

1 **VAPRISOL[®] (conivaptan hydrochloride injection) Ampule**

2 and

3 **VAPRISOL[®] (conivaptan hydrochloride injection) Premixed in 5% Dextrose in**
4 **INTRAVIA[®] Plastic Container**

5

6 **DESCRIPTION**

7

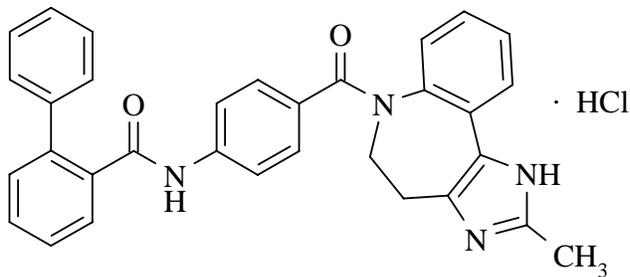
8 VAPRISOL[®] (conivaptan hydrochloride injection) is a nonpeptide, dual antagonist of
9 arginine vasopressin (AVP) V_{1A} and V₂ receptors.

10

11 Conivaptan hydrochloride is chemically [1,1'-biphenyl]-2-carboxamide, *N*-[4-[(4,5-
12 dihydro-2-methylimidazo[4,5-*d*][1]benzazepin-6(1*H*)-yl)carbonyl]phenyl]-,
13 monohydrochloride, having a molecular weight of 535.04 and molecular formula
14 C₃₂H₂₆N₄O₂·HCl. The structural formula of conivaptan hydrochloride is:

15

16



17

18

19 Conivaptan hydrochloride is a white to off-white or pale orange-white powder that is
20 very slightly soluble in water (0.15 mg/mL at 23° C). Conivaptan hydrochloride
21 injection is supplied as a sterile liquid in an ampule and as a sterile premixed solution
22 with dextrose in a flexible plastic container.

23

24 **VAPRISOL (conivaptan hydrochloride injection) Ampule**

25 Each ampule will deliver 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g
26 ethanol and Water for Injection, q.s. Lactic acid is added for pH adjustment to 3.0.

27

28 **VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose**

29 Each container contains a clear, colorless, sterile, non-pyrogenic solution of conivaptan
30 hydrochloride in dextrose. Each 100 mL, single-use premixed INTRAVIA Container
31 contains 20 mg of conivaptan hydrochloride and 5 g of Dextrose Hydrous, USP. Lactic
32 Acid, USP is added for pH adjustment to pH 3.4 to 3.8. The flexible plastic container is
33 fabricated from a specially designed multilayer plastic (PL 2408). Solutions in contact
34 with the plastic container leach out certain of the chemical components from the plastic in
35 very small amounts; however, biological testing was supportive of the safety of the
36 plastic container materials. The flexible container has a foil overwrap. Water can
37 permeate the plastic into the overwrap, but the amount is insufficient to significantly
38 affect the premixed solution.

39

40 **CLINICAL PHARMACOLOGY**

41 **Pharmacodynamics**

42 Conivaptan hydrochloride is a dual AVP antagonist with nanomolar affinity for human
43 V_{1A} and V_2 receptors in vitro. The level of AVP in circulating blood is critical for the
44 regulation of water and electrolyte balance and is usually elevated in both euvolemic and
45 hypervolemic hyponatremia. The AVP effect is mediated through V_2 receptors, which
46 are functionally coupled to aquaporin channels in the apical membrane of the collecting
47 ducts of the kidney. These receptors help to maintain plasma osmolality within the
48 normal range. The predominant pharmacodynamic effect of conivaptan hydrochloride in
49 the treatment of hyponatremia is through its V_2 antagonism of AVP in the renal collecting
50 ducts, an effect that results in aquaresis, or excretion of free water. The
51 pharmacodynamic effects of conivaptan hydrochloride include increased free water
52 excretion (i.e., effective water clearance [EWC]) generally accompanied by increased net
53 fluid loss, increased urine output, and decreased urine osmolality. Studies in animal
54 models of hyponatremia showed that conivaptan hydrochloride prevented the occurrence
55 of hyponatremia-related physical signs in rats with the syndrome of inappropriate
56 antidiuretic hormone secretion.

57

58 **Pharmacokinetics**

59 The pharmacokinetics of conivaptan have been characterized in healthy subjects, special
60 populations and patients following both oral and intravenous dosing regimens. The
61 pharmacokinetics of conivaptan following intravenous infusion (40 mg/day to 80
62 mg/day) and oral administration are non-linear, and inhibition by conivaptan of its own
63 metabolism seems to be the major factor for the non-linearity. The intersubject
64 variability of conivaptan pharmacokinetics is high (94% CV in CL).

