Exforge®

(amlodipine and valsartan) Tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

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, Exforge® (amlodipine and valsartan) should be discontinued as soon as possible. ***See WARNINGS: Fetal/Neonatal Morbidity and Mortality***

INDICATIONS AND USAGE: Exforge® (amlodipine and valsartan) is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension *(see DOSAGE AND ADMINISTRATION in the full prescribing information).*

CONTRAINDICATIONS: Exforge® (amlodipine and valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS: Fetal/Neonatal Morbidity and Mortality: 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. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have taken valsartan. When pregnancy is detected, valsartan should be discontinued as soon as possible. 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 ateriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system 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, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress 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 means of reversing hypotension and/or substituting for disordered renal function. **Hypotension:** Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Exforge® (amlodipine and valsartan) in placebo-controlled studies. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of Exforge, or the treatment should start under close medical supervision. Caution should be observed when initiating therapy in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis. If excessive hypotension occurs with Exforge, the patient should be placed in a 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. **Increased Angina and/or Myocardial Infarction:** Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/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.

PRECAUTIONS: General: ***Impaired Hepatic Function:*** *Studies with 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, therefore, caution should be exercised when administering amlodipine to patients with severe hepatic impairment. *Studies with valsartan:* As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients. ***Impaired Renal Function – Hypertension:*** In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. ***Congestive Heart Failure:*** *Studies with amlodipine:* In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 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 II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. *Studies with valsartan:* Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. ***Beta-Blocker Withdrawal:*** Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker. **Information for Patients:** ***Pregnancy:*** Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible. **Clinical Laboratory Findings:** ***Creatinine:*** In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving Exforge and 0.6% receiving placebo. In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients. ***Liver Function Tests:*** Occasional elevations (greater than 150%) of liver chemistries occurred in Exforge-treated patients. ***Serum Potassium:*** In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of Exforge-treated patients compared to 3.4% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients. ***Blood Urea Nitrogen (BUN):*** In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of Exforge-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients. **Drug Interactions:** No drug interaction studies have been conducted with Exforge and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below: ***Studies 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. Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine. Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine. Sildenafil: A single 100 mg dose of sildenafil (Viagra®*) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect. Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. ***Studies with Valsartan:*** No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone. Warfarin: Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin. ***CYP 450 Interactions:*** The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown. As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. **Drug/Food Interactions:** *Studies with amlodipine:* The bioavailability of amlodipine is not altered by the presence of food. *Studies with valsartan:* Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. **Carcinogenesis/Mutagenesis/Impairment of Fertility:** *Studies with amlodipine:* Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m² basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m² basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.) Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m² basis). *Studies with valsartan:* There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m² basis. (Calculations based on a 60 kg patient.) Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli*, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test. Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the maximum recommended human dose on a mg/m² basis. **Pregnancy:** ***Pregnancy Category C (first trimester) and D (second and third trimesters):*** *See WARNINGS, Fetal/Neonatal Morbidity and Mortality. Studies with amlodipine:* No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m² basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Studies with valsartan:* No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses of up to 600 mg/kg/day and to pregnant rabbits at oral doses of up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits, respectively, are about 9, 6 and 0.1 times the MRHD of 320 mg/day on a mg/m² basis. (Calculations based on a patient weight of 60 kg.) *Studies with amlodipine besylate and valsartan:* In the oral embryo-fetal development study in rats using amlodipine besylate plus valsartan at doses equivalent to 5 mg/kg/day amlodipine plus 80 mg/kg/day valsartan, 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan, and 20 mg/kg/day amlodipine plus 320 mg/kg/day valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. The no-observed-adverse-effect level (NOAEL) for embryo-fetal effects was 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan. On a systemic