Aliskiren (Tekturna)

Manufacturer: Novartis, East Hanover, NJ

Indication: Aliskiren is a potent, orally active, potent nonpeptide direct renin inhibitor for the treatment of hypertension. Aliskiren is known as Rasilez in Europe.

Drug Class: This salt is chemically described as \((2S,4S,5S,7S)-(2\text{-carbamoyl-2-methylpropyl})-5\text{-amino-4-hydroxy-2,7-di-isopropyl} 8-[4\text{-meth-oxy-3-(3-methoxy-propoxy)-phenyl}]\text{-octanamide hemifumarate.}

Uniqueness of Drug: The tablet is a once-daily medication used as monotherapy, or it can be taken in combination with other antihypertensive agents. In clinical trials, aliskiren demonstrated significant blood pressure reductions for 24 hours.

Boxed Warning: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin–angiotensin system (RAS) can cause injury and even death to the developing fetus. When pregnancy is detected, aliskiren should be discontinued as soon as possible.

Warnings:

Pregnancy: Drugs that act directly on the RAS can cause fetal and neonatal morbidity and death when they are administered to pregnant women. Several dozen cases have been reported throughout the world in patients who were taking angiotensin-converting enzyme (ACE)–inhibitors. Aliskiren should be discontinued in pregnant women as soon as pregnancy is suspected or confirmed.

Drugs that act directly on the RAS during the second and third trimesters of pregnancy have been associated with fetal and neonatal hypotension, neonatal hypoplasia of the skull, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; in this setting, oligohydramnios has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences resulted from exposure to the drug.

These adverse effects do not appear to be a result of intrauterine drug exposure that was limited to the first trimester. Women whose embryo or fetus has been exposed to a renin inhibitor only during the first trimester should be informed about aliskiren. Nonetheless, when patients become pregnant, physicians should advise patients to discontinue the use of aliskiren as soon as possible.

In rare instances (probably less often than one in 1,000 pregnancies), no alternative to a drug acting on the RAS is found; that is, there are no other RAS inhibitors on the market. In these rare cases, pregnant women should be apprised of the potential hazards to the fetus, and serial ultrasound examina-

Pharmaceutical Approval Update

Marvin M. Goldenberg, PhD, RPh, MS

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Hypotension: In patients with uncomplicated hypertension...
who received aliskiren alone, an excessive drop in blood pressure was rarely seen (in 0.1%). Hypotension was also infrequent during combination therapy with other antihypertensive agents (less than 1%). In patients with an activated RAS, such as those with volume or salt depletion (i.e., as in those receiving high doses of diuretics), symptomatic hypotension can occur after aliskiren therapy is initiated. This condition should be corrected before aliskiren is administered, or treatment should start with the patient under close medical supervision.

If blood pressure drops excessively, the patient should be placed in the supine position. If necessary, the patient should receive an intravenous (IV) infusion of normal saline solution. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty after blood pressure has been stabilized.

Precautions: Patients were excluded from clinical trials of aliskiren involving hypertension:

- if they had had more than moderate renal dysfunction (i.e., creatinine, 1.7 mg/dl for women and 2 mg/dl for men, or an estimated glomerular filtration rate of less than 30 ml/minute).
- if they had a history of dialysis, nephritic syndrome, or renovascular hypertension.

Caution should be exercised in these patients because of the paucity of safety information about the drug and because of the potential for other drugs acting on the RAS to cause elevated serum creatinine and blood urea nitrogen (BUN).

Hyperkalemia: Increases in serum potassium levels above 5.5 mEq/L were infrequent with aliskiren alone (0.9%), compared with 0.6% for placebo. However, when used in combination with an ACE-inhibitor in diabetic patients, elevated serum potassium levels occurred more frequently (5.5% of the time).

Dosage and Administration: The usual recommended starting dose of aliskiren is 150 mg once daily. For patients with inadequately controlled blood pressure, the daily dose may be increased to 300 mg. Doses above 300 mg did not bring about an increased blood pressure response but did result in an increased rate of diarrhea. The antihypertensive effect of a given dose is usually attained by two weeks 85% to 90% of the time.

Aliskiren may be administered with other antihypertensive agents. Most data on exposure to date come from studies of diuretics and an angiotensin-receptor blocker, such as valsartan (Diovan, Novartis); the drugs together have a greater effect at their maximum recommended doses than either drug alone. It is not known whether additive effects are present when aliskiren is used with ACE-inhibitors or beta blockers.

No initial dosage adjustment is required for elderly patients, patients with mild-to-severe renal impairment, or patients with mild-to-severe hepatic insufficiency. Care should be exercised in patients with severe renal impairment, because clinical experience with such patients is limited.

In terms of meals, patients should establish a routine pattern for taking aliskiren. High-fat meals substantially decrease the drug’s absorption.