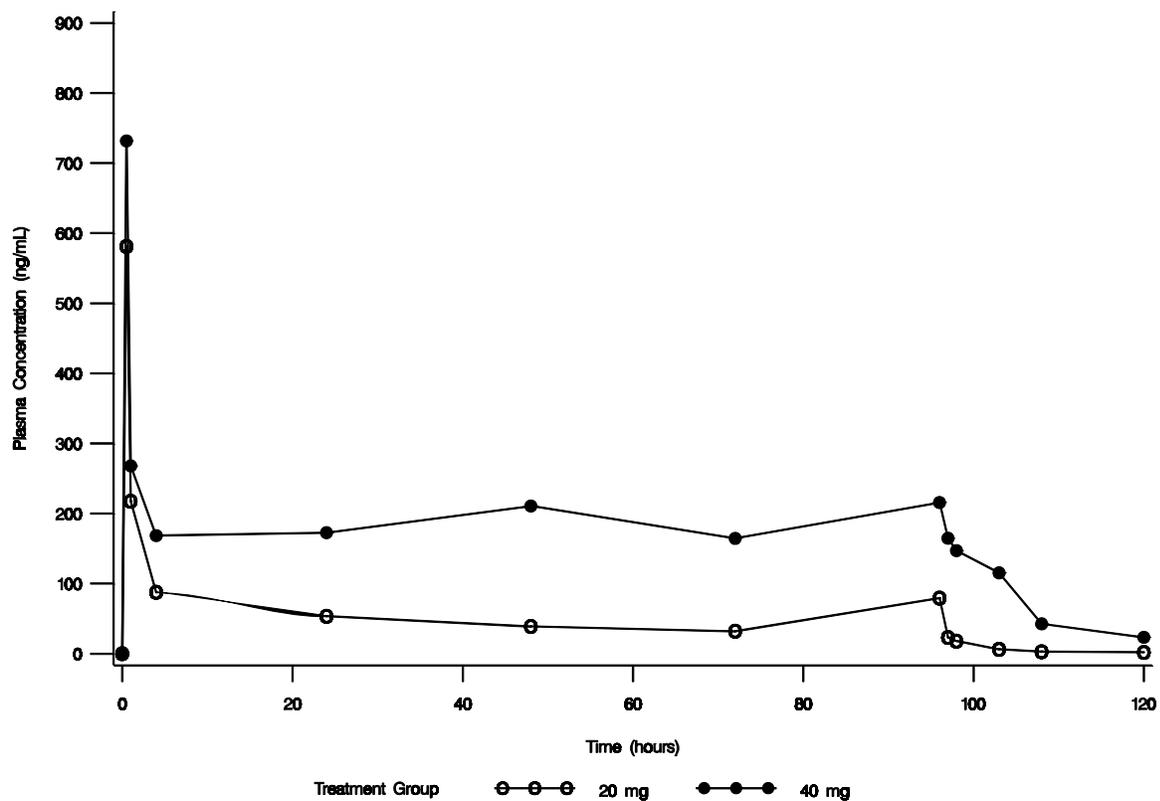
65
66 The pharmacokinetics of conivaptan and its metabolites were characterized in healthy
67 male subjects administered conivaptan hydrochloride as a 20 mg loading dose (infused
68 over 30 minutes) followed by a continuous infusion of 40 mg/day for 3 days. Mean C_{max}
69 for conivaptan was 619 ng/mL and occurred at the end of the loading dose. Plasma
70 concentrations reached a minimum at approximately 12 hours after start of the loading
71 dose, then gradually increased over the duration of the infusion to a mean concentration
72 of 188 ng/mL at the end of the infusion. The mean terminal elimination half-life after
73 conivaptan infusion was 5.0 hours, and the mean clearance was 15.2 L/h.

74
75 In an open-label safety and efficacy study, the pharmacokinetics of conivaptan were
76 characterized in hypervolemic or euvolemic hyponatremia patients (ages 20 - 92 years)
77 receiving conivaptan hydrochloride as a 20 mg loading dose (infused over 30 minutes)
78 followed by a continuous infusion of 20 or 40 mg/day for 4 days. The median-plasma
79 conivaptan concentrations are shown in Figure 1 and pharmacokinetic parameters are
80 summarized in Table 1.

81

82 **Figure 1. Median Plasma Concentration-Time Profiles From Rich PK Sampling**
83 **After 20 mg Loading Dose and 20 mg/day (open circle) or 40 mg/day (closed circle)**
84 **Infusion for 4 Days**

85



86

Table 1. Pharmacokinetic Parameters After 20 mg Loading Dose for 30 Minutes and 20 mg/day or 40 mg/day Infusion for 4 Days		
Parameter	IV Conivaptan 20 mg/day	IV Conivaptan 40 mg/day
Conivaptan concentration at the end of loading dose (ng/mL, at 0.5 hours) N* Median (range)	31 659.4 (144.5-1587.6)	170 679.5 (0.0-1910.8)
Conivaptan concentration at the end of infusion (ng/mL, at 96 hours) N* Median (range)	30 117.6 (4.9-938.3)	172 215.7 (2.1-1999.3)
Elimination half-life (hr) N** Median (range)	8 5.3 (3.3-9.3)	8 8.1 (4.1-22.5)
Clearance (L/hr) N** Median (range)	8 16.1 (7.2-37.6)	8 8.73 (2.1-20.9)

88 *: number from the rich and the sparse PK sampling

89 **: number from the rich PK sampling

90

91 Distribution

92 Conivaptan is extensively bound to human plasma proteins, being 99% bound over the
93 concentration range of approximately 10 to 1000 ng/mL.

94

95 Metabolism and Excretion

96 CYP3A4 was identified as the sole cytochrome P450 isozyme responsible for the
97 metabolism of conivaptan. Four metabolites have been identified. The pharmacological
98 activity of the metabolites at V_{1A} and V₂ receptors ranged from approximately 3-50% and
99 50-100% that of conivaptan, respectively. The combined exposure of the metabolites
100 following intravenous administration of conivaptan is approximately 7% that of
101 conivaptan and hence, their contribution to the clinical effect of conivaptan is minimal.

102

103 After intravenous (10 mg) or oral (20 mg) administration of conivaptan hydrochloride in
104 a mass balance study, approximately 83% of the dose was excreted in feces as total
105 radioactivity and 12% in urine over several days of collection. Over the first 24 hours
106 after dosing, approximately 1% of the intravenous dose was excreted in urine as intact
107 conivaptan.

108 **Special Populations**

109 *Hepatic Impairment*

110 The effect of hepatic impairment (including ascites, cirrhosis, or portal hypertension) on
111 the elimination of conivaptan after intravenous administration has not been systematically
112 evaluated. However, increased systemic exposures after administration of oral
113 conivaptan (up to a mean 2.8-fold increase) have been seen in patients with stable
114 cirrhosis and moderate hepatic impairment. Intravenous VAPRISOL resulted in higher
115 conivaptan exposure than did oral conivaptan, in study subjects without hepatic function
116 impairment. Caution should be exercised when administering VAPRISOL to patients
117 with impaired hepatic function.

118

119 *Renal Impairment*

120 The effect of renal impairment on the elimination of conivaptan after intravenous
121 administration has not been evaluated. However, following administration of oral
122 conivaptan, the AUC for conivaptan was up to 80% higher in patients with renal
123 impairment ($CL_{cr} < 60 \text{ mL/min/1.73 m}^2$) as compared to those with normal renal function.
124 Intravenous VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan,
125 in study subjects without renal function impairment. Caution should be exercised when
126 administering VAPRISOL to patients with impaired renal function.

