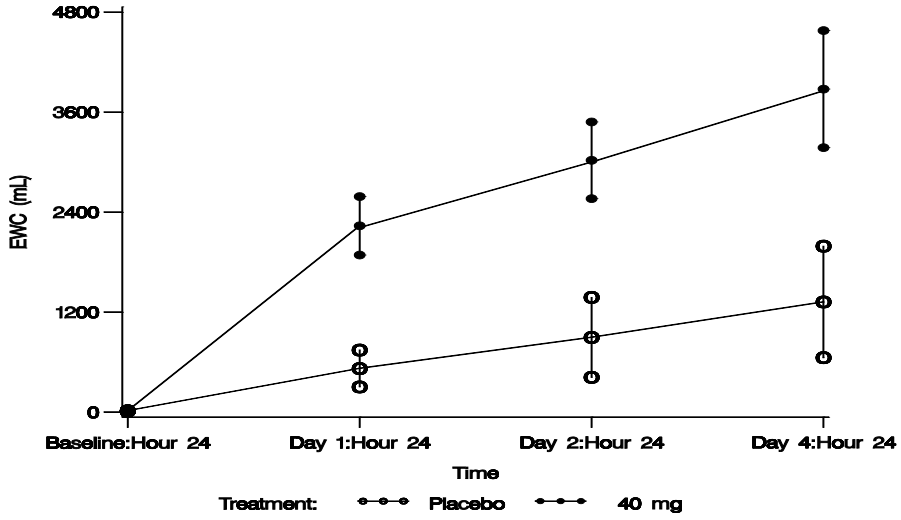
The aquaretic effect of VAPRISOL is shown in Figure 3. VAPRISOL produced a baseline-corrected cumulative increase in effective water clearance of over 3800 mL compared to approximately 1300 mL with placebo by Day 4.

Figure 3. Baseline-Corrected Mean (SE) Cumulative Effective Water Clearance (EWC)



$EWC = V \times \left(1 - \frac{U_{Na} + U_K}{P_{Na} + P_K}\right)$, where V is urine volume (mL/d), U_{Na} is urine sodium concentration, U_K is urine potassium concentration, P_{Na} is plasma/serum sodium concentration, and P_K is plasma/serum potassium concentration.

The effect on serum sodium of VAPRISOL (administered as a 20 or 40 mg/day IV continuous infusion for 4 days following a 30 minute IV infusion of a 20 mg loading dose on the first treatment day) was also evaluated in an open-label study of 251 patients with euvolemic or hypervolemic hyponatremia. The results are shown in Table 3.

Table 3. Efficacy Outcomes of Treatment with VAPRISOL 20 or 40 mg/day

Primary Efficacy Endpoint	**20 mg/day N=37**	**40 mg/day N=214**
Baseline adjusted serum Na^+ AUC over duration of treatment (mEq·hr/L) Mean (SD)	753.8 (429.9)	689.2 (417.3)
Secondary Efficacy Endpoints		
Number of patients (%) and median event time (h) from first dose of study medication to a confirmed ≥ 4 mEq/L increase from Baseline in serum Na^+, [95% CI]	29 (78%) 23.8[12.0, 36.0]	178 (83%) 24.4 [24.0, 35.8]
Total time (h) from first dose of study medication to end of treatment in which patients had a confirmed ≥ 4 mEq/L increase in serum Na^+ from Baseline Mean (SD)	60.6 (35.2)	59.5 (33.2)
Serum Na^+ (mEq/L) Baseline mean (SD) Mean (SD) at end of treatment Mean Change (SD) from Baseline to End of Treatment Mean (SD) at Follow-up Day 11 Mean Change (SD) from Baseline to Follow-up Day 11 Mean (SD) at Follow-up Day 34 Mean Change (SD) from Baseline to Follow-up Day 34	 122.5 (5.2) 131.8 (3.9) 9.4 (5.3) 129.9 (6.2) 7.1 (8.2) 134.3 (4.5) 11.5 (7.3)	 123.8 (4.6) 132.5 (4.6) 8.8 (5.4) 131.8 (5.8) 8.0 (6.5) 134.3 (5.2) 10.7 (6.7)
Number (%) of patients who obtained a confirmed ≥ 6 mEq/L increase from Baseline in serum Na^+ or a normal serum Na^+ concentration ≥135 mEq/L during treatment	26 (70%)	154 (72%)

14.2 Heart Failure

The effectiveness of VAPRISOL for the treatment of congestive heart failure has not been established. In 10 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, 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) *[see Indications and Usage (1)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

VAPRISOL (conivaptan hydrochloride) Injection is supplied as a single-use, premixed solution, containing 20 mg of conivaptan hydrochloride in 5% Dextrose in 100 mL INTRAVIA Plastic Containers.

- 1 container/carton (NDC 66220-160-10)

VAPRISOL in INTRAVIA Plastic Containers should be stored at 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat. Protect from freezing. Protect from light until ready to use.

17 PATIENT COUNSELING INFORMATION

Inform patients about the common adverse effects of VAPRISOL including infusion site effects (edema, erythema, pain, and phlebitis), pyrexia, hypokalemia, headache, orthostatic hypotension and potential for overly rapid increase in serum sodium which can cause serious neurologic sequelae. Instruct patients to inform their healthcare provider if they develop any unusual symptoms, or if any known symptom persists or worsens, with special attention to potential manifestations of osmotic demyelination syndrome.

Ask patients about what other medications they are currently taking with VAPRISOL, including over-the-counter medications.

Lactation

Advise women not to breastfeed during treatment with VAPRISOL *[see Use in Specific Populations (8.2)]*.

Marketed by:
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