumatriptan is its inactive indole acetic acid analog, which is formed by oxidative *N*-deamination of the *N*-dimethyl side chain.[1, 2, 13, 14, 104, 148, 166] The indole acetic acid metabolite of sumatriptan achieves plasma concentrations 6-7 times higher than those of sumatriptan but has a half-life similar to that of the parent compound, suggesting that clearance of this metabolite is formation-rate limited.[2, 45, 166] Other minor metabolites of sumatriptan, an ester glucuronide of the indole acetic acid derivative and an indole ethyl alcohol derivative, also have been identified.[2, 14, 104] Data in a limited number of patients with hepatic impairment indicate that the area under plasma concentration-time curve (AUC) and peak concentration of sumatriptan increase by 70%, and time to peak plasma concentration occurs 40 minutes earlier compared with such values in healthy individuals receiving a single 50-mg oral dose of sumatriptan.[148, 236] (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Sumatriptan is excreted in urine via glomerular filtration and tubular secretion,[89, 146, 168] but renal plasma clearance accounts for only 22% of the systemic clearance of 1176-1200 mL/minute.[1, 2, 3, 6, 13, 45, 78, 146, 166, 168] Since the major route of elimination is by metabolism in the liver, reduction of renal elimination is unlikely to be clinically important.[1, 13, 14, 146, 148] Following subcutaneous administration of a single 6-mg dose of sumatriptan, approximately 22 and 38-53% of the dose is excreted in urine as unchanged drug and as the indole acetic acid metabolite, respectively.[1, 45, 168] Approximately 0.6 and 3.3% of the sumatriptan dose is excreted in feces as unchanged sumatriptan and as the indole acetic acid metabolite, respectively, after subcutaneous administration.[2, 13, 14, 45]

Following administration of a single oral radiolabeled dose of sumatriptan (200 mg) in healthy individuals, 37-40 and 57-60% of the dose is excreted in feces and urine, respectively.[14, 45, 148] Only 3 and 9% of the dose of radiolabeled sumatriptan is excreted unchanged in urine and feces, respectively, after oral administration.[13, 45, 148, 166, 168] Urinary and fecal recovery of sumatriptan metabolites average 46 and 11% of the administered dose, respectively.[45, 166] It is not known whether sumatriptan metabolites excreted in feces are the metabolic product of MAO enzymes present in the GI tract or are derived from biliary excretion.[166]

Chemistry and Stability

• Chemistry

Sumatriptan is a selective agonist of vascular serotonin (5-hydroxytryptamine; 5-HT) type 1-like receptors.[1, 2, 3, 4, 5, 6, 7, 8, 223, 224, 249] Sumatriptan is structurally and pharmacologically related to serotonin, differing structurally from serotonin principally by the substitution of methane sulfonamide for the alcohol group on the indole ring of serotonin.[2, 3, 6]

Sumatriptan and sumatriptan succinate occur as white to off-white powders and are freely soluble in water and in 0.9% sodium chloride. The drug reportedly has pK_as of 4.21 and 5.67 (succinic acid), 9.63 (tertiary amine group), and 12 or greater (sulfonamide group).[1, 2, 236]

Sumatriptan succinate is commercially available as a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection and as tablets for oral administration.[1, 148] Each 0.5 mL of the 8 mg/mL injection contains 4 mg of sumatriptan and 3.8 mg of sodium chloride.[273] Each 0.5 mL of the 12 mg/mL injection contains 6 mg of sumatriptan and 3.5 mg of sodium chloride.[1] The commercially available injection has a pH of approximately 4.2-5.3 and an osmolality of 291 mOsm/kg.[1, 236] Commercially available sumatriptan tablets contain 35, 70, or 140 mg of sumatriptan succinate equivalent to 25, 50 or 100 mg, respectively, of sumatriptan.[148]

Sumatriptan nasal spray is commercially available as aqueous buffered solutions in single-use delivery devices.[249] The solutions have a pH of approximately 5.5 and osmolalities of 372 and 742 mOsm/kg for the 5 and 20 mg per 0.1 mL single-use doses, respectively.[249]

• Stability

Sumatriptan succinate injection and tablets and sumatriptan nasal spray should be protected from light and stored at 2-30°C.[1, 148]

Preparations

Sumatriptan

Routes Dosage Strengths Brand Names Manufacturer Forms Nasal Solution 5 mg/0.1 mL **Imitrex® Nasal Spray** GlaxoSmithKline 20 mg/0.1 mL **Imitrex® Nasal Spray** GlaxoSmithKline

Sumatriptan Succinate

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Tablets, film- 25 mg (of sumatriptan) **Imitrex®** GlaxoSmithKline coated 50 mg (of sumatriptan) **Imitrex®** GlaxoSmithKline 100 mg (of **Imitrex®** GlaxoSmithKline sumatriptan) Parenteral Injection, for 4 mg/0.5 mL (of **Imitrex®** (available in 0.5-mL GlaxoSmithKline subcutaneous sumatriptan) [4-mg] unit-of-use syringes) use only 6 mg/0.5 mL (of **Imitrex®** (available in 0.5-mL GlaxoSmithKline sumatriptan) [6-mg] unit-of-use syringes and as 0.5 mL[6 mg] single- dose vials)

• **Comparative Pricing**
Pricing information provided by drugstore.com.

Imitrex 20MG/ACT SOLN (GLAXO SMITH KLINE): 6/$176.64 or 18/$505.27

Imitrex 5MG/ACT SOLN (GLAXO SMITH KLINE): 1/$31.16 or 6/$174.04

Imitrex 6MG/0.5ML SOLN (GLAXO SMITH KLINE): 2/$337.72 or 7/$979.4

Imitrex STATdose 6MG/0.5ML KIT (GLAXO SMITH KLINE): 1/$138.99 or 3/$398.8

Imitrex STATdose Pen 6MG/0.5ML KIT (GLAXO SMITH KLINE): 1/$145.48 or 3/$419.58

[#] Use is not currently included in the labeling approved by the US Food and Drug Administration.

References

1. Glaxo Wellcome. Imitrex® (sumatriptan succinate) injection prescribing information. Research Triangle Park, NC; 2001 Mar.

2. Hsu VD. Sumatriptan: a new drug for vascular headache. *Clin Pharm*. 1992; 11:919-29. [IDIS 303852] [PubMed 1334452]

3. Bateman DN. Sumatriptan. *Lancet*. 1993; 341:221-4. [IDIS 308640] [PubMed 8093509]

4. Peroutka SJ. Serotonin receptor subtypes and neuropsychiatric diseases: focus on 5-HT_{1D} and 5-HT_3 receptor agents. *Pharmacol Rev*. 1991; 43:579-86. [IDIS 296518] [PubMed 1663621]

5. MacIntyre PD, Bhargava B, Hogg KJ et al. Effect of subcutaneous sumatriptan, a selective $5HT_1$ agonist, on the systemic, pulmonary, and coronary circulation. *Circulation*. 1993; 87:401-5. [IDIS 309421] [PubMed 8381056]

6. Fullerton T, Gengo FM. Sumatriptan: a selective 5-hydroxytryptamine receptor agonist for the acute treatment of migraine. *Ann Pharmacother*. 1992; 26:800-8. [IDIS 298261] [PubMed 1319244]

7. Anon. Sumatriptan for migraine. *Med Lett Drugs Ther*. 1992; 34:91-3. [PubMed 1326077]

8. Ferrari MD and the Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med*. 1991; 325:316-21. [IDIS 283296] [PubMed 1647495]

9. Cady RK, Wendt JK, Kirchner JR et al. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA*. 1991; 265:2831-5. [IDIS 281579] [PubMed 1851894]

10. Friberg L, Olesen J, Iversen HK et al. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. *Lancet*. 1991; 338:13-7. [IDIS 282832] [PubMed 1676084]

11. Fox AW, Poe TE. Use and safety of sumatriptan. *Clin Pharm*. 1993; 12:258. [IDIS 311529] [PubMed 8384541]

12. Glaxo, Research Triangle Park, NC: Personal communication.

13. Plosker GL, McTavish D. Sumatriptan: a reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs*. 1994; 47:622-51. [PubMed 7516861]

14. Dixon CM, Saynor DA, Andrew PD et al. Disposition of sumatriptan in laboratory animals and humans. *Drug Metabol Disp*. 1993; 21:761-9.

15. Dechant KL, Clissold SP. Sumatriptan: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the acute treatment of migraine and cluster headache. *Drugs*. 1992; 43:776-98. [PubMed 1379152]

16. D'Arcy PF. Adverse drug reaction (ADR) problems with sumatriptan. *Intl Pharm J*. 1992; 6:264-5.

17. D'Arcy PF. Warnings from the UK committee on safety of medicines: chest pain with sumatriptan. *Intl Pharm J*. 1992; 6:217-8.

18. Willett F, Curzen N, Adams J et al. Coronary vasospasm induced by subcutaneous sumatriptan. *BMJ*. 1992; 304:1415. [IDIS 297248] [PubMed 1320974]

19. Price LH, Charney DS, Delgado PL et al. Lithium treatment and serotoninergic function. *Arch Gen Psych*. 1989; 46:13-9.

20. Castle WM, Simmons VE. Coronary vasospasm and sumatriptan. *BMJ*. 1992; 305:117-8. [IDIS 299098] [PubMed 1322216]

21. Stricker BHC. Coronary vasospasm and sumatriptan. *BMJ*. 1992; 305:118.

22. Inman W, Kubota K. Cardiorespiratory distress after sumatriptan given by injection. *BMJ*. 1992; 305:714. [IDIS 302441] [PubMed 1327369]

23. Curtin T, Brooks AP, Roberts JA. Cardiorespiratory distress after sumatriptan given by injection. *BMJ*. 1992; 305:713-4. [IDIS 302439] [PubMed 1327368]

24. Pilgrim AJ, Lloyd DK, Simmons VE. Cardiorespiratory distress after sumatriptan given by injection. *Br Med J*. 1992;305:714. Letter. (IDIS 302439)

25. Lloyd DK, Pilgrim AJ, Simmons VE. Coronary vasospasm and sumatriptan. *BMJ*. 1992; 305:310-1. [IDIS 300103] [PubMed 1327366]

26. Anon. New medicines: sumatriptan. *Intl Pharm J*. 1992; 6:55-7.

27. Ottervanger JP, Paalman HJA, Boxma GL et al. Transmural myocardial infarction with sumatriptan. *Lancet*. 1993; 341:861-2. [IDIS 312131] [PubMed 8096565]

28. Hillis WS, Macintyre PD. Sumatriptan and chest pain. *Lancet*. 1993; 342:683. [IDIS 320009] [PubMed 8103169]

29. Hillis WS, MacIntyre PD. Sumatriptan and chest pain. *Lancet*. 1993; 341:1564-5. [IDIS 316435] [PubMed 8099643]

30. Ottervanger JP, Stricker BHC. Sumatriptan and chest pain. *Lancet*. 1993; 342:176.

31. Chester AH, O'Neil GS, Yacoub MH. Sumatriptan and ischaemic heart disease. *Lancet*. 1993; 341:1419-20. [IDIS 315064] [PubMed 8098831]

32. Bax WA, Saxena PR. Sumatriptan and ischaemic heart disease. *Lancet*. 1993; 341:1420. [IDIS 315065] [PubMed 8098832]

33. Myerburg RJ, Kessler KM, Mallon SM et al. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary artery spasm. *N Engl J Med*. 1992; 326:1451-5. [IDIS 296579] [PubMed 1574091]

34. MacLean MR, Smith GCS, Templeton AGB. Adverse reactions associated with sumatriptan. *Lancet*. 1993; 341:1092.

35. Lloyd DK, Simmons V. Adverse reactions associated with sumatriptan. *Lancet*. 1993; 341:1092. [IDIS 313075] [PubMed 8096981]

36. Cavazos JE, Caress JB, Chilukuri VR et al. Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet*. 1994; 343:1105-6. [IDIS 330002] [PubMed 7909130]

37. Cerenex Pharmaceuticals, Div. of Glaxo, Inc., Research Triangle Park, NC: Personal communication.

38. Humphrey PPA, Feniuk W. Mode of action of the anti-migraine drug sumatriptan. *Trends Pharmacol Sci*. 1991; 12:444-6. [PubMed 1665260]

39. Lovenberg TW, Erlander MG, Baron BM et al. Molecular cloning and functional expression of 5-HT_{1E}-like rat and human 5-hydroxytryptamine receptor genes. *Proc Natl Acad Sci USA*. 1993; 90:2184-8. [PubMed 8384716]

40. Cerenex Pharmaceuticals, Div. of Glaxo, Inc., Research Triangle Park, NC: Personal communication.

41. Sullivan JT, Preston KL, Testa MP et al. Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther*. 1992; 52:635-42. [IDIS 307784] [PubMed 1333934]

42. Luman W, Gray RS. Adverse reactions associated with sumatriptan. *Lancet*. 1993; 341:1091-2. [IDIS 313073] [PubMed 8096980]

43. Caekebeke JFV, Ferrari MD, Zwetsloot CP et al. Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks. *Neurology*. 1992; 42:1522-6. [IDIS 300080] [PubMed 1322512]

44. Lacey LF, Fowler PA. The clinical pharmacology of sumatriptan. *Cephalalgia*. 1993; 13(Suppl 13):156.

45. Fowler PA, Lacey LF, Thomas M et al. The clinical pharmacology, pharmacokinetics, and metabolism of sumatriptan. *Eur Neurol*. 1991; 31:291-4. [PubMed 1653135]

46. Dahlof C. Headache recurrence after subcutaneous sumatriptan and early treatment. *Lancet*. 1992; 340:909. [IDIS 303758] [PubMed 1357313]

47. Ferrari MD, Saxena PR. Clinical and experimental effects of sumatriptan in humans. *Trends Pharmacol Sci*. 1993; 14:129-33. [PubMed 8390743]

48. Anon. Sumatriptan: a new approach to migraine. *Drug Ther Bull*. 1992; 30:85-7. [PubMed 1330474]

49. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med*. 1991; 325:322-6. [IDIS 283297] [PubMed 1647496]

50. Lloyd DK, Pilgrim AJ. Sumatriptan and recurrence of migraine. *Lancet*. 1992; 340:1110. [IDIS 304617] [PubMed 1357515]

51. Blau JN. Sumatriptan and recurrence of migraine. *Lancet*. 1992; 340:1110. [IDIS 304618] [PubMed 1357514]

52. Black P, Caldwell J. Skin sensitivity to sumatriptan. *N Z Med J*. 1994; 107:20- 1. [IDIS 325657] [PubMed 8295755]

53. Sykes RS, Castle W, Palmer J. Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet*. 1994; 343:1299-300. [IDIS 330600] [PubMed 7910310]

54. Carp H, Singh PJ, Vadhera R et al. Effects of the serotonin-receptor agonist sumatriptan on postdural puncture headache: report of six cases. *Anesth Analg*. 1994; 79:180-2. [IDIS 332633] [PubMed 8010433]

55. Solbach MP, Waymer RS. Treatment of menstruation-associated migraine headache with subcutaneous sumatriptan. *Obstet Gynecol*. 1993; 82:769-72. [IDIS 321578] [PubMed 8414324]

56. Cady RK, Dexter J, Sargent JD et al. Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. *Neurology*. 1993; 43:1363-8. [IDIS 317183] [PubMed 8392150]

57. Thomson AN, Arthur GP, Bergin PS et al. Subcutaneous sumatriptan in acute treatment of migraine: a multicentre New Zealand trial. *N Z Med J*. 1993; 106:171-3. [IDIS 316753] [PubMed 8389026]

58. Bousser MG, d'Allens H, Richard A et al. Efficacy of subcutaneous sumatriptan in the acute treatment of early-morning migraine: a placebo-controlled trial. *J Int Med*. 1993; 234:211-6.

59. Goadsby PJ, Zagami AS, Donnan GA et al. Oral sumatriptan in acute migraine. *Lancet*. 1991; 338:782-3. [IDIS 286705] [PubMed 1681162]

60. Tfelt-Hansen P, Sperling B, Winter PDO'B. Transient additional effect of sumatriptan on ergotamine-induced constriction of peripheral arteries in man. *Clin Pharmacol Ther*. 1992; 51:149.

61. Posner JB. Disorders of sensation: headache and other pain. In: Wyngaarden JB, Smith LH Jr, Bennett JC, eds. Cecil textbook of medicine. 19th ed. Philadelphia: WB Saunders Company; 1992:2116-24.

62. Scott AK, Walley T, Breckenridge AM et al. Lack of an interaction between propranolol and sumatriptan. *Br J Clin Pharmacol*. 1991; 32:581-4. [IDIS 294713] [PubMed 1659437]

63. Kaube H, May A, Diener HC et al. Sumatriptan. *BMJ*. 1994; 308:1573-4.

64. Osborne MJ, Austin RCT, Dawson KJ et al. Is there a problem with long term use of sumatriptan in acute migraine? *Br Med J*. 1994; 308:113. (IDIS 325298)

65. den Boer MO, Somers JAE, Saxena PR. Lack of effect of the antimigraine drugs, sumatriptan, ergotamine and dihydroergotamine on arteriovenous anastomotic shunting in the dura mater of the pig. *Br J Pharmacol*. 1992; 107:577-83. [PubMed 1330188]

66. Feniuk W, Humphrey PPA, Perren MJ. The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetized dogs. *Br J Pharmacol*. 1989; 96:83-90. [PubMed 2538184]

67. Kaube H, Hoskin KL, Goadsby PJ. Inhibition by sumatriptan of central trigeminal neurones only after blood-brain barrier disruption. *Br J Pharmacol*. 1993; 109:788-92. [PubMed 8395298]

68. den Boer MO, Villalon CM, Heiligers JPC et al. Role of 5-HT_1-like receptors in the reduction of porcine cranial arteriovenous anastomotic shunting by sumatriptan. *Br J Pharmacol*. 1991; 102:323-30. [PubMed 1849764]

69. Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D et al. 5-HT receptors mediating contractions of the isolated human coronary artery. *Eur J Pharmacol*. 1993; 239:203-10. [PubMed 7693489]

70. Perren MJ, Feniuk W, Humphrey PPA. The selective closure of feline carotid arteriovenous anastomoses (AVAs) by GR43175. *Cephalalgia*. 1989; 9(Suppl 9):41-6. [PubMed 2544282]

71. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol*. 1993; 33:48-56. [PubMed 8388188]

72. Mathew NT, Dexter J, Couch J et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. *Arch Neurol*. 1992; 49:1271-6. [PubMed 1333181]

73. Jansen I, Olesen J, Edvinsson L. 5-Hydroxytryptamine receptor characterization of human cerebral, middle meningeal and temporal arteries: regional differences. *Acta Physiol Scand*. 1993; 147:141-50. [PubMed 8386424]

74. Nozaki K, Moskowitz MA, Boccalini P. CP-93,129, sumatriptan, dihydroergotamine block c-fos expression within rat trigeminal nucleus caudalis caused by chemical stimulation of the meninges. *Br J Pharmacol*. 1992; 106:409-15. [PubMed 1327382]

75. Ekbom K, Monstad I, Prusinski A et al. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand*. 1993; 88:63-9. [PubMed 8396833]

76. Houghton LA, Fowler P, Keene ON et al. Effect of sumatriptan, a new selective $5HT_1$-like agonist, on liquid gastric emptying in man. *Aliment Pharmacol Ther*. 1992; 6:685-91. [PubMed 1336675]

77. Humphrey PPA, Feniuk W, Perren MJ et al. The pharmacology of the novel 5-HT_1-like receptor agonist, GR43175. *Cephalalgia*. 1989; 9(Suppl 9):23-33. [PubMed 2544280]

78. Gutterman DL, Plachetka JR, Donn K et al. Evaluation of the safety and pharmacokinetic properties of single subcutaneous doses of GR43175C in healthy, adult, male volunteers. *Cephalalgia*. 1989; 9(Suppl 10):412-3.

79. Busch MA, Plachetka JR, Donn KH. Evaluation of the pharmacokinetics and safety of ascending single oral doses of GR43175 administered to healthy male volunteers. *Cephalalgia*. 1989; 9(Suppl 10):414-5.

80. Italian Society for the Study of Headache. Guidelines and recommendations for the treatment of migraine. *Funct Neurol*. 1993; 8:441-6. [PubMed 8150324]

81. Muly EC, McDonald W, Steffens D et al. Serotonin syndrome produced by a combination of fluoxetine and lithium. *Am J Psychiatry*. 1993; 150:1565. [IDIS 321772] [PubMed 8379573]

82. Tansey MJB, Pilgrim AJ, Martin PM. Long-term experience with sumatriptan in the treatment of migraine. *Eur Neurol*. 1993; 33:310-5. [PubMed 8394239]

83. Peroutka SJ, McCarthy BG. Sumatriptan (GR43175) interacts selectively with 5-HT_{1B} and 5-HT_{1D} binding sites. *Eur J Pharmacol*. 1989; 163:133-6. [PubMed 2545459]

84. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. *Eur Neurol*. 1992; 32:177-84. [PubMed 1317294]

85. Chester AH, Martin GR, Bodelsson M et al. 5-Hydroxytryptamine receptor profile in healthy and diseased human epicardial coronary arteries. *Cardiovasc Res*. 1990; 24:932-7. [PubMed 2272071]

86. Sumner MJ, Humphrey PPA. Sumatriptan (GR43175) inhibits cyclic-AMP accumulation in dog isolated saphenous vein. *Br J Pharmacol*. 1990; 99:219-20. [PubMed 2158369]

87. Humphrey PPA, Feniuk W, Perren MJ et al. Serotonin and migraine. *Ann NY Acad Sci*. 1990; 600:587-98. [PubMed 2252337]

88. Parsons AA, Whalley ET. Characterization of the 5-hydroxytryptamine receptor which mediates contraction of the human isolated basilar artery. *Cephalalgia*. 1989; 9(Suppl 9):47-51. [PubMed 2544283]

89. Fowler PA, Thomas M, Lacey LF et al. Early studies with the novel 5-HT_1-like agonist GR43175 in healthy volunteers. *Cephalalgia*. 1989; 9(Suppl 9):57-62. [PubMed 2544285]

90. Perrin VL, Farkkila M, Goasguen J et al. Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. *Cephalalgia*. 1989; 9(Suppl 9):63-72. [PubMed 2544286]

91. Tfelt-Hansen P, Brand J, Dano P et al. Early clinical experience with subcutaneous GR43175 in acute migraine: an overview. *Cephalalgia*. 1989; 9(Suppl 9):73-7. [PubMed 2544287]

92. The Oral Sumatriptan International Multiple-Dose Study Group. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. *Eur Neurol*. 1991; 31:306-13. [PubMed 1653138]

93. The Sumatriptan Auto-Injector Study Group. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. *Eur Neurol*. 1991; 31:323-31. [PubMed 1653140]

94. Brown EG, Endersby CA, Smith RN et al. The safety and tolerability of sumatriptan: an overview. *Eur Neurol*. 1991; 31:339-44. [PubMed 1653142]

95. Moskowitz MA, Macfarlane R. Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev*. 1993; 5:159-77. [PubMed 8217498]

96. Cutler NR, Hussey EK, Sramek JJ et al. Pharmacokinetics (PK) of oral sumatriptan in migraine patients during an attack and while painfree. *Biol Psych*. 1992; 31:180A.

97. Facchinetti F, Nappi RE, Sances G et al. The neuroendocrine effects of sumatriptan, a specific ligand for 5-HT_1-like receptors. *Clin Endocrinol*. 1994; 40:211-4.

