National PBM Drug Monograph

Conivaptan Hydrochloride Injection (Vaprisol®)

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Conivaptan hydrochloride is a nonpeptide, dual V_{1a}/V_2 arginine vasopressin (AVP) receptor antagonist approved for the treatment of euvolemic hyponatremia. Through its actions at the V_2 receptors in the kidney, conivaptan increases free water excretion without significant electrolyte depletion.
- Although conivaptan has been studied in patients with congestive heart failure (CHF), a population where elevated AVP concentrations have been identified, safety has not been established.
- Hyponatremia studies with conivaptan are limited to one pivotal intravenous (IV) study (n=84), two supportive oral trials (n=157 combined), and an open label IV study (n=136). All studies included euvolemic and hypervolemic hyponatremic patients. Of these trials, one supportive oral trial is currently published.
- The pivotal IV trial evaluating 40 mg/day of conivaptan showed a significant increase in serum sodium (Na) at the end of day 4 of treatment over placebo (6.8 ± 0.81mEq/L vs. 2 ± 0.82 mEq/L).
- Mean baseline serum sodium in placebo-controlled hyponatremia trials ranged from 123-126 mEq/L. Little is known about the utility of conivaptan in patients with severe hyponatremia (i.e., Na <120 mEq/L).
- Conivaptan is a potent cytochrome CYP3A4 inhibitor and substrate. Coadministration with known inhibitors of this enzyme including ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated.
- To lessen the potential for drug-drug interactions, conivaptan is only available as an intravenous injection for use in closely monitored, hospitalized patients.
- Conivaptan is administered as a 20 mg IV bolus over 30 minutes followed by a continuous infusion of 20 mg over 24 hours for up to 4 days. If serum sodium is not increasing as desired, the dose of conivaptan may be titrated up to 40 mg/day.
- Infusion site reactions (ISRs) were the most common adverse events reported in clinical trials with conivaptan. To minimize the risk of ISRs, administration through a large vein and changing of the line every 24 hours is recommended. Other adverse reactions may include headache, hypotension, nausea, constipation, and postural hypotension.
- Close monitoring of serum Na and volume status is necessary in patients receiving conivaptan. Overly rapid increases in serum Na, which can result in permanent neurological sequelae, occurred in approximately 9.1% of subjects who received conivaptan in clinical trials. In addition, patients may experience symptoms from hypovolemia including hypotension.
- In summary, conivaptan cannot be recommended for patients with euvolemic hyponatremia until it has been found to be superior to time-proven safe and effective therapies such as free water restriction and/or intravenous saline. Similarly, its use for CHF must await persuasive empiric evidence of a positive risk-benefit ratio compared to standard therapy.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating conivaptan for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Conivaptan is the first arginine vasopressin (AVP) receptor antagonist approved in the U.S. and is indicated for the treatment of euvolemic hyponatremia. Hyponatremia, defined as serum sodium (Na) <135 mEq/L, is classified according to patient volume status: hypovolemic, euvolemic, or hypervolemic. Conivaptan has been studied in euvolemic and hypervolemic states. Common disease processes associated with euvolemic hyponatremia include the syndrome of inappropriate antidiuretic hormone release (SIADH), endocrine disorders (i.e., hypothyroidism or adrenal insufficiency), lung disorders and certain malignancies. Hypervolemic hyponatremia may be associated with edematous states including congestive heart failure (CHF), cirrhosis, and nephrotic syndrome.

Clinical manifestations of hyponatremia are primarily neurological in nature, and symptoms tend to be more prominent in the setting of acute and/or large decreases in serum sodium. Traditional treatments include fluid restriction and intravenous replacement of fluids with normal saline or hypertonic saline. Elevated levels of AVP, also known as antidiuretic hormone, have been identified in several states of hyponatremia. Recently, AVP antagonists, which increase free water excretion while preserving electrolytes, have been shown to effectively correct hyponatremia.

There is also interest in the use of conivaptan and other AVP antagonists in the setting of congestive heart failure (CHF), a population where elevated AVP levels have been identified. However, trials to date evaluating the use of conivaptan in the setting of CHF have not established safety.

Tolvaptan, an oral AVP V_2 receptor antagonist, is currently in development. Two phase 3 studies evaluating this drug have recently been published. The manufacturer expects to file an NDA with the FDA in 2007.

Pharmacology/Pharmacokinetics[1-3]

Conivaptan is a nonpeptide AVP antagonist specifically acting at the V_{1a} and V_2 receptors. AVP is secreted by the pituitary in response to increased serum osmolality or decreased effective circulating blood volume. Three types of vasopressin receptors have been identified: V_{1a} receptors located in the vascular smooth muscle; V_{1b} receptors in the pituitary; and V_2 receptors in the kidney. Stimulation of these receptors results in peripheral and coronary vasoconstriction (V_{1a}), release of adrenocorticotropic hormone [ACTH] (V_{1b}), and water retention (V_2). The predominant action of vasopressin at physiologic concentrations is water retention via V_2 receptor stimulation; higher plasma concentrations are required for vasoconstriction.

In vitro studies show that conivaptan exhibits similar affinity for V_{1a} and V_2 receptor subtypes and no affinity for V_{1b} receptor subtypes. The primary effect of conivaptan, mediated by antagonism at the V_2 receptor in the collecting ducts of the kidney, is aquaresis, an increase in free water excretion without significant increased excretion of electrolytes. Clinically, the result is increased urine output and normalization of serum sodium concentrations.

