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ISMP: Avandia at Top in Drug Deaths

Type 2 diabetes drug rosiglitazone (Avandia) accounted for 1,354 patient deaths in 2009, more than any other prescription drug, according to a June report from the Institute for Safe Medication Practices. However, the institute blamed publicity about the drug's cardiovascular risks in part for the large number of fatalities reported to the Food and Drug Administration (see page 1 article for more on Avandia). "The manufacturer, GlaxoSmithKline, told us earlier that it believed many of the adverse drug event reports for rosiglitazone were associated with possible lawsuits against the company," the report said. The institute excluded reports it knew involved legal claims but said it couldn't rule out the bad publicity as the reason for some other reports of cardiovascular events and deaths associated with rosiglitazone. Other drugs tied to large numbers of deaths last year include deferasirox (1,320 deaths), digoxin (506 deaths), and fentanyl (397). Almost 20,000 medication-associated deaths were reported to the FDA, a 14% increase over 2008 and a threefold increase over 2000, according to the institute. The report attributed the drug-related mortality increase to three factors: increased awareness of drug risks, lack of progress in managing drugs with known risks, and reports of discontinued treatment and death stemming from increasingly common direct company-consumer contacts. The full report is available at www.ismp.org/quarterwatch/2009Q4.pdf.

CMS Reconsiders MRI Coverage

The Centers for Medicare and Medicaid Services is taking another look at its decision to bar coverage of magnetic resonance imaging for people who have cardiac pacemakers or metallic clips on vascular aneurysms. Dr. Robert Russo, director of the cardiac MRI program at

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Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no rechallenge in either case.

The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain and cough.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Valsartan
Valsartan has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials, including over 400 treated for over 6 months, and more than 160 for over 1 year.

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 reactions, 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.

6.2 Clinical Laboratory Test Abnormalities
RBC count, hemoglobin and hematocrit:
Small mean decreases from baseline were seen in RBC count, hemoglobin and hematocrit in both monotherapies and combination therapy. These changes were small, but changes in hemoglobin were slightly more pronounced with the combination therapy (-0.26 g/dL) than with monotherapy regimens (-0.04 g/dL in aliskiren or -0.13 g/dL in valsartan) or placebo (+0.07 g/dL).

Blood Urea Nitrogen (BUN)/Creatinine:
Elevations in BUN (>40 mg/dL) and creatinine (>2.0 mg/dL) in any treatment group were less than 1.0%. For creatinine, 0.5% (3/599) of patients on combination treatment had a creatinine level >1.5 mg/dL at the end of the study and a 30% increase from baseline compared to none in either monotherapy or placebo.

Serum Electrolytes: See Warnings and Precautions (5.7)

6.3 Post-Marketing Experience
The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: angioedema requiring airway management and hospitalization

Peripheral edema

7 DRUG INTERACTIONS
No drug interaction studies have been conducted with Valturna and other drugs, although studies with the individual aliskiren and valsartan components are described below.

Aliskiren
Effects of Other Drugs on Aliskiren
Based on *in vitro* studies, aliskiren is metabolized by CYP 3A4.

Irbesartan: Coadministration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.

P-glycoprotein Effects: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Coadministration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.

Atorvastatin: Coadministration of atorvastatin, a weak Pgp inhibitor, resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole, a moderate Pgp inhibitor, with aliskiren resulted in approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.

Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine, a potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5-fold increase in C_{max} and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.

Verapamil: Coadministration of 240 mg of verapamil, a moderate Pgp inhibitor, with 300 mg aliskiren resulted in an approximately 2-fold increase in C_{max} and AUC of aliskiren. However, no dosage adjustment is necessary.

Drugs with no clinically significant effects: Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.

Effects of Aliskiren on Other Drugs
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.

Furosemide: When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Drugs with no clinically significant effects: Coadministration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

Warfarin: The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

Valsartan
No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with aliskiren, 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: Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: In vitro metabolism studies have indicated that CYP450 mediated drug interactions between valsartan and coadministered

the Scripps Clinic in San Diego asked the CMS to reopen the issue of coverage for those patients. He is seeking to have it approved if the MRI is performed on people bearing the devices as part of an FDA-approved, prospective trial to determine the risk of the procedure. Comments on the proposal were being accepted through July 28, and the CMS said that it expected to issue a preliminary decision by Dec. 28.

FDA to Share Drug-Risk Findings

The FDA will post on its Web site summaries of postmarketing safety analyses on recently approved drugs and biologics, including brief discussions of steps being taken to address identified safety issues. The new summaries will cover side effects that might not become apparent until after a medicine becomes available to a large, diverse population, including previously unidentified risks and known adverse events that occur more frequently than expected. The initial reports will contain information on drugs and biologics approved since September 2007, including several drugs for infections, hypertension, and depression, the agency said.

J&J Discloses Physician Payments

Following in the footsteps of Pfizer, GlaxoSmithKline, and, most recently, Medtronic, Johnson & Johnson said that it is disclosing how much it pays physician speakers and consultants, at least for a number of its pharmaceutical subsidiaries. Unlike at other companies, however, the data cover only J&J divisions that were subject to corporate integrity agreements with the federal government, according to a company spokesman. Those divisions are PriCara, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Janssen, and McNeil Pediatrics. Payment disclosures are listed at those units' individual Web sites, such as www.janssen.com/transparency.html. Quarterly updates will give way to semiannual and then annual updates by 2012 for all the divisions. The company will start disclosing payments for medical devices and diagnostics by June 30, 2011, said the spokesman.

Men Less Likely to Get Care

Men are much less likely than are women to seek routine medical care: Just over half of U.S. men see a doctor, nurse practitioner, or physician assistant for routine care, compared with nearly three-quarters of women, according to the Agency for Healthcare Research and Quality. Only about 35% of Hispanic men and 43% of black men made routine appointments, compared with 63% of white men, and uninsured people were only about half as likely as were those with private insurance to make a routine care appointment, the agency said.

State Expands Medicaid to Adults

Connecticut has added low-income, childless adults to its Medicaid program under the nation's new health care reform law. It's the first state to take advantage of the law's incentives to expand "permanent" coverage to such individuals, which could previously be covered only under Medicaid waivers. Connecticut said it initially will cover childless adults who make up to 56% of the federal poverty level, or $6,650 per year, estimated to be about 45,000 extra people. Health care reform requires states to cover all low-income individuals in Medicaid starting in 2014, but also allows states to get federal funding to enroll them early.

—Alicia Ault

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