

POLICY & PRACTICE

Cardio Surgery Network Launches

The Cardiothoracic Surgery Investigations Network is getting under way, with the designation of the International Center for Health Outcomes and Innovation Research at Columbia University as the coordinating arm of the new seven-site network. The Columbia center received \$23 million from the National Heart, Lung, and Blood Institute to design trials and protocols, to coordinate clinical care, to review data, and to monitor the seven sites: New York–Presbyterian Hospital/Columbia University, New York;

Duke University, Durham, N.C.; the Cleveland Clinic; Albert Einstein College of Medicine/Montefiore Medical Center, New York; Emory University, Atlanta; University of Virginia, Charlottesville; and Montreal Heart Institute. The network was established by the National Institutes of Health and the Canadian Institutes of Health Research to promote the use of evidence-based medicine in surgery, and to quickly evaluate major innovations on a large-scale basis. “This cardiothoracic surgery network is important because it will help answer the

unanswered questions about which patients may benefit most from heart surgeries and when new technologies are appropriate or not,” said Dr. Eric A. Rose, surgeon-in-chief at New York–Presbyterian and lead investigator for the network, in a statement. NHLBI will award a total of \$35 million in grants to the network participants over the next 5 years.

DES Might Be Barred in England

The use of drug-eluting stents could be barred in England and Wales if a draft guidance by the U.K. National Institute for Health and Clinical Excellence is given final approval. NICE makes clinical effec-

tiveness recommendations for the National Health Service. The institute found that drug-eluting stents are not cost effective when compared with bare-metal stents, and said that hospitals participating with the NHS should not implant the devices. Currently, NHS hospitals pay for DES implantation in patients in whom the target artery has an internal diameter smaller than 3 mm or a lesion longer than 15 mm. The guidance was open for public comment through the end of August, and, if approved, would go into effect in January 2008.

Drug Premium About \$25 in 2008

The Centers for Medicare and Medicaid Services said that Medicare beneficiaries will pay about \$25 a month for their Part D pharmaceutical coverage in 2008. This is about a \$3 per month increase over the average premium in 2007, but still 40% lower than what had been projected when the program was established in 2003, according to CMS. The premiums for those who get their benefits through private Medicare Advantage plans will be about \$14, according to CMS. The agency said that almost 10 million low-income beneficiaries are having their premiums subsidized by the federal government. Because Part D is sketching out to cost 30% less in the first 10 years than had been estimated, President Bush's 2009 budget will be retooled to reflect the decline, according to CMS.

Small Practices Decline

Some physicians are shying away from practicing in solo and two-physician practices, according to a new report from the Center for Studying Health System Change. Although these small practices are still the most common practice arrangements, researchers saw a shift between 1996-1997 and 2004-2005 from solo and two-person practices to midsized, single-specialty groups of 6-50 physicians. The percentage of physicians who practiced in solo and two-person practices fell from 40.7% in 1996-1997 to 32.5% in 2004-2005. During the same time period, the percentage of physicians practicing in midsized groups rose from 13.1% to 17.6%. The biggest declines in physicians' choosing small practices have come from medical specialists and surgical specialists, whereas the proportion of primary care physicians in small practices has remained steady at about 36%. The report's findings are based on the group's nationally representative Community Tracking Study Physician Survey.

AMA, PhRMA Big Spenders

Halfway through 2007, the American Medical Association and the Pharmaceutical Research and Manufacturers of America were among the bigger spenders when it came to lobbying Capitol Hill for their causes. The AMA spent \$10.3 million and PhRMA \$10.7 million in the first 6 months of the year, according to lobbying disclosure reports filed with the Senate's public records office. By comparison, the American Heart Association spent \$615,790, the American Academy of Family Physicians spent \$1.2 million, and the American College of Physicians spent \$419,575.

—Alicia Ault

VAPRISOL®
(conivaptan hydrochloride injection)BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

VAPRISOL is indicated for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients.

