

NEWS FROM THE FDA

Botox Approved for Limb Spasticity
OnabotulinumtoxinA (Botox, Allergan) received FDA approval for the treatment of upper limb spasticity in adults, following a series of clinical trials showing that injections of the neurotoxin could significantly improve the tone and function of the flexor muscles of the elbow, wrist, and fingers.

Such spasticity can develop—sometimes after a long delay—following a stroke, spinal cord injury, or traumatic

brain injury, or in advanced multiple sclerosis or cerebral palsy. The approval did not extend to the use of Botox for nonflexural muscles of the upper limbs, spasticity in the legs, or treatment of fixed contracture, the FDA noted.

The most common side effects experienced by study subjects were nausea, fatigue, bronchitis, muscle weakness, and pain in the arms. A black box warning says that the effects of Botox may extend beyond the area of injection, resulting in

temporary paralysis that could affect swallowing and breathing.

Myopathy Occurs With Simvastatin

The risk of myopathy is increased when the highest dose of simvastatin is used, according to the Food and Drug Administration, which is conducting a safety review of the statin.

In a statement, the FDA advises health care professionals to be aware of the potential increased risk of muscle injury as-

sociated with the 80-mg dose of simvastatin, when compared with lower doses of simvastatin and “possibly other statin drugs.” Although myopathy is a known side effect associated with all statins, this warning “highlights the greater risk of developing muscle injury, including rhabdomyolysis,” when patients use higher doses of simvastatin.

Simvastatin is marketed as Zocor and is also available as a generic formulation. The drug also is combined with ezeti-



40/5 • 40/10 • 80/5 • 80/10 mg

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.

Consider the patient's baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared with monotherapy when deciding whether to use TWYNSTA tablets as initial therapy.

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-anniotic 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

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 III 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.

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 noted 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.

mibe (Vytorin) and with niacin (Simcor).

Preliminary data from more than 6,000 patients taking simvastatin for almost 7 years showed that 52 (0.9%) of patients on the 80-mg dose developed myopathy, compared with 1 patient (0.02%) on the 20-mg dose. Eleven patients (0.02%) taking the 80-mg dose developed rhabdomyolysis, but none in the low-dose group developed the condition.

Plavix Not for Poor Metabolizers

The FDA updated the labeling for clopidogrel to emphasize that new data definitively show that the antiplatelet

agent is less effective—and may not work at all—in patients defined as “poor metabolizers.”

The agency, which is notifying physicians that testing is available for the genotypes that are associated with poor metabolism, stopped short of recommending that all patients receive such testing before starting a course of clopidogrel (Plavix, Sanofi-Aventis). An estimated 2%-14% of the population probably have those alleles and are poor metabolizers, according to the FDA.

The FDA urges physicians to consider use of other antiplatelet agents in

poor metabolizers, such as ticlopidine (Ticlid) or prasugrel (Effient), or potentially increasing the clopidogrel dose. Prasugrel did not seem to have the same metabolism issue.

Lung Drug Gets Okay From Panel

The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 9-3 to recommend approval of pirfenidone for the reduction in the decline of lung function in idiopathic pulmonary fibrosis (IPF). Those who voted in favor of approval agreed that the data on the drug showed that treatment was beneficial in

slowing the progression of the disease.

Panelists said, however, that more data are needed to help identify which subsets of patients with IPF may benefit the most from treatment. The panel also recommended that safety of the drug should be monitored long term, possibly in a patient registry.

There is no FDA-approved treatment for IPF, a progressive, irreversible diffuse parenchymal lung disease of unknown etiology that is typically diagnosed after age 50. Approximately 100,000 people in the United States have the disease, according to pirfenidone's manufacturer, InterMune.

Panel Votes Yes on DBS for Seizures

The FDA's Neurological Devices Advisory Panel voted 7-5 to recommend approval, with conditions, of an implantable device that delivers electrical stimulation to the brain as an adjunctive treatment for adults with refractory seizures.

The panel reviewed the data from one study of 109 patients on the Deep Brain Stimulation (DBS) System for Epilepsy, manufactured by Medtronic, which provides bilateral stimulation of the anterior thalamic nucleus. The proposed indication for the device is as adjunctive therapy for reducing the frequency of seizures in adults with epilepsy characterized by partial-onset seizures that are refractory to antiepileptic medications.

Panel members voting in favor of approval agreed that the study provided adequate efficacy and safety data on the device in this patient population. Those voting against approval were satisfied with the safety data, but said they did not consider the efficacy data robust enough to support approval.

The components of the DBS system include a neurostimulator that connects to two leads that are implanted in the anterior nucleus of the thalamus. The same system is already approved for treating essential tremor of Parkinson's disease.

Safety of Insulin Pumps Reviewed

Members of the FDA's General Hospital and Personal Use Devices Panel agreed that although there are technological issues with insulin infusion pumps, these are outweighed by user-related issues.

During 2006-2009, the FDA received 16,849 reports of adverse events (including 310 deaths) associated with insulin pumps; most were reported by the manufacturers. The reports were far from complete: In most cases the problem with the pump was not described, and the cause of death had not been thoroughly evaluated, according to the FDA. The most common device problems were listed as unknown (20%), replace (9%), display of an error message (almost 5%), failure to deliver (3%), and repair (3%).

Of the 310 deaths, the most commonly listed causes were diabetic coma, hyperglycemia, hypoglycemia, diabetic ketoacidosis, and unresponsiveness. There were 29 deaths associated with a motor vehicle.

—From staff reports

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.

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 Dose-Related Adverse 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 Effects 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	07.8
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:** hyposthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, 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.

DRUG INTERACTIONS

Drug Interactions with TWYNSTA Tablets

The pharmacokinetics of amlodipine and telmisartan are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with TWYNSTA tablets and other drugs, although studies have been conducted with the individual amlodipine and telmisartan components of TWYNSTA tablets, as described below:

Drug Interactions with Telmisartan

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Co-administration of telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized

by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Drug Interactions with Amlodipine

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, Maalox®, sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

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.

Rx only



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