

Table 7.1.5.2 Number and Percentage of Hypervolemic Hyponatremic Patients With CHF Who Had Treatment-emergent Adverse Events¹, Intravenous Studies 027, 071, 080

System Organ Class (SOC)	Preferred Term	Pbo	20 mg	40 mg	80 mg	120 mg	Any Coni Dose
		N=10 n(%)	N=8 n(%)	N=50 n(%)	N=11 n(%)	N=10 n(%)	N=79 n(%)
	Infusion site phlebitis	2 (20.0)	2 (25.0)	18 (36.0)	3 (27.3)	4 (40.0)	27 (34.2)
	Infusion site reaction	0	1 (12.5)	5 (10.0)	1 (9.1)	0	7 (8.9)
	Pyrexia	1 (10.0)	2 (25.0)	4 (8.0)	0	1 (10.0)	7 (8.9)
Infections and infestations	Any AE	4 (40.0)	2 (25.0)	15 (30.0)	5 (45.5)	3 (30.0)	25 (31.6)
	Pneumonia NOS	0	1 (12.5)	1 (2.0)	1 (9.1)	0	3 (3.8)
	Sepsis NOS	0	1 (12.5)	3 (6.0)	1 (9.1)	1 (10.0)	6 (7.6)
Injury, poisoning and procedural complications	Any AE	0	2 (25.0)	6 (12.0)	0	0	8 (10.1)
Investigations	Any AE	2 (20.0)	2 (25.0)	11 (22.0)	5 (45.5)	2 (20.0)	20 (25.3)
	Blood creatinine increased	0	0	3 (6.0)	2 (18.2)	0	5 (6.3)
	Blood potassium decreased	0	0	3 (6.0)	0	0	3 (3.8)
	Blood urea increased	0	0	3 (6.0)	0	0	3 (3.8)
	Urine output decreased	0	0	2 (4.0)	0	1 (10.0)	3 (3.8)
	Weight decreased	0	0	1 (2.0)	2 (18.2)	0	3 (3.8)
Metabolism and nutrition disorders	Any AE	5 (50.0)	6 (75.0)	22 (44.0)	5 (45.5)	3 (30.0)	36 (45.6)
	Dehydration	0	0	2 (4.0)	0	1 (10.0)	3 (3.8)
	Hyperglycemia NOS	0	0	1 (2.0)	0	2 (20.0)	3 (3.8)
	Hypoglycemia NOS	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
	Hypokalemia	3 (30.0)	4 (50.0)	10 (20.0)	1 (9.1)	0	15 (19.0)
	Hypomagnesemia	2 (20.0)	2 (25.0)	2 (4.0)	0	1 (10.0)	5 (6.3)
	Hyponatremia	1 (10.0)	0	7 (14.0)	0	0	7 (8.9)
Musculoskeletal and connective tissue disorders	Any AE	1 (10.0)	0	7 (14.0)	2 (18.2)	3 (30.0)	12 (15.2)
	Muscle cramp	0	0	2 (4.0)	1 (9.1)	0	3 (3.8)
	Pain in extremity	0	0	3 (6.0)	0	1 (10.0)	4 (5.1)
Nervous system disorders	Any AE	1 (10.0)	2 (25.0)	6 (12.0)	3 (27.3)	1 (10.0)	12 (15.2)
	Headache	0	1 (12.5)	1 (2.0)	1 (9.1)	0	3 (3.8)
Psychiatric disorders	Any AE	3 (30.0)	1 (12.5)	9 (18.0)	3 (27.3)	1 (10.0)	14 (17.7)
	Confusional state	1 (10.0)	0	6 (12.0)	1 (9.1)	0	7 (8.9)
	Insomnia	1 (10.0)	1 (12.5)	2 (4.0)	1 (9.1)	1 (10.0)	5 (6.3)
Renal and urinary disorders	Any AE	2 (20.0)	4 (50.0)	11 (22.0)	3 (27.3)	2 (20.0)	20 (25.3)
	Hematuria	1 (10.0)	1 (12.5)	1 (2.0)	1 (9.1)	0	3 (3.8)
	Polyuria	0	1 (12.5)	3 (6.0)	0	0	4 (5.1)
	Renal failure NOS	0	1 (12.5)	1 (2.0)	0	1 (10.0)	3 (3.8)
	Renal failure acute	0	0	4 (8.0)	0	0	4 (5.1)
Respiratory, thoracic and mediastinal disorders	Any AE	5 (50.0)	4 (50.0)	18 (36.0)	4 (36.4)	2 (20.0)	28 (35.4)
	Dyspnea exacerbated	0	0	4 (8.0)	1 (9.1)	0	5 (6.3)
	Pulmonary congestion	0	0	3 (6.0)	1 (9.1)	0	4 (5.1)
Vascular disorders	Any AE	1 (10.0)	2 (25.0)	12 (24.0)	5 (45.5)	2 (20.0)	21 (26.6)
	Hypotension NOS	1 (10.0)	2 (25.0)	5 (10.0)	4 (36.4)	1 (10.0)	12 (15.2)
	Orthostatic hypotension	0	0	3 (6.0)	1 (9.1)	0	4 (5.1)
	Phlebitis NOS	0	0	3 (6.0)	0	0	3 (3.8)