Clinical pharmacology studies demonstrate pharmacodynamic effects consistent with V_{1a} antagonism (increased skin blood flow and inhibition of AVP-induced platelet aggregation), although these effects would not be expected to disturb normal physiology in otherwise healthy nonhypovolemic patients.

Table 1. Pharmacokinetics

Parameter	Drug
Bioavailability	~30% absorption with oral conivaptan formulation
Cmax (at 0.5 hr)	619 ng/mL – median, healthy males (20 mg loading dose/20 mg/day) 575.8 (144.5-764.3) ng/mL – median, hyponatremic patients (20 mg loading dose/20 mg/day) 781.1 (194.5-1373.5) ng/mL – median, hyponatremic patients (20 mg loading dose/40 mg/day)
Protein Binding	99%
Metabolism	CYP3A4 (substrate and potent inhibitor); 4 active metabolites identified with minimal clinical effect
Elimination	Eliminated primarily as metabolites (<1% recovered intact drug in urine) 83% feces 12% urine
Clearance	15.2 L/hr
Half-life	5 hrs mean terminal elimination half-life

- Conivaptan exhibits nonlinear pharmacokinetics, which appears to be due to inhibition of its own metabolism. Intersubject variability of conivaptan is high (94% CV).
- Conivaptan has not been systematically studied in renal or hepatic impairment, although increased exposure following administration of oral conivaptan has been observed in these populations.
- In the elderly, a nearly 2-fold increase in AUC was observed following a single dose of 60 mg of oral conivaptan compared to younger subjects, although similar AUCs were observed at lower doses.

FDA Approved Indication and Off-label Uses[1]

Conivaptan is indicated for the treatment of euvolemic hyponatremia (i.e., SIADH, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.) in hospitalized patients. Although conivaptan has been evaluated in patients with hypervolemic hyponatremia (mainly in patients with CHF), safety has not been established.

Dosage and Administration[1]

Conivaptan is available for intravenous (IV) use only. To minimize the risk of vascular irritation, conivaptan should be administered through large veins. Changing the infusion site every 24 hours is recommended.

Conivaptan therapy should be initiated with a loading dose of 20 mg IV infused over 30 minutes, followed by a continuous IV infusion of 20 mg per day for up to 4 days. If serum sodium is not rising as desired, the infusion may be titrated up to 40 mg per day. The total duration of infusion should not exceed 4 days.

Monitoring

Frequent monitoring of serum sodium and volume status is necessary in patients receiving conivaptan. An overly rapid rise in serum sodium (>12 mEq/L/24 hrs) may result in serious sequelae. If patients develop an undesirably rapid rise in serum sodium, conivaptan should be discontinued and serum sodium and neurologic status carefully monitored. If serum sodium continues to rise, conivaptan should not be resumed. If hyponatremia persists or recurs, and the patient has no evidence of neurologic sequelae of rapid rise in serum sodium, conivaptan may be resumed at a reduced dose. For patients who develop hypotension or hypovolemia while receiving conivaptan, the drug should be discontinued and volume status and vital signs monitored. Once the patient is euvolemic and no longer hypotensive, conivaptan may be resumed at a reduced dose if patient remains hyponatremic.

Preparation

Conivaptan should be diluted with 5% Dextrose Injection only, and is stable up to 24 hours after mixing. Conivaptan should not be mixed or administered with other solutions (i.e., Lactated Ringer's Injection or 0.9% Sodium Chloride Injection) or drugs.

The loading dose should be prepared by adding 4 ml (20 mg) of conivaptan hydrochloride injection to an infusion bag containing 100 ml of 5% Dextrose Injection and infused over 30 minutes. To prepare the continuous infusion, either 4 ml (20 mg) or 8 ml (40 mg) of conivaptan hydrochloride injection should be

added to a 250 ml bag of 5% Dextrose Injection and administered over 24 hours. The drug should be used immediately and administration completed within 24 hours of mixing.

How Supplied/Storage
Conivaptan hydrochloride is available in single use ampules containing 4 ml (20 mg) of drug. Conivaptan should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F), controlled room temperature. Do not store below 15°C (59°F).

Efficacy

Efficacy Measures
The primary efficacy endpoint in clinical trials with conivaptan was change in serum sodium.

Summary of Efficacy Findings *(See Appendix 1 for details)*
Hyponatremia
There are three randomized, double-blinded, placebo-controlled clinical trials evaluating the efficacy of conivaptan in hyponatremia; one pivotal study with intravenous conivaptan and two supportive trials using oral conivaptan. Of these trials, only one supportive oral trial is currently published. All three trials conducted were similar in design. The primary efficacy endpoint was the mean change in serum sodium over the duration of treatment, as measured by the area under the serum sodium effect curve (AUC), corrected for baseline serum sodium. Secondary endpoints are reported in Tables 2 and 3.

In the pivotal phase 3 trial conducted with IV conivaptan, 84 nonhypovolemic hyponatremic patients were randomized to receive conivaptan 40 mg/day, 80 mg/day, or placebo for 4 days. The continuous infusion of conivaptan was preceded by a 20 mg intravenous loading dose. Of 84 total patients included in the analysis, 66 completed treatment. Of the patients who withdrew early, 11 (13%) were reported to be due to adverse events. Both doses of conivaptan were associated with significant improvements in serum sodium compared to placebo as measured by both the primary and secondary efficacy endpoints (Table 2).

