Key Standards and Rules

Chapter FastFACTS

1. **Physicians are likely to see changes in standards for measuring clinical success.**
2. **Revising your emergency preparedness plan now will help ready your practice to meet new guidelines.**
3. **More attention is being paid to how medical practices dispose of biohazardous waste.**
4. **Changes in medical practice by 2015 may increase employee fatigue and stress.**
5. **Prevention-and-control best practices may change because of issues with MRSA, sepsis, and other infectious diseases.**

Although primary care physicians strive to be up-to-date on new guidelines and rules that govern their office processes, it can be a challenge given the everyday pressure-cooker environment of a busy medical practice. However, this may become easier in 2015 when information about new standards from organizations like OSHA and the Joint Commission could come as a link through your EMR and would include alert notices when information is updated. That program will include background information and resources that will be readily available at the time of a patient visit to help you provide the best diagnostic and treatment options.

The system is already underway. In 2008 the Joint Commission released an electronic version of its accreditation manual

7 out of 10 patients

with untreated hypertension present with an

overactive RAAS[1,2]

NOVARTIS

IN HYPERTENSION

VALTURNA offers both superior BP efficacy and more comprehensive RAAS inhibition than valsartan[3]

A SMART VALTURNATIVE

Indication

VALTURNA is indicated for the treatment of hypertension in adults.

VALTURNA may be substituted for the titrated components. VALTURNA may be used in patients whose blood pressure is not adequately controlled on aliskiren or any ARB monotherapy and as initial therapy in patients who are likely to need multiple medications to achieve their blood pressure goals.

The choice of VALTURNA as initial therapy should be based on an assessment of potential benefits and risks. The decision to use a combination medication as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination product compared to monotherapy.

Important Safety Information

WARNING: AVOID USE IN PREGNANCY: When pregnancy is detected, discontinue VALTURNA as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause injury and even death to the developing fetus. [See *Warnings and Precautions* (5.1)]

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors (ACEIs) or angiotensin receptor antagonists. Discontinue aliskiren immediately in patients who develop angioedema, and provide appropriate therapy and monitoring until signs and symptoms resolve. Aliskiren should not be readministered.

Hypotension: In clinical trials, an excessive fall in blood pressure (hypotension) was seen rarely (<0.5%) in patients with uncomplicated hypertension treated with VALTURNA. Initiate therapy cautiously in patients with heart failure or recent myocardial infarction (MI) and in patients undergoing surgery or dialysis.

Volume- and/or Salt-depletion: Volume- and/or salt-depletion should be corrected in patients prior to administering VALTURNA or symptomatic hypotension may occur. Patients taking VALTURNA should be observed for clinical signs of fluid or electrolyte imbalance.

Renal Considerations: Care should be used when dosing VALTURNA in patients with severe renal impairment. As a consequence of inhibiting the RAAS, changes in renal function may be observed in susceptible individuals (eg, patients with renal artery stenosis or severe heart failure). Patients with severe renal impairment were excluded from clinical trials with VALTURNA in hypertension.

In studies of ACEIs in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. 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 ACEIs should be anticipated.

In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACEIs and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

- Greater SBP reductions vs valsartan
- More comprehensive RAAS inhibition than an ARB
- Established safety and tolerability
- Single-tablet dosing
- $15 co-pay available for most patients*

The clinical implications of differences in effect on RAAS components are not known.

***Valid for those patients with private insurance only.**

Not valid for patients whose prescription is paid for in part or in full under Medicare, Medicaid or any other federal or state program, self-paying patients (those without private insurance), or for residents of MA. Limitations apply. This card is the property of Novartis and must be returned upon request.

Novartis reserves the right to rescind, revoke, or amend this program without notice.

Patient is responsible for reporting receipt of program rewards to any private insurer that pays for or reimburses any part of the prescriptions filled with this program.

This offer will expire on 12/31/2010.

To learn more about Valturna, talk to your Novartis sales representative.

Important Safety Information (cont)

Hepatic Considerations: As a majority of valsartan is eliminated in the bile, valsartan should be used with care in patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, because of lower valsartan clearance.