exposure [$AUC_{(0-\infty)}$] basis, these doses are, respectively, 4.3 and 2.7 times the systemic exposure [$AUC_{(0-\infty)}$] in humans receiving the MRHD (10/320 mg/60 kg). **Labor and Delivery:** The effect of Exforge on labor and delivery has not been studied. **Nursing Mothers:** It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered. It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of Exforge in pediatric patients have not been established. **Geriatric Use:** In controlled clinical trials, 323 hypertensive patients treated with Exforge were ≥65 years and 79 were ≥75 years. No overall differences in the efficacy or safety of Exforge was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Exforge: Exforge® (amlodipine and valsartan) has been evaluated for safety in over 2,600 patients with hypertension; over 1,440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall frequency of adverse experiences was neither dose-related nor related to gender, age, or race. In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in the Exforge-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with Exforge were peripheral edema (0.4%), and vertigo (0.2%). The adverse experiences that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Exforge but at a higher incidence in amlodipine/valsartan patients (n=1,437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs. 2.1%) and dizziness (2.1% vs. 0.9%). Orthostatic events (orthostatic hypotension and postural dizziness) were seen in less than 1% of patients. Other adverse experiences that occurred in placebo-controlled clinical trials with Exforge (≥0.2%) are listed below. It cannot be determined whether these events were causally related to Exforge. ***Blood and Lymphatic System Disorders:*** Lymphadenopathy. ***Cardiac Disorders:*** Palpitations, tachycardia. ***Ear and Labyrinth Disorders:*** Ear pain. ***Gastrointestinal Disorders:*** Diarrhea, nausea, constipation, dyspepsia, abdominal pain, abdominal pain upper, gastritis, vomiting, abdominal discomfort, hemorrhoids, abdominal distention, dry mouth, flatulence, toothache, colitis. ***General Disorders and Administration Site Conditions:*** Fatigue, chest pain, asthenia, pitting edema, pyrexia, edema, pain. ***Immune System Disorders:*** Seasonal allergies. ***Infections and Infestations:*** Nasopharyngitis, sinusitis, influenza, bronchitis, pharyngitis, urinary tract infection, gastroenteritis, pharyngotonsillitis, bronchitis acute, viral infection, tonsillitis, tooth abscess, cystitis, pneumonia. ***Injury, Poisoning and Procedural Complications:*** Contusion, epicondylitis, joint sprain, limb injury, post procedural pain. ***Investigations:*** Cardiac murmur. ***Metabolism and Nutrition Disorders:*** Gout, non-insulin dependent diabetes mellitus, hypercholesterolemia. ***Musculoskeletal and Connective Tissue Disorders:*** Arthralgia, back pain, muscle spasms, pain in extremity, myalgia, osteoarthritis, joint swelling, musculoskeletal chest pain. ***Nervous System Disorders:*** Headache, sciatica, parasthesia, cerviocobrachial syndrome, carpal tunnel syndrome, hypoaesthesia, sinus headache, somnolence. ***Psychiatric Disorders:*** Insomnia, anxiety, depression. ***Renal and Urinary Disorders:*** Hematuria, nephrolithiasis, pollakiuria. ***Reproductive System and Breast Disorders:*** Erectile dysfunction. ***Respiratory, Thoracic and Mediastinal Disorders:*** Cough, pharyngolaryngeal pain, sinus congestion, dyspnea, epistaxis, productive cough, dysphonia, nasal congestion. ***Skin and Subcutaneous Tissue Disorders:*** Pruritus, rash, hyperhidrosis, eczema, erythema. ***Vascular Disorders:*** Flushing, hot flush. Isolated cases of the following clinically notable adverse events were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, and hypotension. **Amlodipine:** Norvasc®** has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse events that have been reported <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 were: ***Cardiovascular:*** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, postural hypotension, vasculitis. ***Central and Peripheral Nervous System:*** neuropathy peripheral, tremor. ***Gastrointestinal:*** anorexia, dysphagia, pancreatitis, gingival hyperplasia. ***General:*** allergic reaction, hot flushes, malaise, rigors, weight gain, weight loss. ***Musculoskeletal System:*** arthrosis, muscle cramps. ***Psychiatric:*** sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization. ***Respiratory System:*** dyspnea. ***Skin and Appendages:*** angioedema, erythema multiforme, rash erythematous, rash maculopapular. ***Special Senses:*** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. ***Urinary System:*** micturation frequency, micturation disorder, nocturia. ***Autonomic Nervous System:*** sweating increased. ***Metabolic and Nutritional:*** hyperglycemia, thirst. ***Hemopoietic:*** leukopenia, purpura, thrombocytopenia. Other events reported with amlodipine at a frequency of ≤0.1% of patients include: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, 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. Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®. ***Post-Marketing Experience:*** 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. **Valsartan:** Diovan® has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p<0.001). Other adverse events, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are: ***Body as a Whole:*** allergic reaction, asthenia. ***Musculoskeletal:*** muscle cramps. ***Neurologic and Psychiatric:*** paresthesia. ***Respiratory:*** sinusitis, pharyngitis. ***Urogenital:*** Impotence. Other reported events seen less frequently in clinical trials were: angioedema. Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan. ***Post-Marketing Experience:*** The following additional adverse events have been reported in post-marketing experience with valsartan: ***Blood and Lymphatic:*** There are very rare reports of thrombocytopenia. ***Hypersensitivity:*** There are rare reports of angioedema. ***Digestive:*** Elevated liver enzymes and very rare reports of hepatitis. ***Renal:*** Impaired renal function. ***Clinical Laboratory Tests:*** Hyperkalemia. ***Dermatologic:*** Alopecia. Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