127

128 *Geriatric Patients*

129 Following a single oral dose of conivaptan hydrochloride (15, 30 or 60 mg), drug
130 exposure (AUC) in elderly male and female volunteers (65 to 90 years of age) compared
131 to that seen in young male subjects was similar for the 15 and 30 mg doses but increased
132 nearly 2-fold at the 60 mg dose.

133

134 In an open label study to assess the safety and efficacy of conivaptan, a subset of geriatric
135 hypervolemic or euvolemic hyponatremia patients (65 to 92 years of age) received a 20
136 mg intravenous loading dose followed by a 20 mg/day (N=27) or 40 mg/day (N=135)
137 intravenous infusion for 4 days. The median conivaptan plasma concentration in these
138 patients at the end of the loading dose infusion was 654 ng/mL. The median conivaptan
139 plasma concentrations at the end of the 4-day continuous infusion were 118 and 215
140 ng/mL for the 20 mg/day and 40 mg/day regimens, respectively.

141

142 *Pediatric Patients*

143 The pharmacokinetics of conivaptan in pediatric patients have not been studied.

144

145 **Drug-Drug Interactions**

146 (See **CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions**)

147 **CYP3A4**

148 Conivaptan is a sensitive substrate of CYP3A4. The effect of ketoconazole, a potent
149 CYP3A4 inhibitor, on the pharmacokinetics of intravenous conivaptan has not been
150 evaluated. Coadministration of oral conivaptan hydrochloride 10 mg with ketoconazole
151 200 mg resulted in 4- and 11-fold increases in C_{max} and AUC of conivaptan,
152 respectively.

153

154 Conivaptan is a potent inhibitor of CYP3A4. The effect of conivaptan on the
155 pharmacokinetics of CYP3A4 substrates has been evaluated with the coadministration of
156 conivaptan with midazolam, simvastatin, and amlodipine. Intravenous conivaptan
157 hydrochloride 40 mg/day increased the mean AUC values by approximately 2- and 3-fold
158 for 1 mg intravenous or 2 mg oral doses of midazolam, respectively. Intravenous
159 conivaptan hydrochloride 30 mg/day resulted in a 3-fold increase in the AUC of
160 simvastatin. Oral conivaptan hydrochloride 40 mg twice daily resulted in a 2-fold
161 increase in the AUC and half-life of amlodipine.

162 **Digoxin**

163 Coadministration of a 0.5-mg dose of digoxin, a P-glycoprotein substrate, with oral
164 conivaptan hydrochloride 40 mg twice daily resulted in a 30% reduction in clearance and
165 79% and 43% increases in digoxin C_{max} and AUC values, respectively.

166

167 **Warfarin**

168 The effect of intravenous conivaptan on warfarin pharmacokinetics or
169 pharmacodynamics has not been evaluated. The potential drug-drug interaction of oral
170 conivaptan with warfarin, which undergoes major metabolism by CYP2C9 and minor
171 metabolism by CYP3A4, was investigated in a clinical study.

172

173 The effects of oral conivaptan hydrochloride 40 mg twice daily on prothrombin time was
174 assessed in patients receiving stable oral warfarin therapy. After 10 days of oral
175 conivaptan administration, the S- and R-warfarin concentrations were 90% and 98%,
176 respectively, of those prior to conivaptan administration. The corresponding prothrombin
177 time values after 10 days of oral conivaptan administration were 95% of baseline. No
178 effect of oral conivaptan on the pharmacokinetics or pharmacodynamics of warfarin was
179 observed.

180

181 **Captopril and Furosemide**

182

183 The effects of captopril (25 mg) on the pharmacokinetics of conivaptan hydrochloride (30
184 mg) and furosemide (40 mg or 80 mg once daily for 6 days) on the pharmacokinetics of
185 conivaptan hydrochloride (20 mg, and 40 mg) were assessed in separate studies. The
186 pharmacokinetics of conivaptan were unchanged with coadministration of either captopril
187 or furosemide.

188

189 **Electrophysiology**

190 The effect of VAPRISOL 40 mg IV and 80 mg IV on the QT interval was evaluated after
191 the first dose (Day 1) and at the last day during treatment (Day 4) in a randomized,
192 single-blind, parallel group, placebo- and positive-controlled (moxifloxacin 400 mg IV)
193 study in healthy male and female volunteers aged 18 to 45 years. Digital ECGs were
194 obtained at baseline and on Days 1 and 4. The placebo-corrected changes from baseline
195 in individualized QT correction (QTcI) in the VAPRISOL 40 mg and 80 mg dose groups
196 on Day 1 were -3.5 msec and -2.9 msec, respectively, on Day 1, and -2.1 msec for both
197 dose groups on Day 4. Similar results were obtained using either the Bazett's or
198 Fridericia's correction methods. Moxifloxacin elicited placebo-corrected changes from
199 baseline in QTcI of +7 to +10 msec on Days 1 and 4, respectively.

200

Drug and Dose	QTcI
Placebo	-3 msec
Vaprisol 40 mg IV	-5.1 msec
Vaprisol 80 mg IV	-5.1 msec
Moxifloxacin 400 mg IV	+7.4 msec

201

202 The results of the central tendency analysis of QTc indicate that VAPRISOL had no
203 effect on cardiac repolarization.