Source: Applicant's Table 6.2, pg 42, response document

¹ Adverse events which occurred in at least three patients and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group

In the population of hypervolemic hyponatremic patients who also had CHF, adverse events occurred more commonly among conivaptan patients than among placebo patients. This

difference was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. Other events which occurred with greater frequency in the overall conivaptan-treated population than in the placebo population, and which occurred with greater frequency in the majority of the conivaptan groups than in the placebo group, included anemia NOS, nausea and sepsis NOS. For the System Organ Classes "Cardiac Disorders", "General Disorders and Administration Site Conditions", "Musculoskeletal and Connective Tissue Disorders", "Nervous System Disorders", "Renal and Urinary System Disorders" and "Vascular Disorders", events within the SOC were more common among conivaptan patients overall than among placebo patients, and occurred more frequently in the majority of the individual conivaptan dose groups. Events which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan patients, included "congestive cardiac failure aggravated", diarrhea NOS, nausea, peripheral edema, sepsis NOS, blood creatinine increased, and "dyspnea exacerbated".

Because the event categories of atrial dysrhythmias and cardiac failure events were concerns in the previous review cycle for conivaptan, those events are discussed separately in Section 7.1.3.3.1 above.

7.1.5.3 Common Adverse Events Among All Patients With Hypervolemic Hyponatremia Who Did Not Have Heart Failure and Who Were Treated with Intravenous Conivaptan

The following table lists adverse events which occurred in at least 1% of patients and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group.

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Table 7.1.5.3 Number and Percentage of Hypervolemic Hyponatremic Patients Without Heart Failure Who Had Treatment-emergent Adverse Events¹, Intravenous Studies 027, 071, 080

System Organ Class (SOC)	Preferred Term	Pbo	20 mg	40 mg	80 mg	Any Coni Dose
		N=4 n (%)	N=6 n (%)	N=23 n (%)	N=4 n (%)	N=33 n (%)
All SOCs	Any AE	2 (50.0)	5 (83.3)	23 (100.0)	3 (75.0)	31 (93.9)
Gastrointestinal disorders	Any AE	1 (25.0)	1 (16.7)	8 (34.8)	0	9 (27.3)
	Constipation	0	1 (16.7)	2 (8.7)	0	3 (9.1)
	Vomiting NOS	0	0	3 (13.0)	0	3 (9.1)
General disorders and administration site conditions	Any AE	1 (25.0)	4 (66.7)	18 (78.3)	1 (25.0)	23 (69.7)
	Infusion site erythema	0	0	3 (13.0)	0	3 (9.1)
	Infusion site phlebitis	0	2 (33.3)	10 (43.5)	0	12 (36.4)
	Infusion site reaction	0	2 (33.3)	3 (13.0)	0	5 (15.2)
	Pyrexia	0	0	2 (8.7)	1 (25.0)	3 (9.1)
Hepatobiliary disorders	Any AE	0	0	3 (13.0)	0	3 (9.1)
Metabolism and nutrition disorders	Any AE	2 (50.0)	2 (33.3)	6 (26.1)	0	8 (24.2)
	Hypokalemia	0	1 (16.7)	2 (8.7)	0	3 (9.1)
Nervous system disorders	Any AE	0	1 (16.7)	8 (34.8)	0	9 (27.3)
	Dizziness	0	0	3 (13.0)	0	3 (9.1)
Skin and subcutaneous tissue disorders	Any AE	0	1 (16.7)	2 (8.7)	0	3 (9.1)
Vascular disorders	Any AE	1 (25.0)	2 (33.3)	9 (39.1)	2 (50.0)	13 (39.4)
	Orthostatic hypotension	0	1 (16.7)	4 (17.4)	0	5 (15.2)