Table 2. Efficacy Results from Study 027 (IV Conivaptan)[3,4]

	Placebo (n=29)	40 mg/day (n=29)	80 mg/day (n=26)
Baseline serum Na	124.3 ± 4	123.3 ± 4.7	124.8 ± 3.4
Primary Efficacy Endpoint			
Change from baseline serum Na AUC to day 4 (LS mean ± SE, in mEq/L-hr)	12.9 ± 61.2	490.9* ± 56.8	716.6* ±60.5
Secondary Efficacy Endpoints			
Median time to serum Na ≥4mEq/L increase over baseline [hrs (95% CI)]	NE	23.7* (10-24)	23.4* (6-24)
Mean total time serum Na ≥4mEq/L over baseline (LS mean in hrs ± SE)	14.2 ± 5.3	53.2* ± 5.2	72.7* ± 5.4
Mean change in serum Na from baseline to end of day 4 [LS mean in mEq/L ± SE (# of evaluable patients)]	2 ± 0.82 (n=25)	6.8* ± 0.81 (n=24)	9* ± 0.8 (n=24)
Number of patients with ≥6 mEq/L increase in serum Na or increase to normal serum Na (≥135 mEq/L) , (%)	6 (21)	20 (69)*	23 (89)*

*significant vs. placebo; AUC – area under the curve; LS – least squares; NE – not estimable

Of the two supportive oral conivaptan trials, one has been published. Ghali et al.[5] reported on 74 euvolemic and hypervolemic hyponatremic patients who were randomized to receive oral conivaptan 40 mg/day, 80 mg/day, or placebo, all given in two divided doses/day for 5 days. One patient from each treatment arm discontinued the study early. Regarding the primary efficacy endpoint, both doses of conivaptan were associated with significant improvements over placebo. The 80 mg/day dose of conivaptan was also significantly more effective than placebo in all secondary measures (Table 3).

Results from the second oral conivaptan study are available in abstract form only.[6] Study 043 included 83 nonhypovolemic hyponatremic patients randomized to receive oral conivaptan 40 mg/day, 80 mg/day, or placebo, given in two divided doses/day for 5 days. Authors reported that 87% of patients completed the study and reasons for discontinuation were not discussed. Both doses of conivaptan were associated with significant improvements in serum sodium compared to placebo in both the primary and secondary endpoints (Table 3).

Table 3. Efficacy Results from Studies 026 and 043 (Oral Conivaptan^)

	Study 026 (Ghali)			Study 043		
	Placebo (n=23)	**40 mg/day (n=24)**	**80 mg/day (n=27)**	**Placebo (n=30)**	**40 mg/day (n=27)**	**80 mg/day (n=26)**
Baseline serum Na	123.4 ± 4.1	125.3 ± 3.5	125.4 ± 4	125.6 ± 3.9	125.1 ± 5.1	125.6 ± 3.6
Primary Efficacy Endpoint						
Change from baseline serum Na AUC to day 5 (LS mean ± SD, in mEq/L-hr)	309.2 ± 94.8	621.3* ± 89	836.2* ± 87.8	87.5 ± 80.8	634.2* ± 84.2	952.7* ± 85.7
Secondary Efficacy Endpoints						
Median time to Na ≥4mEq/L increase over baseline [hrs (95% CI)]	71.7 (49-NE)	27.5* (12-47)	12.1* (11-28)	NE	23.5* (12-24)	8.7* (4-24)
Mean total time serum Na ≥4mEq/L over baseline (LS mean in hrs ± SE)	46.5 ± 9	69.8 ± 8.5	88.8* ± 8.4	n/a	n/a	n/a
Mean change in serum Na from baseline to end of day 5 (LS mean in mEq ± SE)	3.4 ± 1.1	6.4 ±1	8.2* ± 1	1 ± 0.9	6.8* ± 0.9	8.8* ± 0.9
Patients with ≥6 mEq/L increase in serum Na or normal serum Na (>135 mEq/L) , n (%)	11 (48)	17 (71)	22 (82)*	6 (20)	18 (67)*	23 (89)*

^Bioavailability of oral conivaptan is ~30%; *significant vs. placebo; NE – not estimable; LS – least squares; n/a – not available

In an open-label study conducted in nonhypovolemic hyponatremic patients (Study 080), intravenous conivaptan was administered as a 20 mg intravenous bolus followed by continuous infusion of 20 mg or 40 mg/day for 4 days. Similar endpoints as in the above trials were used. The 20 mg/day arm was added in response to FDA's request to evaluate efficacy of the drug at lower doses. Interim results, available for 136 patients (n=21 in 20 mg/day group; n=115 in 40 mg/day group), showed that numerically, 20 mg/day of conivaptan was associated with similar or better improvements in serum sodium than the 40 mg dose (p values not stated).

Duration of Effect

Although the duration of conivaptan's effect on serum sodium was not directly determined, serum sodium was evaluated in two of the trials after treatment. In study 027, mean serum sodium, measured one time at day 10-13 was 131 mEq/L, 129 mEq/L, and 134 mEq/L in placebo, 40 mg/day, and 80 mg/day groups respectively. In the open label trial, serum sodium levels measured at day 11 and day 34 and were similar to levels at the end of treatment. Significant hyponatremia did not seem to recur in either of these studies following treatment, although it is unknown whether this effect was due to conivaptan or other factors (i.e., treatment of the underlying cause of hyponatremia).