98. McCarthy BG, Peroutka SJ. Comparative neuropharmacology of dihydroergotamine and sumatriptan (GR43175). *Headache*. 1989; 29:420-2. [PubMed 2547733]

99. Galer BS, Lipton RB, Solomon S et al. Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache*. 1991; 31:446-50. [PubMed 1774159]

100. Panconesi A, Anselmi B, Curradi C et al. Comparison between venoconstrictor effects of sumatriptan and ergotamine in migraine patients. *Headache*. 1994; 34:194-7. [PubMed 8014033]

101. Peroutka SJ, Havlik S, Oksenberg D. Wolff award presentation 1993. Anti-migraine drug interactions with cloned human 5-hydroxytryptamine$_1$ receptor subtypes. *Headache*. 1993; 33:347-50. [PubMed 8397171]

102. Connor HE, Feniuk W, Humphrey PPA. 5-Hydroxytryptamine contracts human coronary arteries predominantly via 5-HT$_2$ receptor activation. *Eur J Pharmacol*. 1989; 161:91-4. [PubMed 2542039]

103. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache: neuropeptide changes and effects of acute attacks therapies. *Brain*. 1994; 117:427-34. [PubMed 7518321]

104. Dixon CM, Park GR, Tarbit MH. Characterization of the enzyme responsible for the metabolism of sumatriptan in human liver. *Biochem Pharmacol*. 1994; 47:1253-7. [PubMed 8161354]

105. Humphrey PPA, Feniuk W, Perren MJ et al. GR43175, a selective agonist for the 5- HT$_1$-like receptor in dog isolated saphenous vein. *Br J Pharmacol*. 1988; 94:1123-32. [PubMed 2850055]

106. Rebeck GW, Maynard KI, Hyman BT et al. Selective 5-HT$_{1D\,\alpha}$ serotonin receptor gene expression in trigeminal ganglia: implications for antimigraine drug development. *Proc Natl Acad Sci USA*. 1994; 91:3666-9. [PubMed 8170966]

107. Totaro R, De Matteis G, Marini C et al. Effect of sumatriptan on cerebral blood flow velocity measured by transcranial doppler. *Stroke*. 1993; 24:516.

108. Nappi G, Sicuteri F, Byrne M et al. Oral sumatriptan compared with placebo in the acute treatment of migraine. *J Neurol*. 1994; 241:138-44. [PubMed 8164015]

109. Ebersole BJ, Diglio CA, Kaufman DW et al. 5-Hydroxytryptamine$_1$-like receptors linked to increases in intracellular calcium concentration and inhibition of cyclic AMP accumulation in cultured vascular smooth muscle cells derived from bovine basilar artery. *J Pharmacol Exp Ther*. 1993; 266:692-9. [PubMed 8394913]

110. Den Boer MO, Villalon CM, Saxena PR. 5-HT$_1$-like receptor mediated changes in porcine carotid haemodynamics: are 5-HT$_{1D}$ receptors involved? *Arch Pharmacol*. 1992; 345:509-15.

111. Ensink FBM for the Sumatriptan International Study Group. Subcutaneous sumatriptan in the acute treatment of migraine. *J Neurol*. 1991; 238(Suppl 1):S66-9.

112. Wayne VS. A possible relationship between migraine and coronary artery spasm. *Aust N Z J Med*. 1986; 16:708-10. [PubMed 3469972]

113. Saper JR. Ergotamine dependency: a review. *Headache*. 1987; 27:435-8. [PubMed 3117735]

114. Lloyd DK, Arnold WSG. Long term use of sumatriptan. *BMJ*. 1994; 308:533.

115. Miller D, Waters DD, Warnica W et al. Is variant angina the coronary manifestation of a generalized vasospastic disorder? *N Engl J Med*. 1981; 304:763-6.

116. Leviton A, Malvea B, Graham JR. Vascular diseases, mortality, and migraine in the parents of migraine patients. *Neurology*. 1974; 24:669-72. [PubMed 4858091]

117. Moskowitz MA, Buzzi MG. Neuroeffector functions of sensory fibres: implications for headache mechanisms and drug actions. *J Neurol*. 1991; 238(Suppl 1):S18-22. [PubMed 2045826]

118. Saxena PR, Den Boer MO. Pharmacology of antimigraine drugs. *J Neurol*. 1991; 238(Suppl 1):S28-35. [PubMed 1646288]

119. Feniuk W, Humphrey PPA, Perren MJ et al. Rationale for the use of 5-HT_1- like agonists in the treatment of migraine. *J Neurol*. 1991; 238(Suppl 1):S57-61. [PubMed 1646289]

120. Bax WA, Van Heuven-Nolsen D, Bos E et al. 5-hydroxytryptamine-induced contractions of the human isolated saphenous vein: involvement of 5-HT_2 and 5-HT_{1D}-like receptors, and a comparison with grafted veins. *Arch Pharmacol*. 1992; 345:500-8.

121. Buzzi MG, Carter WB, Shimizu T et al. Dihydroergotamine and sumatriptan attenuate levels of CGRP in plasma in rat superior sagittal sinus during electrical stimulation of the trigeminal ganglion. *Neuropharmacology*. 1991; 30:1193-200. [PubMed 1663596]

122. Franceschini R, Cataldi A, Garibaldi A et al. The effects of sumatriptan on pituitary secretion in man. *Neuropharmacology*. 1994; 33:235-9. [PubMed 8035909]

123. The Finnish Sumatriptan Group and the Cardiovascular Clinical Research Group. A placebo-controlled study of intranasal sumatriptan for the acute treatment of migraine. *Eur Neurol*. 1991; 31:332-8. [PubMed 1653141]

124. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan and cafergot in the acute treatment of migraine. *Eur Neurol*. 1991; 31:314-22. [PubMed 1653139]

125. Buzzi MG, Dimitriadou V, Theoharides TC et al. 5-Hydroxytryptamine receptor agonists for the abortive treatment of vascular headaches block mast cell, endothelial

and platelet activation within the rat dura mater after trigeminal stimulation. *Brain Res.* 1992; 583:137-49. [PubMed 1324091]

126. Bruinvels AT, Lery H, Nozulak J et al. 5-HT_{1D} binding sites in various species: similar pharmacological profile in dog, monkey, calf, guinea-pig and human brain membranes. *Arch Pharmacol*. 1992; 346:243-8.

127. De Keyser J, Vauquelin G, De Backer JP et al. What intracranial tissues in humans contain sumatriptan-sensitive serotonin 5-HT_1-type receptors? *Neurosci Lett*. 1993; 164:63-6.

128. Waeber C, Hoyer D, Palacios JM. GR43175: a preferential 5-HT_{1D} agent in monkey and human brains as shown by autoradiography. *Synapse*. 1989; 4:168-70. [PubMed 2551055]

129. Bruinvels AT, Landwehrmeyer B, Probst A et al. A comparative autoradiographic study of 5-HT_{1D} binding sites in human and guinea-pig brain using different radioligands. *Molecul Brain Res.* 1994; 21:19-29.

130. Cocks TM, Kemp BK, Pruneau D et al. Comparison of contractile responses to 5- hydroxytryptamine and sumatriptan in human isolated coronary artery: synergy with the thromboxane A_2-receptor agonist, U46619. *Br J Pharmacol*. 1993; 110:360-8. [PubMed 8220898]

131. Edvinsson L, Jansen I, Olesen J. Characterization of human craniovascular 5-hydroxytryptamine receptors. *Front Headache Res*. 1992; 2:129-36.

132. Beer MS, Stanton JA, Bevan Y et al. L-694,247: a potent 5-HT_{1D} receptor agonist. *Br J Pharmacol*. 1993; 110:1196-200. [PubMed 8298808]

133. Huang Z, Byun B, Matsubara T et al. Time-dependent blockade of neurogenic plasma extravasation in dura mater by 5-$HT_{1B/D}$ agonists and endopeptidase 24.11. *Br J Pharmacol*. 1993; 108:331-5. [PubMed 8383561]

134. Brennum J, Kjeldsen M, Olesen J. The 5-HT_1-like agonist sumatriptan has a significant effect in chronic tension-type headache. *Cephalalgia*. 1992; 12:375-9. [PubMed 1335361]

135. Hamblin MW, Metcalf MA, McGuffin RW et al. Molecular cloning and functional characterization of a human 5-HT_{1B} serotonin receptor: a homologue of the rat 5- HT_{1B} receptor with 5-HT_{1D}-like pharmacological specificity. *Biochem Biophys Res Comm*. 1992; 184:752-9. [PubMed 1315531]

136. Sleight AJ, Cervenka A, Peroutka SJ. In vivo effects of sumatriptan (GR 43175) on extracellular levels of 5-HT in the guinea pig. *Neuropharmacology*. 1990; 29:511-3. [PubMed 2166920]

137. Adham N, Kao HT, Schechter LE et al. Cloning of another human serotonin receptor (5-HT_{1F}): a fifth 5-HT_1 receptor subtype coupled to the inhibition of adenylate cyclase. *Proc Natl Acad Sci USA*. 1993; 90:408-12. [PubMed 8380639]

138. Connor HE, Stubbs CM, Feniuk W et al. Effect of sumatriptan, a selective 5-HT_1-like receptor agonist, on pial vessel diameter in anaesthetised cats. *J Cerebral Blood Flow Metabol*. 1992; 12:514-9.

139. Maura G, Thellung S, Andrioli GC et al. Release-regulating serotonin 5-HT_{1D} autoreceptors in human cerebral cortex. *J Neurochem*. 1993; 60:1179-82. [PubMed 8382263]

140. Diener HC, Haab J, Peters C et al. Subcutaneous sumatriptan in the treatment of headache during withdrawal from drug-induced headache. *Headache*. 1991; 31:205-9. [PubMed 1646775]

141. Mills KC. Serotonin syndrome. *Am Fam Physician*. 1995; 52:1474-82.

142. Henry P, d'Allens H, French Migraine Network Bordeaux-Lyon-Grenoble. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache*. 1993; 33:432-5. [PubMed 8262783]

143. Schoenen J, Bulcke J, Caekebeke J et al. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device: comparison with customary treatment in an open, longitudinal study. *Cephalalgia*. 1994; 14:55-63. [PubMed 8200027]

144. Lloyd DK, Pilgrim AJ. The safety of sumatriptan in asthmatic migraineurs. *Cephalalgia*. 1993; 13:201-4. [PubMed 8395345]

145. Banerjee M, Findley LJ. Sumatriptan in the treatment of acute migraine with aura. *Cephalalgia*. 1992; 12:39-44. [PubMed 1313746]

146. Scott AK. Sumatriptan: clinical pharmacokinetics. *Clin Pharmacokinet*. 1994; 27:337-44. [PubMed 7851052]

147. Bartsch P, Maggi S, Kleger GR et al. Sumatriptan for high altitude headache. *Lancet*. 1994; 344:1445. [IDIS 338591] [PubMed 7968111]

148. GlaxoSmithKline. Imitrex® (sumatriptan succinate) tablets prescribing information. Research Triangle Park, NC; 2001 Jun.

149. Chiari M, Manzoni GC, van de Geijn EJ. Ischemic optic neuropathy after sumatriptan in a migraine with aura patient. *Headache*. 1994; 34:237-8. [PubMed 8014044]

150. Palmer J, Feldman R, Mancini GB et al. Glyceryl trinitrate reversal of post-sumatriptan coronary artery narrowing. *Lancet*. 1995; 345:1366. [IDIS 348711] [PubMed 7752771]

151. Szabo CP. Fluoxetine and sumatriptan: possibly a counterproductive combination. *J Clin Psychiatry*. 1995; 56:37-8. [IDIS 342757] [PubMed 7836342]

152. Jayamaha JEL, Street MK. Fatal cerebellar infarction in a migraine sufferer whilst receiving sumatriptan. *Intensive Care Med*. 1995; 21:82-3. [IDIS 341704] [PubMed 7560482]

153. La Porta LD. Recurrent depression after sumatriptan administration for treatment of migraine. *J Clin Psychopharmacol*. 1995; 15:81-2. [IDIS 341600] [PubMed 7714232]

154. Anon. Sumatriptan: rebound headache and migraine exacerbation. *CMAJ*. 1995; 152:66.

155. Evers S, Husstedt IW, Enbergs A. Coronary angiography in migraine patient after subcutaneous sumatriptan. *Lancet*. 1995; 345:198. [IDIS 341082] [PubMed 7823698]

156. Garcia G, Kaufman MB, Colucci RD. Dystonic reaction associated with sumatriptan. *Ann Pharmacother*. 1994; 28:1199. [IDIS 337083] [PubMed 7841582]

157. Shane R. Development and implementation of practice guidelines (part 1). *Hosp Formul*. 1994; 29:711-9. [IDIS 336987] [PubMed 10137848]

158. Bates D, Ashford E, Dawson R et al. Subcutaneous sumatriptan during the migraine aura. *Neurology*. 1994; 44:1587-92. [IDIS 335543] [PubMed 7936279]

159. Houghton LA, Foster JM, Whorwell PJ et al. Is chest pain after sumatriptan oesophageal in origin? *Lancet*. 1994; 344:985-6.

160. Hood S, Birnie D, MacIntyre PD et al. Sumatriptan-induced chest pain. *Lancet*. 1994; 344:1500-1. [IDIS 339304] [PubMed 7832891]

161. Entwisle SJ, Fowler PA, Thomas M et al. The effects of oral sumatriptan, a 5-HT_1 receptor agonist, on circulating ACTH and cortisol concentrations in man. *Br J Clin Pharmacol*. 1995; 39:389-95. [IDIS 345219] [PubMed 7640145]

162. Akpunonu BE, Mutgi AB, Federman DJ et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. *Ann Emerg Med*. 1995; 25:464-9. [IDIS 345053] [PubMed 7710149]

163. Boyd IW, Rohan AP. Sumatriptan-induced chest pain. *Lancet*. 1994; 344:1704-5. [IDIS 339816] [PubMed 7996981]

164. Bhanji NH. Sumatriptan and chest pain. *Can J Hosp Pharm*. 1994; 47:232-4.

165. Gaist D, Sindrup S, Hallas J et al. Misuse of sumatriptan. *Lancet*. 1994; 344:1090. [IDIS 337456] [PubMed 7934471]

166. Warner PE, Brouwer KLR, Hussey EK et al. Sumatriptan absorption from different regions of the human gastrointestinal tract. *Pharm Res*. 1995; 12:138-43. [PubMed 7724476]

167. Anon. Drugs for migraine. *Med Lett Drugs Ther*. 1995; 37:17-20. [PubMed 7862023]

168. Lacey LF, Hussey EK, Fowler PA. Single dose pharmacokinetics of sumatriptan in healthy volunteers. *Eur J Clin Pharmacol*. 1995; 47:543-8. [IDIS 345294] [PubMed 7768259]

169. Ferrari MD, Haan J, Blokland AK et al. Cerebral blood flow during migraine attacks without aura and effect of sumatriptan. *Arch Neurol*. 1995; 52:135-9. [PubMed 7848120]

170. Pini LA, Trenti T. Does chronic use of sumatriptan induce dependence? *Headache*. 1994; 34:600.

171. Gross MLP, Kay J, Turner AM et al. Sumatriptan in acute migraine using a novel cartridge system self-injector. *Headache*. 1994; 34:559-63. [PubMed 7843948]

172. Catarci T, Fiacco F, Argentino C et al. Ergotamine-induced headache can be sustained by sumatriptan daily intake. *Cephalalgia*. 1994; 14:374-5. [PubMed 7828198]

173. Ferrari MD, James MH, Bates D et al. Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia*. 1994; 14:330-8. [PubMed 7828190]

174. Russell MB, Holm-Thomsen OE, Nielsen MR et al. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia*. 1994; 14:291-6. [PubMed 7954759]

175. Doenicke A, Melchart D, Bayliss EM. Effective improvement of symptoms in patients with acute migraine by GR43175 administered in dispersible tablets. *Cephalalgia*. 1989; 9(Suppl 9):89-92. [PubMed 2544290]

176. Ferrari MD, Saxena PRS. Clinical effects and mechanism of action of sumatriptan in migraine. *Clin Neurol Neurosurg*. 1992; 94(Suppl):S73-7.

177. Hoyer D, Clarke DE, Fozard JR et al. International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). *Pharmacol Rev*. 1994; 46:157-203. [PubMed 7938165]

178. Tansey MJB, Pilgrim AJ, Lloyd K. Sumatriptan in the acute treatment of migraine. *J Neurol Sci*. 1993; 114:109-16. [PubMed 8381852]

179. MacDonald JT. Treatment of juvenile migraine with subcutaneous sumatriptan. *Headache*. 1994; 34:581-2. [PubMed 7843952]

180. The Oral Sumatriptan Dose-Defining Study Group. Sumatriptan—an oral dose-defining study. *Eur Neurol*. 1991; 31:300-5. [PubMed 1653137]

181. Cady RK, Rubino J, Crummett D et al. Oral sumatriptan in the treatment of recurrent headache. *Arch Fam Med*. 1994; 3:766-72. [PubMed 7987510]

182. Suchowersky O. Rebound headaches due to sumatriptan. *Neurology*. 1993; 43(Suppl 2):A326.

183. Ekbom K, Krabbe A, Micelli G et al et al. Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). *Cephalalgia*. 1995; 15:230-6. [PubMed 7553814]

184. Hardebo JE. Subcutaneous sumatriptan in cluster headache: a time study of the effect on pain and autonomic symptoms. *Headache*. 1993; 33:18-21. [PubMed 8382200]

185. Monstad I, Krabbe A, Micieli G et al. Preemptive oral treatment with sumatriptan during a cluster period. *Headache*. 1995; 35:607-13. [PubMed 8550362]

186. Fanciullacci M, Alessandri M, Figini M et al. Increase in plasma calcitonin gene-related peptide from the extracerebral circulation during nitroglycerin-induced cluster headache attack. *Pain*. 1995; 60:119-23. [PubMed 7540279]

187. Rani PU, Naidu MUR, Rao TRK et al. Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest*. 1996; 11:300-4.

188. Drummond PD, Lance JW. Thermographic changes in cluster headache. *Neurology*. 1984; 34:1292-8. [IDIS 191821] [PubMed 6541301]

189. Rapoport AM, Visser WH, Cutler NR et al. Oral sumatriptan in preventing headache recurrence after treatment of migraine attacks with subcutaneous sumatriptan. *Neurology*. 1995; 45:1505-9. [IDIS 351281] [PubMed 7644049]

190. Cutler N, Mushet GR, Davis R et al. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. *Neurology*. 1995; 45(Suppl 7):S5-9.

191. Rederich G, Rapoport A, Cutler N et al. Oral sumatriptan for the long-term treatment of migraine: clinical findings. *Neurology*. 1995; 45(Suppl 7):S15-20.

192. Blier P, Bergeron R. The safety of concomitant use of sumatriptan and antidepressant treatments. *J Clin Psychopharmacol*. 1995; 15:106-9. [IDIS 345845] [PubMed 7782482]

193. Diamond S. The use of sumatriptan in patients on monoamine oxidase inhibitors. *Neurology*. 1995; 45:1039-40. [IDIS 348476] [PubMed 7783861]

194. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology*. 1995; 45:1211-3. [IDIS 348482] [PubMed 7783891]

195. Goadsby PJ, Olesen J. Diagnosis and management of migraine. *BMJ*. 1996; 312:1279-83. [IDIS 365075] [PubMed 8634619]

196. Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. *Cephalalgia*. 1994; 14:320-7. [PubMed 7828188]

197. Moskowitz MA. Neurogenic inflammation in the pathophysiology and treatment of migraine. *Neurology*. 1993; 43(Suppl 3):S16-20. [PubMed 8389008]

198. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*. 1988; 8(Suppl 7):19-28.

199. Robbins L. Intranasal lidocaine for cluster headache. *Headache*. 1995; 35:83- 4. [PubMed 7737866]

200. Kudrow L, Kudrow DB. Intranasal lidocaine. *Headache*. 1995; 35:565-6. [PubMed 8530286]

201. Kittrelle JP, Grouse DS, Seybold ME. Cluster headache: local anesthetic abortive agents. *Arch Neurol*. 1985; 42:496-8. [PubMed 3994568]

202. Ghose RR. SUNCT syndrome. *Med J Aust*. 1995; 162:667-8. [IDIS 349917] [PubMed 7603383]

203. Choi A, Laurito CE, Cunningham FE. Pharmacologic management of postdural puncture headache. *Ann Pharmacother*. 1996; 30:831-9. [IDIS 369043] [PubMed 8826568]

204. Burtscher M, Likar R, Nachbauer W et al. Ibuprofen versus sumatriptan for high-altitude headache. *Lancet*. 1995; 346:254-5. [IDIS 351898] [PubMed 7616830]

205. Mathew NT. Long-term subcutaneous sumatriptan in cluster headache. *Cephalalgia*. 1995; 15:164. [PubMed 7553802]

206. Benson JM, Zorn SL, Book LS. Sumatriptan in the treatment of cyclic vomiting. *Ann Pharmacother*. 1995; 29:997-9. [IDIS 354740] [PubMed 8845562]

207. Maizels M, Scott B, Cohen W et al. Intranasal lidocaine for treatment of migraine. *JAMA*. 1996; 276:319-21. [IDIS 368694] [PubMed 8656545]

208. Kudrow L, Kudrow DB, Sandweiss JH. Rapid and sustained relief of migraine attacks with intranasal lidocaine: preliminary findings. *Headache*. 1995; 35:79-82. [PubMed 7737865]

209. Ekbom K, Waldenlind E, Cole J et al. Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. *Cephalalgia*. 1992; 12:254-6. [PubMed 1326405]

210. Stovner LJ, Sjaastad O. Treatment of headache and its variants. *Curr Opin Neurol*. 1995; 8:243-7. [PubMed 7551127]

211. Stratton SJ. Sumatriptan: a clinical standard? *Ann Emerg Med*. 1995; 25:538- 9. Letter. (IDIS 345057)

212. Stratton SJ. Sumatriptan and migraine. *Ann Emerg Med*. 1996; 27:388. [IDIS 361196] [PubMed 8599507]

213. Akpunonu BE, Mutgi AB. Sumatriptan and migraine. *Ann Emerg Med*. 1996; 27:387-8. [IDIS 361195] [PubMed 8599506]

214. Dahlof C, Ekbom K, Persson L. Clinical experiences from Sweden on the use of subcutaneously administered sumatriptan in migraine and cluster headache. *Arch Neurol*. 1994; 51:1256-61. [PubMed 7986182]

215. Anthony M, Hinterberger H, Lance JW. Plasma serotonin in migraine and stress. *Arch Neurol*. 1967; 16:544-52. [PubMed 5297855]

216. Kimball RW, Friedman AP, Vallejo E. Effect of serotonin in migraine patients. *Neurology*. 1960; 10:107-11. [PubMed 14409092]

217. Wilkinson M, Pfaffenrath V, Schoenen J et al. Migraine and cluster headache—their management with sumatriptan: a critical review of the current clinical experience. *Cephalalgia*. 1995; 15:337-57. [PubMed 8536293]

218. Mueller L, Gallagher RM, Ciervo CA. Vasospasm-induced myocardial infarction with sumatriptan. *Headache*. 1996; 36:329-31. [PubMed 8682677]

219. Shader RI. I read a recent report suggesting a causal relationship between a dystonic reaction in a patient and her use of sumatriptan. Is this likely? *J Clin Psychopharmacol*. 1995; 15:231. Commentary. (IDIS 347590)

220. Ottervanger JP, van Witsen TB, Valkenburg HA et al. Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol*. 1994; 47:305-9. [IDIS 340281] [PubMed 7875179]

221. Dachs R, Vitillo J. Angioedema associated with sumatriptan administration. *Am J Med*. 1995; 99:684-5. [PubMed 7503094]

222. Bakshi R, Yan-Go FL. Prolonged marijuana-like dysphoria after subcutaneous sumatriptan. *Ann Pharmcother*. 1996; 30:683.