Patients With CHF or Post-MI: Include assessment of renal function when evaluating patients with heart failure or post-MI. Dosage reduction and/or discontinuation of a diuretic and/or valsartan may be required.

Hyperkalemia: In short-term controlled trials of VALTURNA, the incidence of hyperkalemia (K^+ >5.5 mEq/L) was about 1%-2% higher than with corresponding monotherapies or placebo.

Electrolyte Imbalance: Periodic determinations of serum electrolytes to detect possible electrolyte imbalances is advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Cyclosporine or Itraconazole: It is not recommended to prescribe VALTURNA for patients who also take cyclosporine or itraconazole.

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.

Common AEs: The most common adverse events (AEs) that occurred more frequently with VALTURNA than placebo were fatigue (2.6% vs 1.4%), nasopharyngitis (2.6% vs 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs 1.1%), urinary tract infection (1.4% vs 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs 0.3%).

Please see Brief Summary of Prescribing Information, including **Boxed WARNING**, on following pages.

References: 1. Blumenfeld JD, Laragh JH. Renin system analysis: a rational method for the diagnosis and treatment of the individual patient with hypertension. *Am J Hypertens.* 1998;11(7): 894-896. **2.** Alderman MH, Cohen HW, Sealey JE, Laragh JH. Plasma renin activity levels in hypertensive persons: their wide range and lack of suppression in diabetic and in most elderly patients. *Am J Hypertens.* 2004;17(1):1-7. **3.** Valturna [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2010.

Valturna®
(aliskiren and valsartan, USP) tablets
150/160 • 300/320 mg

A smart option in BP lowering

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Printed in USA 10/10 VAT-1009817

Valturna *(aliskiren and valsartan, USP)* Tablets

Initial U.S. Approval: 2009

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

WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue Valturna as soon as possible. When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus. *[See Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Valturna is indicated for the treatment of hypertension.

Add-on Therapy

A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan (or another angiotensin receptor blocker) alone may be switched to combination therapy with Valturna.

Replacement Therapy

Valturna may be substituted for the titrated components.

Initial Therapy

Valturna may be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of Valturna as initial therapy should be based on an assessment of potential benefits and risks.

Patients with Stage 2 hypertension are at a relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study *[see Clinical Studies (14) in the full prescribing information]* provide estimates of the probability of reaching a target blood pressure with Valturna compared to aliskiren or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Valturna 300/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable because of a small number of subjects with high baseline blood pressures.

Figure 1: Probability of Achieving Systolic Blood Pressure (SBP) <140 mm Hg in Patients at Endpoint

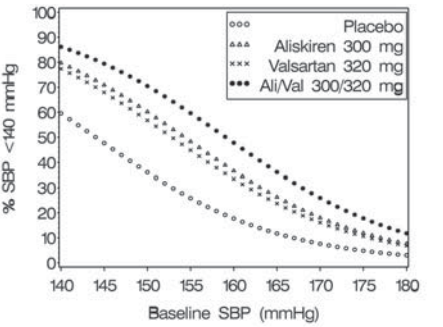


Figure 2: Probability of Achieving Diastolic Blood Pressure (DBP) <90 mm Hg in Patients at Endpoint

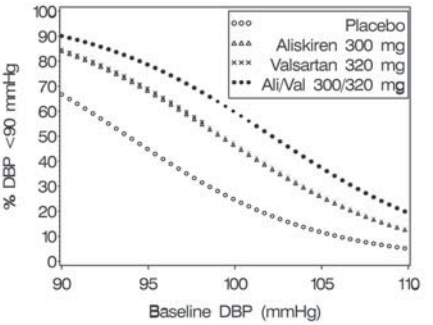


Figure 3: Probability of Achieving Systolic Blood Pressure (SBP) <130 mm Hg in Patients at Endpoint