Heart Failure

In a double-blind, dose-ranging pilot study,[7] 162 hospitalized patients with acute decompensated heart failure, New York Heart Association (NYHA) Class III/IV, were randomized to receive conivaptan 20 mg by intravenous bolus followed by continuous infusion of 40 mg/day, 80 mg/day, 120 mg/day, or placebo for 2 days. Efficacy endpoints included change in respiratory symptoms, urine output and weight. Ten patients in the conivaptan groups and one in the placebo group discontinued the drug due to adverse events. Conivaptan did not improve severity of respiratory symptoms as assessed by the patient using a visual analog scale (VAS). Significant increases in urine output and changes in body weight were observed with all doses of conivaptan compared to placebo.

Hemodynamic effects of conivaptan were evaluated in a double-blind, single dose study in patients with NYHA Class III/IV heart failure.[8] A total of 142 patients were randomized to receive intravenous conivaptan 10 mg, 20 mg, 40 mg or placebo. Conivaptan administration was associated with a significant reduction in pulmonary capillary wedge pressure (PCWP), right atrial pressure, and an increased urine output compared to placebo. No differences were seen in other parameters evaluated including cardiac index (CI), pulmonary artery pressure (PAP), mean arterial pressure (MAP), and pulmonary vascular resistance (PVR). Reports of adverse events were similar or slightly lower in the conivaptan groups. No serious adverse events or drug-related deaths occurred.

Adverse Events (Safety Data)

The overall patient safety population was comprised of 1,160 subjects exposed to conivaptan. Of these, 404 patients and healthy volunteers received intravenous conivaptan ≥40 mg/day for 2-4 days. However,

the safety information from placebo-controlled hyponatremia trials with IV conivaptan is limited to only 55 patients from the pivotal Phase 3 study. Several subpopulations were analyzed in the FDA safety review.

Deaths[3]

The overall incidence of death among conivaptan-treated patients reported in the clinical development program was 5.5% (63/1148) vs. 3.2% (12/372) in the placebo groups. These were deaths that occurred either during treatment or within 30 days of treatment or later but due to an adverse event that occurred during treatment. When investigated by subpopulation, there appears to be a dose-related increased risk of death in patients with CHF treated with conivaptan. According to the FDA review, there does not appear to be an increased risk of death for conivaptan when used in the absence of CHF.

In the placebo-controlled IV and oral hyponatremia studies (Study 027, 026, and 043), there were 8 deaths in 159 conivaptan-treated patients summarized in Table 4.

Table 4. Summary of Deaths in Conivaptan-treated Patients in Phase 3 Controlled IV/Oral Hyponatremia Trials (Studies 027, 026, and 043)

Study	Age	Gender	Description
027	81	F	Metastatic gallbladder cancer, sepsis, hypotension, liver failure
027	91	M	Pneumonia, CHF
027	59	F	Out of hospital death, unknown cause
027	90	F	CHF, pneumonia, renal failure
026	45	F	End stage CHF, renal failure
026	54	F	Cardiorespiratory arrest, CHF; was hypotensive on conivaptan
043	78	F	Refractory heart failure
043	67	M	Hypovolemic shock after marked aquaresis

Serious Adverse Events[3]

In table 5, the incidence of serious adverse events is listed by event for the full safety population. Table 6 includes the full patient sets (euvolemic and hypervolemic patients) from the placebo controlled hyponatremia trials.

Table 5. Overall Safety Population: Serious Adverse Events occurring in ≥1% of Conivaptan Treated Subjects

	All IV		All Oral		All IV + Oral	
Event	**Placebo (n=132)**	**Coni (n=445)**	**Placebo (n=240)**	**Coni (n=715)**	**Placebo (n=372)**	**Coni (n=1160)**
Total cardiac events (includes CHF, CMP)	9.8%	8.3%	3.3%	6.7%	5.6%	7.3%
CHF, aggravated	0.8%	1.3%	0.8%	2.4%	0.8%	2%
CHF, total	3%	4.7%	1.7%	4.1%	2.2%	4.1%
Total infusion site reactions		1.3%				0.5%
Total infection events	4.5%	7%	0.4%	1.8%	1.9%	3.8%
Total metabolic and nutrition events	2.3%	2.7%	0.4%	2.2%	1.1%	2.4%
Total nervous system events	0.8%	1.6%		2.2%	0.3%	2%

CMP=cardiomyopathy

Table 6. Serious Treatment-Emergent Adverse Events, Phase 3 Controlled IV and Oral Hyponatremia Trials

		Study 027 (IV)			Studies 026 and 043 (Oral)		
Body System	**Adverse Event**	**Placebo n=29**	**Coni 40 n=29**	**Coni 80 n=26**	**Placebo n=53**	**Coni 40 n=51**	**Coni 80 n=53**
Cardiac	acute MI, AV block, cardiac failure, SVT, V tach, sick sinus syndrome	10.3%	10.3%	7.7%	1.9%	9.8%	1.9%
Cardiac Procedures	cardioversion, heart transplant				1.9%	2%	
Vascular Disorders	arterial occlusion, DVT, hypertension, hypotension	6.9%	6.9%			3.9%	1.9%
GI	GI bleed	3.4%					
General Disorders	anasarca, edema, peripheral edema, pain		3.4%		3.8%		1.9%
Hepatic Disorders	elevated LFTs, cholestasis, hepatic failure		3.4%	3.8%	1.9%	5.9%	
Infection	pneumonia, sepsis		3.4%	7.7%			

Metabolic/ Nutritional Disorders	dehydration, hypovolemia, hyperkalemia, hyponatremia	6.8%	6.8%			3.9%	
Neurological	confusional state		3.4%				
Renal	renal disorder, renal failure, acute renal injury	3.4%	13.8%	11.5%		5.9%	1.9%
Reproductive	ovarian mass			3.8%			
Respiratory	COPD exacerbation, dyspnea, hypercapnea, PE, respiratory arrest	3.4%	3.4%			3.9%	1.9%

COPD=chronic obstructive pulmonary disease; DVT=deep venous thrombosis; GI=gastrointestinal; LFTs=liver function tests; MI=myocardial infarction; PE=pulmonary embolism; SVT=supraventricular tachycardia; V tach=ventricular tachycardia

Other Adverse Events of Interest[3]

Signals detected in the original NDA or pre-clinically warranted further evaluation of the below events of interest.

