HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VAPRISOL safely and effectively. See full prescribing information for VAPRISOL.

VAPRISOL® (conivaptan hydrochloride) injection, for intravenous use
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------
Dosage and Administration, Hepatic Impairment (2.3) 10/2016

----------INDICATIONS AND USAGE----------
VAPRISOL® is a vasopressin receptor antagonist indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia (1).

Limitations of Use:
VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure (1).
It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients (1).

----------DOSAGE AND ADMINISTRATION----------
- Loading Dose: 20 mg IV administered over 30 minutes (2.1), followed by:
- Continuous infusion: 20 mg/day over 24 hours, for 2 to 4 days (2.1).
- Following initial day of treatment, dosage may be increased to 40 mg/day continuous infusion as needed to raise serum sodium (2.1).
- Monitor volume status and serum sodium frequently and discontinue if patient develops hypovolemia, hypotension or undesirable rapid rate of increase in serum sodium (2.1, 5.2).
- Hepatic impairment: Decrease the dose in patients with moderate or severe hepatic impairment (8.6, 12.3).

----------DOSAGE FORMS AND STRENGTHS----------
- Intravenous injection solution: conivaptan hydrochloride 20 mg/100 mL premixed in 5% Dextrose (2.2, 3).

----------CONTRAINDICATIONS----------
- Hypovolemic hyponatremia (4.1).
- Coadministration with potent CYP3A inhibitors (4.2, 5.3, 7.1).
- Anuria: no benefit can be expected (4.3).

----------WARNINGS AND PRECAUTIONS----------
- Hypervolemic hyponatremia associated with heart failure: Data are limited. Consider other treatment options (5.1, 6.1).
- Overly rapid correction of serum sodium: Monitor serum sodium and neurologic status as serious neurologic sequelae can result from over rapid correction of serum sodium (2.1, 5.2).
- Infusion site reactions: Serious reactions have occurred. Administer through large veins and change infusion site every 24 hours (2.1, 5.4, 6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 10%) are infusion site reactions (including phlebitis), pyrexia, hypokalemia, headache and orthostatic hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-887-484-2700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Potent CYP3A inhibitors may increase the exposure of conivaptan and are contraindicated (4.2, 7.1).
- Generally avoid CYP3A substrates (5.3, 7.1).
- Exposure to coadministered digoxin may be increased and digoxin levels should be monitored (7.2).

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding not recommended (8.2).
- Pediatric Use: There are no studies (8.4).
- Severe renal impairment: VAPRISOL is not recommended (8.7, 12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VAPRISOL® is indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.

Limitations of Use:

VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication.

It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

VAPRISOL is for intravenous use only.

VAPRISOL is for use in hospitalized patients only.

Administer VAPRISOL through large veins and change of the infusion site every 24 hours to minimize the risk of vascular irritation *[see Warnings and Precaution (5.4)]*.

Initiate with a loading dose of 20 mg VAPRISOL administered intravenously over 30 minutes.

Follow the loading dose with 20 mg VAPRISOL administered in a continuous intravenous infusion over 24 hours. After the initial day of treatment, administer VAPRISOL for an additional 1 to 3 days in a continuous infusion of 20 mg/day. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to a maximum dose of 40 mg daily, administered in a continuous intravenous infusion over 24 hours.

The total duration of infusion of VAPRISOL (after the loading dose) should not exceed four days.

Patients receiving VAPRISOL must have frequent monitoring of serum sodium and volume status *[see Warnings and Precautions (5.2, 5.3)]*.

2.2 Preparation, Compatibility and Stability

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter, discoloration or cloudiness is observed, the drug solution should not be used.

VAPRISOL is supplied ready-to-use; no further dilution of this preparation is necessary.

VAPRISOL is compatible with 5% Dextrose Injection. VAPRISOL is physically and chemically compatible with 0.9% Sodium Chloride Injection for up to 48 hours when the two solutions are co-administered via a Y-site connection at a flow rate for VAPRISOL of 4.2 mL/hour and at flow rates for 0.9% Sodium Chloride Injection of either 2.1 mL/hour or 6.3 mL/hour.