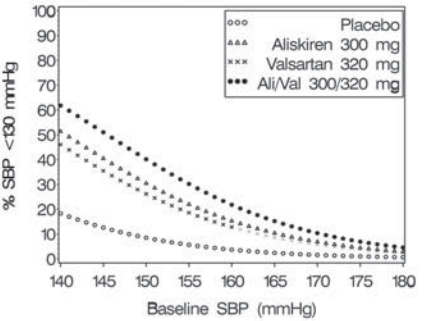
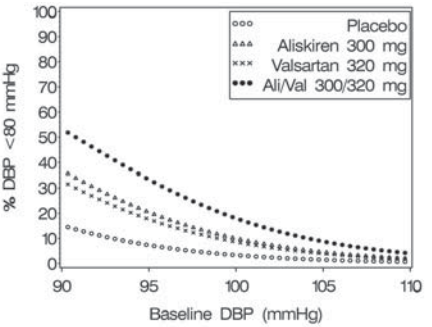


Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) <80 mm Hg in Patients at Endpoint



At all levels of baseline blood pressure, the probability of achieving any given diastolic or systolic goal is greater with the combination than for either monotherapy. For example, the mean baseline SBP/DBP for patients participating in this multifactorial study was 154/100 mm Hg. A patient with a baseline blood pressure of 154/100 mm Hg has about 51% likelihood of achieving a goal of <140 mm Hg (systolic) and 46% likelihood of achieving <90 mm Hg (diastolic) on aliskiren alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) and 47% (diastolic). The likelihood of achieving these goals on Valturna

rises to about 62% (systolic) and 60% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) and 25% (diastolic) *[see Dosage and Administration (2) and Clinical Studies (14) in the full prescribing information]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*. In several dozen published cases, use of ACE inhibitors during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. In addition, first trimester use of ACE inhibitors has been associated with birth defects in retrospective data.

5.2 Head and Neck Angioedema

Aliskiren

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren and has necessitated hospitalization and intubation. This may occur at any time during treatment and has occurred in patients with and without a history of angioedema with ACE inhibitors or angiotensin receptor antagonists. If angioedema involves the throat, tongue, glottis or larynx, or if the patient has a history of upper respiratory surgery, airway obstruction may occur and be fatal. Patients who experience these effects, even without respiratory distress, require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Prompt administration of subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and measures to ensure a patent airway may be necessary.

Discontinue aliskiren immediately in patients who develop angioedema, and do not readminister.

5.3 Hypotension

An excessive fall in blood pressure (hypotension) was rarely seen (<0.5%) in patients with uncomplicated hypertension treated with Valturna in controlled trials.

In patients with an activated renin-angiotensin-aldosterone system, such as volume- or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving renin-angiotensin-aldosterone system (RAAS) blockers. Correct these conditions prior to the administration of Valturna, or start the treatment under close medical supervision.

Initiate therapy cautiously 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.

If an excessive fall in blood pressure occurs with Valturna, place the patient in the supine position and, if necessary, give 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.

5.4 Patients with Severe Renal Impairment

Valturna

Patients with severe renal impairment were excluded from clinical trials with Valturna in hypertension.

Aliskiren

Patients with severe renal dysfunction (creatinine 1.7 mg/dL for women and 2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of aliskiren in hypertension. Safety information with aliskiren and the potential for other drugs acting on the renin-angiotensin-aldosterone system to increase serum creatinine and blood urea nitrogen are not available.

Valsartan

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 occur particularly in volume depleted patients. 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 or progressive azotemia and (rarely) with acute renal failure or death. Similar outcomes have been reported with valsartan.

5.5 Patients with Hepatic Impairment

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).

5.6 Patients with Congestive Heart Failure and Post-Myocardial Infarction

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. Include assessment of renal function when evaluating patients with heart failure or post-myocardial infarction.

5.7 Serum Electrolyte Abnormalities

Valturna

In the short-term controlled trials of various doses of Valturna, the incidence of hyperkalemia (serum potassium >5.5 mEq/L) was about 1%-2% higher in the combination treatment group compared with the monotherapies aliskiren and valsartan, or with placebo.

In a long-term, uncontrolled study with median treatment duration of about one year, about 4% of the patients had at least one serum potassium >5.5 mEq/L at some time during the study; about 0.8% of patients discontinued study treatment and had a high serum potassium at some point during the study. Patients with hyperkalemia were older (median age 65 vs. 55) with slightly lower mean baseline estimated creatinine clearance compared to patients without hyperkalemia. While about 25% of the hyperkalemic episodes occurred in the first two months, other initial episodes were reported throughout the study.