223. Fuller RW. Mechanisms and functions of serotonin neuronal systems: opportunities for neuropeptide interactions. *Ann NY Acad Sci*. 1996; 780:176-84. [PubMed 8602731]

224. Pierce PA, Xie GX, Peroutka SJ et al. Dual effect of the serotonin agonist, sumatriptan, on peripheral neurogenic inflammation. *Reg Anesth*. 1996; 21:219-25. [PubMed 8744664]

225. Facchinetti F, Bonellie G, Kangasniemi P et al et al. The efficacy and safety of subcutaneous sumatriptan in the acute treatment of menstrual migraine. *Obstet Gynecol*. 1995; 86:911-6. [IDIS 356476] [PubMed 7501338]

226. Winner P, Ricalde O, Le Force B et al. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol*. 1996; 53:180-4. [PubMed 8639069]

227. Stallard N, Barry P. Another complication of the combined extradural-subarachnoid technique. *Br J Anaesth*. 1995; 75:370-1. [IDIS 352994] [PubMed 7547064]

228. Gawel MJ, Rothbart P, Jacobs H. Subcutaneous sumatriptan in the treatment of acute episodes of posttraumatic headache. *Headache*. 1993; 33:96-7. [PubMed 8384612]

229. Dahlof C. Subcutaneous sumatriptan does not abort attacks of chronic paroxysmal hemicrania (CPH). *Headache*. 1993; 33:201-2. [PubMed 8388371]

230. Hannerz J, Jogestrand T. Intracranial hypertension and sumatriptan efficacy in a case of chronic paroxysmal hemicrania which became bilateral. *Headache*. 1993; 33:320-3. [PubMed 8394301]

231. Hannerz J, Greitz D, Hansson P et al. SUNCT may be another manifestation of orbital venous vasculitis. *Headache*. 1992; 32:384-9. [PubMed 1399559]

232. Bonuccelli U, Nuti A, Lucetti C et al. Amitriptyline and dexamethasone combined treatment in drug-induced headache. *Cephalalgia*. 1996; 16:197-200.

233. Hannington-Kiff JG. Sumatriptan relieves and prevents peri-operative migraine attacks. *Anaesthesia*. 1993; 48:144-6. [PubMed 8384803]

234. Wing Y-K, Clifford EM, Sheehan BD et al. Paroxetine treatment and the prolactin response to sumatriptan. *Psychopharmacology*. 1996; 124:377-9. [PubMed 8739554]

235. Schenker S, Yang Y, Perez A et al. Sumatriptan (Imitrex®) transport by the human placenta. (43941) *Proc Soc Exp Biol Med*. 1995; 210:213-20.

236. Glaxo Wellcome, Research Triangle Park, NC: Personal communication.

237. Reviewers' comments (personal observations).

238. Nielsen TH, Tfelt-Hansen P. Lack of effect of GR43175 on peripheral arteries in man. *Cephalalgia*. 1989; 9(Suppl 9):93-5. [PubMed 2544291]

239. Doenicke A, Brand J, Perrin VL. Possible benefit of GR43175, a novel 5-HT1-like receptor agonist, for the acute treatment of severe migraine. *Lancet*. 1988; 1:1309-11. [IDIS 243109] [PubMed 2897560]

240. Hoerlein M, McMonigle G, Franz DN. Sumatriptan therapy of pediatric migraines. *Ann Neurol*. 1994; 36:548.

241. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first fifty consecutive patients with acute migraine in a pediatric neurology office practice. *Headache*. 1995; 35:292-3.

242. Wojnar-Horton RE, Hackett LP, Yapp P et al. Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol*. 1996; 41:217-21. [IDIS 365036] [PubMed 8866921]

243. Salonen R, Ashford E, Dahlof C et al et al. Intranasal sumatriptan for the acute treatment of migraine. *J Neurol*. 1994; 241:463-9. [PubMed 7964913]

244. Pryse-Phillips WEM, Dodick DW, Edmeads JG et al. Guidelines for the diagnosis and management of migraine in clinical practice. *CMAJ*. 1997; 156:1273-87. [IDIS 384971] [PubMed 9145054]

245. Danish Neurological Society and the Danish Headache Society. Guidelines for the management of headache. *Cephalalgia*. 1998; 18:9-22. [PubMed 9601619]

246. Peroutka SJ. Drugs effective in the therapy of migraine. In: Hardman JG, Limbird LE, Molinoff PB et al, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1995:487-502.

247. Young WB, Silberstein SD, Dayno JM. Migraine treatment. *Semin Neurol*. 1997; 17:325-33. [PubMed 9474712]

248. Anon. New triptans and other drugs for migraine. *Med Lett Drugs Ther*. 1998; 40:97-100. [PubMed 9793036]

249. Glaxo Wellcome. Imitrex® (sumatriptan) nasal spray prescribing information. Research Triangle Park, NC; 2001 Mar.

250. Novartis Pharmaceuticals. Migranal®(dihydroergotamine mesylate) nasal spray prescribing information. East Hanover, NJ; 1997 Dec.

251. Diamond S. Recommendations for primary care providers: diagnosis and treatment of migraine. *Headache Q*. 1997; Suppl: 6-14.

252. Posner JB. Disorders of sensation. In: Wyngaarden JB, Smith LH Jr, Bennett JC, eds. Cecil textbook of medicine. 19th ed. Philadelphia: WB Saunders Company; 1992:2116-2123.

253. Raskin NH. Migraine and the cluster headache syndrome. In: Fauci AS, Braunwald E, Isselbacher KJ et al, eds. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill Company; 1998:2307-11.

254. May A, Bahra A, Buchel C et al. Hypothalamic activation in cluster headache attacks. *Lancet*. 1998; 352:275-8. [PubMed 9690407]

255. Schoenen J. Cluster headaches—central or peripheral in origin? *Lancet*. 1998; 352:253-5.

256. Dahlof C. Placebo controlled trials with ergotamine in the acute treatment of migraine. *Cephalalgia*. 1993; 13:166-71. [PubMed 8358774]

257. Lipton RB, Stewart WF, Ryan RE. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain.: three double-blind, randomized, placebo-controlled trials. *Arch Neurol*. 1998; 55:210-7. [PubMed 9482363]

258. Brown GR. Stadol dependence: another case. *JAMM*. 1985; 254:910.

259. Austin RP. Diversion of butorphanol. *Am J Hosp Pharm*. 1983; 40:1306. [PubMed 6614013]

260. Hoover RC, Williams RB. Survey of butorphanol and nalbuphine diversion in U.S. hospitals. *Am J Hosp Pharm.* 1985; 42:1111-3. [PubMed 4003423]

261. Butorphanol. In: WHO Expert Committee on Durg Dependence. 25th report. Technical report series 775. Geneva: World Health Organization; 1989:24-6.

262. Glaxo Wellcome. Amerge® (naratriptan hydrochloride) tablets prescribing information. Research Triangle Park, NC; 1998 Feb.

263. Merck & Co. Maxalt® (rizatriptan benzoate) tablets prescribing information. West Point, PA; 1998 June.

264. Zeneca Pharmaceuticals. Zomig® (zolmitriptan) tablets prescribing information. Wilmington, DE; 1997 Dec 1.

265. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis; a randomized controlled trial. *Neurology*. 1998; 50:466-70. [IDIS 401485] [PubMed 9484373]

266. Mattimoe D, Newton W. High-dose riboflavin for migraine prophylaxis. *J Fam Pract*. 1998; 47:11. [PubMed 9673596]

267. Diener HC, Kaube H, Limmroth V. A practical guide to the management and prevention of migraine. *Drugs*. 1998; 56:811-24. [PubMed 9829155]

268. Ramadan NM, Silberstein SD, Freitag FG et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. St. Paul, MN; 2001. From the American Academy of Neurology website (http://www.aan.com).

269. Matchar DB, Young WB, Rosenberg JH et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. St. Paul, MN; 2001. From American Academy of Neurology web site (http://www.aan.com).

270. Ryan R, Elkind A, Baker CC et al. Sumatriptan nasal spray for the acute treatment of migraine: Results of two clinical studies. *Neurology*. 1997; 49:1193-5. [IDIS 397203] [PubMed 9371890]

271. Diamond S, Elkind A, Jackson RT et al. Multiple-attack efficacy and tolerability of sumatriptan nasal spray in the treatment of migraine. *Arch Fam Med*. 1997; 130:1-12.

272. Food and Drug Administration. Public health advisory: combined use of 5-hydroxytryptamine receptor agonists (triptans), selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephirne reuptake inhibitors (SNRIs) may result in life-threatening serotonin syndrome. Rockville, MD; 2006 Jul 19. From the FDA website: (http://www.fda.gov/medwatch/safety/2006/safety06.htm#Triptans and http://www.fda.gov/cder/drug/advisory/SSRI_SS200607.htmhttp://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm).

273. GlaxoSmithKline. Imitrex® (sumatriptan succinate) injection prescribing information. Research Triangle Park, NC; 2006 Jun.

274. GlaxoSmithKline. Imitrex® (sumatriptan succinate) tablets prescribing information. Research Triangle Park, NC; 2006 Jun.

275. GlaxoSmithKline. Imitrex® (sumatriptan) nasal spray prescribing information. Research Triangle Park, NC; 2006 Jun.

(+/-) Show / Hide Bibliography

4:04 First Generation Antihistamines

Brompheniramine Maleate, Dexbrompheniramine Maleate

Introduction

• Brompheniramine and dexbrompheniramine are alkylamine (propylamine)-derivative first generation antihistamines.

Uses

Brompheniramine and dexbrompheniramine share the actions and uses of other antihistamines. Fixed-combination preparations containing brompheniramine maleate or dexbrompheniramine maleate and a nasal decongestant (e.g., pseudoephedrine) are used for relief of upper respiratory symptoms, including nasal and/or sinus congestion, associated with allergy (e.g., seasonal or perennial allergic rhinitis) or the common cold.100, 141, 142, 143, 144, 147 Combination preparations generally should only be used when symptoms amenable to each ingredient are present concurrently.100

Dosage and Administration

• **Administration**
Brompheniramine maleate and dexbrompheniramine maleate are administered orally.

• **Dosage**
Dosage of brompheniramine maleate and dexbrompheniramine maleate should be individualized according to the patient's response and tolerance.

Fixed-ratio combination preparations do not permit individual titration of dosages;100 if a fixed combination is used, the precautions and contraindications associated with each drug must be considered.100, 142, 143, 144, 145, 146, 147, 148

Brompheniramine Maleate Combinations

When brompheniramine maleate is used in fixed combination with a nasal decongestant (e.g., pseudoephedrine), the dosage of the fixed-ratio combination should be within the range for the usual therapeutic dosage of each ingredient.100, 141

When brompheniramine maleate is used in fixed combination with pseudoephedrine sulfate for *self-medication*, the usual dosage of brompheniramine maleate in adults and children 12 years of age and older is 4 mg every 4-6 hours, not to exceed 16 mg in 24 hours. Alternatively, these adults and children may receive an extended-release fixed combination containing 12 mg of brompheniramine maleate every 12 hours. Children 6 to younger than 12 years of age may receive this combination for *self-medication* at a dosage of 2 mg every 4-6 hours, not to exceed 8 mg in 24 hours. Alternatively, children 6-12 years of age may receive an extended-release fixed combination containing 6 mg of brompheniramine every 12 hours.

Dexbrompheniramine Maleate Combinations
When dexbrompheniramine maleate is used in fixed combination with pseudoephedrine sulfate as an extended-release tablet, 6 mg of dexbrompheniramine maleate may be administered to adults every 8-12 hours;142, 143, 147 for *self-medication* in adults and children 12 years of age and older, the usual dosage as an extended-release tablet is 6 mg every 12 hours.145, 146, 468

Cautions

Brompheniramine and dexbrompheniramine share the toxic potentials of other antihistamines, and the usual precautions of antihistamine therapy should be observed. (See Cautions in the Antihistamines General Statement 4:00.)

• Pediatric Precautions
Like other antihistamines, brompheniramine and dexbrompheniramine should not be used in premature or full-term neonates. (See Cautions: CNS Effects and Pediatric Precautions, in the Antihistamines General Statement 4:00.) Extended-release fixed-combination preparations of brompheniramine or dexbrompheniramine and a nasal decongestant should be used in children younger than 12 years of age only under the direction of a clinician, and other preparations of one of these fixed combinations should be used in children younger than 6 years of age only under the direction of a clinician.

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) preparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection.693, 694 There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by the US Food and Drug Administration [FDA]) for the symptomatic treatment of cold and cough have not been established.693 Such preparations should be used in children younger than 2 years of age with caution and only as directed by a clinician.693, 694 Clinicians should use caution in prescribing cough and cold preparations in these children and should ask caregivers about use of nonprescription cough and cold preparations to avoid overdosage.693 For additional information on precautions associated with the

use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in the Antihistamines General Statement 4:00

• **Mutagenicity and Carcinogenicity**
Long-term studies to determine the mutagenic and carcinogenic potentials of brompheniramine and dexbrompheniramine have not been performed to date.

• **Pregnancy, Fertility, and Lactation**
Pregnancy
There is inadequate experience with use of brompheniramine or dexbrompheniramine in pregnant women to determine whether the potential for harm to the fetus exists. Because of the risk of severe reactions (e.g., seizures) to antihistamines in neonates, brompheniramine or dexbrompheniramine should not be used during the third trimester; the drugs should be used during the first 2 trimesters only when the potential benefits justify the possible risks to the fetus.

Fertility
Reproduction studies in rats and mice using brompheniramine dosages up to 16 times the maximum human dosage have not revealed evidence of impaired fertility or harm to the fetus. It is not known whether the drug can affect fertility in humans.

Lactation
Because of the potential for serious adverse reactions to antihistamines in nursing infants, a decision should be made whether to discontinue nursing or brompheniramine or dexbrompheniramine, taking into account the importance of the drug to the woman. Excessive crying, irritability, and sleep disturbances occurred in one breast-fed infant whose mother was receiving dexbrompheniramine combined with pseudoephedrine; normal behavior in the infant resumed within 12 hours after the mother discontinued the drug and the infant received 2 formula feedings.264

Pharmacokinetics

• **Absorption**
Brompheniramine and dexbrompheniramine maleates appear to be well absorbed from the GI tract.109, 110, 265

Following oral administration of a single 0.13-mg/kg dose of brompheniramine maleate in healthy, fasting adults in one study, peak serum brompheniramine concentrations of 7.7-15.7 ng/mL occurred within 2-5 hours; in most of these individuals, a second lower peak, possibly secondary to enterohepatic circulation, also was observed.109 The antihistamine effect of brompheniramine, as determined by suppression of the wheal and flare responses induced by intradermal administration of histamine, appears to be maximal within 3-9 hours after a single oral dose of the drug, but suppression of the flare response may persist for up to at least 48 hours; the antipruritic effect appears to be maximal within 9-24 hours.109

Following oral administration of 2 mg of dexbrompheniramine maleate every 4 hours in healthy adults, mean peak plasma concentrations of the drug were about 22 ng/mL on the sixth and seventh days of dosing and mean trough concentrations were about 17 and 18 ng/mL on the sixth and seventh days, respectively.265

• **Distribution**

Distribution of brompheniramine into human body tissues and fluids has not been fully characterized, but the drug appears to be widely distributed.[109] Following oral administration of a single dose of the drug in healthy adults, the apparent volume of distribution reportedly averaged 11.7 L/kg.[109]

• **Elimination**

In healthy adults, the half-life of brompheniramine reportedly ranges from 11.8-34.7 hours.[109] The metabolic and excretory fate of the drug has not been fully characterized.[109, 110, 111] Brompheniramine undergoes *N*-dealkylation to form monodesmethylbrompheniramine and didesmethylbrompheniramine,[110, 111] and is metabolized to the propionic acid derivative, which is partially conjugated with glycine, and to other unidentified metabolites.[110] Brompheniramine and its metabolites are excreted principally in urine.[110, 111] About 40% of an oral dose of brompheniramine is excreted in urine and about 2% in feces within 72 hours in healthy individuals.[110] In healthy individuals, about 5-10% of an oral dose is excreted in urine as unchanged drug, 6-10% as monodesmethylbrompheniramine, 6-10% as didesmethylbrompheniramine,[110, 111] small amounts as the propionic acid derivative and its glycine conjugate, and the remainder as unidentified metabolites.[110]

In healthy adults, dexbrompheniramine reportedly has an elimination half-life of about 22 hours.[265]

Chemistry and Stability

• **Chemistry**

Brompheniramine and dexbrompheniramine are alkylamine (propylamine)-derivative antihistamines. The drugs differ from chlorpheniramine in the substitution of a bromine atom for the chlorine atom of the latter compound. Dexbrompheniramine, the *dextro* isomer which is commercially available only in combination products, is approximately twice as active as racemic brompheniramine on a weight basis. Brompheniramine maleate occurs as a white, odorless, crystalline powder and has solubilities of approximately 200 mg/mL in water and 66.7 mg/mL in alcohol at 25°C. Dexbrompheniramine maleate occurs as a white, odorless, crystalline powder, existing in 2 polymorphic forms, and has solubilities of approximately 833 mg/mL in water and 400 mg/mL in alcohol at 25°C. Brompheniramine has pK_a values of 3.59 and 9.12.

• **Stability**

Preparations containing brompheniramine maleate generally should be stored in tight, light-resistant containers at controlled room temperature between 20 - 25°C.

Additional Information

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, laboratory test interferences, and dosage and administration of brompheniramine and dexbrompheniramine, see the Antihistamines General Statement 4:00.

Preparations

In response to concerns regarding the safety and efficacy of cough and cold preparations in young children, many nonprescription cough and cold preparations specifically formulated for infants have been voluntarily withdrawn from the US market[698] Therefore, some of the preparations described below may no longer be commercially available in the US.

Brompheniramine Maleate Combinations

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Capsules, 6 mg with Pseudoephedrine Hydrochloride **Bromadrine PD®** Rugby extended- 60 mg release **Bromfed-PD®** (with benzyl Muro alcohol and parabens) **Bromfenex® PD** Ethex **Brompheniramine-PSE®** Teva **Dallergy®-JR** Laser **Lodrane® LD** ECR **Respahist®** Respa **Ultrabrom® PD** WE Pharmaceuticals 12 mg with Pseudoephedrine **Allent®** Ascher Hydrochloride 120 mg **Bromadrine®** Rugby **Bromfed®** (with benzyl Muro alcohol and parabens) **Bromfenex®** Ethex **Ultrabrom®** WE Pharmaceuticals Solution 1 mg/5 mL with Pseudoephedrine **Dimetapp® Elixir** Wyeth Hydrochloride 15 mg/5 mL 4 mg/5 mL with Pseudoephedrine **Rondec® Syrup** Biovail Hydrochloride 45 mg/5 mL 4 mg/5 mL with Pseudoephedrine **Andehist® Syrup** Cypress Hydrochloride 60 mg/5 mL **Lodrane®** ECR Suspension 1 mg/5 mL with Acetaminophen 160 mg/5 **Dimetapp® Cold & Fever** Wyeth mL and Pseudoephedrine Hydrochloride (with parabens and 15 mg/5 mL propylene glycol) Tablets 4 mg with Pseudoephedrine Hydrochloride **Bromfed®** (scored) Muro 60 mg

Dexbrompheniramine Maleate Combinations

Routes Dosage Strengths Brand Names Manufacturer Forms Oral Tablets, 3 mg with Acetaminophen 500 **Drixoral® Cold & Flu** (with Schering- extended- mg and Pseudoephedrine parabens) Plough release Sulfate 60 mg **Drixoral® Allergy/Sinus** (with Schering- parabens) Plough 6 mg with Pseudoephedrine **Dexaphen® SA** Major Sulfate 120 mg **Drixoral® Cold & Allergy** (with Schering- butylparaben and povidone) Plough

• **Comparative Pricing**
Pricing information provided by drugstore.com.

Bromfed 4-60MG TABS (MURO): 30/$12.89 or 90/$33.66

Rondec DM 45-4-15MG/5ML SYRP (ALLIANT PHARMACEUTICALS): 480/$103.1 or 1440/$292.18

References

Please see the general statement for a list of references.

(+/-) Show / Hide Bibliography

Cyproheptadine Hydrochloride

Introduction

• Cyproheptadine is a first generation antihistamine and a serotonin antagonist.[5, 6, 27, 40, 43, 50, 51]

Uses

• Allergic Conditions

Cyproheptadine hydrochloride shares the actions and uses of the other antihistamines.[5] In addition, cyproheptadine is used for the treatment of cold urticaria,[5, 11, 12, 13] and some clinicians consider it the drug of choice for the treatment of this condition.[13]

• Cushing's Syndrome

Cyproheptadine has been effective in some patients for the treatment of Cushing's syndrome[#] secondary to pituitary disorders.[14, 15, 16, 17, 18, 19, 20, 21, 48, 52, 53, 63] Clinical remissions and normalization of cortisol indexes (i.e., cortisol secretion rate, plasma cortisol concentration, urinary free cortisol excretion) reportedly occur in up to 60% of patients, generally within 1-3 months after beginning treatment.[14, 15, 17, 18, 48] Although almost all of these patients relapse after discontinuance of cyproheptadine,[14, 15, 48, 52, 53] prolonged remission (e.g., for at least 2.5-3 years) has occurred in a few patients following discontinuance of the drug.[19, 20, 52, 53] If relapse occurs, additional courses of therapy usually produce further responses.[14, 15] The role of cyproheptadine in the treatment of Cushing's syndrome secondary to pituitary disorders remains to be clearly established; in most patients, other therapy (e.g., surgery, radiation therapy) is preferred.[21, 39, 48]

• Sexual Dysfunction

Cyproheptadine has been effective for the management of inhibited male or female orgasm[#] (anorgasmy) induced by tricyclic antidepressants,[55, 57, 58, 66] monoamine oxidase inhibitors,[54, 56] fluoxetine,[68] or antipsychotic agents.[56] Ability to achieve orgasm was restored when cyproheptadine was administered 1-2 hours before anticipated sexual activity (e.g., 4-12 mg)[54, 55, 58, 66, 68] or daily (e.g., 1-16 mg daily).[56, 57, 66, 68] Although not clearly established, the efficacy of cyproheptadine in these patients may be related to its serotonin antagonist or anticholinergic activity.[54, 55, 57, 58, 66] However, the potential for drug interaction (possibly resulting in anticholinergic toxicity or additive CNS depression) in patients receiving any of these drugs concomitantly with cyproheptadine should be kept in mind.[5, 66] In a limited number of patients receiving cyproheptadine for fluoxetine-induced ejaculatory dysfunction, cyproheptadine reversed the antidepressant effects of fluoxetine.[69, 70] The mechanism of this drug interaction is not known, but it has been postulated that cyproheptadine, a serotonin antagonist, may inhibit the serotonergic effects of fluoxetine.[69, 70]

• Anorexia Nervosa

Although there are few indications for clinical use,[40] cyproheptadine has been shown to stimulate appetite and weight gain in children[32, 33] and adults.[34, 35, 36] There is evidence that cyproheptadine may be of some value in the management of anorexia nervosa[#, 37, 38, 41, 46, 47, 59, 60] but the drug may be more effective in patients with anorexia nervosa who do not undertake periodic episodes of binge eating (nonbulimic) than those who do (bulimic).[59]

• Headache

Cyproheptadine reportedly has been effective in some patients for the management of vascular headaches[#] (e.g., migraine).[30, 31, 43, 44, 71] While clinical efficacy of cyproheptadine in the prophylaxis of migraine headache has not been established in randomized controlled studies, some experts consider the drug to be effective based on consensus and clinical experience.[71] For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses in Sumatriptan 28:32.28.