VAPRISOL is incompatible with both Lactated Ringer's Injection and furosemide injection when these products are mixed in the same container; therefore, do not combine VAPRISOL with these products in the same intravenous line or container.

Do not combine VAPRISOL with any other product in the same intravenous line or container.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

Do not remove container from overwrap until ready for use. The overwrap is a moisture and light barrier. The inner container maintains the sterility of the product.

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by

squeezing inner container firmly. If leaks are found, discard solution as sterility may be impaired. Do not use if the solution is cloudy or a precipitate is present.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

2.3 Hepatic Impairment

In patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment, initiate VAPRISOL with a loading dose of 10 mg over 30 minutes followed by 10 mg per day as a continuous infusion for 2 to 4 days. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upward to 20 mg per day *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Intravenous injection solution: conivaptan hydrochloride 20 mg/100 mL premixed in 5% Dextrose in flexible plastic containers.

4 CONTRAINDICATIONS

4.1 Hypovolemic Hyponatremia

VAPRISOL is contraindicated in patients with hypovolemic hyponatremia.

4.2 Coadministration with Potent CYP3A Inhibitors

The coadministration of VAPRISOL with potent CYP3A inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated *[see Drug Interactions (7.1)]*.

4.3 Anuric Patients

In patients unable to make urine, no benefit can be expected *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hyponatremia Associated with Heart Failure

The amount of safety data on the use of VAPRISOL in patients with hypervolemic hyponatremia associated with heart failure is limited. VAPRISOL should be used to raise serum sodium in such patients only after consideration of other treatment options *[see Adverse Reactions (6.1)]*.

5.2 Overly Rapid Correction of Serum Sodium

Osmotic demyelination syndrome is a risk associated with overly rapid correction of hyponatremia (i.e., > 12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, use slower rates of correction. In controlled clinical trials of VAPRISOL, about 9% of patients who received VAPRISOL in doses of 20-40 mg/day IV had rises of serum sodium >12 mEq/L/24 hours, but none of these patients had evidence of osmotic demyelination or permanent neurologic sequelae. 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 *[see Dosage and Administration (2.1)]*.

5.3 Hypovolemia or Hypotension

For patients who develop hypovolemia or hypotension while receiving VAPRISOL, VAPRISOL should be discontinued, and volume status and vital signs should be frequently monitored. Once the patient is again euvolemic and is no longer hypotensive, VAPRISOL may be resumed at a reduced dose if the patient remains hyponatremic.

5.4 Infusion Site Reactions

Infusion site reactions are common and can include serious reactions, even with proper infusion rates *[see Adverse Reactions (6.1)]*. Administer VAPRISOL via large veins, and rotate the infusion site every 24 hours *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling:

- Osmotic demyelination syndrome *[see Warnings and Precautions (5.2)]*
- Infusion site reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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 (2.1) and Warnings and Precautions (5.4)]*.

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.

Table 1. VAPRISOL Injection: Adverse Reactions Occurring in ≥ 5% of Patients or Healthy Volunteers and VAPRISOL Incidence > Placebo Incidence

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%)

Term	Placebo (N=69) N (%)	20 mg (N=37) N (%)	40 mg (N=315) N (%)
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 VAPRISOL was also studied, it was associated with a higher incidence of infusion site reactions and a higher rate of discontinuation for adverse events than was the 40 mg/day VAPRISOL dose. The maximum recommended daily dose of VAPRISOL (after the loading dose) is 40 mg/day.

Heart failure with hypervolemic hyponatremia

In clinical trials where 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) *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors and Substrates

Conivaptan is a sensitive substrate of CYP3A. Coadministration with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir and indinavir) increases conivaptan exposure and is contraindicated *[see Contraindications (4.2) and Clinical Pharmacology (12.3)]*.

Coadministration with CYP3A substrates results in increased exposure of the other drug. Avoid concomitant use with drugs eliminated primarily by CYP3A-mediated metabolism. Subsequent treatment

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