Exforge® (amlodipine and valsartan) Tablets

BRIEF SUMMARY: Please see package insert for full prescribing inform

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 ar valsartan) should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortal

NDICATIONS AND USAGE: Extorge® (amlodipine and valsartan) is indicated for the treatment of hypertension. This ixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRA-

CONTRAINDICATIONS: Exforge® (amlodipine and valsartan) is contraindicated in patients who are hype

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 reported 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 rature, 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 should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraagents utining pringinaricy. Parely procularly reso totel mina on teal mevery indusatin preginancies, fine attentance or adrug 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 oligophydramnios is observed, valsarian should be discontinued unless its considered fifter-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 oligophydramnios and profiling the profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligophydramnios and profiling the profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be closely observed for hypotension, oliguria, and hyper-kalemia 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 hyper-tension treated with Exdorge® (amdiopline and valsatran) 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 Edorge, 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 dalpsis, Patients with heart failure post-myocardial infarctio tinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients. Since the vasodilation induced by amilodipine 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 amilodipine, particularly in patients with severe aortic stenosis. If excessive hypotension occurs with Evforge, 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.

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PRECAUTIONS: General: Impaired Hepatic Function: Studies with amlodipine: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (1;2) is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering amlodipine to patients with impaired hepatic impairment, studies on the valsartan: As the majority of valsartan is eliminated in the bile, patients with milot-on-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 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 dearnous many and angiotensin-receptor antagonists has been associated with oliquria and/or progressive azotenia 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 hard tallure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,135 patients with hard studies. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardic idecontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.5% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Beta-Blocker Withdrawal: Amoligine is not a beta-blocker and therefore gives on 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 childhearing 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: Creatinies: 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. 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 150% increases in serum potassium were observed in 2.8% of Exforge-treated patients. Or hemistries occurred in Exforge-treated patients. Breat failure patients, greater than 50% increases in serum potassium were observed in 1.6% of valsartan-treated patients compared to 5.4% of placebo-treated patients. Breat failure patients, greater than 50% increases in serum potassium were observed in 1.6% of valsartan-treated patients compared to 5.4% of placebo-treated patients. Breat failure patients, greater than 50% increases in serum potassium were observed in 1.6

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) Mutapenicity 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 doout 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. Scale of the maximum candinates 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 valsarian-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and £. coli, a gene mutation test with Chinese harster V79 cells, a cytogenetic test with Chinese harster ovary cells, and a rat micronucleus test. Valsarian had no adverse effects on the reproductive performance or male or female arts 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 (flist trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality; Sudies with amlodipine. New devices of tratogenicity or the embryoffetal toxici 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 ma nursing be discontinued while amilodipine is administered. It is not known whether valsarfan is excreted in human mubur valsarfan 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 ≥55 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.

