

New Drug Bulletin:
Conivaptan (Vaprisol® - Astellas Pharma US, Inc.)

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The Food and Drug Administration approved conivaptan (Vaprisol®) on December 29, 2005. Conivaptan is a dual arginine vasopressin (AVP) V_{1A} and V₂ receptor antagonist. AVP concentrations regulate water and electrolyte balance. The effect of AVP is mediated through V₂ receptors coupled to aquaporin ducts in the collecting tubules of the kidneys. Antagonism of AVP at V₂ receptors in the renal collecting ducts results in excretion of free water (aquaporesis). This results in increased urine output, decreased urine osmolality, and increased net fluid loss. Conivaptan is approved for use only in euvolemic hyponatremia.

Conivaptan displays non-linear pharmacokinetics following IV infusion because of inhibition of its own metabolism. Conivaptan reaches peak plasma concentrations 30 minutes after the loading dose. Conivaptan is 99% bound to human plasma proteins. Metabolism takes place in the liver via CYP3A4 with four resulting active metabolites. Exposure to the metabolites following IV conivaptan administration is approximately 7% that of conivaptan itself; therefore, the contribution to the clinical effect is minimal. After conivaptan infusion, the mean terminal elimination half-life is 5 hours, with a mean clearance of 15.2 L/h. Approximately 83% of dose is excreted in feces and 12% in urine. Approximately 1% is excreted unchanged.

A double-blind, randomized, multi-center, placebo-controlled study was undertaken on 56 patients with euvolemic hyponatremia. Treatment time was 4 days of either placebo or conivaptan at 40 or 80 mg per day IV, and all subjects were fluid restricted. Patients received a conivaptan 20 mg IV loading dose over 30 minutes on the first day, followed by continuous infusion. After 4 days, 67% of the conivaptan 40 mg/day group achieved either a 6 mEq/L or more increase in serum sodium concentrations from baseline or had normal serum sodium concentrations, as compared to 29% for placebo. Effective water clearance for conivaptan recipients was higher than for placebo recipients at day 4.

Contraindications to the use of conivaptan include hypovolemic hyponatremia and hypersensitivity to any of its components. Safety in hyponatremic patients with underlying congestive heart failure is not established.

Infusion site reactions were the most common adverse reactions reported with conivaptan 40 mg administration (52.5%) compared to placebo (3.3%). Infusion site reactions lead to the highest number of conivaptan discontinuations. Adverse reactions occurring in 2% or greater of subjects with incidence greater than placebo include constipation, diarrhea, vomiting, dry mouth, dehydration, thirst, hyperglycemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, headache, insomnia, polyuria, frequent daytime urination, hypertension, hypotension, orthostatic hypotension, and phlebitis.

Conivaptan is both a potent inhibitor of and a substrate of CYP3A4. Coadministration of conivaptan with CYP3A4 inhibitors could lead to conivaptan toxicity. Use with potent CYP3A4 inhibitors such as azole antifungals, macrolide antibiotics, indinavir, and ritonavir are contraindicated. Conivaptan may increase the plasma concentrations of drugs primarily

metabolized by CYP3A4 if they are coadministered. Two cases of rhabdomyolysis have occurred in patients who received both conivaptan and a CYP3A4-metabolized statin.

Digoxin, when coadministered with conivaptan results in increases in digoxin exposure and maximal plasma concentrations, and reduces clearance. Monitor digoxin for toxicity if administered with conivaptan.

Conivaptan is administered intravenously through large veins only. Change infusion site every 24 hours to minimize risk of vascular irritation. Conivaptan loading dose is 20 mg administered IV over 30 minutes. Following the loading dose, 20 mg should be administered by continuous IV infusion over 24 hours. After the first day of treatment, conivaptan should be administered for an additional 1 to 3 days by continuous infusion at 20 mg per day. If sodium levels are not rising at desired rate, then dose may be titrated to 40 mg per day. The total duration of conivaptan infusion should not exceed 4 days. Administer conivaptan cautiously to patients with renal or hepatic failure since the effect of conivaptan is unknown in these patients.

Prepare a loading dose of conivaptan by the addition of 4 mL (20 mg) of conivaptan to an infusion bag containing 100 mL of 5% dextrose injection (D5W). Prepare a continuous IV infusion of conivaptan by adding 4 mL (20 mg) of conivaptan to an infusion bag containing 250 mL of D5W. Conivaptan is stable for up to 24 hours after dilution with D5W. It is not to be administered with or mixed in 0.9% sodium chloride injection or lactated ringer's injection.

Conivaptan will be available in boxes of ten 4 mL ampules, each containing 20 mg of conivaptan hydrochloride. Pricing for Conivaptan is not currently available.

In summary, conivaptan is a dual AVP V_{1A} and V_2 receptor antagonist that is the only agent indicated for the treatment of euvolemic hyponatremia.

References:

1. Vaprisol® (conivaptan hydrochloride injection) [package insert]. Deerfield, IL: Astellas Pharma US, Inc., December 2005.

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