• Other Uses

Cyproheptadine reportedly has been effective in some patients for the management of Nelson's syndrome[#, 22, 23, 24] virilizing congenital adrenal hyperplasia[#] in adult females,[25] galactorrhea-amenorrhea syndrome[#, 26] and carcinoid syndrome[#, 27, 28, 29, 64, 65]

Cyproheptadine has been used as an adjunct to somatropin (human growth hormone) therapy in a limited number of children with somatotropin (endogenous growth hormone) deficiency[#, 49] Combined therapy with the drugs was more effective in promoting weight gain and linear growth in these children than somatropin alone, but additional study is necessary.[49]

Dosage and Administration

• Administration

Cyproheptadine hydrochloride is administered orally.[5]

• Dosage

Dosage of cyproheptadine hydrochloride should be individualized according to the patient's response and tolerance.[5] For geriatric patients, the manufacturer suggests that cyproheptadine hydrochloride dosage be initiated in the lower end of the usual range.[5]

Allergic Conditions

For the treatment of allergic conditions, the usual initial adult dosage of cyproheptadine hydrochloride is 4 mg 3 times daily.[5] Dosage may be increased, if necessary, but total dosage in adults should not exceed 0.5 mg/kg daily.[5] Most adults require 12-16 mg daily.[5] Some patients may require a dosage as high as 32 mg daily.[5]

The usual dosage of cyproheptadine hydrochloride for children 2-6 years of age is 2 mg 2 or 3 times daily; dosage should not exceed 12 mg daily.[5] For children 7-14 years of age, the usual dosage is 4 mg 2 or 3 times daily; dosage should not exceed 16 mg daily.[5] Alternatively, children may receive 0.25 mg/kg or 8 mg/m^2 daily in divided doses.[5]

Other Uses

For the treatment of Cushing's syndrome[#] secondary to pituitary disorders, the usual initial adult dosage of cyproheptadine hydrochloride is 8 mg daily in divided doses; dosage is gradually increased to up to 24 mg daily in divided doses.[14, 17, 18, 21, 48, 52]

For the management of anorexia nervosa[#] in adults and children 13 years of age and older, cyproheptadine hydrochloride has been administered at an initial dosage of 2 mg 4 times daily and then gradually increased over a 3-week period to up to 8 mg 4 times daily.[38, 46, 47, 59]

Cautions

Cyproheptadine hydrochloride shares the toxic potentials of other antihistamines, and the usual precautions of antihistamine therapy should be observed. (See Cautions in the Antihistamines General Statement 4:00.)

• Pediatric Precautions

Safety and efficacy of cyproheptadine in children younger than 2 years of age have not been established and, like other antihistamines, the drug should not be used in premature or full-term neonates.[5] (See Cautions: CNS Effects and Pediatric Precautions, in the Antihistamines General Statement 4:00.)

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) preparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection.[72, 73] There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by the US Food and Drug Administration [FDA]) for the symptomatic treatment of cold and cough have not been established.[72] Such preparations should be used in children younger than 2 years of age with caution and only as directed by a clinician.[72, 73] Clinicians should use caution in prescribing cough and cold preparations in these children and should ask caregivers about use of nonprescription cough and cold preparations to avoid overdosage.[72] For additional information on precautions associated with the use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in the Antihistamines General Statement 4:00.

• Geriatric Precautions

Clinical studies of cyproheptadine did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients.[5] While clinical experience generally has not revealed age-related differences in response to the drug, care should be taken in dosage selection of cyproheptadine.[5] Because of the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy in geriatric patients, the manufacturer suggests that patients in this age group receive initial dosages of the drug in the lower end of the usual range.[5]

• Mutagenicity and Carcinogenicity

Long-term studies to determine the carcinogenic potential of cyproheptadine have not been performed to date.[5] No evidence of cyproheptadine-induced mutagenic activity was seen in vitro in the Ames microbial mutagen test, although concentrations of the drug greater than 0.5 mg/plate inhibited bacterial growth.[5] Chromosomal

abnormalities also were not evident in in vitro mammalian (human lymphocytes or fibroblasts) test systems, but high concentrations were cytotoxic.[5]

• Pregnancy, Fertility, and Lactation

Pregnancy

Reproduction studies in rabbits, mice, and rats using oral or subcutaneous cyproheptadine hydrochloride dosages up to 32 times the maximum recommended human oral dosage have not revealed evidence of harm to the fetus.[5] Although the drug has been fetotoxic in rats when administered intraperitoneally at dosages 4 times the maximum recommended human oral dosage, experience in a limited number of women who received cyproheptadine orally during the first, second, and/or third trimesters of pregnancy did *not* reveal evidence of an increased risk of fetal abnormalities, nor were teratogenic effects observed in neonates born to these women.[5, 20, 64] No evidence of adverse fetal effect was evident in an infant born to a woman who had received 12 mg of cyproheptadine hydrochloride daily throughout pregnancy for the treatment of Cushing's syndrome; the infant developed normally until 4 months of age when he developed gastroenteritis and died.[20] Nevertheless, because the reported experience to date in humans cannot exclude the possibility of adverse fetal effects of the drug, cyproheptadine should be used during pregnancy only when clearly needed.[5]

Fertility

Reproduction studies in animals using cyproheptadine hydrochloride dosages up to 32 times the maximum recommended human oral dosage have not revealed evidence of impaired fertility.[62] Successful pregnancy has occurred in several women who received cyproheptadine for the treatment of Cushing's syndrome[#]; the women were amenorrheic prior to therapy with the drug.[19, 20]

Lactation

It is not known whether cyproheptadine hydrochloride is distributed into milk.[5] Because of the potential for serious adverse reactions to cyproheptadine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.[5]

Pharmacology

Cyproheptadine has potent antihistaminic and serotonin antagonist properties; the drug also has anticholinergic and sedative effects[5, 6, 40, 50, 51] and reportedly has calcium-channel blocking activity.[42] While the exact mechanisms of action are complex and have not been fully elucidated, the beneficial effects of cyproheptadine in the treatment of Cushing's syndrome[#] are generally believed to result from the drug's serotonin antagonist activity.[14, 17, 18, 21, 40, 52, 53]

Pharmacokinetics

• Absorption

Cyproheptadine hydrochloride appears to be well absorbed following oral administration.[1, 7] Following a single oral dose of radiolabeled drug in fasting healthy adults in one study, peak plasma concentrations of radioactivity occurred 6-9 hours after administration;[7] the radioactivity appeared to represent cyproheptadine metabolites.[7]

• **Distribution**
Distribution of cyproheptadine into human body tissues and fluids has not been characterized.[7] It is not known if the drug is distributed into milk.[5]

• **Elimination**
The metabolic and excretory fate of cyproheptadine has not been fully elucidated.[5, 7, 8, 9, 10] The drug appears to be almost completely metabolized,[7, 8, 9, 10] principally to the quaternary ammonium glucuronide conjugate.[8, 9, 10] The drug also undergoes aromatic ring hydroxylation, *N*-demethylation, and heterocyclic ring oxidation.[8] Most cyproheptadine metabolites appear to be conjugated with glucuronic acid or sulfate.[7, 8]

Cyproheptadine metabolites are excreted principally in urine, almost completely as conjugates.[7, 8, 9, 10] The drug does not appear to be excreted unchanged in urine.[9, 10] Cyproheptadine and some metabolites are excreted in feces following oral administration;[5, 7] whether such excretion occurs via biliary elimination remains to be established. Following a single oral dose of cyproheptadine hydrochloride in healthy adults, about 30% of the dose is excreted as metabolites in urine within 24 hours, about 50% within 48 hours, and about 65-75% within 6 days;[7] the remainder of the dose is excreted in feces.[7] The principal urinary metabolite is the quaternary ammonium glucuronide conjugate;[8, 9, 10] during chronic administration of 12-20 mg of cyproheptadine daily in patients with anorexia nervosa who had normal renal and hepatic function, an average of 24% of the daily dose was excreted in urine as this metabolite.[9] Elimination of cyproheptadine is reduced in renal insufficiency.[5]

Chemistry and Stability

• **Chemistry**
Cyproheptadine is an antihistamine and a serotonin antagonist.[5, 6, 27, 40, 43, 50, 51] The drug is structurally and pharmacologically related to azatadine.[1, 5] Cyproheptadine hydrochloride occurs as a white to slightly yellow, odorless or practically odorless, crystalline powder.[2] The drug has solubilities of approximately 3.64 mg/mL in water and 28.6 mg/mL in alcohol.[2] Cyproheptadine has a pK_a of 9.3.[3] Commercially available cyproheptadine hydrochloride oral solution occurs as a clear, yellow, syrupy liquid and has a pH of 3.5-4.5.[2, 5, 67]

• **Stability**
Cyproheptadine hydrochloride oral solution and tablets should be stored in tight or well-closed containers, respectively,[2, 4, 5] at a temperature less than 40°C,[4, 5] preferably at 15-30°C;[4, 5, 61] freezing (i.e., storage at temperatures colder than -20°C) of the oral solution should be avoided.[4, 5]

Additional Information

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, laboratory test interferences, and dosage and administration of cyproheptadine hydrochloride, see the Antihistamines General Statement 4:00.

Preparations

* Available generically.

Cyproheptadine Hydrochloride

Routes Dosage Strengths Brand Names Manufacturer Forms Oral Solution 2 mg/5 mL **Cyproheptadine Hydrochloride Syrup** Actavis, Alpharma (with alcohol 5% and sorbic acid 0.1%) Tablets 4 mg* **Cyproheptadine Hydrochloride Tablets** Corepharma, Major, Par, Rising, Teva

• **Comparative Pricing**
Pricing information provided by drugstore.com.

Cyproheptadine HCl 2MG/5ML SYRP (ACTAVIS MID ATLANTIC): 120/$14.99 or 360/$38.46

Cyproheptadine HCl 4MG TABS (IVAX PHARMACEUTICALS, INC.): 30/$9.99 or 90/$23

[#] Use is not currently included in the labeling approved by the US Food and Drug Administration.

References

1. Schering. Optimine® prescribing information. In: Huff BB, ed. Physicians' desk reference. 38th ed. Oradell, NJ: Medical Economics Company Inc; 1984:1795-7.

2. The United States pharmacopeia, 21st rev, and The national formulary, 16th ed. Rockville, MD: The United States Pharmacopeial Convention, Inc; 1984:267, 1450, 1484.

3. Hoffman JP (Merck, Sharp and Dohme): Personal communication; 1978 May 15.

4. United States Pharmacopeia Dispensing Information (USP DI). Vol I. Drug information for the health care provider. Rockville, MD: The United States Pharmacopeial Convention, Inc; 1983:142.

5. Merck & Co. Periactin ® (cyproheptadine) tablets and syrup prescribing information. West Point, PA; 1999 Sept.

6. Stone CA, Wenger HC, Ludden CT et al. Antiserotonin-antihistaminic properties of cyproheptadine. *J Pharmacol Exp Ther*. 1961; 131:73-84.

7. Hintze KL, Wold JS, Fischer LJ. Disposition of cyproheptadine in rats, mice, and humans and identification of a stable epoxide metabolite. *Drug Metab Dispos*. 1975; 3:1-9. [PubMed 234828]

8. Porter CC, Arison BH, Gruber VF et al. Human metabolism of cyproheptadine. *Drug Metab Dispos*. 1975; 3:189-97. [PubMed 238818]

9. Kennedy KA, Halmi KA, Fischer LJ. Urinary excretion of a quaternary ammonium glucuronide metabolite of cyproheptadine in humans undergoing chronic drug therapy. *Life Sci*. 1977; 21:1813-20. [PubMed 604709]

10. Fischer LJ, Thies RL, Charkowski D et al. Formation and urinary excretion of cyproheptadine glucuronide in monkeys, chimpanzees, and humans. *Drug Metab Dispos*. 1980; 8:422-4. [PubMed 6109610]

11. Wanderer AA, St. Pierre JP, Ellis EF. Primary acquired cold urticaria: double-blind comparative study of treatment with cyproheptadine, chlorpheniramine, and placebo. *Arch Dermatol*. 1977; 113:1375-7. [PubMed 334082]

12. Sigler RW, Evans R III, Horakova Z et al. The role of cyproheptadine in the treatment of cold urticaria. *J Allergy Clin Immunol*. 1980; 65:309-12. [PubMed 6102102]

13. Buckley RH, Mathews KP. Common "allergic" skin diseases. *JAMA*. 1982; 248:2611-22. [PubMed 7143623]

14. Krieger DT, Amorosa L, Linick F. Cyproheptadine-induced remission of Cushing's disease. *N Engl J Med*. 1975; 293:893-6. [PubMed 1177986]

15. Krieger DT. Cyproheptadine for pituitary disorders. *N Engl J Med*. 1976; 295:394-5. [PubMed 934231]

16. Grant DB, Atherden SM. Cushing's disease presenting with growth failure: clinical remission during cyproheptadine therapy. *Arch Dis Child*. 1979; 54:466-8. [PubMed 475431]

17. Hsu TH, Gann DS, Tsan KW et al. Cyproheptadine in the control of Cushing's disease. *Johns Hopkins Med J*. 1981; 149:77-83. [PubMed 6265685]

18. Jimenez-Alonso J, Munoz-Avila J, Jaimez L et al. Cyproheptadine-induced remission of Cushing's disease due to pituitary basophil adenoma. *Drug Intell Clin Pharm*. 1982; 16:962-5. [PubMed 6295736]

19. Griffith DN, Rose EJ. Pregnancy after cyproheptadine treatment for Cushing's disease. *N Engl J Med*. 1981; 305:893-4. [PubMed 7278892]

20. Kasperlik-Zaluska A, Migdalska B, Hartwig W et al. Two pregnancies in a woman with Cushing's syndrome treated with cyproheptadine: case report. *Br J Obstet Gynaecol*. 1980; 87:1171-3. [PubMed 7437385]

21. Gold EM. The Cushing syndromes: changing views of diagnosis and treatment. *Ann Intern Med*. 1979; 90:829-44. [PubMed 219743]

22. Hartwig W, Kasperlik-Zaluska A, Wilczynska J et al. Cyproheptadine for pituitary disorders. *N Engl J Med*. 1976; 295:394. [PubMed 934231]

23. Krieger DT, Condon EM. Cyproheptadine treatment of Nelson's syndrome: restoration of plasma ACTH circadian periodicity and reversal of response to TRF. *J Clin Endocrinol Metab*. 1978; 46:349-52. [PubMed 220278]

24. Aronin N, Krieger DT. Sustained remission of Nelson's syndrome after stopping cyproheptadine treatment. *N Engl J Med*. 1980; 302:453-5. [PubMed 6243392]

25. Hsu TH. Management of virilizing congenital adrenal hyperplasia with cyproheptadine. *Ann Intern Med*. 1980; 92:628-30. [PubMed 7387003]

26. Wortsman J, Soler NG, Hirschowitz J. Cyproheptadine in the management of the galactorrhea-amenorrhea syndrome. *Ann Intern Med*. 1979; 90:923-5. [PubMed 571691]

27. Vroom FQ, Brown RE, Dempsey H et al. Studies on several possible antiserotonin compounds in a patient with the functioning carcinoid syndrome. *Ann Intern Med*. 1962; 56:941-5. [PubMed 13926919]

28. Berry EM, Maunder C, Wilson M. Carcinoid myopathy and treatment with cyproheptadine (Periactin). *Gut*. 1974; 15:34-8. [PubMed 4274414] [Free Fulltext PMC]

29. Harris AL, Smith IE. Regression of carcinoid tumour with cyproheptadine. *BMJ*. 1982; 285:475. [PubMed 6809131] [Free Fulltext PMC]

30. Curran DA, Lance JW. Clinical trial of methysergide and other preparations in the management of migraine. *J Neurol Neurosurg Psychiatry*. 1964; 27:463-9. [PubMed 14213477]

31. Lance JW, Curran DA, Anthony M. Investigations into the mechanism and treatment of chronic headache. *Med J Aust*. 1965; 2:909-14. [PubMed 5322372]

32. Lavenstein AF, Decaney EP, Lasagna L et al. Effect of cyproheptadine on asthmatic children. *JAMA*. 1962; 180:912-6. [PubMed 14462919]

33. Bergen SS. Appetite stimulating properties of cyproheptadine. *Am J Dis Child*. 1964; 108:270-3. [PubMed 14168064]

34. Noble RE. Effect of cyproheptadine on appetite and weight gain in adults. *JAMA*. 1969; 209:2054-5. [PubMed 4897366]

35. Silverstone T, Schuyler D. The effect of cyproheptadine on hunger, calorie intake, and body weight in man. *Psychopharmacologia*. 1975; 40:335-40. [PubMed 1096217]

36. Pawlowski GJ. Cyproheptadine: weight-gain and appetite stimulation in essential anorexic adults. *Curr Ther Res Clin Exp*. 1975; 18:673-8. [PubMed 812645]

37. Goldberg SC, Halmi KA, Eckert ED. Cyproheptadine in anorexia nervosa. *Br J Psychiatry*. 1979; 134:67-70. [PubMed 367480]

38. Halmi KA, Eckert E, Falk JR. Cyproheptadine for anorexia nerovsa. *Lancet*. 1982; 1:1357-8. [PubMed 6123657]

39. Vaughan GM, Taylor TJ. Cushing's syndrome. In: Conn HF, ed. Current therapy: latest approved methods of treatment for the practicing physician, 1983. Philadelphia: WB Saunders Company; 1983:472-7.

40. Anon. Cyproheptadine. *Lancet*. 1978; 1:367-8.

41. Goldberg SC, Eckert ED, Halmi KA et al. Effects of cyproheptadine on symptoms and attitudes in anorexia nervosa. *Arch Gen Psychiatry*. 1980; 37:1083. [PubMed 7416909]

42. Peroutka SJ, Allen GS. The calcium antagonist properties of cyproheptadine: implications for antimigraine action. *Neurology*. 1984; 34:304-9. [PubMed 6538269]

43. Lance JW, Anthony M, Somerville B. Comparative trial of serotonin antagonists in the management of migraine. *Br Med J*. 1970; 1:327-30. [PubMed 4906701] [Free Fulltext PMC]

44. Bille B, Ludvigsson J, Sanner G. Prophylaxis of migraine in children. *Headache*. 1977; 17:61-3. [PubMed 324951]

45. Greenberger P, Patterson R. Safety of therapy for allergic symptoms during pregnancy. *Ann Intern Med*. 1978; 89:234-7. [PubMed 28058]

46. Falk JR, Halmi KA, Tyron WW. Activity measures in anorexia nervosa. *Arch Gen Psychiatry*. 1985; 42:811-4. [PubMed 4015326]

47. Herzog DB, Copeland PM. Eating disorders. *N Engl J Med*. 1985; 313:295-303. [PubMed 2861566]

48. Burch WM. Cushing's disease: a review. *Arch Intern Med*. 1985; 145:1106-11. [PubMed 3923962]

49. Kaplowitz PB, Jennings S. Enhancement of linear growth and weight gain by cyproheptadine in children with hypopituitarism receiving growth hormone therapy. *J Pediatr*. 1987; 110:140-3. [PubMed 3794875]

50. Douglas WW. Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: Gilman AG, Goodman LS, Rall TW et al, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 7th ed. New York: Macmillan Publishing Company; 1985:605-38.

51. Anthony M. Serotonin antagonists. *Aust N Z J Med*. 1984; 6:888-95.

52. Wiesen M, Ross F, Kreiger DT. Prolonged remission of a case of Cushing's disease following cessation of cyproheptadine therapy. *Acta Endocrinol (Copenh)*. 1983; 102:436-8. [PubMed 6829265]

53. Couch RM, Smail PJ, Dean HJ et al. Prolonged remission of Cushing disease after treatment with cyproheptadine. *J Pediatr*. 1984; 104:906-8. [PubMed 6327962]

54. DeCastro RM. Reversal of MAOI-induced anorgasmia with cyproheptadine. *Am J Psychiatry*. 1985; 142:783. [PubMed 4039897]

55. Riley AJ, Riley EJ. Cyproheptadine and antidepressant-induced anorgasmia. *Br J Psychiatry*. 1986; 148:217-8. [PubMed 3697592]

56. Jeffries JJ. Cyproheptadine and drug-induced anorgasmia. *Can J Psychiatry*. 1987; 32:79. [PubMed 2880654]

57. Sovner R. Treatment of tricyclic antidepressant-induced orgasmic inhibition with cyproheptadine. *J Clin Psychopharmacol*. 1984; 4:169. [PubMed 6736278]

58. Steele TE, Howell EF. Cyproheptadine for imipramine-induced anorgasmia. *J Clin Psychopharmacol*. 1986; 6:326-7. [PubMed 3771824]

59. Halmi KA, Eckert E, LaDu TJ et al. Anorexia nervosa: treatment efficacy of cyproheptadine and amitriptyline. *Arch Gen Psychiatry*. 1986; 43:177-81. [PubMed 3511877]

60. Johnson C, Stuckey M, Mitchell J. Psychopharmacological treatment of anorexia nervosa and bulimia: review and synthesis. *J Nerv Ment Dis*. 1983; 171:524-34. [PubMed 6310046]

61. Mylan Pharmaceuticals Inc. Cyproheptadine hydrochloride tablets, USP prescribing information. Morgantown, WV; 1985 Feb.

62. Merck Sharp & Dohme. Periactin® prescribing information. In: Huff BB, ed. Physicians' desk reference. 41st ed. Oradell, NJ: Medical Economics Company Inc; 1987 (Suppl A):A43.

63. Khir ASM, How J, Bewsher PD. Successful pregnancy after cyproheptadine treatment for Cushing's disease. *Eur J Obstet Gynecol Reprod Biol*. 1982; 13:343-7. [PubMed 7128894]

64. Padfield NL. Carcinoid syndrome: comparison of pretreatment regimes in the same patient. *Ann R Coll Surg Engl*. 1987; 69:16-7. [PubMed 2952043]

65. Kvols LK. Metastatic carcinoid tumors and the carcinoid syndrome: a selective review of chemotherapy and hormonal therapy. *Am J Med*. 1986; 81(Suppl 6B):49-55. [PubMed 2432781]

66. Pontius EB. Case report of an anticholinergic crisis associated with cyproheptadine treatment of desipramine-induced anorgasmia. *J Clin Psychopharmacol*. 1988; 8:230-1. [PubMed 3379154]

67. Merck Sharp & Dohme. Periactin® tablets and syrup prescribing information. In: Physician's desk reference. 52nd ed. Montvale, NJ: Medical Economics Company Inc; 1998:1720-1.

68. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. *J Clin Psychiatry*. 1990; 51:383-4. [PubMed 2211550]

69. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry*. 1991; 52:163-4. [PubMed 2016249]

70. Fluoxetine/cyproheptadine. In: Tatro DS, Olin BR, Hebel SK eds. Drug interaction facts. St. Louis: JB Lippincott Co; 1992(Jan):344c.

71. Ramadan NM, Silberstein SD, Freitag F et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. St. Paul, MN; 2001. From the American Academy of Neurology web site: (http://www.aan.com).

72. Srinivasan A, Budnitz D, Shehab N et al. Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007; 56:1-4.

73. Food and Drug Administration. Cough and cold medications in children less than two years of age. MedWatch drug labeling changes. Rockville, MD; January 2007. From FDA website (http://www.fda.gov/medwatch/safety/2007/safety07.htm#coughcold).

(+/-) Show / Hide Bibliography

Desloratadine

Introduction

$C_{19}H_{19}ClN_2$

• Desloratadine, the active descarboethoxy metabolite of loratadine, is a second generation antihistamine.[1, 2, 3, 9]

Uses

Desloratadine, an active metabolite of loratadine, is used for the management of allergic rhinitis and chronic idiopathic urticaria.[1, 9] The drug also has been used in patients with seasonal allergic rhinitis who have concomitant mild to moderate asthma.[1, 2, 6, 9] For additional information on these and other uses of antihistamines, see Uses in the Antihistamines General Statement 4:00.