Renal Adverse Events

Overall (serious and nonserious combined) renal adverse events occurred more frequently among conivaptan treated patients compared to placebo. Most events were moderate, reversible increases in serum creatinine, which may be due to volume depletion and a prerenal state. A direct nephrotoxic effect of conivaptan was not detected. Most cases of renal failure occurred in patients with underlying CHF. A review of the safety data available does not indicate that conivaptan is associated with an increased risk of serious renal adverse events.

Overly Rapid Correction of Serum Sodium

In evaluating the patient population in clinical trials that received conivaptan in doses of 20-40 mg/day IV equivalent as in the product labeling, 9.1% (n=27/297) of patients met criteria for overly rapid rise of serum sodium. Of these, one patient experienced a seizure with no permanent deficits.

Hypotension and Hypovolemia

In various subpopulations reviewed, including controlled and non-controlled studies, hypovolemia related adverse events occurred more frequently in IV conivaptan treated patients than in placebo. Intravenous conivaptan appears to be associated with an increase risk of both serious and nonserious hypotension and hypovolemic related events, which may be due to intravascular volume depletion.

Adverse Events in CHF Patients

Adverse events that occurred more frequently in patients with CHF included atrial arrhythmias, bleeding, ISRs, and cardiac failure events. With the data available at the time of original approval, the FDA recommended that the use of conivaptan in CHF patients be limited to the clinical trial setting.

Common Adverse Events[2]

Infusion site reactions (ISRs) were the most commonly reported adverse events reported in clinical trials. In the overall safety population, 57% of subjects who received conivaptan IV reported ISRs vs. 7.3% of placebo groups. Most reactions were mild; however some serious ISRs did occur. ISRs with conivaptan appear to be dose and concentration related. Other commonly reported adverse reactions included headache, hypotension, nausea, constipation, and postural hypotension.

Table 7. Adverse Events Occurring in ≥2% of Volunteers and Patients with Euvolemic Hyponatremia (FDA labeled indication only)[2]

Body System	Adverse Event	Placebo (n=61) n (%)	Conivaptan 40mg/day IV (n=183) n (%)
Blood Disorders	Anemia	2 (3.3)	7 (3.8)
Cardiac Disorders	Atrial fibrillation	0	5 (2.7)
Gastrointestinal Disorders	Constipation	2 (3.3)	9 (4.9)
	Diarrhea	0	10 (5.5)
	Dry mouth	2 (3.3)	8 (4.4)
	Nausea	2 (3.3)	7 (3.8)
	Vomiting	0	12 (6.6)
General Disorders and Administration Site Conditions	Infusion site reactions, all	2 (3.3)	96 (52.5)
	Edema, peripheral	1 (1.6)	10 (5.5)
	Pain	0	4 (2.2)

	Pyrexia	0	7 (3.8)
	Thirst	1 (1.6)	18 (9.8)
	Erythema, skin	0	5 (2.7)
Infections	Oral candidiasis	0	4 (2.2)
	Pneumonia	0	5 (2.7)
	Urinary tract infection	1 (1.6)	6 (3.3)
Metabolic and Nutritional Disorders	Dehydration	0	4 (2.2)
	Hyperglycemia	0	5 (2.7)
	Hypoglycemia	0	6 (3.3)
	Hypokalemia	1 (1.6)	18 (9.8)
	Hypomagnesemia	0	4 (2.2)
	Hyponatremia	0	6 (3.3)
Nervous System Disorders	Headache	2 (3.3)	22 (12)
Psychiatric Disorders	Confusional state	1 (1.6)	7 (3.8)
	Insomnia	0	6 (3.3)
Renal and Urinary Disorders	Hematuria	1 (1.6)	4 (2.2)
	Pollakiuria	0	11 (6)
	Polyuria	0	9 (4.9)
Vascular Disorders	Hypertension	0	10 (5.5)
	Hypotension	1 (1.6)	5 (2.7)
	Orthostatic hypotension	0	10 (5.5)
	Phlebitis	1 (1.6)	9 (4.9)

Precautions

CHF
The safety of conivaptan has not been established in hyponatremic patients with CHF. Until further information is available, conivaptan should not be used in patients with underlying CHF outside of the clinical trial setting.

Overly Rapid Correction of Serum Sodium
Central pontine myelinolysis leading to serious, sometimes permanent neurological damage and death is an established risk of correcting serum sodium too rapidly. As defined in the clinical trials, an undesirable rate of rise of serum sodium was an increase of >12mEq/L in a 24 hour period, an increase of ≥24mEq/L over baseline, or an increase to ≥145mEq/L at any time. Approximately 9.1% of patients in clinical trials who received doses approved for labeling met criteria for overly rapid correction of serum sodium. Close monitoring of serum sodium and neurologic status is recommended in patients receiving conivaptan.

Hepatic or Renal Impairment
The effect of conivaptan in patients with hepatic or renal impairment has not been extensively studied. Increased exposure following oral administration of conivaptan in patients with hepatic and renal impairment has been observed. Caution should be used when administering conivaptan to patients with hepatic or renal impairment.