patient population, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Extorge: Extorge® (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 with hypertension; over 1,440 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 Extorge-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with Extorge 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 Extorge but at a higher incidence in amlodipine/valsartan patients (n=1,437) than placebo (n=337) included peripheral edema (0.4%), 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. Bload and Lymphatic System Disorders: Lymphadenopathy, Cardiac Disorders: Papilitations, tachycardia. Ear and Labyrinth Disorders: Ear pain. Gastrointestinal Disorders: Darnhea, nausea, constipation, dyspepsia, abdominal apin, abdominal plain upper, gastrist, vomiting, abdominal discomfort, hemorrhoids, abdominal distention, dry mouth, flatulence, toothache, colitis. General Disorders: Darnhea, nausea, constipation, dyspepsia, abdominal 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 Demonstratis, pharyngotonsillitis, bronchitis acute, viral infection, tonsillitis, tooth abscess, cystitis, pneumonia. Injury, Poisoning and Procedural Complications: Contusion, epicondylitis, joint syralin, limb injury, post procedural pain. Investigations: Cardiac murruur. Metabolism and Nutrition Disorders: Gout, non-insulin dependent diabetes mellitus, hypercholesterolemia. Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, pain in extremity, myagia, osteoarthritis, joint swelling, musculoskeletal chest pain. Nervous System Disorders: Headache, scalatica, parasthesia, cervicocorbachial syndrome, carpal tunnel syndrome, hypoaesthesia, sinus headache, somnolence. Psychiatric Disorders: Insomnia, anxiety, depression. Renal and Urinary Disorders: Henaturia, nephrolithiasis, polakiuria. 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: Puritus, rash, hyperhidrosis, eczema, erythema. Vascular Disorders: Husing, hof tilush, Isolated cases of the following clinically notable adverse events were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, and hypotension. Amiodijine: Norvasco²⁰⁻¹ 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 dreams, depersonalization. Respiratory System: dyspnea. Skin and Appendages: anjoiedema, 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 Nutritionat: hyperglycemia, thirst. Hemopoletic: leukopenia, purpura, thrombocytopenia. Other events reported with amhodipine at a frequency of soil. 9% of patients include: cardiac failure, pulse irrepularity, 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 verophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Adverse reactions reported for amhodipine for indications other than hypertension may be found in the prescribing information for Norvasce. 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 amilodipine. Valsartan: Diovan® has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials in which valsartan was compared to an 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, HCT2, or lisinopril were 20%, 19%, and 69% respectively (pc.0.001). Other adverse events, not listed above,

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

Reference: 1. Data on file. Study CVAA489A2403. Novartis Pharmaceuticals Corporation

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1 NOVARTIS

Subtle Shift in Guidelines for **Prediabetes**

BY SHERRY BOSCHERT

San Francisco Bureau

SAN FRANCISCO — Take time to read the updates of guidelines for the management of prediabetes or diabetes carefully, because little pearls can be buried in the text, Dr. Richard M. Bergenstal said at a meeting sponsored by the American Diabetes Association.

He says he has noticed a shift, for example, in nutrition recommendations for the prevention of diabetes in the latest update of the American Diabetes Association's major position statement, "Standards of Medical Care in Diabetes," which states that for weight loss, "either low-carbohydrate or low-fat calorie-restricted diets may be effective in the short term (up to 1 year)" (Diabetes Care 2008;31:S1-S108).

'This is a huge change," said Dr. Bergenstal, executive director of the International Diabetes Center, Minneapolis. We've always just said it's got to be lowfat calorie-restricted diets.

The new recommendation is more patient centered and gives providers more leeway to figure out what patients might be willing to do to change their diets and to match the pros and cons of different diets to individual patients.

For the first year, let people do what they're going to do to lose some weight," he paraphrased. "I thought that was an interesting and significant change, but it just shows up as a little bullet in the standards of care, so read them carefully."

The updated guidelines state that for patients with prediabetes, counseling for lifestyle modifications is the standard of care for patients with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The goal should be a weight loss of 5%-10% and an increase in physical activity to at least 150 minutes a week of moderate activity such as walking. Follow-up counseling is recommended.

In addition to lifestyle counseling, treatment with metformin may be considered for people at very high risk of developing diabetes: those who are obese, are younger than 60 years old, and have both IFG and IGT plus other risk factors for diabetes (such as a family history of the disease). Patients with prediabetes should be monitored yearly for the development of diabetes.

The guidelines eschewed the use of thiazolidinediones or incretin mimetics in these patients because more data are needed about the risks and benefits of these agents for preventing diabetes, Dr. Bergenstal noted.

In recent studies, other suggested therapies for prediabetes have included walking; combining aerobic exercise and weight lifting; getting adequate sleep; surgery; monitoring caffeine intake and diet; and medications.

Dr. Bergenstal is an advisor to or has received research funding from multiple companies that make medications or devices for diabetes.

^{*}Viagra® is a registered trademark of Pfizer, Inc. **Norvasc® is a registered trademark of Pfizer, Inc