• Allergic Rhinitis

Desloratadine alone or in fixed combination with pseudoephedrine sulfate is used to provide symptomatic (nasal and nonnasal) relief of seasonal (e.g., hay fever) allergic rhinitis.[1, 9, 18] Desloratadine also is used to provide symptomatic (nasal and nonnasal) relief of perennial (nonseasonal) allergic rhinitis.[1] The fixed-combination preparation generally should be used only when both the antihistaminic and nasal decongestant activity of the combination preparation are needed concurrently.[18]

Antihistamines are not curative and merely provide palliative therapy; since seasonal allergic rhinitis may be a chronic, recurrent condition, successful therapy often may require long-term, intermittent use of these drugs.[10, 11, 12, 13] In the treatment of seasonal allergic rhinitis, antihistamines are more likely to be beneficial when therapy is initiated at the beginning of the hay fever season when pollen counts are low.[11, 13, 14, 15] Antihistamines are less likely to be effective when pollen counts are high, when pollen exposure is prolonged, and when nasal congestion is prominent.[13, 16] Chronic

nasal congestion and headache caused by edema of the paranasal sinus mucosa often are refractory to antihistamine therapy.[11, 12, 13, 17]

Safety and efficacy of desloratadine in the management of seasonal allergic rhinitis were established in several randomized, double-blind, placebo-controlled studies of 2-4 weeks' duration in more than 2300 patients (12-75 years of age) with seasonal allergic rhinitis.[1, 3, 4] In these studies, treatment with desloratadine 5 mg daily during the spring or fall allergy season was more effective than placebo in reducing nasal (e.g., rhinorrhea, sneezing, nasal itching, nasal stuffiness/congestion) and nonnasal (e.g., ocular itching or burning, ocular redness or tearing, itching of ears or palate) symptoms (as assessed by reduction in total symptom scores) in patients with seasonal allergic rhinitis.[1, 2, 4, 9] Results of several studies indicate that treatment with desloratadine (5 mg daily) for 2-4 weeks also was associated with reduced nasal congestion/stuffiness.[2, 3, 5, 9]

Desloratadine also appears to be more effective than placebo in improving symptoms in patients with seasonal allergic rhinitis who have concomitant mild to moderate asthma.[1, 2, 6, 9] In 2 randomized, controlled studies in 924 patients (15-75 years of age) with seasonal allergic rhinitis and mild to moderate asthma, treatment with desloratadine 5 mg daily for 2-4 weeks improved nasal (e.g., rhinorrhea, sneezing, nasal itching, nasal stuffiness/congestion) and nonnasal (e.g., ocular itching or burning, ocular redness, tearing/watery eyes, itching of ears and/or palate) symptoms without impairing pulmonary function.[1, 2, 6] Limited data indicate that treatment with desloratadine also may improve total asthma symptom score (i.e., sum of individual scores for coughing, wheezing, and breathing difficulties) and/or reduce use of inhaled β_2-agonist bronchodilators.[2, 6]

Safety and efficacy of desloratadine in the management of perennial (nonseasonal) allergic rhinitis were established in 2 randomized, double-blind, placebo-controlled studies of 4 weeks' duration in more than 1300 patients (12-80 years of age) with perennial allergic rhinitis.[1] In one of these studies, treatment with desloratadine 5 mg daily was more effective than placebo in reducing nasal and nonnasal symptoms (as assessed by reduction in total symptom scores) in patients with perennial allergic rhinitis.[1]

In most studies, symptomatic (i.e., nasal and nonnasal) improvement was observed as early as 1 day after initiation of desloratadine therapy and maintained over the 24-hour dosage interval and throughout the entire treatment period.[2, 4, 5, 6, 9]

Safety and efficacy of the extended-release fixed-combination preparation containing desloratadine and pseudoephedrine sulfate were established in two 2-week randomized, parallel-group studies in adults and children 12 years of age and older with seasonal allergic rhinitis.[18, 19] The fixed combination was more effective in providing symptomatic relief of seasonal allergic rhinitis than either drug alone.[18, 19] However, the fixed combination generally should be used only when both the antihistaminic and nasal decongestant activity of the combination preparation are needed concurrently.[18]

Desloratadine also is used to provide symptomatic relief in the treatment of seasonal and perennial allergic rhinitis in pediatric patients.[1] Efficacy of the drug for symptomatic relief of seasonal allergic rhinitis in children 2-12 years of age and

perennial allergic rhinitis in pediatric patients 6 months of age and older is supported by adequate and well-controlled studies in adults.[1] In addition, the course of seasonal and perennial allergic rhinitis and the drug's effects are similar in adults and pediatric patients.[1]

• Chronic Idiopathic Urticaria

Desloratadine is used for the symptomatic treatment of pruritus and urticaria associated with chronic idiopathic urticaria.[1] Safety and efficacy of desloratadine were evaluated in several randomized, double-blind, placebo-controlled studies of 6 weeks' duration in more than 400 patients (12-84 years of age) with chronic idiopathic urticaria.[1, 2, 7] In these studies, treatment with desloratadine 5 mg daily was more effective than placebo in decreasing the severity of pruritus, the number of hives, and the size of the largest hive.[1, 2, 7, 9] Treatment with the drug also was associated with improved sleep and daytime performance compared with placebo.[2, 7]

Desloratadine also is used for relief of symptoms of chronic idiopathic urticaria (e.g., pruritus, hives) in pediatric patients.[1] Efficacy of the drug for symptomatic relief of chronic idiopathic urticaria in pediatric patients 6 months of age and older is supported by adequate and well-controlled studies in adults.[1] In addition, the course of chronic idiopathic urticaria and the drug's effects are similar in adults and pediatric patients.[1]

Dosage and Administration

• Administration

Desloratadine is administered orally once daily without regard to meals.[1, 9, 18]

Desloratadine orally disintegrating tablets are administered by placing a tablet on the tongue, allowing it to disintegrate, and then subsequently swallowing with or without water.[1] Patients receiving desloratadine orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing.[1] Desloratadine oral solution should be administered using a commercially available dropper or syringe that is calibrated to deliver 2 or 2.5 mL.[1] Extended-release tablets containing desloratadine in fixed combination with pseudoephedrine sulfate should be swallowed intact and should not be chewed, broken, or crushed.[18]

Commercially available desloratadine conventional tablets and oral solution are bioequivalent.[1] The currently available *reformulated* orally disintegrating tablets containing 5 mg of desloratadine are bioequivalent to the *original* orally disintegrating formulation (no longer commercially available),[1] which previously was shown to be bioequivalent to desloratadine conventional tablets and oral solution.[20]

• Dosage

Allergic Rhinitis and Chronic Idiopathic Urticaria

The recommended dosage of desloratadine for symptomatic relief of seasonal allergic rhinitis, perennial allergic rhinitis, or chronic idiopathic urticaria in adults and children 12 years of age and older is 5 mg once daily.[1, 9] When the fixed combination containing desloratadine and pseudoephedrine sulfate is used for symptomatic relief of seasonal allergic rhinitis in adults and children 12 years of age and older, the recommended dosage is 5 mg of desloratadine once daily.[18] Clinical studies in patients with seasonal allergic rhinitis indicate that higher desloratadine dosages (i.e.,

dosages exceeding 5 mg daily) provide no additional benefit but may increase the risk of adverse effects (e.g., somnolence).[1, 9]

The recommended dosage of desloratadine for symptomatic relief of seasonal allergic rhinitis, perennial allergic rhinitis, or chronic idiopathic urticaria in pediatric patients 6-11 years of age is 2.5 mg once daily (as an oral solution or orally disintegrating tablet).[1] For symptomatic relief of seasonal allergic rhinitis in pediatric patients 2-5 years of age, perennial allergic rhinitis in pediatric patients 1-5 years of age, or chronic idiopathic urticaria in pediatric patients 1-5 years of age, the recommended dosage of desloratadine is 1.25 mg once daily (as an oral solution).[1] For symptomatic relief of perennial allergic rhinitis or chronic idiopathic urticaria in pediatric patients 6-11 months of age, the recommended dosage of desloratadine is 1 mg once daily (as an oral solution).[1]

• **Special Populations**
The recommended initial dosage of desloratadine in adults with renal or hepatic impairment is 5 mg every *other* day.[1, 18] There are no specific dosage recommendations for pediatric patients with renal or hepatic impairment at this time because of lack of data.[1] The manufacturer states that the fixed-combination preparation containing desloratadine and pseudoephedrine sulfate generally should be avoided in patients with hepatic impairment.[18]

Although peak plasma concentrations and areas under the plasma concentration-time curve (AUCs) of desloratadine reportedly were higher in women, black patients, and geriatric patients, the manufacturer states that these differences do not appear to be clinically important, and that dosage adjustment based on gender, race, or age generally is not necessary.[1, 3] (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

• **Contraindications**
Known hypersensitivity to desloratadine, loratadine, or any ingredient in the formulation.[1, 18]

• **Warnings/Precautions**
General Precautions
Desloratadine shares the toxic potentials of loratadine and other second generation antihistamines, and the usual precautions related to therapy with such drugs should be observed.[1]

Use of Fixed Combinations. When desloratadine is used in fixed combination with pseudoephedrine sulfate, the usual cautions, precautions, and contraindications associated with pseudoephedrine must be considered in addition to those associated with desloratadine.[18]

Phenylketonuria. Individuals who must restrict their intake of phenylalanine should be warned that Clarinex® Reditabs® contain aspartame, which is metabolized in the GI tract following oral administration, to provide 1.4 or 2.9 mg of phenylalanine per 2.5- or 5-mg tablet, respectively. [1]

Specific Populations
Pregnancy. Category C.[1, 18] (See Users Guide.)

Lactation. Desloratadine is distributed into milk.[1, 18] Discontinue nursing or the drug, taking into account the importance of the drug to the woman.[1, 18] Exercise caution if the fixed-combination preparation containing desloratadine and pseudoephedrine sulfate is used in nursing women.[18]

Pediatric Use. Safety and efficacy have not been established for symptomatic management of seasonal allergic rhinitis in children younger than 2 years of age.[1]

Safety and efficacy have not been established for symptomatic management of perennial allergic rhinitis or chronic idiopathic urticaria in children younger than 6 months of age.[1]

Safety and efficacy of the fixed-combination preparation containing desloratadine and pseudoephedrine sulfate for symptomatic management of seasonal allergic rhinitis have not been established in children younger than 12 years of age.[18]

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) preparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection.[22, 23] There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by the US Food and Drug Administration [FDA]) for the symptomatic treatment of cold and cough have not been established.[22] Such preparations should be used in children younger than 2 years of age with caution and only as directed by a clinician.[22, 23] Clinicians should use caution in prescribing cough and cold preparations in these children and should ask caregivers about use of nonprescription cough and cold preparations to avoid overdosage.[22] For additional information on precautions associated with the use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in the Antihistamines General Statement 4:00.

Geriatric Use. Experience with desloratadine in those 65 years of age and older is insufficient to determine whether they respond differently from younger adults.[1, 18] In one study, peak plasma concentrations and area under the plasma concentration-time curve (AUC) of desloratadine were increased (by 20%) and plasma elimination half-life was prolonged in geriatric patients compared with younger adults; however, these age-related differences do not appear to be clinically important.[1, 18] Nevertheless, dosage should be selected with caution because of the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in geriatric patients.[1, 18]

Hepatic Impairment. In clinical studies, AUC of desloratadine was increased by 2.4-fold in patients with hepatic impairment relative to that in patients with normal hepatic function; decreased clearance and increased elimination half-life also were observed.[1] Dosage reduction recommended for patients with hepatic impairment.[1] (See Dosage and Administration: Special Populations.) Avoid use of the fixed-combination preparation containing desloratadine and pseudoephedrine sulfate.[18]

Renal Impairment. Peak plasma concentrations or AUC of desloratadine increased by 1.2- or 1.9-fold, respectively, in patients with mild to moderate renal impairment and by 1.7- or 2.5-fold, respectively, in patients with severe renal impairment or in those who required hemodialysis compared with that in patients with normal renal function.[1] Dosage reduction recommended for patients with renal impairment.[1, 18] (See Dosage and Administration: Special Populations.)

• Common Adverse Effects

Adverse effects reported in 2% or more of patients 12 years of age and older receiving desloratadine for management of allergic rhinitis and occurring more frequently than placebo include pharyngitis,[1, 3, 4, 9] dry mouth,[1, 3, 4, 9] myalgia,[1, 3, 9] fatigue,[1, 3, 9] somnolence,[1, 3, 4, 9] and dysmenorrhea.[1] Adverse effects reported in at least 2% of patients 12 years of age and older receiving desloratadine for management of chronic idiopathic urticaria and more frequently than placebo include headache,[1, 7, 9] nausea,[1] fatigue,[1, 7] dizziness,[1, 7] pharyngitis,[1, 7] dyspepsia,[1] and myalgia.[1]

Adverse effects reported in 2% or more of pediatric patients (2-5 years of age) receiving desloratadine and occurring more frequently than placebo include fever, urinary tract infection, and varicella (chicken pox).[1] Adverse effects reported in 2% or more of patients 12-23 months of age and occurring more frequently than placebo include fever, diarrhea, upper respiratory tract infection, coughing, increased appetite, emotional lability, epistaxis, parasitic infection, pharyngitis, and maculopapular rash.[1] Adverse effects reported in 2% or more of patients 6-11 months of age and occurring more frequently than placebo include upper respiratory tract infection, diarrhea, fever, irritability, coughing, somnolence, bronchitis, otitis media, vomiting, anorexia, pharyngitis, insomnia, rhinorrhea, erythema, and nausea.[1]

Adverse effects reported in 2% or more of patients 12 years of age and older receiving the fixed combination of desloratadine and pseudoephedrine sulfate include dry mouth, headache, insomnia, fatigue, pharyngitis, somnolence, nausea, dizziness, nervousness, hyperactivity, and anorexia.[18]

Drug Interactions

No formal drug interaction studies have been performed with the fixed-combination preparation containing desloratadine and pseudoephedrine sulfate.[18] When using this preparation, consider the drug interactions associated with pseudoephedrine (e.g., monoamine oxidase [MAO] inhibitors).[18]

• Drugs Affecting Hepatic Microsomal Enzymes

Potential pharmacokinetic interaction (increased plasma concentrations of desloratadine and active metabolite) when desloratadine is used with drugs affecting hepatic microsomal enzymes (e.g., azithromycin, cimetidine, erythromycin, fluoxetine, ketoconazole).[1, 9] No clinically important changes in ECG or laboratory evaluations, vital signs, or adverse effects were reported.[1, 9]

• Grapefruit Juice

Pharmacokinetic interaction unlikely.[1, 3]

Pharmacokinetics

• **Absorption**

Bioavailability

Conventional tablets and oral solution are bioequivalent.[1] Orally disintegrating tablets (recently reformulated) are bioequivalent to original orally disintegrating formulation (no longer commercially available);[1] original formulation previously shown to be bioequivalent to conventional tablets and oral solution.[20]

Peak plasma concentrations occur at approximately 3 or 6-7 hours following administration of conventional tablets, or fixed-combination extended-release preparation, respectively.[1, 18]

Onset

Following single- and multiple-dose administration, antihistaminic effects occur within 1 hour.[1] Symptomatic (nasal and nonnasal) improvement observed as early as 1 day after initiation of therapy.[2, 4, 5, 6, 9]

Duration

Following single- and multiple-dose administration, antihistaminic effects persist for up to 24 hours.[1] No evidence of histamine-induced skin wheal tachyphylaxis over 28-day treatment period.[1]

Food

Food or grapefruit juice does not appear to affect bioavailability following administration as conventional tablets, oral solution,[1] or fixed-combination tablets;[18] water does not appear to affect bioavailability following administration as orally disintegrating tablets.[1]

Special Populations

In patients with renal impairment and those who require hemodialysis, peak plasma desloratadine concentrations and AUC are increased.[1]

• **Distribution**

Plasma Protein Binding

Approximately 82-87% (for desloratadine) and 85-89% (for 3-hydroxydesloratadine).[1]

Special Populations. Protein binding not altered in patients with renal impairment.[1]

• **Elimination**

Metabolism

Extensively metabolized to 3-hydroxydesloratadine (active metabolite), which subsequently undergoes glucuronidation; enzyme(s) responsible for metabolism of desloratadine not identified.[1]

Elimination Route

Approximately 87% excreted as metabolic products in urine and feces in equal proportions.[1]

Desloratadine and 3-hydroxydesloratadine are poorly removed by hemodialysis.[1]

Half-life

27 hours for desloratadine and 3-hydroxydesloratadine.[1]

Special Populations
Approximately 6% of patients are poor metabolizers (decreased ability to form 3-hydroxydesloratadine); higher frequency of poor metabolizers in blacks (17%) than in Caucasians (2%) or Hispanics (2%).[1, 18] Substantially (approximately sixfold) greater drug exposure in poor metabolizers than in normal metabolizers;[1] however, no overall differences in safety observed between these groups.[1, 18] Nevertheless, an increased risk of adverse effects in poor metabolizers cannot be ruled out.[1, 18]

In patients ≥65 years of age, plasma desloratadine concentrations are increased and elimination half-life is prolonged.[1]

In patients with hepatic impairment, AUC and elimination half-life are increased and clearance is decreased.[1]

Description

Desloratadine, the active descarboethoxy metabolite of loratadine, is a long-acting tricyclic antihistamine.[1, 2, 3, 9] The drug has been characterized as a specific, selective peripheral H_1-receptor antagonist.[1, 2, 3, 4, 6, 9] Experimental evidence indicates that desloratadine also suppresses the release of histamine from human mast cells.[1, 9] Because desloratadine does not readily cross the blood-brain barrier,[1, 2, 3] the drug has been referred to as a relatively "nonsedating" or second generation antihistamine.[2, 5, 6, 7, 9]

Desloratadine is commercially available for oral administration as conventional tablets, orally disintegrating tablets, oral solution, and as an extended-release tablet containing desloratadine in fixed combination with pseudoephedrine sulfate.[1, 18] Desloratadine orally disintegrating tablets recently have been reformulated to improve palatability.[9, 21]

Following oral administration of desloratadine 5 mg once daily for 10 days as conventional tablets, peak plasma concentrations of the drug were achieved in approximately 3 hours.[1] Following oral administration of a single 5-mg dose of desloratadine as a fixed-combination, extended-release tablet also containing pseudoephedrine sulfate, peak plasma concentrations of desloratadine were achieved in approximately 6-7 hours.[18] Food or grapefruit juice does not appear to affect bioavailability of desloratadine following administration as conventional tablets, oral solution, or extended-release fixed-combination tablets; water does not appear to affect bioavailability of desloratadine following administration as orally disintegrating tablets.[1]

The manufacturer states that desloratadine conventional tablets and oral solution are bioequivalent.[1] The currently available *reformulated* orally disintegrating tablets containing 5 mg of desloratadine are bioequivalent to the *original* orally disintegrating formulation (no longer commercially available),[1] which previously was shown to be bioequivalent to desloratadine conventional tablets and oral solution.[20] The extended-release fixed-combination tablets are not bioequivalent with desloratadine conventional tablets. Following oral administration of the fixed-combination preparation containing 5 mg of desloratadine and 240 mg of

pseudoephedrine sulfate, plasma concentrations of desloratadine and 3-hydroxydesloratadine were 15-20% lower than those achieved with the 5-mg conventional tablets.[18]

Following single- and multiple-dose administration, antihistaminic effects of desloratadine occur within 1 hour and persist for up to 24 hours.[1] There is no evidence of histamine-induced skin wheal tachyphylaxis following 28 days of treatment with desloratadine 5 mg daily; the clinical relevance of histamine wheal skin testing has not been established.[1]

Desloratadine is extensively metabolized to 3-hydroxydesloratadine, an active metabolite that subsequently undergoes glucuronidation; the enzyme(s) responsible for metabolism of desloratadine has not been identified.[1, 18] Data from clinical trials and pharmacokinetic studies indicate that approximately 6% of patients receiving desloratadine exhibit a decreased ability to form 3-hydroxydesloratadine and, therefore, are classified as poor metabolizers of the drug; the frequency of poor metabolizers appears to be higher in blacks (17%) than in Caucasians (2%) or Hispanics (2%).[1, 18] Poor metabolizers experience a substantially (approximately sixfold) greater exposure to desloratadine than normal metabolizers; however, no overall differences in safety were observed between these groups.[1, 18] Nevertheless, the manufacturer states that an increased risk of adverse effects in poor metabolizers cannot be ruled out.[1, 18]

Approximately 87% of a radiolabeled oral dose of desloratadine is excreted as metabolic products in urine and feces in equal proportions.[1]

Advice to Patients

Importance of adhering to prescribed dosage regimen and directions for use; increase in dosage or dosing frequency not recommended since higher dosages provide no additional benefit but may increase the risk of adverse effects (e.g., somnolence).[1]

For phenylketonurics, importance of informing them that desloratadine orally disintegrating tablets contain aspartame.[1]

Importance of advising patients to avoid concomitant use of fixed-combination preparation with OTC antihistamines and/or decongestants.[18]

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs.[1]

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.[1]

Importance of informing patients of other important precautionary information. (See Cautions.)

Additional Information

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more

detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Desloratadine

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Solution 0.5 mg/mL **Clarinex® Syrup** (with propylene Schering glycol and sorbitol) Tablets, film- 5 mg **Clarinex®** Schering coated Tablets, orally 2.5 mg **Clarinex® RediTabs®** (with aspartame) Schering disintegrating 5 mg **Clarinex® RediTabs®** (with aspartame) Schering

Desloratadine Combinations

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Tablets, extended- release core 5 mg with **Clarinex-D® 24-Hour** Schering (pseudoephedrine sulfate only) Pseudoephedrine (with povidone) Sulfate 240 mg

• **Comparative Pricing**
Pricing information provided by drugstore.com.

Clarinex 0.5MG/ML SYRP (SCHERING): 473/$155.38 or 1419/$445.42

Clarinex 5MG TABS (SCHERING): 30/$91.47 or 90/$267.29

Clarinex Reditabs 2.5MG TBDP (SCHERING): 90/$294.28 or 180/$573.26

Clarinex-D 12 Hour 2.5-120MG TB12 (SCHERING): 100/$218.62 or 300/$605.97

Clarinex-D 24 Hour 5-240MG TB24 (SCHERING): 30/$93.23 or 90/$271.91

References

1. Schering Corporation. Clarinex® (desloratadine) tablets, syrup, RediTabs® tablets prescribing information. Kenilworth, NJ; 2005 Apr.

2. McClellan K and Jarvis B. Desloratadine. *Drugs*. 2001; 61:789-96. [PubMed 11398910]

3. Agrawal DK. Pharmacology and clinical efficacy of desloratadine as an anti-allergic and anti-inflammatory drug. *Expert Opin Investig Drugs*. 2001; 10:547-60. [PubMed 11424898]

4. Meltzer EO, Prenner BM, Nayak A for the Desloratadine Study Group. Efficacy and tolerability of once-daily 5 mg desloratadine, an H_1-receptor antagonist, in

patients with seasonal allergic rhinitis assessment during the spring and fall allergy seasons. *Clin Drug Invest*. 2001; 21:25-32.

5. Nayak AS and Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. *Allergy*. 2001; 56:1077-80. [PubMed 11703222]

6. Baena-Cagnani CE. Desloratadine activity in concurrent seasonal allergic rhinitis and asthma. *Allergy*. 2001; 56(Suppl):21-7. [PubMed 11243501]

7. Ring J, Hein R, Gauger A et al. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol*. 2001; 40:1-5. [PubMed 11277944]

8. Gupta S, Banfield C, Kantesaria B et al. Pharmacokinetic and safety profile of desloratadine and fexofenadine when coadministered with azithromycin: a randomized, placebo-controlled, parallel-group study. *Clin Ther*. 2001; 23:451-66. [PubMed 11318079]

9. Schering, Kenilworth, NJ: Personal communication.

10. Borge PA. Problems in allergic rhinitis. *Arzneimittelforschung*. 1982; 32:1199-201. [PubMed 6891258]

11. Anon. Treatment of seasonal and perennial rhinitis. *BMJ*. 1981; 283:808-10. [PubMed 6117350] [Free Fulltext PMC]

12. Food and Drug Administration. Over-the-counter drugs: establishment of a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic products. [21 CFR 341] *Fed Regist*. 1976; 41:38312-424.