Contraindications

- Hypovolemic hyponatremia
- Co-administration with potent CYP3A4 inhibitors including ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir
- Hypersensitivity to ingredients

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for conivaptan:

Ativan (lorazepam) injection, tablets – benzodiazepine
Coumadin (warfarin) tablets – anticoagulant
Sumatriptan (Imitrex) injection, tablets – 5-hydroxytryptamine$_1$ receptor agonist
Carboplatin (Paraplatin) injection – antineoplastic agent

LA/SA for Vaprisol:

Valproate sodium (Depacon) injection – anticonvulsant
Pantoprazole sodium (Protonix) injection – proton pump inhibitor
Allopurinol (Zyloprim) tablets – xanthine oxidase inhibitor

Drug Interactions[1-3]

CYP3A4

Conivaptan is a sensitive substrate of CYP3A4. Coadministration of conivaptan with known inhibitors of CYP 3A4 may result in elevated concentrations of conivaptan, the effects of which are unknown. Concurrent use of potent inhibitors of CYP3A4 including ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir is contraindicated.

Due to its potent inhibitory effects on CYP3A4, conivaptan coadministered with drugs metabolized by this enzyme may result in significantly elevated concentrations of that drug. Concomitant use of conivaptan and drugs metabolized by CYP3A4 should be avoided if possible or closely monitored.

There were 4 cases of marked creatinine kinase elevation/myopathy, including 2 cases of rhabdomyolysis, in clinical trials of oral conivaptan. One patient was on lovastatin, two were on simvastatin, and one was on gemfibrozil/cerivastatin. To reduce the potential for serious drug interactions, the manufacturer restricted conivaptan development to the intravenous form for use in short durations in hospitalized patients.

Digoxin

Coadministration of digoxin and oral conivaptan resulted in a 30% reduction in digoxin clearance and an increase in digoxin Cmax (79%) and AUC (43%).

Warfarin

In a 10-day duration drug interaction study, oral conivaptan did not significantly alter R- or S- warfarin concentrations or bleeding time. However, there have been reports of increased bleeding times with coadministration of warfarin and conivaptan in other clinical trials.

Table 8. Drug Interaction Studies[3]

n	Subjects	Conivaptan dose, duration	Coadministered Drug	Results
84	Healthy	PO – 20 or 40mg/day, 2 days	PO midazolam 2 mg	Conivaptan 20 and 40mg/day increased midazolam AUC by 2.8 and 3.9-fold
37	Healthy	IV – 40 or 80mg/day, days 3-5	PO or IV midazolam 2mg or 1 mg days 1, 5	Conivaptan increased midazolam metabolite exposure by 1.6 to 2-fold
12	Healthy	PO – 40mg BID, 12 days	PO amlodipine 5mg/day	Conivaptan increased amlodipine AUC 2.4-fold
12	Stable on warfarin	PO – 40mg BID, 10 days	PO warfarin	Conivaptan did not significantly effect R- or S-warfarin concentrations or on PT
16	Healthy	PO – 20 or 40mg/day, days 2-6	PO simvastatin 60mg, days 1, 6	Conivaptan 40mg/day increased simvastatin AUC 5.9-fold
4	Healthy	IV – 15mg BID, days 3-5	PO simvastatin 60mg, days 1, 5	Conivaptan increased simvastatin AUC increased 3-fold
12	Healthy	PO – 10mg/day, day 1, 5	PO ketoconazole 200mg BID, days 4-6	Ketoconazole increased conivaptan Cmax and AUC by 4-fold and 11-fold
14	Healthy	PO – 40mg/day, 2 days	IV digoxin 0.5mg	Conivaptan had no significant effect on digoxin PK parameters
12	Healthy	PO – 40mg BID, 10 days	PO digoxin 0.25mg/day	Conivaptan increased digoxin Cmax and AUC by 79% and 43% and reduced clearance by 30%
15	Healthy	PO – 30mg/day, 2 days	PO captopril 25mg/day	Captopril had no effect on PK of conivaptan
24	CHF	PO – 20 or 40mg/day, 3 days	PO furosemide 40 or 80mg/day	Furosemide had no effect on PK of conivaptan

CHF – congestive heart failure; PT – prothrombin time; AUC – area under the curve; PK - pharmacokinetic

Acquisition Costs

The FSS price for conivaptan is $219.31 per 20 mg vial for injection.

Table 9. Conivaptan Costs

Dose	Cost/day	Cost/treatment course
20 mg loading dose, then 20 mg/day x4	$438.62 for day 1, then $219.31/day	$1096.55
20 mg loading dose, then 40 mg/day x4	$438.62 for days 1-4	$1754.48

Pharmacoeconomic Analysis

There are currently no available pharmacoeconomic analyses available for conivaptan.

Conclusions

Conivaptan is the first FDA approved AVP receptor antagonist for the treatment of euvolemic hyponatremia. Although data is limited, clinical trials thus far demonstrate efficacy of conivaptan in euvolemic hyponatremic patients compared to placebo and that close monitoring of sodium and volume status is necessary. ISRs are the most commonly reported adverse events with conivaptan. Due to the potential for serious drug-drug interactions, concurrent administration with drugs known to be substrates or inhibitors of CYP3A4 should be avoided. The duration of effect of conivaptan has not been directly determined, and therapy beyond 4 days has not been studied.