204

205 **CLINICAL STUDIES**

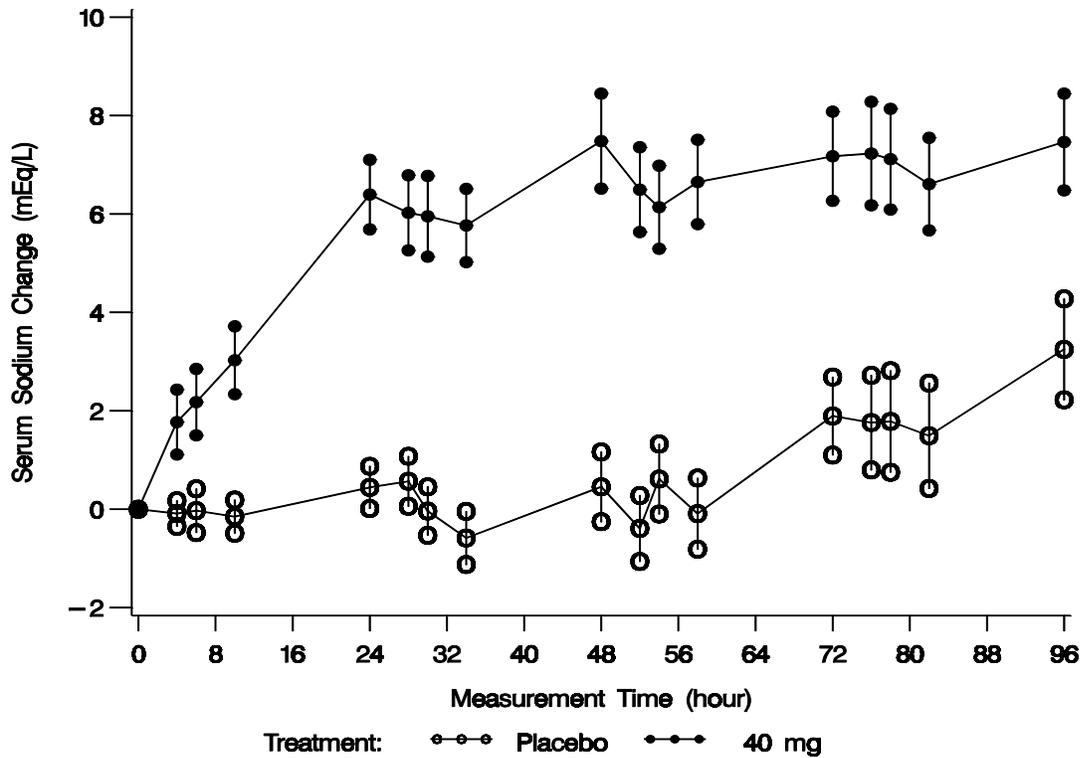
206 In a double-blind, placebo-controlled, randomized, multicenter study, 84 patients with
207 euvolemic or hypervolemic hyponatremia (serum sodium 115 -130 mEq/L) due to a
208 variety of underlying causes (malignant or nonmalignant diseases of the central nervous
209 system, lung, or abdomen; congestive heart failure [CHF]; hypertension; myocardial
210 infarction; diabetes; osteoarthritis; or idiopathic) were treated for 4 days with VAPRISOL
211 or placebo. All patients received standard care for hyponatremia, primarily fluid
212 restriction (daily fluid intake restricted to less than or equal to 2.0 liters). Study
213 participants were randomized to receive either placebo IV (N=29), or VAPRISOL
214 40 mg/day IV (N=29), or VAPRISOL 80 mg/day IV (N=26). VAPRISOL was
215 administered as a continuous infusion following a 30 minute IV infusion of a 20 mg
216 loading dose on the first treatment day. Serum or plasma sodium concentrations were
217 assessed at predose (Hour 0) and at 4, 6, 10, and 24 hours post dose on all treatment days.
218 Mean serum sodium concentration was 123.3 mEq/L at study entry.

219

220 The mean change in serum sodium concentration from baseline over the 4-day treatment
221 period is shown in Figure 2.

222

223 **Figure 2. Mean (SE) Change from Baseline in Sodium Concentrations with**
224 **VAPRISOL 40 mg/day**



225

226

227 Following treatment with 40 mg/day of intravenous VAPRISOL, 79% of patients
228 achieved an increase of ≥ 4 mEq/L in serum sodium concentration. The mean change
229 from baseline in serum sodium concentration at the end of 2 days of treatment with
230 VAPRISOL was 5.3 mEq/L (mean concentration 128.6 mEq/L). At the end of the 4-day
231 treatment period, the mean change from baseline was 6.5 mEq/L (mean concentration
232 129.8 mEq/L). In addition, after 2 days and 4 days of treatment with VAPRISOL, 41%
233 (after 2 days) and 69% (after 4 days) of patients achieved a ≥ 6 mEq/L increase in serum
234 sodium concentration or a normal serum sodium of ≥ 135 mEq/L. Although 80 mg/day
235 was also studied, it was not significantly more effective than 40 mg/day. The maximum
236 daily dose of VAPRISOL (after the loading dose) is 40 mg/day. Additional efficacy data
237 are summarized in Table 3.

Efficacy Variable	Placebo N=29		VAPRISOL 40 mg/d N=29	
	Day 2‡	Day 4	Day 2‡	Day 4
Baseline adjusted serum Na ⁺ AUC over duration of treatment (mEq·hr/L)				
Mean (SD)	6.2 (81.8)	61.4 (242.3)	205.9 (171.6)	500.8 (365.5)
LS Mean ± SE	3.8 ± 26.9	12.9 ± 61.2	205.6 ± 26.6*	490.9 ± 56.8*
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]	2 (7%) Not estimable Not estimable	9 (31%) Not estimable Not estimable	22 (76%) 23.7* [10, 2]	23 (79%) 23.7* [10, 2]
Total time (h) from first dose of study medication to Day 2 or Day 4 end of treatment during which patients had a confirmed ≥ 4 mEq/L increase in serum Na ⁺ from Baseline				
Mean (SD)	2.2 (5.9)	13.7 (20.5)	22.3 (16.0)	53.4 (34.3)
LS Mean ± SE	2.1 ± 2.3	14.2 ± 5.3	22.3 ± 2.3*	53.2 ± 5.2*
Serum Na ⁺ (mEq/L)				
Baseline mean (SD)	124.3 (4.1)	124.3 (4.1)	123.3 (4.7)	123.3 (4.7)
Mean (SD) at end of treatment	124.5 (4.7)	125.8 (4.9)	128.6 (5.9)	129.8 (4.8)
Change from Baseline to end of treatment				
Mean change (SD)	0.2 (2.5)	1.5 (4.6)	5.3 (4.4)	6.5 (4.4)
LS Mean change ± SE	0.1 ± 0.7	0.8 ± 0.8	5.2 ± 0.7*	6.3 ± 0.7*
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	0 (0)	6 (21%)	12 (41%)*	20 (69%)*

