

Guidelines Call for Celiac Screening in IBS

BY SUSAN BIRK

CHICAGO — All irritable bowel syndrome patients with the diarrhea and mixed diarrhea-constipation phenotypes should be screened for celiac disease, according to guidelines issued by the American College of Gastroenterology earlier this year.

The guidelines were developed in response to emerging evidence showing a

three- to fourfold greater prevalence of celiac disease in IBS patients than in the general population, Dr. William D. Chey said at a meeting on celiac disease sponsored by the American Gastroenterological Association.

Celiac disease and IBS can have virtually identical symptoms, and mistaking one for the other or not knowing that both are present can lead to expensive, unnecessary tests, ineffective therapies,

and pointless repeat visits, said Dr. Chey, professor of internal medicine and director of the gastrointestinal physiology laboratory at the University of Michigan, Ann Arbor.

“Most important, people with untreated celiac disease have higher mortality and are at higher risk of developing cancer, osteoporosis, and a variety of other metabolic abnormalities than people who have been treated. There are

clear cost consequences of not doing this correctly, but there are even more profound health consequences for the patients who are incorrectly diagnosed and treated,” said Dr. Chey, co-editor in chief of the American Journal of Gastroenterology.

A systematic review by Dr. Chey and his colleagues of seven studies from around the world involving 2,978 people (1,052 with IBS) found that 3% of the

Twynsta® (telmisartan/amlodipine) Tablets

WARNING: AVOID USE IN PREGNANCY

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, TWYNSTA tablets should be discontinued as soon as possible. See Warnings and Precautions.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Twynsta® (telmisartan/amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents.

TWYNSTA tablets may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Base the choice of TWYNSTA tablets as initial therapy for hypertension on an assessment of potential benefits and risks including whether the patient is likely to tolerate the starting dose of TWYNSTA tablets.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Fetal/Neonatal Morbidity and Mortality

Telmisartan

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue TWYNSTA tablets as soon as possible [see Boxed Warning].

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second or third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, physicians should have the patient discontinue the use of TWYNSTA tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, TWYNSTA tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Hypotension

Telmisartan

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with TWYNSTA tablets. Either correct this condition prior to administration of TWYNSTA tablets, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Amlodipine

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, observe patients with severe aortic stenosis closely when administering amlodipine, as one should with any vasodilator.

Hyperkalemia

Telmisartan

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Patients with Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine at 2.5 mg in patients with hepatic impairment. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients.

Renal Function Impairment

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone

system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

The ONTARGET trial enrolled 25,620 patients ≥ 55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

Risk of Myocardial Infarction or Increased Angina

Amlodipine

Uncommonly, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Heart Failure

Amlodipine

Closely monitor patients with heart failure.

Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class II or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class I/II heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. In the PRAISE-2 study, 1654 patients with NYHA class III (80%) or IV (20%) heart failure without evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%), and diuretics (99%) were randomized 1:1 to receive placebo or amlodipine and followed for a mean of 33 months. While there was no statistically significant difference between amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine), there were more reports of pulmonary edema in the patients on amlodipine.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

TWYNSTA Tablets

The concomitant use of telmisartan and amlodipine has been evaluated for safety in more than 3700 patients with hypertension; approximately 1900 of these patients were exposed for at least 6 months and over 160 of these patients were exposed for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In the placebo-controlled factorial design study, the population treated with a telmisartan and amlodipine combination had a mean age of 53 years and included approximately 50% males, 79% were Caucasian, 17% Blacks, and 4% Asians. Patients received doses ranging from 20/2.5 mg to 80/10 mg orally, once daily.

The frequency of adverse reactions was not related to gender, age, or race.

The adverse reactions that occurred in the placebo-controlled factorial design trial in $\geq 2\%$ of patients treated with TWYNSTA and at a higher incidence in TWYNSTA-treated patients ($n=789$) than placebo-treated patients ($n=46$) were peripheral edema (4.8% vs 0%), dizziness (3.0% vs 2.2%), clinically meaningful orthostatic hypotension (defined as a decrease in DBP >10 mmHg and/or decrease in SBP >20 mmHg) (6.3% vs 4.3%), and back pain (2.2% vs 0%). In addition, other adverse reactions that occurred in more than 1% of the patients treated with TWYNSTA tablets ($n=789$) were dizziness (2.0% vs 2.2% on placebo) and headache (1.4% vs 4.3% on placebo).