Important Limitation:

VAPRISOL is not indicated for the treatment of congestive heart failure. VAPRISOL should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the increased risk of adverse events for heart failure patients. (See PRECAUTIONS AND ADVERSE REACTIONS.)

CONTRAINDICATIONS

VAPRISOL is contraindicated in patients with hypovolemic hyponatremia.

The coadministration of VAPRISOL with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. (See PRECAUTIONS: Drug Interactions for details and other important considerations.)

PRECAUTIONS

Congestive Heart Failure: The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in patients with underlying congestive heart failure. (See ADVERSE REACTIONS.)

Overly Rapid Correction of Serum Sodium: An overly rapid increase in serum sodium concentration (>12 mEq/L/24 hours) may result in serious sequelae. In controlled clinical trials of VAPRISOL, about 9% of patients who received VAPRISOL in doses of 20-40 mg/day IV met laboratory criteria for overly rapid correction of serum sodium, but none of these patients had permanent neurologic sequelae. Although not observed in the clinical studies with VAPRISOL, osmotic demyelination syndrome has been reported following rapid correction of low serum sodium concentrations. Serum sodium concentration and neurologic status should be monitored appropriately during VAPRISOL administration, and VAPRISOL administration should be discontinued if the patient develops an undesirably rapid rate of rise of serum sodium. If the serum sodium concentration continues to rise, VAPRISOL should not be resumed. If hyponatremia persists or recurs (after initial discontinuation of VAPRISOL for an undesirably rapid rate of rise of serum sodium concentration), and the patient has had no evidence of neurologic sequelae of rapid rise in serum sodium, VAPRISOL may be resumed at a reduced dose.

Hepatic Impairment: The use of VAPRISOL in patients with hepatic impairment (including 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. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without hepatic function impairment. Caution should be used when administering VAPRISOL to patients with hepatic impairment.

Renal Impairment: The effect of renal impairment on the elimination of conivaptan after intravenous administration has not been evaluated. However, following oral administration of conivaptan, the AUC for conivaptan was up to 80% higher after a single oral dose and 35% higher with repeated oral dosing in patients with renal impairment (CL_{CR} 60 mL/min/1.73 m²) as compared to those with normal renal function. Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without renal function impairment. Caution should be used when administering VAPRISOL to patients with renal impairment.

Injection Site Reactions: Conivaptan may cause significant injection site reactions, even with proper dilution and infusion rates. (See ADVERSE REACTIONS.) Conivaptan must only be administered when properly prepared and diluted (see Preparation) via large veins, and the infusion site should be rotated every 24 hours. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions

(See CLINICAL PHARMACOLOGY: Drug-Drug Interactions.)

CYP3A4: Conivaptan is a substrate of CYP3A4. Coadministration of VAPRISOL with CYP3A4 inhibitors could lead to an increase in conivaptan concentrations. The consequences of increased conivaptan concentrations are unknown. Concomitant use of VAPRISOL with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated.

Conivaptan is a potent inhibitor of CYP3A4. VAPRISOL may increase plasma concentrations of coadministered drugs that are primarily metabolized by CYP3A4. In clinical trials of oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in patients who were also receiving a CYP3A4-metabolized HMG-CoA reductase inhibitor. Concomitant use of VAPRISOL with drugs that are primarily metabolized by CYP3A4 should be closely monitored or the combination should be avoided. If a clinical decision is made to discontinue concomitant medications at recommended doses, allow an appropriate amount of time following the end of VAPRISOL administration before resuming these medications.