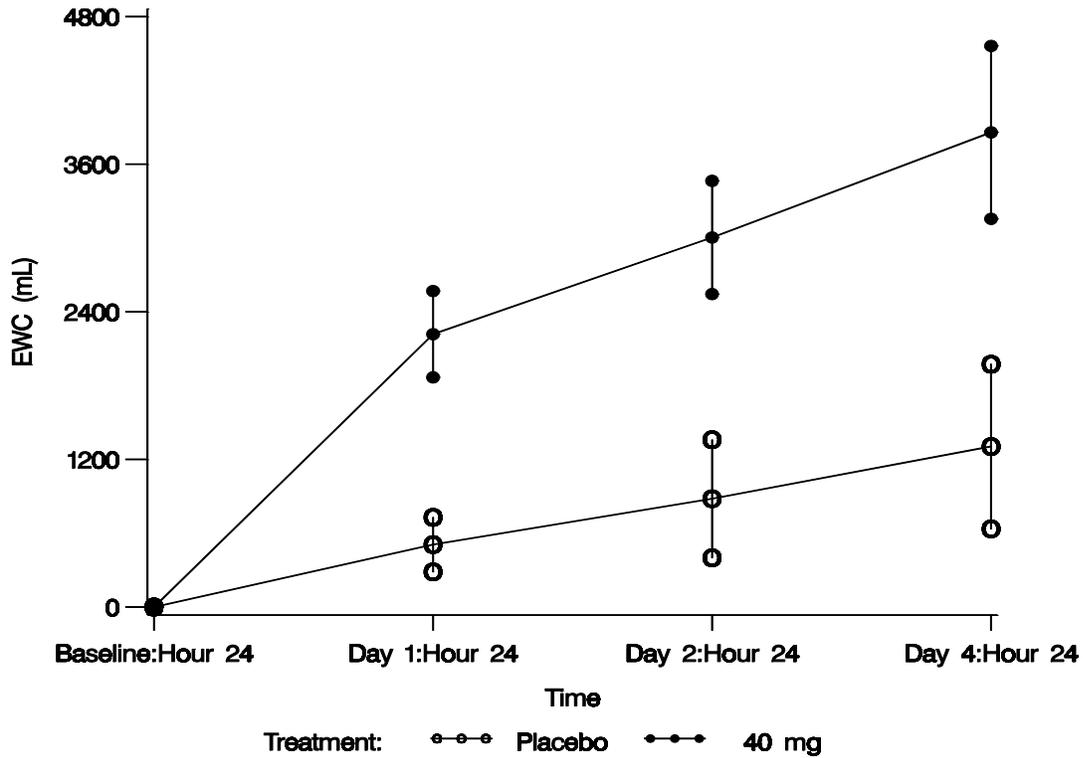
239 *P ≤ 0.001 vs placebo

240 ‡efficacy variables were assessed on Day 2 of a 4-day treatment period

241

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

245 **Figure 3. Baseline-Corrected Cumulative Effective Water Clearance**
 246 **(EWC)**



247
 248 $EWC = V \times \left(1 - \frac{U_{Na} + U_K}{P_{Na} + P_K} \right)$, where V is urine volume (mL/d), U_{Na} is urine sodium concentration, U_K is urine potassium
 249 concentration, P_{Na} is plasma/serum sodium concentration, and P_K is plasma/serum potassium concentration.
 250

251 In an open-label study in patients with euvolemic or hypervolemic hyponatremia, 251
 252 patients were treated for 4 days with VAPRISOL 20 or 40 mg/day IV as a continuous
 253 infusion following a 30 minute IV infusion of a 20 mg loading dose on the first treatment
 254 day. The results are shown in Table 4.

Table 4. 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%) 24.0[24.0, 35.8]
Total time (h) from first dose of study medication to end of treatment during 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)	122.5 (5.2)	123.8 (4.6)
Mean (SD) at end of treatment	131.8 (3.9)	132.5 (4.6)
Mean Change (SD) from Baseline to End of Treatment	9.4 (5.3)	8.8 (5.4)
Mean (SD) at Follow-up Day 11	129.9 (6.2)	131.8 (5.8)
Mean Change (SD) from Baseline to Follow-up Day 11	7.1 (8.2)	8.0 (6.5)
Mean (SD) at Follow-up Day 34	134.3 (4.5)	134.3 (5.2)
Mean Change (SD) from Baseline to Follow-up Day 34	11.5 (7.3)	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%)

256

257

258 The effectiveness of VAPRISOL for the treatment of congestive heart failure has not
259 been established.

260

261 **INDICATIONS AND USAGE**

262 VAPRISOL is indicated for the treatment of euvolemic and hypovolemic hyponatremia
263 in hospitalized patients.

264

265 **Important Limitation:**

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

271

272 **CONTRAINDICATIONS**

273 VAPRISOL is contraindicated in patients with hypovolemic hyponatremia.

274 The coadministration of VAPRISOL with potent CYP3A4 inhibitors, such as

275 ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated.

276 (See **PRECAUTIONS: Drug Interactions** for details and other important

277 considerations)

278 **VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose**

279 Solutions containing dextrose may be contraindicated in patients with known allergy to

280 corn or corn products.