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Flop: Episodic Amiodarone

BY BRUCE JANCIN
Denver Bureau

DENVER — Episodic amiodarone therapy is a losing strategy for maintenance of sinus rhythm in patients with persistent atrial fibrillation, according to the first randomized trial comparing this approach to continuous amiodarone.

"Episodic amiodarone therapy is no option for pharmacologic rhythm control," Dr. Isabelle C. Van Gelder said at the annual meeting of the Heart Rhythm Society.

She presented the results of the Continuous Versus Episodic Amiodarone Therapy for Prevention of Permanent Atrial Fibrillation (CONVERT) trial. In this multicenter Dutch study, 206 patients with persistent atrial fibrillation (AF) underwent cardioversion followed by a loading dose of amiodarone at 600 mg/day for 4 weeks and were then randomized to continuation of the drug at 200 mg/day or to discontinuation. Patients in the episodic treatment arm who experienced AF recurrences went back on amiodarone for up to 1 month following each cardioversion.

Amiodarone is widely recognized as the most effective antiarrhythmic agent at maintaining sinus rhythm in AF patients. It is also the antiarrhythmic drug least likely to cause proarrhythmias. But it causes a wide variety of noncardiac side effects in what has been thought to be a cumulative dose-related fashion. The hypothesis in CONVERT was episodic amiodarone would be as effective as continuous therapy at suppressing AF, because the drug has a very long half-life of up to 100 days, but that episodic therapy would be associated with markedly less toxicity.

Contrary to expectation, however, CONVERT showed episodic amiodarone brings significantly more morbidity, not less, said Dr. Van Gelder of the University of Groningen (the Netherlands).

After a median 1.8 years of follow-up, 32% of the episodic amiodarone group and 25% on continuous therapy had progressed to permanent atrial fibrillation. Seventy percent in the episodic treatment arm experienced AF recurrences and cardioversions, compared with 39% of controls. The primary CONVERT end point—a composite of adverse drug-related cardiac and noncardiac effects—occurred at a rate of 21.5 cases per 100 person-years with episodic therapy and 16.7 cases per 100 person-years with continuous amiodarone, a nonsignificant difference.

"What was surprising to us was there were more events related to underlying heart disease in the episodic amiodarone group. They had more hospitalizations for heart failure because of atrial fibrillation after discontinuation of amiodarone and not that much rate control," she explained.

Indeed, 13% of patients in the episodic amiodarone arm experienced an end point related to AF or underlying heart disease, compared with only 3% on continuous amiodarone. ■