Digoxin: Coadministration of digoxin, a P-glycoprotein substrate, with oral conivaptan resulted in a reduction in clearance and increases in digoxin C_{max} and AUC values. Therefore, if digoxin is administered with VAPRISOL, the clinician should be alert to the possibility of increases in digoxin levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of 3, 10 or 30 mg/kg/day in males and 1, 3 or 10 mg/kg/day in females by gavage. Rats were given oral doses of 0.3, 1, 3 or 10 mg/kg/day in males and 1, 3, 10 or 30 mg/kg/day in females by gavage. No increased incidence of tumors was observed at doses up to 30 mg/kg/day in mice (6 times human systemic exposure of an IV bolus of 20 mg on Day 1 followed by IV infusion 40 mg/day for 3 days based on AUC comparison) or rats (2 times human systemic exposure of an IV bolus of 20 mg on Day 1 followed by IV infusion 40 mg/day for 3 days based on AUC comparison).

Conivaptan was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, in human peripheral blood lymphocytes, or *in vivo* rat micronucleus assay.

In fertility studies after 4 weeks treatment by intravenous bolus at 0.5, 1.25 or 2.5 mg/kg/day, male fertility was unaffected. However, in females given IV bolus conivaptan 15 days before mating through gestation day 7 there was prolonged diestrus, decreased fertility and increased pre- and post-implantation loss at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Pregnancy: **Pregnancy Category C**
Conivaptan has been shown to have adverse effects on the fetus when given to animals during pregnancy at systemic exposures less than those achieved at a therapeutic dose based on AUC comparisons. There are no adequate and well-controlled studies in pregnant women. VAPRISOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The patient should be apprised of the potential hazard to the fetus. Conivaptan crosses the placenta and is found in fetal tissue in rats. Fetal tissue levels were <10% of maternal plasma concentrations while placental levels were 2.2-fold higher than maternal plasma concentrations indicating that conivaptan can be transferred to the fetus. Conivaptan that is taken up by fetal tissue is slowly cleared, suggesting that fetal accumulation is possible. Milk levels were up to 3 times higher than maternal plasma levels following an intravenous dose of 1 mg/kg (systemic exposures less than therapeutic based on AUC comparisons).

In female rats given an intravenous bolus dose of 0.5, 1.25 or 2.5 mg/kg/day conivaptan hydrochloride before mating and continuing through gestation day 7, prolonged diestrus, decreased fertility and increased pre- and post-natal implantation loss occurred at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

In pregnant rats given intravenous doses of 0.5, 1.25 or 2.5 mg/kg/day from gestation day 7 through 17 (organogenesis), no significant maternal or fetal effects were observed at systemic exposures less than therapeutic exposure based on AUC comparisons.

Pregnant rats were administered intravenous conivaptan hydrochloride at a dose of 2.5 mg/kg/day (systemic exposures less than therapeutic based on AUC) from gestation day 7 through lactation day 20 (weaning), and the pups showed decreased neonatal viability, weaning indices, delayed growth and physical development (including sexual maturation), and delayed reflex development. No discernible changes were seen in pups from dams administered conivaptan hydrochloride at 0.5 or 1.25 mg/kg/day from this same period. No maternal adverse effects were seen with conivaptan hydrochloride administration (0.5, 1.25, or 2.5 mg/kg/day from gestation day 7 through lactation day 20; systemic exposures less than therapeutic dose based on AUC comparisons). In pregnant rabbits given intravenous doses of 3, 6 or 12 mg/kg/day from gestation day 6 through 18 (organogenesis) there were no fetal findings; however, maternal toxicity was observed in all groups (systemic exposures less than the therapeutic dose.)

In bolus intravenous postnatal rat studies, decreased neonatal viability, decreased weaning indices, delayed growth/physical development and delayed sexual maturation of offspring were observed at 2.5 mg/kg/day (systemic exposures less than the therapeutic dose).

Labor and Delivery
The effect of conivaptan on labor and delivery in humans has not been studied. Conivaptan hydrochloride delayed delivery in rats dosed orally at 10 mg/kg/day by oral gavage (systemic exposures equivalent to the therapeutic dose based on AUC comparisons.) Administration of conivaptan hydrochloride at 2.5 mg/kg/day intravenously increased peripartum pup mortality (systemic exposures were less than the therapeutic dose based on AUC comparisons). These effects may be associated with conivaptan activity on oxytocin receptors in the rat. The relevance to humans is unclear.