Commentary: One in four American adults has hypertension; this puts them at an increased risk of cardiovascular disease, currently the world’s number one killer. Despite more than 100 different antihypertensive drugs on the market, almost 70% of Americans with high blood pressure are unable to control it. Many patients use two or three drugs and still struggle to get their blood pressure down. Physicians need more weapons in their armamentarium, and aliskiren may offer a novel therapeutic option for treating hypertension.

Aliskiren is the first in a new class of hypertension drugs known as direct renin inhibitors. The drug solves a puzzle that has vexed the industry for more than 30 years: how to block renin, a kidney enzyme that raises blood pressure, at its origin. The hope is that aliskiren might ultimately reduce both cardiovascular complications and the progression of kidney failure in hypertensive patients. Unlike existing antihypertensive drugs such as ACE-inhibitors, aliskiren suppresses renin at the beginning of the process, lowering plasma renin activity. This approach is one of the most effective ways of reducing the progression of kidney disease.

Once-daily administration provides an advantage in helping to improve patient compliance. The most important benefit is sustained blood pressure control over 24 hours, with fewer side effects than in existing treatments.


Conivaptan HCl Injection (Yaprisol)

Manufacturer: Astellas Pharma, Deerfield IL

Indication: Conivaptan HCl injection is indicated for the treatment of euvolemic hyponatremia in hospitalized patients (e.g., the syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders). This product is not indicated for patients with congestive heart failure.

Drug Class: Conivaptan is a nonpeptide dual antagonist of arginine vasopressin V1A and V2 receptors. Chemically, it is represented as [1,1’-biphenyl]-2-carboxamide, N-[4-[(4,5-dihydro-2-methylimidazo[4,5-d][1]benzazepin-6(1H)-yl)carbonyl]phenyl]-, monohydrochloride. Its molecular weight is 535.04.

Uniqueness of Product: This is the first drug specifically indicated for the treatment of both euvolemic and hypervolemic hyponatremia. These potentially life-threatening conditions occur when the body’s blood sodium levels fall significantly below normal.

Precautions:

Hyponatremia and Congestive Heart Failure. The safety of conivaptan in hyponatremic patients with underlying congestive heart failure has not been established.

Overly Rapid Correction of Serum Sodium Levels: An overly rapid elevation in serum sodium levels (more than 12 mEq/L per 24 hours) may result in serious sequelae. In controlled clinical trials, about 9% of patients who received IV conivaptan in doses of 20 to 40 mg/day met the laboratory criteria for the overly rapid correction of sodium, but none of the patients had permanent neurological sequelae.

Osmotic demyelination syndrome was not observed in clinical studies of conivaptan, but it was reported after low serum
sodium levels were quickly corrected. Serum sodium concentrations and neurological status should be monitored appropriately while conivaptan is being administered. If serum sodium levels rise at an undesirably rapid rate, conivaptan therapy should be discontinued. If the sodium level continues to rise, the injection should not be resumed.

If hyponatremia persists or recurs after the initial discontinuation of conivaptan HCl injection because of an undesirably rapid rate in the rise of serum sodium levels, and if the patient has no evidence of neurological sequelae as a result of this rapid elevation, conivaptan may be resumed at a reduced dose.

**Hepatic Impairment:** The use of conivaptan in patients with hepatic impairment (e.g., ascites, cirrhosis, or portal hypertension) has not been systematically evaluated.

Increased systemic exposures after oral administration of conivaptan have been seen in patients with stable cirrhosis and moderate hepatic impairment. In study subjects without hepatic function impairment, IV conivaptan, when compared with the oral formulation, resulted in higher exposure to the agent. Caution should be used in patients with hepatic impairment.

**Renal Impairment:** The effect of renal impairment on the elimination of conivaptan after IV administration has not been evaluated. However, following oral administration of conivaptan, the area-under-the-curve (AUC) concentration for conivaptan was up to 80% higher after a single oral dose and 35% higher with repeated oral dosing in patients with renal impairment (creatinine clearance below 60 ml/minute per 1.73 m²), compared with subjects with normal renal function. In study subjects without renal function impairment, IV conivaptan resulted in higher conivaptan exposure than did oral conivaptan. Caution should be used in patients with renal impairment.

**Injection-Site Reactions:** Conivaptan may cause significant injection-site reactions, even when rates of dilution and infusion are correct. Conivaptan must be administered only when it is properly prepared and diluted via large veins, and the infusion site should be rotated every 24 hours.

**Dosage and Administration:** Conivaptan HCl injection is indicated for IV use only. Injecting through large veins and changing the infusion site every 24 hours are recommended to minimize the risk of vascular irritation. Therapy should begin with a loading dose of 20 mg IV administered over 30 minutes.

The loading dose should be followed by 20 mg of conivaptan, administered in a continuous IV infusion over a period of 24 hours. After the first day of treatment, conivaptan should be given for an additional one to three days in a continuous infusion of 20 mg/day.

If serum sodium levels do not rise at the desired rate, the dose may be titrated upward to 40 mg daily, again administered in a continuous IV infusion. The total duration of the infusion after the loading dose should not exceed four days.