Conivaptan has not been compared to time-proven safe and effective therapies such as free water restriction and/or intravenous saline use. Little is known about the utility of conivaptan in patients with severe hyponatremia (Na <120 mEq/L) i.e. those most likely to be hospitalized because of this condition. While there is great interest in the potential use of AVP antagonists in the treatment of CHF, safety of conivaptan has not been established. Thus, conivaptan cannot be recommended for patients with euvolemic hyponatremia or CHF until its utility and safety advantages compared to standard therapy are demonstrated.

References:

1. Product package insert for conivaptan (Vaprisol). February 2006.
2. Astellas Vaprisol Clinical Product Monograph.
3. FDA review of conivaptan (http://www.fda.gov/cder/foi/nda/2005/021697s000_Vaprisol_MEDR.pdf).
4. Verbalis JG, Bisaha JG, Smith N. Novel vasopressin V1a and V2 antagonist (conivaptan) increases serum sodium concentration and effective water clearance in patients with hyponatremia. Circulation. 2004;110(Suppl 3):723. [Abstract].
5. Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Kaisheng F, Long WA, Smith N. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. J Clin Endocrinol Metab. 2006; 91:2145-52.
6. Gross P, Bisaha JG, Smith N. Conivaptan, a novel V1a and V2 antagonist, increases serum sodium and effective water clearance in patients with hyponatremia. Circulation. 2004;110(suppl 3):723. [abstract]
7. Goldsmith SR. Efficacy and safety of conivaptan in acute decompensated heart failure; a dose-ranging pilot study. J Card Fail. 2006;12(6) Suppl: S72.
8. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, et al. Acute hemodynamic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist, in patients with advanced heart failure. Circulation. 2001;104:2417-23.

Prepared 12/2006 Contact person: Lisa S. Longo, Pharm.D., BCPS

Appendix 1. Placebo Controlled Trials

<table>
<tr><th>Study</th><th>Inclusion/Exclusion Criteria</th><th>Dose</th><th>Demographics and Baseline Values</th><th>Results</th></tr>
<tr>
<td>Study 027
Phase 3 trial
FDA transcripts/ Product package insert

n=84

MC, DB, PC, RCT

Placebo (n=29)
CONI 40mg (n=29)
CONI 80mg (n=26)</td>
<td>Inclusion criteria
≥18 years old
Euvolemic or hypervolemic Hyponatremia (serum Na 115-<130mEq/L)
Serum osmolality <290mOsm/kg H_20

Exclusion criteria
Dehydration or hypovolemia, pregnancy or lactation, FBS ≥275mg/dL, supine SBP <85mmHg, orthostatic hypotension (SBP drop >20mmHg supine to standing or <80mmHg SBP standing), uncontrolled HTN or arrhythmias, untreated hypo- or hyper-thyroidism or adrenal insufficiency, CrCl <20 mL/min, urinary outflow obstruction unless catheterized, ALT or AST >5x ULN, INR >2 not on or INR >3 on anticoagulant therapy, albumin <1.5g/dL, WBC <3K/uL, HIV or hepatitis infection

Other treatments for hyponatremia not permitted</td>
<td>Loading (IV)
CONI 20mg

Maintenance (CIV)
CONI 40mg/day vs.
CONI 80mg/day vs.
Placebo

Duration
4 days

All patients
Fluid restriction of 2L/d</td>
<td>Values for Placebo/40mg/80mg
Mean age (yrs): 76/74/73
% Male: 52/41/54
% White (non-Hispanic): 90/93/73
% Black (non-Hispanic): 7/3/23

Cause of hyponatremia
% COPD: 7/0/0
% Malignancy: 7/10/8
% Idiopathic: 14/17/23
% CHF: 24/35/31
% Post surgical: 3/3/4

Volume status
% Hypervolemic: 28/38/35
% Euvolemic: 72/62/65

Mean days since first diagnosis: 485/360/313

Mean days since current episode began: 43/15/28

Mean baseline serum Na (mEq/L): 124/123/125</td>
<td>
<table>
<tr><th></th><th>Placebo</th><th>CONI 40</th><th>CONI 80</th></tr>
<tr><td># drop-outs</td><td>7/29</td><td>7/29</td><td>6/26</td></tr>
<tr><td>Change in Na AUC (LS mean ± SE in mEq-hr/L)</td><td>12.9 ± 61.2</td><td>490.9* ± 56.8</td><td>716.6* ± 80.5</td></tr>
<tr><td>Time to Na increase ≥4mEq/L over baseline (median in hrs) [95% CI]</td><td>NE</td><td>23.7* (10-24)</td><td>23.4* (6-24)</td></tr>
<tr><td>Mean total time Na ≥4mEq/L over baseline (LS mean ± SE in hr)</td><td>14.2 ± 5.3</td><td>53.2* ± 5.2</td><td>72.7* ± 5.4</td></tr>
<tr><td>Change in Na at end of treatment (LS mean ± SE in mEq/L)</td><td>0.8 ± 0.8</td><td>6.8* ± 0.81</td><td>9* ± 0.8</td></tr>
<tr><td>% patients with Na ≥135mEq/L or increase of ≥6mEq/L</td><td>20.7</td><td>69*</td><td>88.5*</td></tr>
</table>
*significant vs. placebo
</td>
</tr>
<tr>
<td>Ghali JK
(Study 026)

MC, DB, PC, RCT

n=74

Placebo (n=23)
CONI 40mg (n=24)
CONI 80mg (n=27)</td>
<td>same as above</td>
<td>CONI 40mg PO/day* vs.
CONI 80mg PO/day* vs.
Placebo*