In the placebo-controlled factorial design trial, discontinuation due to adverse events occurred in 2.2% of all treatment cells of patients in the telmisartan/amlodipine-treated patients and in 4.3% in the placebo-treated group. The most common reasons for discontinuation of therapy with TWYNSTA tablets were peripheral edema, dizziness, and hypotension (each $\leq 0.5\%$).

Peripheral edema is a known, dose-dependent adverse reaction of amlodipine, but not of telmisartan. In the factorial design study, the incidence of peripheral edema during the 8 week, randomized, double-blind treatment period was highest with amlodipine 10 mg monotherapy. The incidence was notably lower when telmisartan was used in combination with amlodipine 10 mg.

Table 1: Incidence of Peripheral Edema during the 8 Week Treatment Period

		Telmisartan		
		Placebo	40 mg	80 mg
Amlodipine	Placebo	0%	0.8%	0.7%
	5 mg	0.7%	1.4%	2.1%
	10 mg	17.8%	6.2%	11.3%

Telmisartan

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of telmisartan (20-160 mg) monotherapy for up to 12 weeks, an overall incidence of adverse events was similar to the patients treated with placebo.

Adverse events occurring at an incidence of $\geq 1\%$ in patients treated with telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 2.

Table 2: Adverse Events Occurring at an Incidence of $\geq 1\%$ in Patients Treated with Telmisartan and at a Greater Rate than Patients Treated with Placebo

	Telmisartan (n=1455) %	Placebo (n=380) %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of $\geq 1\%$ but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy due to adverse events was required in 2.8% of 1455 patients treated with telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

IBS cohort versus 0.7% of controls were positive for antiendomysial antibody (EMA), tissue-transglutaminase antibody (tTG), or both (odds ratio 2.94, 95% confidence interval 1.36-6.35). In a separate analysis of five studies, 3.6% of IBS patients (34 of 952) versus 0.7% of controls (12 of 1,798) tested positive for EMA, anti gliadin antibody, or tTG and showed small bowel biopsy evidence of celiac disease (OR 4.34, 95% CI 1.78-10.6) (Arch. Intern. Med. 2009;169:651-8; Am. J. Gastroenterol. 2009;104[suppl 1]:S1-35).

There are limited data on this issue

from the United States. Dr. Chey cited a retrospective study (Am. J. Gastroenterol. 2008;103[suppl 1]:S472) and a prospective study (Gastroenterology 2007;132:A-147) that found only small absolute differences in celiac disease prevalence among IBS patients versus controls, and the differences did not reach statistical significance in either study.

However, the patient populations in these studies were relatively small. "If we had a larger study, those differences probably would be significant. We had about 500 IBS patients [in the prospec-

tive study], but for those types of differences we would need an even larger study."

Two decision analytic models used as a basis for the ACG guidelines showed that serologic screening for celiac disease in the IBS patient population is cost effective, even though the disease's prevalence among IBS patients actually is low, Dr. Chey said. According to these models, screening is cost effective as long as disease prevalence exceeds 1%, and both the prospective and retrospective studies from the United States met that criterion.

"It sounds impressive to say there's a three- to fourfold increase, and that is true, but overall, the prevalence of celiac disease among IBS patients is still pretty low," Dr. Chey emphasized. "It's really important for doctors to understand that they're only going to find celiac disease in 1 or 2 out of 100 patients."

They're going to do a lot of testing and not find a lot of celiac disease. However, the benefits to patients and the time and costs saved with an accurate diagnosis and appropriate care make this routine testing worthwhile," he said.

At present, the ACG guidelines do not recommend screening for celiac disease in constipation-predominant IBS patients because there are "virtually no data" showing that these patients are at increased risk, Dr. Chey said. "We didn't feel comfortable making a sweeping recommendation. It may be



'There are ... profound health consequences for the patients who are incorrectly diagnosed and treated.'

DR. CHEY

reasonable to screen in this population, but we need prospective data." The guidelines have been published in the American Journal of Gastroenterology (2009;104 [suppl 1]:S1-35).

Dr. Chey also reported recent findings regarding patients who develop gastrointestinal symptoms related to the ingestion of gluten who do not have celiac disease. Some of these patients have a sensitivity to gluten, but in many cases do not show the intestinal inflammation on biopsy that is the hallmark of celiac disease, or they have mild abnormalities on biopsy but totally normal serology.