Periodic determinations of serum electrolytes to detect possible electrolyte imbalances are advised, particularly in patients at risk for hyperkalemia such as those with renal impairment.

Caution is advised with concomitant use of Valturna with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels as this may lead to increases in serum potassium.

5.8 Renal Artery Stenosis

Aliskiren

No data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Valsartan

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.

5.9 Cyclosporine or Itraconazole

Aliskiren

When aliskiren was given with cyclosporine or itraconazole, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine or itraconazole is not recommended *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Risk of fetal/neonatal morbidity and mortality *[see Warnings and Precautions (5.1)]*
- Head and neck angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Valturna

Valturna has been evaluated for safety in more than 1,225 patients, including over 316 patients for over 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event (including uncontrolled hypertension) occurred in 1.4% of patients treated with Valturna versus 2.7% of patients given placebo.

Adverse events in placebo-controlled trials that occurred in at least 1% of patients treated with Valturna and at a higher incidence than placebo included fatigue (2.6% vs. 1.4%), nasopharyngitis (2.6% vs. 2.2%), diarrhea (1.4% vs 0.9%), upper respiratory tract infection (1.4% vs. 1.1%), urinary tract infection (1.4% vs. 0.6%), influenza (1.1% vs 0.2%), and vertigo (1.1% vs. 0.3%).

Hyperkalemia has been observed as a serum electrolyte abnormality in Valturna clinical trials *[see Warnings and Precautions (5.7)]*.

Aliskiren

Aliskiren has been evaluated for safety in 6,460 patients, including 1,740 treated for longer than 6 months, and 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension, occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.

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 estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: angioedema requiring airway management and hospitalization

Peripheral edema

Blood creatinine increased

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.

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

Ketoconazole: Coadministration of 200 mg twice-daily ketoconazole 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.

Itraconazole: Coadministration of 100 mg itraconazole with 150 mg aliskiren resulted in approximately 5.8-fold increase in C_{max} and 6.5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with itraconazole is not recommended.

Cyclosporine: Coadministration of 200 mg and 600 mg cyclosporine 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 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 drugs are unlikely because of low extent of metabolism *[see Pharmacokinetics – Valsartan (12.3) in the full prescribing information]*.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.1)]

Valturna contains both aliskiren (a direct renin inhibitor) and valsartan (an angiotensin II receptor blocker). When administered during the second or third trimester of pregnancy, drugs that act directly on the renin-angiotensin-aldosterone system can cause fetal and neonatal morbidity and death. Valturna can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin-converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin-aldosterone system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also 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-aldosterone system, has been associated with a potential risk of birth defects in retrospective data.

When pregnancy occurs in a patient using Valturna, discontinue Valturna treatment as soon as possible. Inform the patient about potential risks to the fetus based on the time of gestational exposure to Valturna (first trimester only or later). If exposure occurs beyond the first trimester, perform an ultrasound examination.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, perform serial ultrasound examinations to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Valturna treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to Valturna for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension or support decreased renal function.

No reproductive toxicity studies have been conducted with the combination of aliskiren and valsartan. However, these studies have been conducted for aliskiren as well as valsartan alone *[see Nonclinical Toxicology (13) in the full prescribing information]*.

8.3 Nursing Mothers

It is not known whether aliskiren is excreted in human milk, but aliskiren was secreted in the milk of lactating rats. It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. 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.

8.4 Pediatric Use

Safety and effectiveness of Valturna in pediatric patients have not been established.

8.5 Geriatric Use

In the short-term controlled clinical trials of Valturna, 99 (15.9%) patients treated with Valturna were ≥65 years and 14 (2.2%) were ≥75 years.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Aliskiren

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension occurs, provide supportive treatment.

Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

16 STORAGE

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

Protect from moisture.

Dispense in tight container (USP).