Lactating Women
It is not known whether conivaptan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VAPRISOL is administered to a lactating woman. Conivaptan is excreted in milk and detected in neonates when given by intravenous administration to lactating rats. Milk levels of conivaptan in rats reached maximal levels at 1 hour post dose following intravenous administrations and were up to 3 times greater than maternal plasma levels. Administration of conivaptan hydrochloride at 2.5 mg/kg/day intravenously increased peripartum pup mortality; systemic exposures were less than the therapeutic dose based on AUC comparisons.

Pediatric Use
The safety and effectiveness of VAPRISOL in pediatric patients have not been studied.

Geriatric Use
In clinical studies of intravenous VAPRISOL administered as a 20 mg IV loading dose followed by 20 mg/day or 40 mg/day IV for 2 to 4 days, 89% (20 mg/day regimen) and 60% (40 mg/day regimen) of participants were greater than or equal to 65 years of age and 60% (20 mg/day regimen) and 40% (40 mg/day regimen) were greater than or equal to 75 years of age. In general, the adverse event profile in elderly patients was similar to that seen in the general study population.

ADVERSE REACTIONS
The most common adverse reactions reported with VAPRISOL administration were infusion site reactions. In studies in patients and healthy volunteers, infusion site reactions occurred in 73% and 63% of subjects treated with VAPRISOL 20 mg/day and 40 mg/day, respectively, compared to 4% in the placebo group. Infusion site reactions were the most common type of adverse event leading to discontinuation of VAPRISOL. Discontinuations from treatment due to infusion site reactions were more common among VAPRISOL-treated patients (3%) than among placebo-treated patients (0%). Some serious infusion site reactions did occur. (See DOSAGE AND ADMINISTRATION in full Prescribing Information.)

The adverse reactions presented in Table 1 are derived from 72 healthy volunteers and 243 patients with euvolemic or hypervolemic hyponatremia who received VAPRISOL 20 mg IV as a loading dose followed by 40 mg/day IV for 2 to 4 days, from 37 patients with euvolemic or hypervolemic hyponatremia who received VAPRISOL 20 mg IV as a loading dose followed by 20 mg/day IV for 2 to 4 days in an open-label study, and from 40 healthy volunteers and 29 patients with euvolemic or hypervolemic hyponatremia who received placebo. The adverse reactions occurred in at least 5% of patients treated with VAPRISOL and at a higher incidence for VAPRISOL-treated patients than for placebo-treated patients.

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Table 1
IV VAPRISOL: Adverse Reactions Occurring in ≥5% of Patients or Healthy Volunteers and VAPRISOL Incidence > Placebo Incidence Hyponatremia and Healthy Volunteer Studies

