## INDICATIONS

#### Rocket Man-Er, Fish

Putting aside efforts to cure real diseases (cancer? AIDS?), researchers from the University of Stuttgart-Hohenheim's Department of Wasting Time and Money, in Germany, launched 60 baby cichlid fish into space to decode the causes of motion sickness, Reuters reports. The fish will take off from the Esrange Space Centre in Sweden, above the Arctic Circle, and journey 160 miles into the atmosphere, where they will become weightless for 6 minutes. Cameras will record the fish's actions. After the fish land, the researchers will examine the subjects' otolith organs, which sense gravity and acceleration. "Fish, when they get motion sick, begin tumbling around, swimming in circles, and miss their balance," a researchers told the news outlet. Hey, that happens to us sometimes, too, though under slightly different circumstances. Said one space traveler: "All this science, I don't understand. It's just my job, 5 days a week. I'm a Rocket Man." Um, right.

### **Top Gun, Chemically Enhanced**

You've heard of airplane pilots hitting the bar before takeoff. Now for the newest trend: Israeli fighter pilots popping Cialis tablets, supposedly to improve breathing at high altitudes. The Israeli military's weekly magazine, Bamahaneh, recently presented an interview with a retired military general who just happened to have a few pills on hand and conducted a single-subject study of the drug's effects on breathing on Mount Kilimanjaro. A secondhand report in Reuters quoted an unnamed air force officer saying the study's results justify further "testing" of the pills. But an air force spokeswoman said the type of oxygen starvation mountaineers experience is different from that in pilots, and there were no plans to issue the drug to members of the air force. In possibly related news, French customs officials intercepted a shipment of 224,000 fake Viagra and Cialis anti-impotence pills in December, at Paris's Roissy airport. Said a pilot, who remained anonymous for fear of retribution: "Oui, oui! Eet is zee only way to fly. As they say: We have liftoff!"

#### Brain Surgery, Take One ... Action!

In the most compelling story yet to refute the benefits of medical tourism, a Singapore newspaper says students in an immunology class at Nanyang Polytechnic medical school spend half a semester watching television shows like "House" and movies like "Outbreak" in lieu of lectures. Student Constance Chen, aged 18 years, told the newspaper: "As youngsters, we are into TV, and it's great fun to watch ['House'] rather than have regular lectures." As future patients, we feel that no med student ought to be having "great fun" while learning how to perform a colonoscopy, for instance. Neither does a future doctor calling herself a "youngster" really make us want to hop up onto the examining table. Professor Anand Krishnasamy, who has been supplementing his course with the shows for 2 years, said, "I have a collection of movies and programs related to the subject and show them to the students whenever the main themes are connected to what I am teaching in class." Tara Reid, he added, looked totally hot in "Dr. T. and the Women."

-Denise Napoli

# **Exforge**®

(amlodipine and valsartan) Tablets

BRIEF SUMMARY: Please see package insert for full prescribing info

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 Mortaliti

CONTRAINDICATIONS: Extorge® (amlodipine and valsartan) is contraindicated in patients who are hypersensi component of this product.

TION in the full prescribing information).

CONTRAINDICATIONS: Extorgee (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 reports of spontaneous abortion, oligorhydramnios 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 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 oligorydramnios is observed, valastran should be discontinuous during (RPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians

PRECAUTIONS: General: Impaired Hepatic Function: Studies with amlodipine: Amlodipine is extensively metabo-lized 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 himber 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). 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 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 azotenia and (rarely) with acute renal fallure and/or death. Similar outcomes have been reported with valsartan. Congestive Heart Failure: Studies with amiodipine: In general, calcium channel blockers should be used with raution in patients with heart failure. Amiodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Cass III or IV heart failure on stable doses of ACE inhibitor, dipoxin, and diureties. 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). Amiodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class IVIII heart failure, involving a total of 697 pati assessment of renal function. Beta-Blocker Withdrawal: Amlodipine is not a beta-blocker and therefore gives no pro-tection 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 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. In post-myocardial infarction patients, doubling of serum creatinine was observed in 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 2.8% of placebo-treated patients and 3.4% of captorpit-treated patients. In the Function Tests: Cocasional 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 5.5% of placebo-treated patients. Binear than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients. One patients of patients in the patients of patients of patients. In clinical trials, amiodipine as been safely administered with th 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 fid not change serum digoxin levels or digoxin renal clearance in normal volunters: Martarin: 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 valsartanatenolol combination was more antihippertensive than either component, but it did not lower the heart rate more than atenoloi 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 spapiements, 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<sub>max</sub>) 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 12 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 Salmonelia and E. coil, a gene mutation test with Chinese hamster (vary cells, and a rat micronu-cleus 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 flow and were more pregnancy. Pregnancy Category C (first trimester) and D (second and third trimesters): See WARNINGS, Felu/keonatal 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 on a mg/m² basis, during their r 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

aboversa's and 79 were 2/3 years, No overall otherences in the efficacy of satery of extrige was observed in this 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 were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least 6 months and over 540 of these patients in the interest of the safe 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 (5.4% vs. 3.0%). Onthostatic 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 Extorge (a) 2% are listed below. It cannot be determined whether these events were causally related to Extorge. 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, voniting, abdominal disconfort, hemorrhoids, abdominal disection, dyrounth, flattlence, toothache, colitis. General Disorders and Administration Site Conditions: Fatigue, chest pain, asthenia, pitting edema, pyrexia, edema, pain. Immune System Disorders: Seasonal altergies. Infections and Infestations: Nasopharyngitis, sinustis, influenza, bronchitis, pharyngitis, until process. Seasonal altergies. Infections and Infestations: Nasopharyngitis, sinustis, influenza, bronchitis, pharyngitis, until process. Seasonal altergies. Infection, destroenteritis, pharyngotonsillitis, bronchitis acute, viral infection, tonsillitis, tooth abscess, cystitis, pneumonia. Injury, Poisoning and Procedural Complications: Contusion, epi-condylitis, piont sprain, limbi unjury, post procedural pain. Investigations: Cardiac murmur. Metabolism and Mutrition Disorders: Gout, non-insulin dependent diabetes mellitus, hypercholesterolemia. Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, pain in externity, myalgia, obsecurativis, joint swelling, musculoskeletal chest pain. Nervous System Disorders: Haeidache, scialica, parasthesia, cerviocobrachial syndrome, carpal tunnel syndrome, hypoaesthesia, sinus headache, somolence. Psychiatric Disorders: Insomnia, anxiety, depression. Renal and Urinary Disorders: Hematuria, nephrolithiasis, pollakiuria. Reproductive System and Breast Disorders: Terctile 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, ezema, erythema. Vascular Disorders: Hoshing, hot flush. Insolated cases of the following clinically notable adverse events were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, timnitus, and hypotension. Amidipine: Novasco<sup>20-1</sup> 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 <a href="https://docs.org/10.1016/journal-pi.nlm.nitus.nlm.nitus.n dreams, depersonalization. Respiratory System: dyspnea. Skin and Appendages: angloedema, erythema multiforme, rash erythematous, rash maculopapular. Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnifus. Urinary System: micturation frequency, micturation disorder, nocturia. Autonomic Nervous System: sweating increased. Metabolic and Nutritionat: hyperplycemia, thirst. Hemopoletic: leukopenia, purpura, thrombocytopenia. Other events reported with amlodipine at a frequency of <a href="#">other Policy Other Poli To moliciations often than hypertension in large because in the pressrioning information to Dovain. Post-marketing experience with valsarian 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. Renai: 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.]

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

APRIL 2007 Printed in U.S.A. Distributed by: Novartis Pharmaceuticals Corp. East Hanover, New Jersey 07936



<sup>\*</sup>Viagra® is a registered trademark of Pfizer, Inc. \*\*Norvasc® is a registered trademark of Pfizer, Inc