T2010-68

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

called the E-dition. "There is tremendous capacity to link this to other systems and even allow for discussion of standards. The Joint Commission is looking at how to use this capability to link to other documents and systems," says Kenneth Powers, spokesperson for the Joint Commission.

"Some standards that are at the head of the line include medication reconciliation, which is out for field review. Others are still not out for field review as yet. … These include the primary care home initiative and revisions to certain urgent-care standards."

Patrick J. Hurd
Attorney
LeClairRyan
Norfolk, Va.

Although the Joint Commission's standards for ambulatory care were updated in 2009 and 2010, there have been no significant revisions since 2008, says Patrick J. Hurd, attorney at LeClairRyan, a legal strategies and business solution firm in Norfolk, Va. "Some standards that are at the head of the line include medication reconciliation, which is out for field review. Others are still not out for field review as yet. … These include the primary care home initiative and revisions to certain urgent-care standards," he says.

This chapter will focus on changing rules and regulations for those standards that will affect your office processes in such areas as emergency management, hazardous and toxic waste, and human resources.

Environment of Care

Mr. Hurd says physicians are likely to see changes in standards for measuring clinical success. For example, he expects that the Joint Commission will eliminate the reporting of measure-of-success scoring for various elements of performance. "[This is an] encouraging change," he says, noting that it is often

Stricter emergency management guidelines "are all tied to the terrors of the world we live in today, dealing with disaster planning relative to potential terror attacks or bomb threats, and looking at community-planning exercises to be participative with those activities and how they will [evolve]."

Ryan Hellman
Founder and Principal
Hellman & Associates
Wheat Ridge, Colo.

difficult to establish quantifiable measures of effectiveness in implementing these elements. At times, assigning a numerical value becomes arbitrary, and the process can get in the way of providing best care, he says. "While assessment of effectiveness is vital to the improvement of patient care, reducing policies, process, and practices only to that [on] which the success can be assigned a score may eliminate solutions that work well but can only be subjectively analyzed," he explains. "This is not to say that all outcomes measurements should be eliminated."

Areas that Mr. Hurd believes will receive continued attention are smoke-free buildings, grounds, and campuses, and prevention of falls. "Falls continue to be a problem in the office setting, ambulatory surgical centers, dialysis facilities, diagnostic centers, and other healthcare settings," he explains. In addition, physicians may feel the effects of proposed revisions that don't go through the Joint Commissions' standards revision process (e.g., drafting, revising, field review, proposal for comment, etc.). Instead, other guidance from the Joint Commission via its bureau of primary care and its primary care home initiative are

likely to mean changes for practices. "Given the changing dynamics of some healthcare delivery, my overall message is that little will remain static in the months and years to come," Mr. Hurd says.

Emergency Management

While nothing specific is on the horizon for emergency management standards, Mr. Hurd believes that the various natural and man-made disasters around the country—and the lessons learned from responses or lack of responses to these disasters—may prompt additional Joint Commission requirements. Community awareness; better communication strategies, policies, infrastructure and equipment; and improved "downtime" processes in light of increased reliance on EMRs are all ripe for potential action, Mr. Hurd says.

Ryan Hellman, founder and principal of Hellman & Associates of Wheat Ridge, Colo., says stricter emergency management guidelines "are all tied to the terrors of the world we live in today, dealing with disaster planning relative to potential terror attacks or bomb threats, and looking at community-planning exercises to be participative with those activities and how they will [evolve]."

OSHA requires primary care practices to have an emergency action plan and a preparedness plan that identify their critical exposures. Mr. Hellman suggests revising your emergency preparedness plan now in anticipation of these guidelines, which are likely to increase over time. Begin by looking at risk factors in your region. In addition to weather, Mr. Hellman says that physicians should plan for physical injuries, structure fire, building evacuations, power outages, and workplace violence. "Also, how, if at all, will [you deal] with a pandemic communicable disease

outbreak like H1N1 or TB? Have [you] chosen to support any community-based emergency preparedness initiatives?" he asks.

Hazardous and Toxic-waste Materials

Local health departments and the EPA are increasingly examining how medical practices dispose of biohazardous waste; specifically, they are addressing "treatment/drug waste" related to cancer treatments and other progressive drugs, and its disposal, Mr. Hellman says. Although the Joint Commission isn't planning any new standards, it is paying more attention to existing ones.