13. Douglas WW. Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: Gilman AG, Goodman LS, Rall TW et al, eds. Goodman and Gilman's the pharmacologic basis of therapeutics. 7th ed. New York: Macmillan Publishing Company; 1985:605-38.

14. Cirillo VJ, Tempero KF. The pharmacology and therapeutic use of H1 and H2 antihistamines. In: Miller RR, Greenblatt DJ, eds. Drug therapy reviews. Vol 2. New York: Elsevier/North Holland Inc; 1979:24-47.

15. Church JA. Allergic rhinitis: diagnosis and management. *Clin Pediatr (Philadelphia)*. 1980; 19:655-9.

16. AMA Division of Drugs. AMA drug evaluations. 5th ed. Chicago: American Medical Association; 1983:1465-79.

17. Food and Drug Administration. Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use; tentative final monograph for OTC antihistamine drug products. [21 FR Part 341] *Fed Regist*. 1985; 50:2200-18.

18. Schering Corporation. Clarinex-D® 24-Hour (desloratadine 5 mg and pseudoephedrine sulfate) extended-release tablets prescribing information. Kenilworth, NJ; 2005 Mar.

19. Pleskow W, Grubbe R, Weiss S et al. Efficacy and safety of an extended-release formulation of desloratadine and pseudoephedrine vs the individual components in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2005; 94:348-54. [PubMed 15801245]

20. Schering Corporation. Clarinex® (desloratadine) tablets, syrup, RediTabs® tablets prescribing information. Kenilworth, NJ; 2004 Aug.

21. Schering-Plough. FDA approves re-formulated Clarinex® (desloratadine) RediTabs® tablets—orally disintegrating prescription antihistamine. Kenilworth, NJ: 2005 Jul 15. Press release. From website (http://schering-plough.com/schering_plough/news/news_releases.jsp).

22. Srinivasan A, Budnitz D, Shehab N et al. Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007; 56:1-4.

23. Food and Drug Administration. Cough and cold medications in children less than two years of age. Rockville, MD; 2007 Jan 12. From FDA website (http://www.fda.gov/medwatch/safety/2007/safety07.htm#coughcold).

(+/-) Show / Hide Bibliography

Cetirizine Hydrochloride

Introduction

$C_{21}H_{25}ClN_2O_3 \bullet 2ClH$

• Cetirizine, a piperazine-derivative, has been classified as a second generation antihistamine.[1, 2, 3, 12]

Uses

Cetirizine shares the uses of other antihistamines, including the management of seasonal or perennial allergic rhinitis and chronic idiopathic urticaria.[1, 2, 3, 20, 25, 26, 27, 28, 29, 46, 49] For additional information on these and other uses of antihistamines, see Uses in the Antihistamines General Statement 4:00.

• **Allergic Rhinitis**

Cetirizine alone or in fixed combination with pseudoephedrine hydrochloride is used to provide symptomatic relief of seasonal allergic rhinitis (e.g., hay fever).[1, 2, 3, 12, 20, 25, 26, 27, 42, 46, 49, 62, 63] Cetirizine alone or in fixed combination with pseudoephedrine hydrochloride also is used for the symptomatic treatment of perennial allergic

rhinitis.[1, 2, 3, 20, 63] It is recommended that the fixed combination generally be used only when both the antihistamine and nasal decongestant activity of the combination preparation are needed concurrently.[63]

Antihistamines, including cetirizine, are used in the management of seasonal allergic rhinitis.[1, 2, 3, 20, 25, 26, 27, 42, 49, 62] Antihistamines are not curative and merely provide palliative relief; since seasonal allergic rhinitis may be a chronic, recurrent condition, successful therapy often may require long-term intermittent use of these drugs.[7, 8, 9, 10] In the treatment of seasonal allergic rhinitis, antihistamines are more likely to be beneficial when therapy is initiated at the beginning of the hay fever season when pollen counts are low.[8, 10, 50, 52] Antihistamines are less likely to be effective when pollen counts are high, when pollen exposure is prolonged, and when nasal congestion is prominent.[10, 51] Chronic nasal congestion and headache caused by edema of the paranasal sinus mucosa often are refractory to antihistamine therapy.[8, 9, 10, 53] Antihistamines generally are not effective in relieving symptoms of nasal obstruction.[8, 9, 54]

Following oral administration of a 10-mg dose of cetirizine hydrochloride in patients with seasonal allergic rhinitis who were exposed to allergens (e.g., pollen, mold), symptomatic relief of allergic reactions was evident within 2 hours and was maintained for about 24 hours.[27, 62] In short-term (1-6 weeks) controlled clinical trials in patients 12 years of age and older, cetirizine hydrochloride (5-20 mg daily) was more effective than placebo and at least as effective as astemizole (no longer commercially available in the US) (10 mg daily), chlorpheniramine, diphenhydramine (50 mg 3 times daily), loratadine (10 mg daily), or terfenadine (no longer commercially available in the US) (60 mg twice daily) in controlling symptoms of seasonal or perennial allergic rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus, nasal congestion, postnasal drip, itchy throat, cough, otic pruritus, ocular pruritus, tearing).[1, 2, 3, 15, 20, 25, 26, 27, 41, 42, 49, 62]

Cetirizine hydrochloride 5 mg in fixed combination with pseudoephedrine hydrochloride 120 mg (Zyrtec®-D 12 Hour) also was more effective than placebo in controlling symptoms of seasonal allergic rhinitis.[63] In 2 randomized, double-blind, placebo-controlled studies in over 2000 patients 12 years of age and older with seasonal allergic rhinitis, treatment with the fixed-combination preparation for 2 weeks was associated with a substantial reduction in the subject-rated Total Symptom Severity Complex (TSSC) score (which included manifestations such as sneezing, runny nose, itchy nose, itchy eyes, watery eyes, postnasal drip, and nasal congestion) compared with placebo.[63]

In patients with allergic rhinitis and mild to moderate asthma, cetirizine improved symptoms of allergic rhinitis and did not alter pulmonary function.[1, 3, 14, 15, 26] In addition, there is some evidence that asthma symptoms (e.g., self-reported chest tightness, shortness of breath, cough, sputum production) may improve during cetirizine therapy in such patients.[15, 26, 56] Although some clinicians believe that the anticholinergic effects of some antihistamines may cause thickening of bronchial secretions resulting in further airway obstruction in asthmatics, especially those with status asthmaticus, most experts consider complete avoidance of currently available antihistamines in asthmatics unjustified.[15, 16, 17, 18, 19, 40, 46] (See Cautions: Precautions and Contraindications in the Antihistamines General Statement 4:00.)

Cetirizine hydrochloride also is used to provide symptomatic relief in the treatment of seasonal allergic rhinitis and perennial allergic rhinitis in pediatric patients.[1, 2] Efficacy of the drug for symptomatic management of seasonal allergic rhinitis in children 2-11 years of age and perennial allergic rhinitis in pediatric patients 6 months to 11 years of age is based on extrapolation of the demonstrated efficacy of cetirizine in adults and the likelihood that the disease course, pathophysiology, and drug activity are substantially similar between the 2 populations.[1] Safety of cetirizine in infants 6-11 or 12-24 months of age is based on placebo-controlled studies in which 0.25 mg/kg of the drug was administered twice daily for up to 7 days or 18 months, respectively; this dosage corresponds to a range of 3.4-6.2 mg daily in infants 6-11 months of age or 4-11 mg daily in those 12-24 months of age.[1, 64] Safety of cetirizine in children 2-5 years of age is based on placebo-controlled studies in which 0.2-0.4 mg/kg of the drug was administered daily for up to 4 weeks, whereas safety in children 6-11 years of age is based on placebo-controlled and uncontrolled clinical studies in which 5 or 10 mg of the drug was administered orally daily for up to 4 or 12 weeks, respectively.[1, 22, 23, 57, 61] Recommended pediatric doses are based on cross-study comparisons[1] of the pharmacokinetics and pharmacodynamics of cetirizine in adults and children[1, 2, 11, 24] and on safety profiles of the drug from studies in adults and children at recommended or higher doses.[1, 22, 23]

• Chronic Idiopathic Urticaria and Other Urticarias

Cetirizine is used for the symptomatic treatment of chronic idiopathic urticaria.[1, 2, 3, 12, 20, 28, 29, 46] In short-term (2-6 weeks) controlled clinical trials in patients with this condition, cetirizine hydrochloride (5-20 mg daily) was more effective than placebo and at least as effective as astemizole (10 mg daily), hydroxyzine hydrochloride (25-75 mg daily), or terfenadine (60 mg twice daily) in decreasing the incidence, severity, and duration of urticaria and relieving associated pruritus.[1, 2, 3, 12, 20, 28, 29] Limited evidence suggests that clinical benefit may not be improved substantially by the addition of a histamine H_2-receptor antagonist (e.g., cimetidine) to cetirizine therapy in patients with chronic idiopathic urticaria.[21]

Cetirizine also is used to provide symptomatic relief in the treatment of chronic idiopathic urticaria in pediatric patients.[1] Efficacy of the drug in this condition in pediatric patients 6 months to 11 years of age is based on extrapolation of the demonstrated efficacy of cetirizine in adults and the likelihood that the disease course, pathophysiology, and drug activity are substantially similar between the 2 populations.[1] Safety of cetirizine in children 2-5 years of age is based on placebo-controlled studies in which 0.2-0.4 mg/kg of the drug was administered daily for up to 4 weeks, whereas safety in children 6-11 years of age is based on placebo-controlled and uncontrolled clinical studies in which 5 or 10 mg of the drug was administered orally daily for up to 4 or 12 weeks, respectively.[1] Safety of cetirizine in infants 6-11 or 12-24 months of age is based on placebo-controlled studies in which 0.25 mg/kg of the drug was administered twice daily for up to 7 days or 18 months, respectively; this dosage corresponds to a range of 3.4-6.2 mg daily in infants 6-11 months of age or 4-11 mg daily in those 12-24 months of age.[1, 64] Recommended pediatric doses are based on cross-study comparisons[1] of the pharmacokinetics and pharmacodynamics of cetirizine in adults and children[1, 2, 11, 24] and on safety profiles of the drug from studies in adults and children at recommended or higher doses.[1, 22, 23]

Limited data indicate that cetirizine may show some benefit in the management of physical urticaria[#] (e.g., urticaria triggered by mechanical trauma, light, heat, cold, vibration, water), atopic dermatitis[#], and insect (e.g., mosquito) bites[#].[2]

• Common Cold

Nonsedating (second generation) antihistamines do not appear to be effective in relieving rhinorrhea associated with the common cold, suggesting that histamine is not a principal mediator of this manifestation.[32, 37] The extent to which histamine contributes to other manifestations of the common cold currently is unclear, but pathogenesis of the full constellation of symptoms that constitute the common cold appears to be complex, involving a number of mediators and neurologic mechanisms.[32, 33, 34, 35, 36]

Dosage and Administration

• Administration

Cetirizine is administered orally.[1, 3] Cetirizine chewable tablets may be administered with or without water.[1] Tablets containing cetirizine hydrochloride in fixed combination with pseudoephedrine hydrochloride should be swallowed intact and patients should be instructed not to break or chew such tablets.[63]

The manufacturer states that the time of administration of cetirizine may be adjusted for individual patient requirements.[1, 3] Although food may decrease peak plasma concentrations of cetirizine and lengthen the time to achievement of peak plasma concentrations,[1, 2, 3, 12] the manufacturer states that cetirizine may be administered without regard to food because food does not affect the extent of absorption of the drug when administered as conventional or chewable tablets.[1, 2, 3, 12, 14, 20]

The oral bioavailability of cetirizine hydrochloride conventional tablets is comparable to that of the oral solution and to that of the chewable tablets (administered with or without water).[1]

Dispensing and Administration Precautions

Because of similarities in spelling, dosage intervals (once daily), and tablet strengths (5 and 10 mg) of Zyrtec® (cetirizine hydrochloride) and Zyprexa® (olanzapine, an atypical antipsychotic agent), extra care should be exercised in ensuring the accuracy of prescriptions for these drugs.[65] (See Cautions: Precautions and Contraindications.)

• Dosage

Allergic Rhinitis and Chronic Idiopathic Urticaria

For symptomatic relief of seasonal allergic rhinitis, perennial allergic rhinitis, or chronic idiopathic urticaria, the usual initial dosage of cetirizine hydrochloride for adults and children 6 years of age and older is 5 or 10 mg once daily, depending on symptom severity.[1, 2, 3, 15, 20, 22, 23, 25] In clinical trials, most patients 12 years of age and older had cetirizine hydrochloride therapy initiated at a dosage of 10 mg daily.[1] Although dosages ranging from 5-20 mg daily have been used in patients 12 years of age and older,[1, 2, 3, 11, 12, 15, 20, 25, 26, 27, 28, 29] 10 mg daily was more effective than 5 mg daily in this age group in clinical trials, and no additional benefit was observed with the 20-mg daily dosage in these trials.[1]

For symptomatic relief of seasonal allergic rhinitis in pediatric patients 2-5 years of age, perennial allergic rhinitis in pediatric patients 6 months to 5 years of age, or chronic idiopathic urticaria in pediatric patients 6 months to 5 years of age, the usual initial dosage of cetirizine hydrochloride is 2.5 mg once daily (as an oral solution).[1] Dosage in pediatric patients 12-23 months of age may be increased to a maximum dosage of 5 mg daily, given as a 2. 5-mg dose every 12 hours (as an oral solution); the oral solution is the recommended formulation in children younger than 2 years of age.[1] In patients 2-5 years of age, the dosage may be increased to a maximum of 5 mg administered once daily (as an oral solution or chewable tablet) or as a 2. 5-mg dose every 12 hours (as an oral solution).[1] (See Cautions: Pediatric Precautions.)

When cetirizine hydrochloride is used in fixed combination with pseudoephedrine hydrochloride for the symptomatic relief of allergic rhinitis in adults and children 12 years of age or older, the usual dosage is 5 mg of cetirizine hydrochloride twice daily (every 12 hours).[63]

Although the elimination half-life of cetirizine may be prolonged and total body clearance decreased in geriatric adults compared with those in younger adults (see Pharmacokinetics: Elimination), the manufacturer makes no specific recommendations about dosage adjustment of cetirizine hydrochloride in elderly patients except those 77 years of age or older; the recommended dosage in such patients is 5 mg once daily.[1] Because geriatric patients are more likely to have decreased renal function, dosage of cetirizine hydrochloride should be carefully selected in these patients and renal function monitored accordingly.[1] (See Dosage and Administration: Dosage in Renal and Hepatic Impairment and see Cautions: Geriatric Precautions.)

• Dosage in Renal and Hepatic Impairment

The manufacturer states that patients 12 years of age or older who have impaired renal function (e.g., creatinine clearance of 11-31 mL/minute) or hepatic impairment or who are undergoing hemodialysis (creatinine clearance of less than 7 mL/minute), should receive a cetirizine hydrochloride dosage of 5 mg daily.[1, 3] The manufacturer also states that children 6-11 years of age with impaired renal or hepatic function should use the lower recommended dosage (5 mg once daily).[1] The manufacturer states that use of cetirizine hydrochloride in children younger than 6 years of age with impaired renal or hepatic function is not recommended because administration of doses smaller than 2.5 mg is difficult and not reliable, and pharmacokinetic data are lacking in this patient population.[1]

When extended-release tablets of cetirizine hydrochloride in fixed combination with pseudoephedrine hydrochloride are used in patients 12 years of age or older who have impaired renal function (i.e., creatinine clearance of 11-31 mL/minute) or hepatic impairment or who are undergoing hemodialysis (creatinine clearance of less than 7 mL/minute), the recommended cetirizine hydrochloride dosage is 5 mg once daily.[63]

Cautions

During controlled and uncontrolled clinical trials in patients 12 years of age and older receiving oral cetirizine hydrochloride dosages of 5-20 mg daily for 1 week to 6 months (mean duration: 30 days), adverse effects were mild to moderate and the rate of discontinuance of therapy secondary to adverse effects associated with the drug

was similar to that reported with placebo.[1, 3] Discontinuance of therapy because of adverse events was reported in 2.9% of patients receiving cetirizine compared with 2.4% of those receiving placebo.[1, 3, 28] The incidence of adverse effects was not affected by race, age, gender, or body weight.[1, 3]

During controlled and uncontrolled clinical trials in patients 6-11 years of age receiving oral cetirizine hydrochloride dosages of 1.25-10 mg daily for 2-12 weeks and controlled clinical trials in patients 2-5 years of age usually receiving a single 5-mg dose of cetirizine hydrochloride daily for up to 4 weeks, most adverse effects were mild to moderate, and discontinuance of therapy because of adverse events was reported in only 0.4% of the children receiving cetirizine compared with 1% of those receiving placebo.[1] The incidence and nature of adverse effects in children 6-11 years of age were similar to those in children 2-5 years of age.[1] In placebo-controlled studies in pediatric patients 6-11 or 12-24 months of age receiving an oral cetirizine hydrochloride dosage of 0.25 mg/kg twice daily for 7 days or 18 months, respectively, the incidences of adverse effects generally were similar in the cetirizine and placebo groups; however, certain adverse CNS effects (i.e., irritability/fussiness, insomnia) occurred more frequently in patients receiving cetirizine than in those receiving placebo.[1] (See Cautions: Nervous System Effects.)

Adverse effects reported in 2% or more of patients 12 years of age and older who received cetirizine hydrochloride (as conventional tablets) at dosages up to 10 mg daily included somnolence, fatigue, dry mouth, pharyngitis, and dizziness.[1, 63] Adverse effects reported in 2% or more of patients 6-11 years of age who received 5-10 mg of cetirizine hydrochloride daily included headache, pharyngitis, abdominal pain, coughing, somnolence, diarrhea, epistaxis, bronchospasm, nausea, and vomiting.[1]

Adverse effects reported in 1% or more of patients 12 years of age and older with seasonal allergic rhinitis who received extended-release tablets of cetirizine hydrochloride in fixed combination with pseudoephedrine hydrochloride (Zyrtec®-D 12 Hour) included insomnia, dry mouth, fatigue, somnolence, pharyngitis, epistaxis, accidental injury, dizziness, and sinusitis.[63]

• Nervous System Effects

The most frequent adverse effect in patients 12 years of age and older reported during cetirizine therapy is somnolence, occurring in 11, 14, or 6% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively.[1, 2, 3, 5, 6, 27, 28, 39, 41, 42, 43, 49] Overall, somnolence has been reported in 13.7 or 6.3% of patients receiving cetirizine or placebo, respectively.[1, 2, 3] In addition, in clinical trials in patients 6-11 years of age, somnolence occurred in 1.9, 4.2, or 1.3% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively.[1] Discontinuance of therapy because of somnolence has been reported in 1 or 0.6% of patients receiving cetirizine or placebo, respectively.[1, 3] In patients 6-24 months of age, somnolence occurred with essentially the same frequency in those who received cetirizine versus placebo.[1]

Fatigue or dizziness occurred in 5.9 or 2%, respectively, of patients 12 years of age and older receiving cetirizine, whereas these effects occurred in 2.6 or 1.2%, respectively, of patients receiving placebo.[1, 2, 3, 6, 28, 41, 49] Headache was reported in more than 2% of patients 12 years of age and older receiving the drug; however, headache occurred more frequently in patients receiving placebo.[1, 27, 28, 41, 42, 49] In

clinical trials in patients 6-11 years of age, headache occurred in 11, 14, or 12.3% of patients receiving 5-mg doses, 10-mg doses, or placebo, respectively.[1] Abnormal coordination, ataxia, confusion, abnormal thinking, agitation, amnesia, anxiety, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, sleep disorders, nervousness, paroniria, dysphonia, asthenia, malaise, pain, hyperesthesia, hypoesthesia, hyperkinesia, hypertonia, migraine headache, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, and vertigo have been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1] Aggressive reaction, seizures, hallucinations, suicidal ideation, and suicide have been reported rarely during postmarketing surveillance.[1, 63]

In a controlled study of 1 week's duration in patients 6-11 months of age, those receiving cetirizine exhibited greater irritability/fussiness than those receiving placebo.[1] In a controlled study in patients 12 months of age and older, insomnia occurred more frequently with cetirizine than with placebo (9 vs 5.3%, respectively).[1] In those who received 5 mg or more daily, fatigue occurred in 3.6 or 1.3% and malaise in 3.5 or 1.8% of those receiving cetirizine or placebo, respectively.[1]

• Oronasopharyngeal and Pulmonary Effects

Dry mouth or pharyngitis occurred in 5 or 2%, respectively, of those receiving cetirizine, whereas these effects occurred in 2.3 or 1.9%, respectively, of those receiving placebo.[1, 3, 20, 28, 41, 49] In clinical trials in patients 6-11 years of age, pharyngitis, coughing, bronchospasm, or epistaxis occurred in 6.2, 4.4, 3.1, or 3.7%, respectively, of children receiving 5-mg doses of the drug; in 2.8, 2.8, 1.9, or 1.9%, respectively, of children receiving 10-mg doses of the drug; and in 2.9, 3.9, 1.9, or 2.9%, respectively, of children receiving placebo.[1]

Bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, nasal polyp, sinusitis, upper respiratory tract infection, increased salivation, discoloration and/or edema of the tongue, and aggravated dental caries have been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1] Orofacial dyskinesia also has been reported.[1]

• GI Effects

In clinical trials in patients 6-11 years of age, abdominal pain, diarrhea, nausea, or vomiting occurred in 4.4, 3.1, 1.9, or 2.5%, respectively, of children receiving 5-mg doses of the drug; in 5.6, 1.9, 2.8, or 2.3%, respectively, of children receiving 10-mg doses of the drug; and in 1.9, 1.3, 1.9, or 1%, respectively, of children receiving placebo.[1] Nausea was reported in more than 2% of patients 12 years of age and older receiving cetirizine; however, nausea occurred more frequently in patients receiving placebo.[1]

Anorexia, increased appetite, taste loss, taste perversion, dyspepsia, gastritis, stomatitis (including ulcerative stomatitis), enlarged abdomen, eructation, flatulence, constipation, melena, rectal hemorrhage, and hemorrhoids have been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1]

• **Cardiovascular Effects**

Palpitation, tachycardia, hypertension, chest pain, facial edema, generalized edema, leg edema, peripheral edema, hot flashes, or cardiac failure has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1]

Although serious cardiac effects, including ventricular fibrillation and death associated with prolonged QT interval and atypical ventricular tachyarrhythmia (torsades de pointes), have been reported in patients receiving certain other second generation antihistamines (e.g., astemizole [no longer commercially available in the US], terfenadine [no longer commercially available in the US]), administration of cetirizine hydrochloride alone to healthy adult men at dosages of 60 mg daily (6 times the maximum recommended daily dosage) for 1 week has not been associated with significant prolongation of the QT interval corrected for rate (QT_c).[1, 2, 3, 4, 29, 30, 31] In addition, in placebo-controlled studies in pediatric patients 6-11 months or 6-11 years of age who received a cetirizine hydrochloride dosage of 0.25 mg/kg twice daily or 5-10 mg daily, respectively, there was no significant prolongation of the QT_c interval compared with baseline measurements or placebo after 1 or 2 weeks, respectively.[1, 57] Similar findings were reported in other studies in which cetirizine was administered to infants 6-23 months of age.[1] The effect of cetirizine hydrochloride on the QT_c interval in children younger than 12 years of age receiving dosages exceeding 10 mg has not been studied.[1]

The manufacturer states that concomitant administration of cetirizine hydrochloride with drugs known to inhibit cytochrome P-450 microsomal enzymes (e.g., azithromycin, erythromycin, ketoconazole) has not been associated with clinically important changes in ECG parameters (e.g., QT_c intervals) and that no clinically important interactions have been reported in patients receiving cetirizine concomitantly with azithromycin, erythromycin, or ketoconazole.[1, 3, 31, 56, 57] (See Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes.)