Term	Placebo N=69 n (%)	20 mg N=37 n (%)	40 mg N=315 n (%)
Blood and lymphatic system disorders			
Anemia NOS	2 (3%)	2 (5%)	18 (6%)
Cardiac disorders			
Atrial fibrillation	0 (0%)	2 (5%)	7 (2%)
Gastrointestinal disorders			
Constipation	2 (3%)	3 (8%)	20 (6%)
Diarrhea NOS	0 (0%)	0 (0%)	23 (7%)
Nausea	3 (4%)	1 (3%)	17 (5%)
Vomiting NOS	0 (0%)	2 (5%)	23 (7%)
General disorders and administration site conditions			
Edema peripheral	1 (1%)	1 (3%)	24 (8%)
Infusion site erythema	0 (0%)	0 (0%)	18 (6%)
Infusion site pain	1 (1%)	0 (0%)	16 (5%)
Infusion site phlebitis	1 (1%)	19 (51%)	102 (32%)
Infusion site reaction	0 (0%)	8 (22%)	61 (19%)
Pyrexia	0 (0%)	4 (11%)	15 (5%)
Thirst	1 (1%)	1 (3%)	19 (6%)
Infections and infestations			
Pneumonia NOS	0 (0%)	2 (5%)	7 (2%)
Urinary tract infection NOS	2 (3%)	2 (5%)	14 (4%)
Injury, poisoning and procedural complications			
Post procedural diarrhea	0 (0%)	2 (5%)	0 (0%)
Investigations			
Electrocardiogram ST segment depression	0 (0%)	2 (5%)	0 (0%)
Metabolism and nutrition disorders			
Hypokalemia	2 (3%)	8 (22%)	30 (10%)
Hypomagnesemia	0 (0%)	2 (5%)	6 (2%)
Hyponatremia	1 (1%)	3 (8%)	20 (6%)
Nervous system disorders			
Headache	2 (3%)	3 (8%)	32 (10%)
Psychiatric disorders			
Confusional state	2 (3%)	0 (0%)	16 (5%)
Insomnia	0 (0%)	2 (5%)	12 (4%)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	3 (4%)	2 (5%)	3 (1%)
Skin and subcutaneous tissue disorders			
Pruritus	0 (0%)	2 (5%)	2 (1%)
Vascular disorders			
Hypertension NOS	0 (0%)	3 (8%)	20 (6%)
Hypotension NOS	2 (3%)	3 (8%)	16 (5%)
Orthostatic hypotension	0 (0%)	5 (14%)	18 (6%)

Adapted from MedDRA version 6.0

Although a dose of 80 mg/day of intravenous VAPRISOL was also studied, it was associated with a higher incidence of infusion site reactions and a higher rate of discontinuation due to adverse events than was the 40 mg/day intravenous VAPRISOL dose. The maximum daily dose of VAPRISOL (after the loading dose) is 40 mg/day.

Congestive Heart Failure

In clinical trials where intravenous VAPRISOL was administered to 79 hypervolemic hyponatremic patients with underlying heart failure and intravenous placebo administered to 10 patients, adverse cardiac failure events, atrial dysrhythmias, and sepsis occurred more frequently among patients treated with VAPRISOL (32%, 5% and 8% respectively) than among patients treated with placebo (20%, 0% and 0% respectively). The number of heart failure patients with hypervolemic hyponatremia who have been treated with intravenous VAPRISOL is too small to establish safety in this specific population. VAPRISOL should only be used in patients with underlying heart failure when the expected clinical benefit of raising serum sodium outweighs the risk of adverse events.

In ten Phase 2/pilot heart failure studies, VAPRISOL did not show statistically significant improvement for heart failure outcomes, including such measures as length of hospital stay, changes in categorized physical findings of heart failure, change in ejection fraction, change in exercise tolerance, change in functional status, or change in heart failure symptoms, as compared to placebo. In these studies, the changes in the physical findings and heart failure symptoms were no worse in the VAPRISOL-treated group (N=818) compared to the placebo group (N=290).

DRUG ABUSE AND DEPENDENCE

VAPRISOL does not have known potential for psychogenic drug abuse and/or dependence.

OVERDOSAGE

Although no data on overdosage in humans are available, VAPRISOL has been administered as a 20 mg loading dose on Day 1 followed by continuous infusion of 80 mg/day for 4 days in hyponatremia patients and up to 120 mg/day for 2 days in CHF patients. No new toxicities were identified at these higher doses, but adverse events related to the pharmacologic activity of VAPRISOL, e.g. hypotension and thirst, occurred more frequently at these higher doses.

In case of overdose, based on expected exaggerated pharmacological activity, symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is recommended.

Rx only

Marketed by:

Astellas Pharma US, Inc.
Deerfield, IL 60015-2548

Manufactured by:

Astellas Tokai Co., Ltd. Yazu Plant
Shizuoka 425-0072, Japan

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