281

282 **PRECAUTIONS**

283

284 **Congestive Heart Failure**

285

286 The number of heart failure patients with hypervolemic hyponatremia who have been

287 treated with intravenous VAPRISOL is too small to establish safety in patients with

288 underlying congestive heart failure. (See **ADVERSE REACTIONS**)

289

290 **Overly Rapid Correction of Serum Sodium**

291 An overly rapid increase in serum sodium concentration (>12 mEq/L/24 hours) may

292 result in serious sequelae. In controlled clinical trials of VAPRISOL, about 9% of

293 patients who received VAPRISOL in doses of 20-40 mg/day IV met laboratory criteria

294 for overly rapid correction of serum sodium, but none of these patients had permanent

295 neurologic sequelae. Although not observed in the clinical studies with VAPRISOL,

296 osmotic demyelination syndrome has been reported following rapid correction of low

297 serum sodium concentrations. Serum sodium concentration and neurologic status should

298 be monitored appropriately during VAPRISOL administration, and VAPRISOL

299 administration should be discontinued if the patient develops an undesirably rapid rate of

300 rise of serum sodium. If the serum sodium concentration continues to rise, VAPRISOL

301 should not be resumed. If hyponatremia persists or recurs (after initial discontinuation of

302 VAPRISOL for an undesirably rapid rate of rise of serum sodium concentration), and the

303 patient has had no evidence of neurologic sequelae of rapid rise in serum sodium,
304 VAPRISOL may be resumed at a reduced dose.

305

306 **Hepatic Impairment**

307 The use of VAPRISOL in patients with hepatic impairment (including ascites, cirrhosis,
308 or portal hypertension) has not been systematically evaluated.

309

310 Increased systemic exposures after oral administration of conivaptan have been seen in
311 patients with stable cirrhosis and moderate hepatic impairment. Intravenous VAPRISOL
312 resulted in higher conivaptan exposure than did oral conivaptan, in study subjects without
313 hepatic function impairment. Caution should be used when administering VAPRISOL to
314 patients with hepatic impairment.

315

316 **Renal Impairment**

317 The effect of renal impairment on the elimination of conivaptan after intravenous
318 administration has not been evaluated. However, following oral administration of
319 conivaptan, the AUC for conivaptan was up to 80% higher after a single oral dose and
320 35% higher with repeated oral dosing in patients with renal impairment ($CL_{Cr} < 60$
321 $\text{mL}/\text{min}/1.73 \text{ m}^2$) as compared to those with normal renal function. Intravenous
322 VAPRISOL resulted in higher conivaptan exposure than did oral conivaptan, in study
323 subjects without renal function impairment. Caution should be used when administering
324 VAPRISOL to patients with renal impairment.

325

326 **Injection Site Reactions**

327 Conivaptan may cause significant injection site reactions, even with proper dilution and
328 infusion rates. (See **ADVERSE REACTIONS**) The VAPRISOL ampule must only be
329 administered when properly prepared and diluted (see **Preparation**). VAPRISOL should
330 be administered via large veins, and the infusion site should be rotated every 24 hours.

331 (See **DOSAGE AND ADMINISTRATION**)

332

333 **Drug Interactions**

334 (See **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**)

335 **CYP3A4**

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

341

342 Conivaptan is a potent inhibitor of CYP3A4. VAPRISOL may increase plasma
343 concentrations of coadministered drugs that are primarily metabolized by CYP3A4. In
344 clinical trials of oral conivaptan hydrochloride, two cases of rhabdomyolysis occurred in
345 patients who were also receiving a CYP3A4-metabolized HMG-CoA reductase inhibitor.
346 Concomitant use of VAPRISOL with drugs that are primarily metabolized by CYP3A4
347 should be closely monitored or the combination should be avoided. If a clinical decision
348 is made to discontinue concomitant medications at recommended doses, allow an
349 appropriate amount of time (at least 24 hours) following the end of VAPRISOL
350 administration before resuming these medications.

351

352 **Digoxin**

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

357

358 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

359

360 Standard lifetime (104 week) carcinogenicity bioassays were conducted in mice and rats.

361 Mice were given oral doses of 3, 10 or 30 mg/kg/day in males and 1, 3 or 10 mg/kg/day

362 in females by gavage. Rats were given oral doses of 0.3, 1, 3 or 10 mg/kg/day in males

363 and 1, 3, 10 or 30 mg/kg/day in females by gavage. No increased incidence of tumors

364 was observed at doses up to 30 mg/kg/day in mice (6 times human systemic exposure of

365 an IV bolus of 20 mg on Day 1 followed by IV infusion 40 mg/day for 3 days based on

366 AUC comparison) or rats (2 times human systemic exposure of an IV bolus of 20 mg on

367 Day 1 followed by IV infusion 40 mg/day for 3 days based on AUC comparison).

368

369 Conivaptan was not mutagenic or clastogenic with or without metabolic activation in the

370 Ames test with *Salmonella typhimurium* and *Escherichia coli*, in human peripheral blood

371 lymphocytes, or *in vivo* rat micronucleus assay.

372

373 In fertility studies after 4 weeks treatment by intravenous bolus at 0.5, 1.25 or 2.5

374 mg/kg/day, male fertility was unaffected. However, in females given IV bolus

375 conivaptan 15 days before mating through gestation day 7 there was prolonged diestrus,

376 decreased fertility and increased pre- and post-implantation loss at 2.5 mg/kg/day

377 (systemic exposures less than the therapeutic dose).

378

379 **Pregnancy**

380 **Pregnancy Category C**

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

393

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

398

399 In pregnant rats given intravenous doses of 0.5, 1.25 or 2.5 mg/kg/day from gestation day
400 7 through 17 (organogenesis), no significant maternal or fetal effects were observed at
401 systemic exposures less than therapeutic exposure based on AUC comparisons.

402

403 Pregnant rats were administered intravenous conivaptan hydrochloride at a dose of 2.5
404 mg/kg/day (systemic exposures less than therapeutic based on AUC) from gestation day 7
405 through lactation day 20 (weaning), and the pups showed decreased neonatal viability,
406 weaning indices, delayed growth and physical development (including sexual
407 maturation), and delayed reflex development. No discernible changes were seen in pups
408 from dams administered conivaptan hydrochloride at 0.5 or 1.25 mg/kg/day from this
409 same period. No maternal adverse effects were seen with conivaptan hydrochloride
410 administration (0.5, 1.25, or 2.5 mg/kg/day from gestation day 7 through lactation day 20;
411 systemic exposures less than therapeutic dose based on AUC comparisons).