Patients receiving the injection must undergo frequent monitoring of serum sodium levels and volume status. An overly rapid rise in serum sodium (more than 12 mEq/L per 24 hours) may result in serious sequelae.

If sodium levels rise too rapidly at an undesirable rate, the injection should be discontinued, and sodium levels and neurological status should be carefully monitored.

If serum sodium levels continue to rise, conivaptan should not be resumed.

If hyponatremia persists or recurs, and if the patient has had no evidence of neurological sequelae from the rapid rise in serum sodium, the injection may be resumed at a reduced dose.

**Overly Rapid Correction of Serum Sodium:** If hypovolemia or hypotension develops while the patient is receiving conivaptan, therapy with this agent should be discontinued and volume status and vital signs should be frequently monitored. After the patient is again euvoletic and is no longer hypotensive, conivaptan may be resumed at a reduced dose if the patient remains hyponatremic.

**Commentary:** Hyponatremia affects up to 4% of hospitalized patients in the U.S. each year. Although many hyponatremic patients have no symptoms, severe cases are medical emergencies that can result in swelling of the brain, respiratory arrest, and death. Hypervolemic hyponatremia, which occurs when the total body water increase is greater than the body’s sodium levels, results in edema and is often associated with congestive heart failure, severe liver disease, and kidney failure.

In the treatment of hyponatremia associated with congestive heart failure, conivaptan is indicated only in patients for whom the expected benefit of raising serum sodium levels outweighs the increased risk of adverse events. Caution should be used if patients have liver or kidney impairment.

This product provides physicians with an important new treatment option for patients with hyponatremia, a condition that is often serious.

More information on conivaptan is available in the Drug Forecast article in the March 2007 issue of P&T.

**Source:** www.astellas.us/docs/vaprisol.pdf

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**Glucosamine/Chondroitin/Primorine (Relamine) Tablets**

**Manufacturer:** Zylera, Research Triangle Park, NC

**Indication:** A new tablet consisting of glucosamine 400 mg, chondroitin 300 mg, and primorine 425 mg reduces the inflammation, joint swelling, and pain associated with osteoarthritis and may slow its onset and progression.

**Drug Class:** Glucosamine is a form of an amino sugar that is believed to play a role in cartilage formation and repair. Chondroitin sulfate is part of a large-protein molecule that gives cartilage elasticity. Primorine, a novel carbonyl-trapping combination, is used to reduce the toxic effects of highly reactive carbonyl-containing compounds, which are produced under conditions of oxidative stress.

**Uniqueness of Drug:** The combination tablet is the first prescription product that contains these three pharmaceutical-quality constituents. Glucosamine, an amino monosaccharide, is present in chitin, glycoproteins, and glycosaminoglycan (GAGs), such as hyaluronic acid and heparin sulfate. Chondroitin belongs to the GAG family and is composed of linear repeating units containing D-galactosamine and D-glucuronic acid. Primorine is a blend of para-aminobenzoic acid, vitamin E, and alpha-lipoic acid.
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**Precautions:** Glucosamine increases insulin resistance in normal and experimentally diabetic animals. In these animals, IV glucosamine significantly decreases the rate of glucose uptake in skeletal muscle; however, in animals given oral glucosamine, this activity was not observed.

For patients with type-2 diabetes and for patients who are overweight and have problems with glucose tolerance, blood sugar concentrations should be carefully monitored if they are taking glucosamine supplements. Because of insufficient safety data, children, pregnant women, and nursing mothers should avoid using glucosamine.

It is theoretically possible that chondroitin sulfate might have antithrombotic activity; therefore, patients taking warfarin (Coumadin, Bristol-Myers Squibb) and those with hemophilia should exercise caution in using chondroitin.

Patients who need to restrict their salt intake should use salt-free preparations if they take chondroitin.

**Dosage and Administration:** The usual adult dose is two tablets twice daily as directed by a physician.

**Commentary:** Arthritis is one of the most debilitating illnesses in the U.S., and it is the nation's leading cause of disability. There is a significant unmet medical need for safe and effective therapies for the treatment of the pain and inflammation associated with arthritis and osteoarthritis in particular.

Osteoarthritis, the most common form of arthritis, is characterized by chronic and often disabling pain and stiffness of one or more joints, particularly those of the fingers, spine, hips, knees, and feet. According to the Arthritis Foundation, arthritis results in 39 million physician visits, with more than one-half million hospitalizations. Osteoarthritis limits everyday activities such as walking, dressing, and bathing for more than seven million Americans.

Although the glucosamine/chondroitin/primorine tablet appears to be effective for osteoarthritis, patients in clinical trials had been treated for only six months. Thus, additional evidence is needed to confirm that longer-term treatment for at least one to two years can maintain the agent’s effectiveness.

**Source:** [www.zylera.com/pdfs/RELAMINE-package-insert.pdf](http://www.zylera.com/pdfs/RELAMINE-package-insert.pdf)