"The days of dismissing patients who say they have reactions to certain foods in their diets—particularly gluten-containing foods—are over. There is this other condition out there, and we need to understand it," said Dr. Chey, adding that the prevalence of gluten sensitivity could be three or four times that of celiac disease.

"This is a rapidly expanding area and there are groups starting to work hard on understanding gluten sensitivity," he said.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in >0.3% of 3500 patients treated with telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to telmisartan tablets: **Autonomic Nervous System:** impotence, increased sweating, flushing; **Body as a Whole:** allergy, fever, leg pain, malaise; **Cardiovascular:** palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; **CNS:** insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; **Gastrointestinal:** flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; **Metabolic:** gout, hypercholesterolemia, diabetes mellitus; **Musculoskeletal:** arthritis, arthralgia, leg cramps; **Psychiatric:** anxiety, depression, nervousness; **Resistance Mechanism:** infection, fungal infection, abscess, otitis media; **Respiratory:** asthma, bronchitis, rhinitis, dyspnea, epistaxis; **Skin:** dermatitis, rash, eczema, pruritus; **Urinary:** micturition frequency, cystitis; **Vascular:** cerebrovascular disorder; and **Special Senses:** abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Cardiovascular Risk Reduction Trials

In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported.

Amlodipine

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (n=1730) in doses up to 10 mg to placebo (n=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of amlodipine-treated patients and was not significantly different from that seen in placebo-treated patients (about 1%). The most common side effects were headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are presented in Table 3.

Table 3: Incidence (%) of Side Effects with Amlodipine at Doses of 2.5 mg, 5.0 mg, and 10.0 mg or Placebo

Adverse Event	Amlodipine 2.5 mg n=275	Amlodipine 5.0 mg n=296	Amlodipine 10.0 mg n=268	Placebo n=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitations	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1% in placebo-controlled clinical trials are presented in Table 4.

Table 4: Incidence (%) of Adverse Experiences Not Clearly Dose Related but Reported at an Incidence of >1% in Placebo-controlled Clinical Trials

Adverse Event	Amlodipine (n=1730)	Placebo (n=1250)
Headache	7.3	0.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, gastroenteritis, vomiting, gingival hyperplasia; **General:** allergic reaction, asthenia, back pain, hot flashes, malaise, pain, rigors, weight gain, weight decrease; **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia; **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **Respiratory System:** dyspnea, epistaxis; **Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular; **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **Urinary System:** micturition frequency, micturition disorder, nocturia; **Autonomic Nervous System:** dry mouth, sweating increased; **Metabolic and Nutritional:** hyperglycemia, thirst; **Hemopoietic:** leukopenia, purpura, thrombocytopenia.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of telmisartan or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to telmisartan or amlodipine.

Telmisartan

The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK, anaphylactic reaction, and tendon pain (including tendonitis, tenosynovitis).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

Amlodipine

Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects, Pregnancy Categories C (first trimester) and D (second and third trimesters). See Warnings and Precautions. **Nursing Mothers:** Telmisartan: It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Amlodipine:** It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended to discontinue nursing while amlodipine is administered. **Pediatric Use:** Safety and effectiveness of TWYNSTA in pediatric patients have not been established. **Geriatric Use: TWYNSTA Tablets:** Of the total number of 3282 hypertensive patients receiving a telmisartan/amlodipine combination in clinical studies, 605 (18%) patients were 65 years of age or older and of these, 88 (3%) patients were 75 years and older. No overall differences in efficacy or safety of TWYNSTA tablets were observed in this patient population. **Telmisartan:** Of the total number of patients receiving telmisartan in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years and older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **Amlodipine:** Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%; and a lower initial dose may be required. Since patients age 75 and older have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in patients 75 years of age and older. **Hepatic Insufficiency:** Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency. Since patients with hepatic impairment have decreased clearance of amlodipine, start amlodipine or add amlodipine 2.5 mg to telmisartan. The lowest dose of TWYNSTA is 40/5 mg; therefore, initial therapy with TWYNSTA tablets is not recommended in hepatically impaired patients. **Race:** The magnitude of blood pressure lowering in black patients approached that observed in non-black patients but the number of black patients was limited (237 of 1461 patients).

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

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