412

413 In pregnant rabbits given intravenous doses of 3, 6 or 12 mg/kg/day from gestation day 6
414 through 18 (organogenesis) there were no fetal findings; however, maternal toxicity was
415 observed in all groups (systemic exposures less than the therapeutic dose).

416

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

421

422 *Labor and Delivery*

423 The effect of conivaptan on labor and delivery in humans has not been studied.

424 Conivaptan hydrochloride delayed delivery in rats dosed orally at 10 mg/kg/day by oral
425 gavage (systemic exposures equivalent to the therapeutic dose based on AUC
426 comparisons). Administration of conivaptan hydrochloride at 2.5 mg/kg/day
427 intravenously increased peripartum pup mortality (systemic exposures were less than the
428 therapeutic dose based on AUC comparisons). These effects may be associated with
429 conivaptan activity on oxytocin receptors in the rat. The relevance to humans is unclear.

430

431 *Lactating Women*

432 It is not known whether conivaptan is excreted in human milk. Because many drugs are
433 excreted in human milk, caution should be exercised when VAPRISOL is administered to
434 a lactating woman. Conivaptan is excreted in milk and detected in neonates when given
435 by intravenous administration to lactating rats. Milk levels of conivaptan in rats reached
436 maximal levels at 1 hour post dose following intravenous administrations and were up to
437 3 times greater than maternal plasma levels. Administration of conivaptan hydrochloride
438 at 2.5 mg/kg/day intravenously increased peripartum pup mortality; systemic exposures
439 were less than the therapeutic dose based on AUC comparisons.

440

441 **Pediatric Use**

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

443

444 **Geriatric Use**

445 In clinical studies of intravenous VAPRISOL administered as a 20 mg IV loading dose
446 followed by 20 mg/day or 40 mg/day IV for 2 to 4 days, 89% (20 mg/day regimen) and
447 60% (40 mg/day regimen) of participants were greater than or equal to 65 years of age
448 and 60% (20 mg/day regimen) and 40% (40 mg/day regimen) were greater than or equal
449 to 75 years of age. In general, the adverse event profile in elderly patients was similar to
450 that seen in the general study population.

451

452 **ADVERSE REACTIONS**

453

454 The most common adverse reactions reported with VAPRISOL administration were
455 infusion site reactions. In studies in patients and healthy volunteers, infusion site
456 reactions occurred in 73% and 63% of subjects treated with VAPRISOL 20 mg/day and
457 40 mg/day, respectively, compared to 4% in the placebo group. Infusion site reactions
458 were the most common type of adverse event leading to discontinuation of VAPRISOL.
459 Discontinuations from treatment due to infusion site reactions were more common among
460 VAPRISOL-treated patients (3%) than among placebo-treated patients (0%). Some
461 serious infusion site reactions did occur. (See **DOSAGE AND ADMINISTRATION**)

462

463 The adverse reactions presented in Table 5 are derived from 72 healthy volunteers and
464 243 patients with euvolemic or hypervolemic hyponatremia who received VAPRISOL 20
465 mg IV as a loading dose followed by 40 mg/day IV for 2 to 4 days, from 37 patients with
466 euvolemic or hypervolemic hyponatremia who received VAPRISOL 20 mg IV as a
467 loading dose followed by 20 mg/day IV for 2 to 4 days in an open-label study, and from
468 40 healthy volunteers and 29 patients with euvolemic or hypervolemic hyponatremia who
469 received placebo. The adverse reactions occurred in at least 5% of patients treated with
470 VAPRISOL and at a higher incidence for VAPRISOL-treated patients than for placebo-
471 treated patients.

Table 5			
IV VAPRISOL: Adverse Reactions Occurring in \geq 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%)

473 Adapted from MedDRA version 6.0

474

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

479

480 **Congestive Heart Failure**

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

490

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

498

499 **DRUG ABUSE AND DEPENDENCE**

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

502

503 **OVERDOSAGE**

504 Although no data on overdosage in humans are available, VAPRISOL has been
505 administered as a 20 mg loading dose on Day 1 followed by continuous infusion of
506 80 mg/day for 4 days in hyponatremia patients and up to 120 mg/day for 2 days in CHF
507 patients. No new toxicities were identified at these higher doses, but adverse events
508 related to the pharmacologic activity of VAPRISOL, e.g. hypotension and thirst, occurred
509 more frequently at these higher doses.

510
511 In case of overdose, based on expected exaggerated pharmacological activity,
512 symptomatic treatment with frequent monitoring of vital signs and close observation of
513 the patient is recommended.

514

515 **DOSAGE AND ADMINISTRATION**

516

517 VAPRISOL is for intravenous use only.

518

519 VAPRISOL is for use in hospitalized patients only.

520

521 Administration of VAPRISOL through large veins and change of the infusion site every
522 24 hours are recommended to minimize the risk of vascular irritation.

523

524 VAPRISOL therapy should begin with a loading dose of 20 mg IV administered over 30
525 minutes.

526

527 The loading dose should be followed by 20 mg of VAPRISOL administered in a
528 continuous intravenous infusion over 24 hours. Following the initial day of treatment,
529 VAPRISOL is to be administered for an additional 1 to 3 days in a continuous infusion of
530 20 mg/day. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated
531 upward to a dose of 40 mg daily, again administered in a continuous intravenous
532 infusion.

533

534 The total duration of infusion of VAPRISOL (after the loading dose) should not exceed
535 four days. The maximum daily dose of VAPRISOL (after the loading dose) is 40
536 mg/day.