• **Genitourinary and Renal Effects**

Cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary retention, urinary tract infection, dysmenorrhea, intermenstrual bleeding, leukorrhea, menorrhagia, decreased libido, or vaginitis has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1] Glomerulonephritis also has been reported.[1]

• **Dermatologic and Sensitivity Reactions**

Acne, dermatitis, dry skin, eczema, rash (which may be erythematous), urticaria, skin disorder, skin nodules, purpura, bullous eruption, furunculosis, hyperkeratosis, hypertrichosis, alopecia, seborrhea, pruritus, purpura, photosensitivity reactions (which may be toxic), or angioedema has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1] Anaphylaxis also has been reported.[1]

• **Ocular and Otic Effects**

Visual field defect, blindness, conjunctivitis, ocular pain, glaucoma, loss of ocular accommodation, ocular hemorrhage, periorbital edema, xerophthalmia, deafness, otalgia, ototoxicity, or tinnitus has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1]

• Hepatic Effects

Transient, reversible elevations of hepatic aminotransferases (transaminases) occurred during cetirizine therapy.[1, 3, 4] In addition, hepatitis with substantial elevations of aminotransferases and bilirubin has been associated with the use of cetirizine.[1]

• Other Adverse Effects

Accidental injury, back pain, fever, increased weight, cholestasis, pallor, rigors, lymphadenopathy, hemolytic anemia, thrombocytopenia, breast pain in women, or parosmia has been reported in less than 2% of patients 12 years of age and older and children 6-11 years of age receiving cetirizine hydrochloride; however, a causal relationship to the drug has not been established.[1]

No cases of drug abuse or dependence have been reported with cetirizine hydrochloride to date.[1, 56]

• Precautions and Contraindications

The incidence of adverse effects associated with cetirizine use generally appears to be less than that associated with the use of first generation (prototypical, sedating) antihistamines, although evidence from some clinical studies indicates that the incidence of somnolence associated with cetirizine may be higher than that associated with other second generation antihistamines (e.g., loratadine).[2, 20, 56, 57] (See Nervous System Effects in Pharmacology and also in Cautions.) In addition, effects similar to those occurring in patients receiving first generation antihistamines have been reported, and the potential for typical adverse effects induced by these antihistamines should be considered during cetirizine therapy.[56] Pharmacologic studies indicate that cetirizine does not have appreciable anticholinergic effects, although dry mouth has been reported in clinical studies more frequently with the drug than with placebo.[1, 3, 20, 28, 41, 49]

Because somnolence[1, 2, 3, 5, 6, 27, 28, 39, 41, 42, 43, 49] has been reported in some individuals in clinical studies, patients should be warned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).[1, 3] In addition, patients should be warned that additive CNS depression may occur when cetirizine is administered concomitantly with other CNS depressants, including alcohol.[1, 3]

If the fixed combination of cetirizine hydrochloride and pseudoephedrine hydrochloride is used, the precautions and contraindications associated with pseudoephedrine must be considered.[63] (See Pseudoephedrine Hydrochloride 12:12.12.)

Because of similarities in spelling, dose intervals (once daily), and tablet strengths (5 and 10 mg) of Zyrtec® (the trade name for cetirizine hydrochloride) and Zyprexa® (the trade name for olanzapine, an atypical antipsychotic agent), several dispensing or prescribing errors have been reported to the manufacturer of Zyprexa® (Lilly).[65]

These medication errors may result in unnecessary adverse events or a potential relapse in patients with schizophrenia or bipolar disorder.[65] Therefore, the manufacturer of Zyprexa® cautions that extra care should be exercised in ensuring the accuracy of written prescriptions for Zyrtec® and Zyprexa® such as printing both the proprietary (brand) and nonproprietary (generic) names on all prescriptions for these drugs.[65] The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., placing drugs with similar names apart from one another on pharmacy shelves, patient counseling).[65]

Cetirizine is contraindicated in patients who are hypersensitive to cetirizine, hydroxyzine, or any ingredient in the formulation.[1, 3, 63]

• Pediatric Precautions

Safety of cetirizine hydrochloride in pediatric patients 6 months to 5 years of age is based on controlled clinical trials, and safety in children 6-11 years of age is based on both controlled and uncontrolled trials.[1 47] (See Uses.) Efficacy of cetirizine for the treatment of perennial allergic rhinitis and chronic idiopathic urticaria in pediatric patients 6 months to 11 years of age and for seasonal allergic rhinitis in pediatric patients 2-11 years of age is based on extrapolation of demonstrated efficacy in adults and the likelihood that the disease course, pathophysiology, and the drug's effect are substantially similar between these populations.[1] The manufacturer states that safety and efficacy of cetirizine in children younger than 6 months of age have not been established.[1] Cetirizine hydrochloride oral solution is the recommended formulation for children younger than 2 years of age.[1]

Results of placebo-controlled studies in pediatric patients 6-11 months or 6-11 years of age indicate that there is no significant prolongation of the QT_c interval associated with cetirizine use compared with baseline measurements or placebo.[1] Similar findings were reported in other studies in which cetirizine was administered to pediatric patients 6-23 months of age.[1] The effect of cetirizine hydrochloride on the QT_c interval in children younger than 12 years of age receiving dosages exceeding 10 mg has not been studied.[1] (See Cautions: Cardiovascular Effects.)

The dose of pseudoephedrine hydrochloride in fixed combination with cetirizine hydrochloride exceeds the recommended dose in children younger than 12 years of age.[63] In addition, safety and efficacy of this fixed combination have not been established in children younger than 12 years of age, and use of the fixed-combination preparation (Zyrtec®-D 12 Hour) is not recommended in this age group.[63]

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) spreparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection.[66, 67] There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by US Food and Drug Administration [FDA]) for the symptomatic treatment of cold and cough have not been established.[66] Such preparations should be used in children younger than 2 years of age with caution and only as directed by a clinician.[66, 67] Clinicians should use caution in prescribing cough and cold preparations in these children and should ask caregivers about use of

nonprescription cough/cold preparations to avoid overdosage.[66] For additional information on precautions associated with the use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in the Antihistamines General Statement 4:00.

• Geriatric Precautions

Safety and efficacy of cetirizine in geriatric patients have not been specifically studied to date; however, in clinical trials of cetirizine for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, or chronic urticaria involving over 3900 patients, 186 patients were 65 years and older, and 39 patients were 75 years and older.[1] Although no overall differences were observed between geriatric and younger patients in the type or frequency of adverse effects in clinical trials, the possibility that some older patients may exhibit increased sensitivity to the drug cannot be ruled out.[1] With regard to efficacy, clinical trials of cetirizine for each studied indication did not include sufficient numbers of patients 65 years and older to determine whether they respond differently than younger adults.[1]

Because geriatric patients frequently have decreased renal function, cetirizine hydrochloride dosage should be selected with caution, and it may be useful to monitor renal function in these patients.[1, 63] The elimination half-life of cetirizine was prolonged and total body clearance decreased in one study in a limited number of geriatric adults (mean age: 77 years) compared with those in younger adults (mean age: 53 years) (see Pharmacokinetics: Elimination). Therefore, the manufacturer recommends that patients 77 years of age and older receive a lower cetirizine hydrochloride dosage.[1] (See Dosage and Administration: Dosage.)

Clinical trials of cetirizine hydrochloride in fixed combination with pseudoephedrine hydrochloride did not include sufficient numbers of patients 65 years and older to determine whether they respond differently than younger adults.[63] However, geriatric patients may be especially sensitive and are more likely to have adverse effects from administration of sympathomimetic amines than younger patients.[63] For further information about the effects of pseudoephedrine in geriatric patients, see Cautions: Precautions and Contraindications in Pseudoephedrine Hydrochloride 12:12.12.

• Mutagenicity and Carcinogenicity

Cetirizine was not mutagenic in the Ames test and was not clastogenic in the human lymphocyte, mouse lymphoma, and in vivo rat micronucleus assays.[1]

No evidence of carcinogenic potential was observed in a 2-year study in rats receiving oral cetirizine hydrochloride dosages up to 20 mg/kg daily (approximately 15 or 7 times the maximum recommended daily oral dosage in adults or infants, respectively, on a mg/m^2 basis).[1, 57] In mice receiving oral cetirizine hydrochloride dosages of 16 mg/kg daily (approximately 6 or 3 times the maximum recommended daily oral dosage in adults or infants, respectively, on a mg/m^2 basis) for 2 years, there was an increased incidence of benign liver tumors in male mice.[1, 57] However, no increased incidence in liver tumors was observed in mice receiving oral cetirizine dosages of 4 mg/kg daily (approximately 2 times the maximum recommended daily oral dosage in adults and approximately equivalent to the maximum recommended oral dosage in infants on a mg/m^2 basis).[1, 57] The clinical importance of these findings during long-term use of cetirizine is not known.[1]

• **Pregnancy, Fertility, and Lactation**

Pregnancy

Reproduction studies in mice, rats, and rabbits using oral cetirizine hydrochloride dosages up to 96, 225, and 135 mg/kg daily, respectively (approximately 40, 180, and 220 times, respectively, the maximum recommended daily oral dosage in adults on a mg/m^2 basis), have not revealed evidence of teratogenicity.[1, 3, 57] Because there are no adequate and controlled studies to date using cetirizine in pregnant women and animal studies are not always predictive of human response, cetirizine hydrochloride should be used during pregnancy only when clearly needed.[1, 3]

Cetirizine hydrochloride in combination with pseudoephedrine has been shown to increase the number of fetal skeletal malformations (rib distortions) and variants (unossified sternebrae) in rats when given orally in a fixed-combination ratio at a dosage of 6/154 mg/kg (approximately 5 times the maximum recommended adult dosage on a mg/m^2 basis).[63] These effects were not observed at a dosage of 1.6/38 mg/kg (approximately the maximum recommended adult dosage on a mg/m^2 basis).[63] Reproduction studies in rabbits using cetirizine hydrochloride and pseudoephedrine hydrochloride in a fixed-combination ratio at a dosage of up to 6/154 mg/kg (approximately 10 times the maximum recommended adult dosage on a mg/m^2 basis) have not revealed evidence of harm to the fetus.[63] There are no adequate and controlled studies to date using cetirizine hydrochloride and pseudoephedrine hydrochloride in pregnant women, and the fixed combination should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.[63]

Fertility

In a fertility and general reproductive performance study in mice, oral cetirizine hydrochloride did not impair fertility at dosages of 64 mg/kg daily (about 25 times the maximum recommended daily dosage in adults on a mg/m^2 basis).[1, 57] In a reproductive study in rats, oral cetirizine hydrochloride and pseudoephedrine did not impair fertility in a fixed combination at a dosage of 6/154 mg/kg (approximately 5 times the maximum recommended adult dosage on a mg/m^2 basis.[63]

Lactation

In lactating beagles, about 3% of a cetirizine dose was distributed in milk.[1] In mice, cetirizine caused retarded pup weight gain during lactation when dams were receiving a cetirizine hydrochloride dosage of 96 mg/kg daily (about 40 times the maximum recommended daily dosage in adults on a mg/m^2 basis).[1] In rats, cetirizine hydrochloride and pseudoephedrine hydrochloride caused retarded pup weight gain and decreased viability during lactation when administered orally to dams in fixed combination at a dosage of 6/154 mg/kg (approximately 5 times the maximum recommended adult dosage on a mg/m^2 basis) but not when administered at a dosage of 1.6/38 mg/kg (approximately the maximum recommended adult dosage on a mg/m^2 basis).[63] Cetirizine is distributed into human milk.[1 63] Pseudoephedrine also distributes into human milk.[63]Therefore, use of cetirizine hydrochloride alone or in combination with pseudoephedrine hydrochloride in nursing women is not recommended.[1, 3, 57, 63]

Drug Interactions

Because cetirizine is metabolized only minimally in the liver and is excreted mainly unchanged in urine, the drug may have a low potential for adverse drug interactions associated with metabolic enzyme systems.[2]

• **Drugs Affecting Hepatic Microsomal Enzymes**

Concomitant administration of cetirizine hydrochloride with drugs known to inhibit cytochrome P-450 microsomal enzymes (e.g., azithromycin, erythromycin, ketoconazole) has not been associated with clinically important changes in ECG parameters (e.g., QT_c intervals), and no clinically important interactions have been reported in patients receiving cetirizine concomitantly with azithromycin, erythromycin, or ketoconazole.[1, 3, 31, 56] Although concomitant administration of cetirizine hydrochloride (20 mg daily) with ketoconazole (400 mg daily) has been associated with prolongation of the QT_c interval (with an increase of 17.4 msec), such increase is not considered clinically important.[1, 56, 57] It is not known whether cetirizine is metabolized in the liver by the cytochrome P-450 microsomal enzyme system.[48, 56, 57]

• **Other Drugs**

No interactions were observed in pharmacokinetic interaction studies when cetirizine was used concomitantly with pseudoephedrine or antipyrine.[1, 3] A 16% decrease in the clearance of cetirizine was observed in a multiple-dose study when theophylline (400 mg given once daily for 3 days) was administered with cetirizine hydrochloride (20 mg given once daily for 3 days); disposition of theophylline was not altered by the concomitant administration with cetirizine.[1, 3]

Because monoamine oxidase (MAO) inhibitors potentiate the pressor effects of sympathomimetic drugs (e.g., pseudoephedrine), fixed-combination extended-release tablets containing cetirizine hydrochloride and pseudoephedrine hydrochloride are contraindicated in patients receiving an MAO inhibitor, or for 2 weeks after discontinuance of an MAO inhibitor.[63] For further information about drug interactions with pseudoephedrine, see Drug Interactions in Pseudoephedrine Hydrochloride 12:12.12.

Acute Toxicity

• **Pathogenesis**

The acute lethal dose of cetirizine in humans is not known.[1, 57] The acute minimal lethal dose is 237 mg/kg in mice (approximately 95 or 40 times the maximum recommended daily oral dosage in adults or infants, respectively, on a mg/m^2 basis) and 562 mg/kg in rats (approximately 460 or 190 times the maximum recommended daily oral dosage in adults or infants, respectively, on a mg/m^2 basis).[1] In rodents, the target of acute toxicity was the CNS, and the target of multiple-dose toxicity was the liver.[1]

• **Manifestations**

Overdosage has been reported in individuals receiving cetirizine.[1] Somnolence was reported in one adult who ingested 150 mg of cetirizine hydrochloride; no other adverse effects, including clinical manifestations, abnormal blood chemistry, or abnormal hematology, occurred in this individual.[1] Restlessness and irritability followed by drowsiness were reported in an 18-month old child who ingested about 180 mg of cetirizine hydrochloride.[1]

• **Treatment**

In acute cetirizine overdosage, treatment should include symptomatic and supportive measures, taking into account the possibility of any concomitantly ingested drugs.[1]

There is no specific antidote for overdosage of cetirizine.[1] The drug is not effectively removed by dialysis, and therefore, dialysis would not be effective in acute overdosage of cetirizine, unless a drug that is removed by dialysis were ingested concomitantly.[1]

Pharmacology

Cetirizine is a long-acting antihistamine.[1, 2, 3, 12] The drug has been characterized as a selective, peripheral H_1-receptor antagonist.[1, 2, 3, 6, 14, 20, 47, 48] The pharmacology of cetirizine resembles that of other currently available antihistamines.[56, 57] Cetirizine is the carboxylic acid metabolite of hydroxyzine.[1, 2, 3, 11, 12, 20] The increased polarity of cetirizine (compared with hydroxyzine)[2] may decrease distribution of the drug into the CNS,[1, 2, 3] resulting in reduced potential for adverse CNS effects compared with some first generation antihistamines (e.g., diphenhydramine, hydroxyzine).[2, 5, 6, 56, 58] However, it appears that the incidence of certain adverse CNS effects (e.g., somnolence) is higher in patients receiving cetirizine than in those receiving other second generation antihistamines (e.g., loratadine).[2, 20, 56, 57]

• Antihistaminic Effects

In animals and humans, the antihistaminic effect of cetirizine (as measured by suppression of the wheal and flare response induced by intradermal injection of histamine) is comparable to that of astemizole (no longer commercially available in the US), clemastine, chlorpheniramine, diphenhydramine, hydroxyzine, loratadine, pyrilamine, and terfenadine (no longer commercially available in the US).[2, 3, 20, 43] Experimental evidence indicates that the drug exhibits a specific and selective antagonism of histamine H_1-receptors.[1, 2, 3] The manufacturer states that results from several experimental models indicate that cetirizine has inhibitory effects on the acute early phase of immediate hypersensitivity response mediated by the action of H_1-receptors.[3] Results of in vitro studies indicate that cetirizine has no measurable affinity for receptors other than histamine H_1-receptors, including calcium-channel blocking receptors, α_1-adrenergic receptors, or dopamine D_2 receptors.[1, 2, 3] Unlike many other currently available antihistamines, cetirizine does not possess appreciable anticholinergic or antiserotonergic effects,[56, 57] although the incidence of dry mouth in clinical trials was higher in patients receiving cetirizine than in those receiving placebo.[1, 3, 20, 28, 41, 49]

Whereas decreased efficacy (subsensitivity, tolerance), including decreased inhibition in skin reactivity to allergen or histamine, may occur within days or weeks of initiation of therapy with first generation antihistamines,[55] tolerance to the effects of cetirizine usually does not occur.[2] In a 5-week study in children with allergic rhinitis, tolerance to the effects of cetirizine involving histamine skin tests was not reported, and tolerance also did not occur in patients with physical urticarias who were receiving cetirizine for 8-110 weeks.[2] However, in a limited number of patients, the PC_{20} value (the concentration of histamine required to produce a 20% decrease in forced expiratory volume in 1 second [FEV_1]) declined from 118 mmol/L after a single 15-mg dose of cetirizine hydrochloride to 53 mmol/L after administration of 15 mg of cetirizine hydrochloride twice daily for 1 week, although PC_{20} values after 1 week of therapy with cetirizine in such patients remained substantially greater than in patients receiving placebo.[2]

• Respiratory Effects

In animals, cetirizine inhibits histamine-induced nasal airway resistance, and such inhibition appears to be comparable to that of chlorpheniramine.[2, 11] Results of a double-blind, randomized, comparative study in patients with allergic rhinitis indicate that response to nasally inhaled histamine was reduced substantially more by cetirizine than by placebo.[45] In addition, 1.5 and 4 hours after oral administration of the drugs, 10-mg doses of cetirizine hydrochloride were at least as effective as 10-mg doses of loratadine in inhibiting histamine-induced nasal airway resistance.[45] In patients with mild asthma, cetirizine hydrochloride doses of 5-20 mg had a protective effect against nebulized histamine-induced bronchospasm; oral cetirizine may attenuate substantially histamine-induced decreases in FEV_1.[1, 2, 3, 14, 44] Cetirizine also had a protective effect against allergen-induced bronchospasm in patients with allergic asthma; however, such effect was observed only against the late allergic reaction and not against the early allergic reaction.[40]

• Nervous System Effects

In vitro, cetirizine exhibits an affinity for histamine H_1-receptors from brain to peripheral tissues similar to that of terfenadine;[3] however, in vivo, unlike prototypical (first generation) antihistamines, cetirizine (probably because of the polarity of the drug) does not readily cross the blood-brain barrier[1, 2, 3] and, therefore, does not appear to interact appreciably with H_1-receptors within the CNS at usual doses.[2, 56, 58] In some clinical trials, the incidence of certain CNS effects (e.g., somnolence) was higher in patients receiving cetirizine than in those receiving placebo.[1, 2, 3, 20, 27, 28, 39, 41, 43, 49] In addition, some data indicate that the incidence of other CNS effects (e.g., EEG disturbances, impaired psychomotor performance) may be higher in patients receiving cetirizine than in those receiving other second generation antihistamines (e.g., loratadine).[2, 56, 59]

In part, adverse CNS effects of cetirizine reported in these studies may have resulted from use of higher than recommended dosages, indicating a correlation between dose of cetirizine hydrochloride and its description as a nonsedating antihistamine.[56, 59] In several other studies, the CNS effects of cetirizine did not differ from those of placebo or other second generation antihistamines (e.g., astemizole) or, alternatively, no adverse CNS effects were reported with the drug.[5, 56, 58] However, in controlled clinical trials in patients receiving 5- or 10-mg daily dosages of the drug or placebo, the overall incidence of somnolence was 13.7 or 6.3% in patients receiving cetirizine or placebo, respectively.[1, 2, 3] (See Cautions: Nervous System Effects.)