Mr. Hellman says the Colorado Department of Health is already examining how larger medical facilities are managing hazardous waste materials, including expired drugs and chemo-

OSHA Considering Two New Initiatives

OSHA is collecting information in two areas:

Occupational exposure to infectious diseases in healthcare facilities
The agency issued a Federal Register Notice in May 2010 seeking information to better assess the extent of the problem and better understand ways to protect healthcare workers from infectious diseases. OSHA is now reviewing the information that has been submitted. Some of the areas addressed include these:

- Elements of an effective infection prevention-and-control plan
- Technically and economically feasible methods of controlling exposures to infectious diseases
- Availability and use of vaccination and post-exposure prophylaxis
- How to communicate the hazards of infectious diseases
- Recordkeeping
- Economic impacts and specific impacts on small employers

OSHA is particularly interested in the alleged "incomplete adherence to voluntary infection-control measures in traditional healthcare facilities." Another OSHA concern is "the movement of healthcare delivery from the

based drugs that are hazardous. "The change really is this: We know this waste material is hazardous, and proper identification and disposal can prevent the impact in treatment plants associated with larger facilities and municipalities."

Here are steps you can take now to prepare for increased scrutiny of your biohazardous waste compliance:

■ **Know OSHA's core requirements.** Mr. Hellman says common failures occur when physicians or office managers don't completely understand what OSHA requires in their environments. Beyond guidelines governing blood-borne pathogens—which everyone associates with OSHA regulation in clinics or primary care offices—other regulations apply, including emergency preparedness and hazard communication, he says.

traditional hospital setting, with its greater infrastructure and resources to effectively implement infection-control measures, into more diverse and smaller workplace settings with less infrastructure and fewer resources, but with an expanding worker population."

The illness and injury prevention program rule

According to OSHA's Website, key provisions of such a program may include these:

- A requirement that employers systematically identify and remediate risks to workers—for example, to review relevant safety and health information, and to develop procedures for inspecting their workplaces for safety and health hazards and for investigating accidents
- Methods to provide workers with opportunities to participate in the program
- Provisions requiring that the program be made available to workers so they can understand it and help monitor its implementation
- A requirement that employers implement the program so that it protects workers
- Provisions to prevent employers from denying coverage to workers by misclassifying them as independent contractors

■ **Address universal precaution rules.** Provide gloves for phlebotomy activities, and properly label and manage medical and biohazardous waste materials.

"You will see more push to get more healthcare workers properly vaccinated."

Doug Campos-Outcalt, MD
Clinical Sciences Analyst
Scientific Activities Division
American Academy of Family Physicians

■ **Manage expired vaccines with the provider.** Determine whether the pharmaceutical company has a support program for disposing of expired vaccines. If not, contact your local health department to learn the procedures. The same rule applies if you have boxes of expired drug samples.

Needle sticks will continue to be a common hazard in physician offices. "Evaluate what the blood-borne pathogen standards require you to do for alternative-delivery mechanisms, for needles or protective devices that protect the needle following [use]," Mr. Hellman says. According to OSHA standards and guidelines, an exposure control plan must be in place in all medical practices where needles are used.

He recommends the following:

—Develop a written plan that addresses the regulation's essential elements
—Evaluate the plan annually
—Ensure that your staff document exposures to needle sticks and transfer that information to a needle-stick log

"Track any type of workplace injury so you can look at it collectively as an office and see how that can be prevented. If you don't track it ... it tends to be forgotten," Mr. Hellman says.

Human Resources

Human resource issues are likely to play an even bigger role in your office by 2015. There will be issues regarding scope of

practice—i.e., who can do what—which will be largely determined by state rules, says Doug Campos-Outcalt, MD, clinical sciences analyst for the AAFP's Scientific Activities Division and associate chair of the Department of Family and Community Medicine, University of Arizona College of Medicine, Phoenix. He says vaccinating healthcare workers will become an even higher priority. "You will see more push to get more healthcare workers properly vaccinated," he says.