537

538 Patients receiving VAPRISOL must have frequent monitoring of serum sodium and
539 volume status. An overly rapid rise in serum sodium (>12 mEq/L/24 hours) may result in
540 serious neurologic sequelae. For patients who develop an undesirably rapid rate of rise of
541 serum sodium, VAPRISOL should be discontinued, and serum sodium and neurologic
542 status should be carefully monitored. If the serum sodium continues to rise, VAPRISOL
543 should not be resumed. If hyponatremia persists or recurs, and the patient has had no
544 evidence of neurologic sequelae of rapid rise in serum sodium, VAPRISOL may be
545 resumed at a reduced dose. (See **PRECAUTIONS: Overly Rapid Correction of**
546 **Serum Sodium**)

547

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

552

553 **Preparation**

554 **Compatibility and Stability**

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

559

560 **VAPRISOL (conivaptan hydrochloride injection) Ampule**

561 ***Caution: VAPRISOL ampule should be diluted only with 5% Dextrose Injection.***

562

563 The VAPRISOL ampule is compatible with 5% Dextrose Injection and is stable for up to
564 24 hours after mixing. **The VAPRISOL ampule should not be mixed or administered**
565 **with Lactated Ringer's Injection or 0.9% Sodium Chloride Injection.** Compatibility
566 with other drugs has not been studied; therefore, VAPRISOL should not be combined
567 with any other product in the same intravenous line or container.

568

569 The diluted solution of VAPRISOL should be used immediately and administration
570 completed within 24 hours of mixing.

571

572 Loading Dose

573 Withdraw 4 mL (20 mg) of VAPRISOL (4 mL of conivaptan hydrochloride injection)
574 and add to an infusion bag containing 100 mL of 5% Dextrose Injection, USP. Gently
575 invert the bag several times to ensure complete mixing of the solution. The contents of
576 the IV bag should be administered over 30 minutes.

577

578 Continuous Infusion

579 To prepare a continuous IV infusion containing 20 mg conivaptan hydrochloride,
580 withdraw 4 mL (20 mg) from a single ampule of VAPRISOL and dilute into an IV bag
581 containing 250 mL of 5% Dextrose Injection, USP. Gently invert the bag several times
582 to ensure complete mixing of the solution. The contents of the IV bag should be
583 administered over 24 hours.

584

585 To prepare a continuous IV infusion containing 40 mg conivaptan hydrochloride,
586 withdraw 4 mL (20 mg) from each of two ampules of VAPRISOL (8 mL [40 mg] of
587 conivaptan hydrochloride injection) and dilute into an IV bag containing 250 mL of
588 5% Dextrose Injection, USP. Gently invert the bag several times to ensure complete
589 mixing of the solution. The contents of the IV bag should be administered over 24 hours.

590

591 **The VAPRISOL ampule is for single use only. Discard unused contents of the**
592 **ampule.**

593

594 **VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose**

595 VAPRISOL is supplied in a single-use 100 mL flexible INTRAVIA container containing
596 a sterile premixed dilute, ready-to-use, nonpyrogenic solution of conivaptan
597 hydrochloride, 0.2 mg per mL (20 mg/100 mL) in 5% dextrose. **NO FURTHER**
598 **DILUTION OF THIS PREPARATION IS NECESSARY.**

599

600 VAPRISOL is compatible with 5% Dextrose Injection. **VAPRISOL should not be**
601 **administered with Lactated Ringer's Injection.** VAPRISOL should not be combined
602 with any other product in the same intravenous line or container.

603

604 *Loading Dose*

605 Administer 20 mg/100 mL VAPRISOL flexible plastic container over 30 minutes.

606

607 *Continuous Infusion*

608 For patients requiring 20 mg conivaptan hydrochloride injection per day, administer one
609 20 mg/100 mL VAPRISOL flexible plastic container over 24 hours.

610

611 For patients requiring 40 mg conivaptan hydrochloride injection per day, administer two
612 consecutive 20 mg/100 mL VAPRISOL flexible plastic containers over 24 hours.

613

614 **Since the flexible container is for single-use only, any unused portion should be**
615 **discarded.**

616

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

620

621 **Directions for VAPRISOL (conivaptan hydrochloride injection) Premixed in 5%**

622 **Dextrose:**

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

625 Tear overwrap down side at slit and remove solution container. Some opacity of the
626 plastic due to moisture absorption during the sterilization process may be observed. This
627 is normal and does not affect the solution quality or safety. The opacity will diminish
628 gradually. After removing overwrap, check for minute leaks by squeezing inner
629 container firmly. If leaks are found, discard solution as sterility may be impaired. Do not
630 use if the solution is cloudy or a precipitate is present.

631 **DO NOT ADD SUPPLEMENTARY MEDICATION.**

632 Preparation for Administration:

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

636

637 **STORAGE**

638 **VAPRISOL (conivaptan hydrochloride injection) Ampule**

639 Store at 25° C (77° F); excursions permitted to 15 - 30° C (59 - 86° F), controlled room
640 temperature (in accordance with USP). Do not store below 15° C (59° F). Ampules
641 should be stored in their cardboard container protected from light until ready for use.

642

643 **VAPRISOL (conivaptan hydrochloride injection) Premixed in 5% Dextrose**

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

647

648 **HOW SUPPLIED**

649 VAPRISOL (conivaptan hydrochloride injection) ampule is supplied in 4 mL clear glass,
650 one-point cut ampules. Each ampule contains 20 mg conivaptan hydrochloride.
651

652 10 ampules/carton (NDC 0469-1601-04)
653

654 VAPRISOL (conivaptan hydrochloride injection) in 100 mL INTRAVIA Plastic
655 Containers is supplied as a single-use, premixed solution, containing 20 mg of conivaptan
656 hydrochloride in 5% Dextrose.
657

658 10 containers/carton (NDC 0469-1602-11)
659

660 Rx only

661 VAPRISOL is a registered trademark of Astellas Pharma US, Inc.
662 INTRAVIA is a registered trademark of Baxter International Inc.
663

664 Marketed by:
665 Astellas Pharma US, Inc.
666 Deerfield, IL 60015-2548
667

668 VAPRISOL Ampule Manufactured by:
669 **Astellas Tokai Co., Ltd.**
670 Yaizu Plant
671 Shizuoka 425-0072, Japan
672

673 VAPRISOL in INTRAVIA Plastic Container Manufactured by:
674 **Baxter Healthcare Corporation**
675 Deerfield, IL 60015
676

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