• Cardiac Effects

Although serious cardiac effects, including ventricular fibrillation and death associated with prolonged QT interval and atypical ventricular arrhythmia (torsades de pointes), have been reported in patients receiving certain other second generation antihistamines (e.g., astemizole, terfenadine), administration of cetirizine hydrochloride alone to healthy adult men at dosages of up to 60 mg daily (6 times the maximum daily dosage) for 1 week has not been associated with clinically important prolongation of the QT interval corrected for rate (QT_c).[1, 2, 3, 4, 29, 30, 31] (See Cautions: Cardiovascular Effects.) In animals, cetirizine dosages up to 500 times the recommended clinically effective dosage were not associated with important changes in ECG parameters (e.g., QT_c intervals).[4]

• Other Effects

Cetirizine may inhibit mediators other than histamine, including those that release histamine.[1] In one study, cetirizine inhibited cold-induced urticaria in cold-challenged patients.[1, 3]

Cetirizine appears to have some activity against allergic inflammation mediators.[1, 3, 14, 20] In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils, and basophils (components of allergic inflammatory response) was inhibited by 20-mg doses of cetirizine hydrochloride.[1, 3, 14, 20]

Pharmacokinetics

The effect of gender on the pharmacokinetics of cetirizine hydrochloride has not been fully elucidated.[1] In addition, pharmacokinetic studies have not revealed race-related differences in the pharmacokinetics of the drug.[1]

• Absorption

Cetirizine hydrochloride is rapidly absorbed from the GI tract following oral administration.[12, 14, 47, 48] The bioavailability of the conventional tablets appears to be comparable to that of the oral solution or chewable tablets (whether administered with or without water).[1] Following oral administration of 10- or 20-mg doses of cetirizine hydrochloride (tablets or oral solution) in healthy adults, peak plasma concentrations of 257-384 or 580 ng/mL, respectively, are achieved in about 1 hour;[1, 2, 3, 4, 14, 39, 46, 47, 48] following administration of cetirizine hydrochloride chewable tablets, peak plasma concentrations also are achieved within 1 hour.[1] Considerable interindividual variation in peak plasma concentrations of cetirizine does not appear to occur.[3, 48] In healthy individuals receiving 10 mg of cetirizine hydrochloride daily for 10 days, apparent steady-state plasma concentrations of the drug reportedly were achieved by the second day of administration.[3] With multiple daily dosing, steady-state plasma concentrations averaging approximately 311 ng/mL (range: 271-351 ng/mL) usually were achieved within 1 hour (range: 0.5-1.5 hours) after administration of a dose and there was minimal accumulation of drug.[1, 3, 39] Pharmacokinetics of the drug appear to be linear for oral doses ranging from 5-60 mg, with plasma concentrations of the drug increasing proportionately with increasing doses.[1, 3, 4, 14]

Administration of cetirizine hydrochloride and pseudoephedrine hydrochloride as fixed-combination extended-release tablets reportedly does not affect the bioavailability of either drug substantially.[63] Following oral administration of a single 5-mg dose of cetirizine hydrochloride (given as an extended-release tablet in fixed combination with pseudoephedrine hydrochloride 120 mg), mean peak plasma cetirizine concentration of 114 ng/mL was reached in about 2.2 hours.[63] Following multiple-dose administration of the 12-hour fixed-combination tablet (at a cetirizine hydrochloride dosage of 5 mg twice daily for 7 days) in healthy individuals, steady-state peak plasma concentrations of cetirizine reportedly averaged 178 ng/mL.[63]

Following oral administration of cetirizine hydrochloride 5-mg oral capsules in children 7-12 years of age, peak plasma concentration of the drug averaged 275 ng/mL, whereas peak plasma concentration of the drug averaged 660 ng/mL in children 2-5 years of age receiving a 5-mg oral dose of the drug.[1] The manufacturer states that the area under the plasma concentration-time curve (AUC) and peak plasma concentrations in children 2-5 and 6-11 years of age receiving 5- and 10-mg

doses of cetirizine hydrochloride, respectively, were estimated to be intermediate between those observed in adults receiving single 10- and 20-mg doses of the drug.[1] Following oral administration of a single cetirizine hydrochloride dose of 0.25 mg/kg in a limited number of children 6-24 months of age, peak plasma concentrations of 390 ng/mL (range: 255-525 ng/mL) were achieved in about 2 hours (range: 0.7-3.3 hours).[1, 47] The average AUC in pediatric patients 6 months to less than 2 years of age receiving dosages of 2.5 mg twice daily is expected to be 2-fold higher than that observed in adults receiving a dosage of 10 mg once daily.[1] The manufacturer states that the AUC and peak plasma concentrations in pediatric patients 6-23 months of age receiving a single 0.25 mg/kg dose (mean: 2.3 mg) of cetirizine hydrochloride were estimated to be intermediate between those observed in adults receiving single 10- and 20-mg doses of the drug.[1]

Peak plasma concentrations and AUCs may be increased in geriatric adults (mean age: 77 years).[3] Following administration of a 10-mg dose of cetirizine hydrochloride in geriatric adults, peak plasma concentrations of 460 ng/mL were achieved in about 0.9 hours.[3] Peak plasma concentrations, time to achieve peak plasma concentrations, and AUCs of cetirizine may be increased in patients with renal impairment compared with those in healthy individuals.[2, 3] Mean peak plasma concentrations of cetirizine reportedly were 356 (range: 292-420 ng/mL) and 357 ng/mL (range: 185-529 ng/mL) in patients with mild (creatinine clearance of 42-77 mL/minute) and moderate (creatinine clearance of 11-31 mL/minute) renal impairment, respectively; time to achieve peak plasma concentrations in patients with moderate renal impairment was increased to about 2.2 hours.[1, 3] In addition, peak plasma concentrations and AUCs may be increased in patients with hepatic impairment.[39] In one study in patients with primary biliary cirrhosis who received a single 10-mg oral dose of cetirizine hydrochloride, mean peak plasma concentrations of 498 ng/mL (range: 380-616 ng/mL) occurred within about 1 hour; cetirizine was still detectable in some patients 96 hours after dosing.[39]

Although food may decrease peak plasma concentrations of cetirizine (by 23, 37, or 30%, respectively, for conventional tablets, chewable tablets, or extended-release tablets in fixed combination with pseudoephedrine hydrochloride) and lengthen the time (by about 1.7, 2.8, or 1.8 hours, respectively) to achievement of peak plasma concentrations,[1, 2, 3, 12, 20] food does not affect the extent of absorption (measured by the AUC) of the drug.[1, 2, 3, 12, 20, 63]

Following oral administration of a single 10-mg dose of cetirizine hydrochloride in healthy adults, the antihistaminic effect of the drug (as measured by suppression of the wheal and flare response induced by intradermal injection of histamine) was apparent within 20 and 60 minutes in 50 and 95% of individuals, respectively, and persisted for about 24 hours.[1, 2, 3, 6, 14, 20, 43] In addition, following oral administration of a single 5- or 10-mg dose of cetirizine hydrochloride in healthy children (5-10 years of age), the antihistaminic effect of the drug (as measured by suppression of the wheal and flare response induced by intradermal injection of histamine) was apparent within 20-60 minutes and persisted for at least 24 hours.[1, 14] In infants 7-25 months of age receiving oral cetirizine hydrochloride at a dosage of 0.25 mg/kg twice daily for 4-9 days, 90% inhibition of histamine-induced cutaneous wheal and 87% inhibition of the flare occurred 12 hours following administration of the last dose.[1] The antihistaminic effect of the drug may persist longer in patients with hepatic

impairment; limited data indicate that suppression of wheal and flare response persisted for 48 and 72 hours, respectively, in such patients.[39] The manufacturer states that the clinical relevance of suppressing histamine-induced wheal and flare response on skin testing is unknown.[1]

• Distribution

Distribution of cetirizine and its metabolites into human body tissues and fluids has not been fully elucidated.[1, 3] In animals, the drug appears to be extensively distributed into many body tissues and fluids with highest concentrations obtained in the liver, kidneys, and lungs.[3] However, the volume of distribution of cetirizine is relatively low compared with that of many other H_1-receptor antagonists.[20] The volume of distribution is about 0.39-0.6, 0.46, 0.54, 0.44, or 0.38-0.56 L/kg in healthy adults, patients with mild renal impairment (creatinine clearance of 42-77 mL/minute), patients with moderate renal impairment (creatinine clearance of 11-31 mL/minute), patients with hepatic impairment, or geriatric patients (mean age: 77 years), respectively.[2, 3, 39, 47]

The substantial polarity of cetirizine[2] apparently limits distribution of the drug into the CNS.[1, 2, 3, 6, 20, 46] Animal studies indicate that brain cetirizine concentrations were less than 10% of those measured in plasma.[2]

Cetirizine is distributed into milk in humans and animals.[1] In lactating beagles, about 3% of a cetirizine dose was distributed into milk.[1]

Cetirizine is approximately 93% bound to plasma proteins; protein binding appears to be independent of the concentration of the drug ranging from 25-1000 ng/mL, which includes usual therapeutic plasma concentrations.[1, 3]

• Elimination

Following oral administration of a single 10-mg dose of cetirizine hydrochloride in healthy adults, the drug may undergo biphasic elimination,[47, 56, 57] with an initial distribution half-life of about 3 hours[48] and a mean terminal elimination half-life of about 8.3 hours (range: 6.5-10 hours).[1, 2, 4, 12, 14, 20, 39, 47, 48, 57] In pediatric patients 7-12 years, 2-5 years, or 6-23 months of age, the elimination half-life of the drug corrected for weight was 33, 33-41, or 63% shorter, respectively, than that observed in adults.[1, 46, 47] In addition, the elimination half-life of the drug in geriatric adults (mean age: 77 years) receiving a single 10-mg oral dose of cetirizine hydrochloride was prolonged by about 50% compared with that in younger adults (mean age: 53 years).[1, 3, 20, 39, 46] The manufacturer states that plasma elimination half-life of cetirizine following multiple oral doses in healthy adults is similar to that reported following a single oral dose.[2]

Although a small fraction of cetirizine undergoes oxidative *O*-dealkylation to a metabolite with negligible antihistaminic activity, the drug undergoes a low degree of first-pass metabolism in the liver.[1, 2, 3, 11, 14, 39, 46, 47, 56, 57] Two unidentified metabolites also were recovered from urine; however, the enzyme(s) responsible for the metabolism of the drug has not been identified.[1, 2, 3, 39, 47] Following oral administration of a single 10-mg dose of cetirizine hydrochloride in healthy individuals, about 80% of the dose is excreted within 5 days, mainly (more than 50%) as unchanged drug;[1, 2, 4, 12, 14, 20, 39, 46, 47, 48, 57] most excretion occurs within 24 hours.[1, 2, 3, 12, 48]

In healthy individuals, about 70 and 10% of a radiolabeled dose was recovered in urine and feces, respectively.[1, 2, 3, 14, 48] Fecal excretion has not been well characterized, and it is not known whether fecal excretion of the drug represents unabsorbed drug or if the drug is excreted via biliary elimination.[48, 56, 57] In animals, cetirizine and its metabolites undergo extensive biliary elimination.[48]

In healthy adults, total body clearance of cetirizine reportedly was about 53 mL/minute, whereas in children 7-12 years of age, those 2-5 years of age, or those 6-24 months of age, the apparent total body clearance corrected for weight was 33, 81-111, or 304% greater, respectively, than that observed in adults.[1, 47] The apparent total body clearance in geriatric adults (mean age: 77 years) receiving a single 10-mg oral dose of cetirizine hydrochloride was 33-45% lower than in younger adults (mean age: 53 years).[1, 3, 39] The decreased apparent total body clearance in geriatric adults may be related to decreased renal function in this age group.[1]

Following oral administration of 10-mg doses of cetirizine hydrochloride daily for 7 days, elimination of the drug in patients with mild renal impairment (creatinine clearance of 42-77 mL/minute) appears to be similar to that in healthy young adults (creatinine clearance of 89-128 mL/minute). Patients with moderate renal impairment (creatinine clearance of 11-31 mL/minute) receiving this dose daily for 7 days and those on hemodialysis receiving a single 10-mg dose of the drug had a threefold increase in half-life and a 70% decrease in clearance compared with those in healthy young adults.[1, 3, 20, 46, 60] Less than 10% of a 10-mg dose of cetirizine hydrochloride is removed by hemodialysis.[1, 2]

Although cetirizine appears to be minimally metabolized by liver enzymes,[1, 11, 14, 20, 39] a 50-85% increase in half-life and a 40-60% decrease in clearance occurred in patients with chronic hepatic impairment following oral administration of a single 10- or 20-mg dose of cetirizine hydrochloride.[1, 3, 20, 39]

Chemistry and Stability

• Chemistry

Cetirizine, a piperazine derivative, is a long-acting antihistamine.[1, 2, 3, 12] The drug is the carboxylic acid metabolite of hydroxyzine.[1, 2, 3, 11, 12, 20, 48] The increased polarity of cetirizine (compared with hydroxyzine)[2] may decrease distribution of the drug into the CNS,[1, 2, 3] resulting in a reduced potential for adverse CNS effects compared with some first generation antihistamines (e.g., diphenhydramine, hydroxyzine).[2, 5, 6, 56, 58]

Cetirizine hydrochloride occurs as a white crystalline powder that is soluble in water.[1] Commercially available cetirizine hydrochloride oral solution is a colorless to slightly yellow syrup and has a pH of 4-5.[1] Cetirizine hydrochloride occurs as a racemic mixture.[1]

The fixed-combination tablets contain 5 mg of cetirizine hydrochloride in an immediate-release layer and 120 mg of pseudoephedrine hydrochloride in an extended-release layer that slowly releases the drug.[63]

• Stability

Cetirizine hydrochloride oral solution and tablets should be stored at a room temperature of 20-25°C but may be exposed to temperatures ranging from 15-30°C;

cetirizine hydrochloride oral solution also may be refrigerated at 2-8°C.[1] The fixed-combination cetirizine hydrochloride and pseudoephedrine hydrochloride extended-release tablets should be stored at a controlled room temperature of 20-25°C but may be exposed to temperatures ranging from 15-30°C.[63]

Preparations

Cetirizine Hydrochloride

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Solution 5 mg/5 mL **Zyrtec® Syrup** (with Pfizer (also promoted by UCB) parabens and propylene glycol) Tablets, 5 mg **Zyrtec®** Pfizer (also promoted by UCB) chewable 10 mg **Zyrtec®** Pfizer (also promoted by UCB) Tablets, 5 mg **Zyrtec®** (with povidone) Pfizer (also promoted by UCB) film-coated 10 mg **Zyrtec®** (with povidone) Pfizer (also promoted by UCB)

Cetirizine Hydrochloride Combinations

Routes Dosage Forms Strengths Brand Names Manufacturer Oral Tablets, extended-5 mg with Pseudoephedrine **Zyrtec®-D 12** Pfizer (also release Hydrochloride 120 mg **Hour** promoted by UCB)

• **Comparative Pricing**
Pricing information provided by drugstore.com.

Zyrtec 1MG/ML SYRP (PFIZER U.S.): 120/$37.39 or 360/$106.13

Zyrtec 1MG/ML SYRP (PFIZER U.S.): 480/$141.74 or 1440/$375.84

Zyrtec 10MG CHEW (PFIZER U.S.): 30/$69.42 or 90/$190.92

Zyrtec 5MG CHEW (PFIZER U.S.): 30/$71.74 or 90/$205.95

Zyrtec 5MG TABS (PFIZER U.S.): 30/$72.99 or 90/$212.97

Zyrtec-D 5-120MG TB12 (PFIZER U.S.): 30/$40.79 or 90/$118.63

[#] Use is not currently included in the labeling approved by the US Food and Drug Administration.

References

1. Pfizer Labs. Zyrtec® (cetirizine hydrochloride) tablets, chewable tablets, and syrup prescribing information. New York, NY; 2004 Jul.

2. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs*. 1993; 46:1055-80. [PubMed 7510611]

3. Pfizer Laboratories. Zyrtec® (cetirizine hydrochloride) tablets product monograph. New York, NY: Undated.

4. Sale ME, Barbey JT, Woosley RL et al. The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther*. 1994; 56:295-301. [PubMed 7924125]

5. Schweitzer PK, Muehlbach MJ, Walsh JK. Sleepiness and performance during three- day administration of cetirizine or diphenhydramine. *J Allergy Clin Immunol*. 1994; 94:716-24. [PubMed 7930305]

6. Gengo FM, Dabronzo J, Yurchak A et al. The relative antihistaminic and psychomotor effects of hydroxyzine and cetirizine. *Clin Pharmacol Ther*. 1987; 42:265-72. [PubMed 2887328]

7. Borge PA. Problems in allergic rhinitis. *Arzneimittelforschung*. 1982; 32:11199-201.

8. Anon. Treatment of seasonal and perennial allergic rhinitis. *BMJ*. 1981; 283:808-10. [PubMed 6117350] [Free Fulltext PMC]

9. Food and Drug Administration. Over-the-counter drugs: establishment of a monograph for OTC cold, cough, allergy, bronchodilator and antihistaminic products. [21 CFR 341]. *Fed Regist*. 1976; 41:38312-424.

10. Douglas WW. Histamine and 5-hydroxytryptamine (serotonin) and their antagonists. In: Gilman AG, Goodman LS, Rall TW et al eds. Goodman and Gilman's the pharmacologic basis of therapeutics. 7th ed. New York: Macmillan Publishing Company. 1985:605-638.

11. Campoli-Richards DM, Buckley MMT, Fitton A. Cetirizine: a review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma, and chronic urticaria. *Drugs*. 1990; 40:762-81. [PubMed 1981354]

12. Barnes CL, McKenzie CA, Webster KD et al. Cetirizine: a new, nonsedating antihistamine. *Ann Pharmacother*. 1993; 27:464-70. [PubMed 8477125]

13. Reviewers' comments (personal observations).

14. Pfizer, New York, NY: Personal communication.

15. Grant JA, Nicodemus CF, Findlay SR et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 1995; 95:923-32. [PubMed 7751511]

16. Food and Drug Administration. Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use; final monograph for

OTC antihistamine drug products. Final rule. [21 CFR Parts 201, 310, 341, 369] *Fed Regist*. 1992; 57:58356-8.

17. Meltzer EO. To use or not to use antihistamines in patients with asthma. *Ann Allergy*. 1990; 64:183-6. [PubMed 1967918]

18. Pierson WE, Virant FS. Antihistamines in asthma. *Ann Allergy*. 1989; 63:601-3. [PubMed 2574551]

19. Simons FER, Simons KJ. The pharmacology and use of H_1-receptor antagonist drugs. *N Engl J Med*. 1994; 330:1663-70. [PubMed 7909915]

20. Anon. Cetirizine—a new antihistamine. *Med Lett Drugs Ther*. 1996; 38:21-3. [PubMed 8598822]

21. Simons FE, Sussman GL, Simons KJ. Effect of the H_2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H_1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. *J Allergy Clin Immunol*. 1995; 95:685-93. [PubMed 7897151]

22. Jobst S, van den Wijngaart W, Schubert A et al. Assessment of the efficacy and safety of three dose levels of cetirizine given once daily in children with perennial allergic rhinitis. *Allergy*. 1994; 49:598-604. [PubMed 7653736]

23. Masi M, Candiani R, van de Venne H. A placebo-controlled trial of cetirizine in seasonal allergic rhino-conjunctivitis in children aged 6-12 years. *Pediatr Allergy Immunol*. 1993; 4(Suppl):47-52. [PubMed 8353660]

24. Watson WTA, Simons KJ, Chen XY et al. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1989; 84:457-64. [PubMed 2571627]

25. Lockey RF, Widlitz MD, Mitchell DQ et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 1996; 76:448-54. [PubMed 8630719]

26. Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allergy Asthma Immunol*. 1996; 76:440-6. [PubMed 8630718]

27. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1996; 97:617-26. [PubMed 8621847]

28. Breneman D, Bronsky EA, Bruce S et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative study. *J Am Acad Dermatol*. 1995; 33(2 Part 1):192-8. [PubMed 7622644]

29. Andri L, Senna GE, Betteli C et al. A comparison of the efficacy of cetirizine and terfenadine: a double-blind, controlled study of chronic idiopathic urticaria. *Allergy*. 1993; 48:358-65. [PubMed 8368464]

30. Woosley RL. Cardiac actions of antihistamines. *Annu Rev Pharmacol Toxicol*. 1996; 36:233-52. [PubMed 8725389]

31. Simons FER. H_1-Receptor antagonists: comparative tolerability and safety. *Drug Saf*. 1994; 10:350-80. [PubMed 7913608]

32. Turner RB, Sperber SJ, Sorrentino JV et al. Effectiveness of clemastine fumarate for treatment of rhinorrhea and sneezing associated with the common cold. *Clin Infect Dis*. 1997; 25:824-30. [PubMed 9356796]

33. Douglass JA, Dhami D, Gurr CE et al. Influence of interleukin-8 challenge in the nasal mucosa in atopic and nonatopic subjects. *Am J Respir Crit Care Med*. 1994; 150:1108-13. [PubMed 7921444]

34. Proud D, Naclerio RM, Gwaltney JM et al. Kinins are generated in nasal secretions during natural rhinovirus colds. *J Infect Dis*. 1990; 161:120-3. [PubMed 2295843]

35. Proud D, Gwaltney JM Jr, Hendley JO et al. Increased levels of interleukin-1 are detected in nasal secretions of volunteers during experimental rhinovirus colds. *J Infect Dis*. 1994; 169:1007-13. [PubMed 8169385]

36. Turner RB. Elaboration of interleukin 8 from fibroblast cells and human nasal epithelium in response to rhinovirus challenge. Program and abstracts of the thirty-fourth Interscience Conference on Antimicrobial Agents and Chemotherapy. Orlando, FL: 1994. Abstract No. B43.

37. Berkowitz RB, Tinkelman DG. Evaluation of oral terfenadine for treatment of the common cold. *Ann Allergy*. 1991; 67:593-7. [PubMed 1750722]

38. Lambert D, Hantzperg M, Danglas P et al. Double-blind comparative study of terfenadine and cetirizine in chronic idiopathic urticaria. *Allerg Immunol*. 1993; 25:235- 40.

39. Simons FER, Watson WTA, Minuk GY et al. Cetirizine pharmacokinetics and pharmacodynamics in primary biliary cirrhosis. *J Clin Pharmacol*. 1993; 33:949-54. [PubMed 7693767]

40. Wasserfallen JB, Leuenberger P, Pecoud A. Effect of cetirizine, a new H_1 antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. *J Allergy Clin Immunol*. 1993; 91:1189-97. [PubMed 8099593]

41. Berkowitz RB, Dockhorn R, Lockey R et al. Comparison of efficacy, safety, and skin test inhibition of cetirizine and astemizole. *Ann Allergy Asthma Immunol*. 1996; 76:363- 8. [PubMed 8612120]

42. Harcup JW, Hawkes G, Saul PA. The efficacy and sedative profile of astemizole and cetirizine in the treatment of grass pollen hayfever in general practice. *Br J Clin Pract*. 1993; 47:131-5. [PubMed 8347437]

43. Simons FER, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine

versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol*. 1990; 86:540-7. [PubMed 1977781]

44. Brik A, Tashkin DP, Gong H Jr et al. Effect of cetirizine, a new histamine H_1 antagonist, on airway dynamics and responsiveness to inhaled histamine in mild asthma. *J Allergy Clin Immunol*. 1987; 80:51-6. [PubMed 2885355]

45. Frossard N, Lacronique J, Melac M et al. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. *Allergy*. 1997; 52:205- 9. [PubMed 9105526]

46. Simons FER, Simons KJ. Second-generation H_1-receptor antagonists. *Ann Allergy*. 1991; 66:5-19. [PubMed 1670985]

47. Spicak V, Dab I, Hulhoven R et al. Pharmacokinetics and pharmacodynamics of cetirizine in infants and toddlers. *Clin Pharmacol Ther*. 1997; 61:325-30. [PubMed 9084458]

48. Wood SG, John BA, Chasseaud LF et al. The metabolism and pharmacokinetics of ^{14}C-cetirizine in humans. *Ann Allergy*. 1987; 59:31-4. [PubMed 2892447]

49. Falliers CJ, Brandon ML, Buchman E et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Ann Allergy*. 1991; 66:257-62. [PubMed 1672494]

50. Cirillo VJ, Tempero KF. The pharmacology and therapeutic use of H1 and H2 antihistamines. In: Miller RR, Greenblatt DJ, eds. Drug therapy reviews. Vol 2. New York: Elsevier/North Holland Inc; 1979:24-47.

51. AMA Division of Drugs. AMA drug evaluations. 5th ed. Chicago: American Medical Association; 1983:1465-79.

52. Church JA. Allergic rhinitis: diagnosis and management. *Clin Pediatr (Philadelphia)*. 1980; 19:655-9.

53. Food and Drug Administration. Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use; tentative final monograph for OTC antihistamine drug products. [21 R Part 341] Fed Regist. 1985; 50:2200-18. (IDIS 195256)

54. Holgate S. Comparative trial of two non-sedative H1 antihistamines, terfenadine and astemizole, for hay fever. *Thorax*. 1985; 40:399.

55. Bousquet J, Chanal I, Skassa-Brociek W et al. Lack of subsensitivity to loratadine during long-term dosing during 12 weeks. *J Allergy Clin Immunol*. 1990; 86:248-53. [PubMed 1974561]

56. Reviewers' comments.

57. Pfizer Inc. Manufacturer's comments.

58. Seidel WF, Cohen S, Bliwise NG et al. Cetirizine effects on objective measures of daytime sleepiness and performance. *Ann Allergy*. 1987; 59(part II):58-62. [PubMed 2892452]

59. Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol*. 1992; 42:363-9. [PubMed 1355427]

60. Matzke GR, Yeh J, Awni WM et al. Pharmacokinetics of cetirizine in the elderly and patients with renal insufficiency. *Ann Allergy*. 1987; 59(part II):25-30. [PubMed 2892446]

61. Tinkelman DG, Kemp J, Mitchell DQ et al. *Ped Allergy, Immunol*. 1996; 10:9- 17.

62. Day JH, Briscoe MP, Clark RH et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Ann Allergy Asthma Immunol*. 1997; 79:163-72. [PubMed 9291422]

63. Pfizer Labs. Zyrtec-D 12 hour® (cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg) extended release tablets prescribing information. New York, NY; 2003 Aug.

64. Simons FE, Silas P, Portnoy JM et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol*. 2003; 111(6):1244-8. [PubMed 12789224]

65. Eisenberg P. Dear healthcare provider letter regarding dispensing errors involving Zyprexa® (olanzapine). Indianapolis, IN: Eli Lilly and Company; 2005 Jan.

66. Srinivasan A, Budnitz D, Shehab N et al. Infant deaths associated with cough and cold medications—two states, 2005. *MMWR Morb Mortal Wkly Rep*. 2007; 56:1-4.

67. Food and Drug Administration. Cough and cold medications in children less than two years of age. MedWatch drug labeling changes. Rockville, MD; January 2007. From FDA website (http://www.fda.gov/medwatch/safety/2007/safety07.htm#coughcold).

(+/-) Show / Hide Bibliography