The amount of change alone can lead to employee issues. Any work environment under pressure or understaffed will be at increased risk for employee fatigue and stress. Be alert to symptoms of employee burnout, fatigue, or sleep deprivation. Does a nurse need a personal day to recharge after a draining week? Don't wait for a staff member to ask for relief.

It will also be essential for you to consider the physical fitness of your staff. "You want the people you hire to be physically fit to manage the tasks the office is doing. They carry higher risks," Mr. Hellman says. He advises evaluating your job descriptions and reviewing the physical demands of each in order to establish minimum physical-function requirements. "Working with your occupational physician, you can develop a functional-capacity evaluation. … This will help ensure your new hires are capable of performing the required physical tasks," he says. "This is particularly important for positions that require significant patient-movement efforts."

Infection Prevention and Control

The H1N1 flu last year was a wake-up call to many physician practices to show how essential it is to have an infectious disease plan in place. While there is still much to learn about infection prevention, education, and practices in the office setting, these issues are likely to become increasingly important. "MRSA, sep-

sis, and other critical infectious disease problems may result in further revisions to best practices, training and education, and other aspects of prevention and control," Mr. Hurd says. He points out that state licensing boards are seeing more complaints

"Continuing best practices for infection prevention control really needs to be on the forefront of [physicians'] minds."

Ryan Hellman
Founder and Principal
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Wheat Ridge, Colo.

of poor reporting of culture results and inadequate or inappropriate antibiotic prescribing. As a result, he says we should expect to see a focus on assuring timely reporting of culture results and see timely and accurate diagnosis and treatment based on those results.

Key Compliance Standards

Make sure you manage the compliance requirements for the following regulations that apply to primary care offices, according to Hellman & Associates, which offers environmental health and safety management services:

OSHA's 29 CFR* 1910.1030, Blood-borne Pathogens

OSHA's 29 CFR 1910.38, Emergency Action Plans

OSHA's 29 CFR 1910.39, Fire Prevention Plans

OSHA's 29 CFR 1910.1200, Hazard Communication

OSHA's 29 CFR 1910.132, Personal Protection Equipment

OSHA's 29 CFR 1910.120, Hazardous Waste Operations and Emergency Response Standards, When Applicable

**CFR: Code of Federal Regulations.*

Practices that are now providing face masks and other standard methods for control of contact will probably need to do even more to be prepared for clusters of infections. "Continuing best practices for infection prevention control really need to be at the forefront of [physicians'] minds," Mr. Hellman says.

Keeping Up

To stay current on standards for your practice, sign up for OSHA's comprehensive biweekly newsletter, *QuickTakes*, at *http://www.osha.gov/pls/quicktakes/e_subscribe.subscribe*. In addition, check out the Joint Commission at *http://www.jcrinc.com*, and the Centers for Disease Control and Prevention at *http://www.cdc.gov*. Finally, read trade journals or hire a third party to help. Hellman Associates, for example, charges $200 to $300 per month for physician offices and $500 to $800 for larger care/outpatient surgical centers (based on a two-year contract) to write plans, develop and deliver training, provide updates, and walk through a practice to identify hazards and help manage its compliance and loss-prevention program.

The key is making sure you're keeping up with current OSHA regulations (see "OSHA Considering Two New Initiatives"). "It requires an act of Congress to change the OSHA act. For OSHA to promulgate and publish a new regulation is a very challenging task that just doesn't happen very often," Mr. Hellman says. "The regulations that are on the books now are the ones physicians need to focus on; and if there is a change, believe me, because of the necessary steps to make a change, there will be a lot of information published … in trade journals."

Correction

In the Sept/Oct 2010 *Doctor's Digest's* issue, "Top-tier Communication," two quotes were misattributed. The quote, "Instead of engaging patients and preaching to [your patients] …don't interrupt them. Sit down, use open-ended questions, listen actively, and be sincere," that appears on p. 29 and highlighted on p. 28 should have been attributed to Richard F. Multack, DO, not Craig M. Wax, DO. The quote "It's also a clear sign that your communication skills need work," on p. 29 should have been attributed to Dr. Wax, not Dr. Multack.