

Law Ensures Right to Appeal Coverage Denials

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New federal regulations mandated by the Affordable Care Act will give patients rights to appeal claims denials made by their health plans.

The rules will allow consumers in new health plans to appeal decisions both through their insurer's internal process and to an outside, independent entity. Most health plans already provide for an

internal appeals process, but not all offer an external review of plan decisions, said the U.S. Department of Health and Human Services. The types of appeals processes often depend on state laws.

HHS officials estimate that in 2011 there will be about 31 million people in new employer plans and another 10 million in new individual market plans who will be able to take advantage of these new appeals opportunities. The rules do

not apply to grandfathered health plans.

Health plans that begin on or after Sept. 23, 2010, must have an internal appeals process for consumers to appeal whenever the plan denies a claim for a covered service or rescinds coverage. The appeals process must offer consumers detailed information about the grounds for their denial and information on filing an appeal.

The rules aim to make internal appeals more objective by ensuring that the per-

son considering the appeal does not have a conflict of interest. Health plans will also have to provide an expedited appeals process, which would allow urgent cases to be reviewed within 24 hours.

The appeals regulations also standardize rules for external appeals. Health plans must provide clear information about external appeals and expedited access to the process. The decisions made through external appeals will be binding. ■

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 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 Valtorna 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