

2009 CMS Outpatient Pay Will Be Based on Quality

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The Centers for Medicare and Medicaid Services has proposed an overall 3% increase in payments for outpatient hospital care in 2009, almost a full percent below the update for 2008. As expected, reporting on quality of care is being tied to the amount of increase hospitals and other outpatient providers will receive.

For the first time, hospitals and other recipients of payments under the outpatient system that do not report data on seven quality measures on emergency department and perioperative care will see only a 1% increase.

The proposed rule, issued in July, also outlines changes for ambulatory surgery centers (ASCs) that are part of a 4-year transition to a new payment system that began this year. In 2009, as was the case this year, ASCs would be paid 65% of the rate paid for the same service in an outpatient hospital department.

The agency estimates it will spend \$29 billion in 2009 on payments to acute care hospitals, inpatient rehabilitation facilities, inpatient psychiatric facilities, long-term acute-care hospitals, community mental health centers, children's hospitals, and cancer hospitals. That's a \$2 billion increase from the estimated \$27 billion CMS will spend on outpatient services this year. Payments to ambulatory surgery centers will increase from an estimated \$3.5 billion in 2008 to \$3.9 billion in 2009, according to CMS.

"The changes proposed for 2009 are intended to give hospitals greater flexibility to manage their resources and give them incentives to improve efficiency so that both beneficiaries and taxpayers get the most value for their health care dollar," said CMS Acting Administrator Kerry Weems in a statement.

CMS is proposing to more aggressively penalize hospitals and other outpatient providers that do not report quality data. Providers must report on 7 measures in 2008 and on 11 in 2009, including 4 imaging efficiency measures. In addition, the agency is seeking to reduce copayments for beneficiaries who are treated at hospitals that do not report quality data.

By law, Medicare is gradually changing the payment system so that beneficiaries will be liable for only 20% of a covered service. The coinsurance rate has varied widely over the last 8-10 years. In 2009, about 25% of services will be subject to the 20% coinsurance, up from 23% in 2008, CMS said.

For imaging—a huge and growing portion of Medicare expenditures—CMS would make a single payment for multiple imaging procedures performed in a single hospital session, including ultrasound, CT, and MRI.

CMS also proposes reducing pay for some of the higher-cost device-oriented procedures: a 48% reduction in pay for the placing of left ventricular pacing add-on leads; a 3% decrease for replacing pace-makers, electrodes, or pulse generators; 4% for stent placement; and just 1% for drug-eluting stents.

A small increase is proposed for most neurology devices, as well as for urologic and gynecologic procedures and drug infusion devices, but placement of neurostimulator electrodes would be slashed by 52%.

For ASCs, reimbursement would decrease for 92 procedures, but increase for 2,475 procedures, according to the Ambulatory Surgery Center Association. Gastrointestinal procedures as a whole are slated for a 6% reduction, and nervous sys-

tem procedures and pain management would be reduced by 3%, according to Washington Analysis, a firm that advises investors on health policy developments.

CMS proposes adding nine surgical procedures to the list of services covered at an ASC. Three have brand new current procedural terminology (CPT) codes, and six—nasal/sinus endoscopy surgery; removal of vein clot; blood exchange/transfuse, non-nb; laparoscopic insertion of a permanent intraperitoneal catheter; la-

paroscopic revision of a permanent intraperitoneal catheter; and laparoscopy with omentopexy add-on—were previously excluded from coverage. Five procedures will be added to the list of office-based procedures, which are paid at either the ASC rate or the office practice expense payment rate, whichever is lower.

CMS is accepting public comments on the outpatient and ASC proposals until Sept. 2 and expects to issue the final rule Nov. 1. ■

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 euvoletic 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 **DOSE 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 **DOSE AND ADMINISTRATION** in full Prescribing Information)

The adverse reactions presented in Table 1 are derived from 72 healthy volunteers and 243 patients with euvoletic 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 euvoletic 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 euvoletic 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.

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. Yaizu Plant
Shizuoka 425-0072, Japan

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References: 1. Vaprisol Prescribing Information. Astellas Pharma US, Inc. 2. Data on file. Astellas Pharma US, Inc.