*given in 2 divided doses

Duration
5 days

All patients
Fluid restriction of 2L/d</td>
<td>Values for Placebo/40mg/80mg
Mean age (yrs): 73/66/69
% Male: 44/50/52
% White (non-Hispanic): 96/79/93
% Black (non-Hispanic): 4/13/0

Cause of hyponatremia
% COPD: 4/0/7
% Malignancy: 13/8/11
% Idiopathic: 13/21/26
% CHF: 48/42/41
% Other: 22/29/15

Volume status
% Hypervolemic: 26/33/18
% Euvolemic: 74/67/82

Mean baseline serum Na (mEq/L): 123/125/125</td>
<td>
<table>
<tr><th></th><th>Placebo</th><th>CONI 40</th><th>CONI 80</th></tr>
<tr><td># drop-outs</td><td>1/23</td><td>1/24</td><td>1/27</td></tr>
<tr><td>Change in Na AUC (LS mean ± SE in mEq-hr/L)</td><td>309.2 ± 94.8</td><td>621.3* ± 89</td><td>836.2* ± 87.8</td></tr>
<tr><td>Time to Na increase ≥4mEq/L over baseline (median in hrs)</td><td>71.7</td><td>27.5*</td><td>12.1*</td></tr>
<tr><td>Mean total time Na ≥4mEq/L over baseline (LS mean ± SE in hrs)</td><td>46.5 ± 9</td><td>69.8 ± 8.5</td><td>88.8* ± 8.4</td></tr>
<tr><td>Change in Na to end of treatment (LS mean ± SE in mEq/L)</td><td>3.4 ±1.1</td><td>6.4 ± 1</td><td>8.2* ± 1</td></tr>
<tr><td>% patients with Na ≥135mEq/L or increase of ≥6mEq/L</td><td>48</td><td>71</td><td>82*</td></tr>
</table>
*significant vs. placebo
</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Inclusion/Exclusion Criteria</th><th>Dose</th><th>Demographics and Baseline Values</th><th>Results</th></tr>
<tr>
<td>Study 043
(abstract only)
n=83</td>
<td>Same as above</td>
<td>CONI 40mg PO/day* vs.
CONI 80mg PO/day* vs.
Placebo*
*given in two divided doses
Duration
5 days
All patients
Fluid restriction of 2L/d</td>
<td>% Male: 66
Mean baseline serum Na (mEq/L):
Placebo: 126
40mg/day: 125
80mg/day: 126
Volume status
% Hypervolemic: 37
% Euvolemic: 63</td>
<td>
<table>
<tr><th></th><th>Placebo</th><th>CONI 40</th><th>CONI 80</th></tr>
<tr><td>Change in Na AUC (LS mean ± SE in mEq-hr/L)</td><td>87.5 ± 80.8</td><td>634.2* ± 84.2</td><td>952.7* ± 85.7</td></tr>
<tr><td>Time to Na increase ≥4mEq/L over baseline (median in hrs) [95% CI]</td><td>NE</td><td>23.5* (12-24)</td><td>8.7* (4-24)</td></tr>
<tr><td>Change in Na to end of treatment (LS mean ± SE in mEq/L)</td><td>1 ± 0.9</td><td>6.8* ± 0.9</td><td>8.8* ± 0.9</td></tr>
<tr><td>% patients with Na ≥135mEq/L or increase of ≥6mEq/L</td><td>20</td><td>67*</td><td>89*</td></tr>
</table>
*significant vs. placebo
</td>
</tr>
<tr>
<td>Study 080
OL
n=136
CONI 20mg (n=21)
CONI 40mg (n=115)</td>
<td>Same as above</td>
<td>Loading (IV)
CONI 20mg
Maintenance (CIV)
CONI 20mg/day vs.
CONI 40mg/day vs.
Duration
4 days</td>
<td>Values for 20mg/40mg:
Mean baseline serum Na (mEq/L):
122/124
Volume status:
%Hypervolemic: 47/19
%Euvolemic: 53/81</td>
<td>
<table>
<tr><th></th><th>CONI 20</th><th>CONI 40</th></tr>
<tr><td>Change in Na AUC (Mean ± SD in mEq-hr/L)</td><td>770.5 ± 446.9</td><td>651.4 ± 403.4</td></tr>
<tr><td>Time to Na increase ≥4mEq/L over baseline (median in hrs) [95% CI]</td><td>24 (6.8-60)</td><td>24.6 (24-36)</td></tr>
<tr><td>Change in Na to end of treatment (Mean ± SD in mEq/L)</td><td>10.2 ± 5.5</td><td>8.3 ± 5.3</td></tr>
<tr><td>Change in Na at Day 11 (Mean ± SD in mEq/L)</td><td>7.9 ± 9.6</td><td>8 ± 6.55</td></tr>
<tr><td>Change in Na at Day 30 (Mean ± SD in mEq/L)</td><td>13.1 ± 7</td><td>10.3 ± 6.5</td></tr>
<tr><td>% patients with Na ≥135mEq/L or increase of ≥6mEq/L</td><td>71.4</td><td>84</td></tr>
</table>
(interim results; p values not given)
</td>
</tr>
</table>

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the curve; CIV=continuous intravenous infusion; CONI=conivaptan; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; DB=double-blind; FBS=fasting blood sugar; HTN=hypertension; INR=international normalized ratio; LS=least squares; MC=multicenter; Na=sodium; NE=not estimable; OL=open-label; PC=placebo controlled; RCT=randomized clinical trial; SBP=systolic blood pressure; ULN=upper limit of normal