Source: Applicant's Table 6.3, pg 50, response document

¹ Adverse events which occurred in at least three patients and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group

In the population of hypervolemic hyponatremic patients who did not have CHF, adverse events occurred more commonly among conivaptan patients than among placebo patients. Interpretation of the significance of adverse event findings in this group was difficult due to the small size of the placebo group (N=4), and the conivaptan dose groups other than the 40 mg/day group. The difference in overall frequency of adverse events was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. The only individual type of adverse event which occurred with greater frequency in the conivaptan-treated population than in the placebo population, and which occurred with greater frequency in the majority of the conivaptan groups than in the placebo group, was orthostatic hypotension. For the System Organ Classes "General Disorders and Administration Site Conditions", "Nervous System Disorders", and "Vascular Disorders", events within the SOC were more common among conivaptan patients overall than among placebo patients, and occurred more frequently in the majority of the individual conivaptan dose groups. The only individual event which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan patients, was orthostatic hypotension.

Because the event categories of atrial dysrhythmias and cardiac failure events were concerns in the previous review cycle for conivaptan, those events are discussed separately in Section 7.1.3.3.1 above. However, there were no cardiac failure events among conivaptan-treated patients who did not have cardiac failure at baseline in Studies 027, 071 and 080.

7.1.5.4 Comparison of Adverse Event Profiles for the Overall Hypervolemic Hyponatremic Patient Population, and the Subpopulations With and Without Congestive Heart Failure, Intravenous Studies 027, 071, and 080

The following table lists adverse events of note from each of the three populations in Tables 7.1.5.1-7.1.5.3. In order for an adverse event (or System Organ Class of events) to be placed in this list, it had to meet one of the following criteria:

- It was an event which occurred in at least 3 patients, and occurred with a frequency at least 1% higher in the majority of the conivaptan dose groups compared to placebo, or
- It was an event which did not occur in the placebo group, but occurred in at least 5 conivaptan patients.

The table includes a notation for which of these criteria were met by a given event. This allows a rough comparison between populations for types of events potentially attributable to conivaptan. It has limitations related to the differing size of the populations.

7.1.5.4 Comparison of Occurrence of Adverse Events of Note Among Analysis Populations by Heart Failure Status, Hypervolemic Hyponatremic Patients from Intravenous Studies 027, 071, and 080

Event or System Organ Class	Criterion ¹ Met for Events Possibly Attributable to Conivaptan		
	Overall Hypervolemic Hyponatremic Population	Hypervolemic Hyponatremia Patients With Heart Failure	Hypervolemic Hyponatremia Patients Without Heart Failure
Anemia NOS		a	
Congestive cardiac failure aggravated		b	
Dyspnea exacerbated		b	
Constipation	a		
Diarrhea NOS		b	
Nausea		a, b	
Pyrexia	a		
Sepsis NOS	a, b	a, b	
Headache	a, b		
Orthostatic hypotension	a, b		a, b
Asthenia	b		
Edema peripheral	b	b	
Blood creatinine increased	b	b	
Dizziness	b		
Polyuria	b		
Acute renal failure	b		
Infusion site-related events	a	a	a
SOC General Disorders and Administration Site Conditions	a	a	a
SOC Musculoskeletal and Connective Tissue Disorders	a	a	

7.1.5.4 Comparison of Occurrence of Adverse Events of Note Among Analysis Populations by Heart Failure Status, Hypervolemic Hyponatremic Patients from Intravenous Studies 027, 071, and 080

	Criterion¹ Met for Events Possibly Attributable to Conivaptan		
Event or System Organ Class	Overall Hypervolemic Hyponatremic Population	Hypervolemic Hyponatremia Patients With Heart Failure	Hypervolemic Hyponatremia Patients Without Heart Failure
SOC Nervous System Disorders	a	a	a
SOC Vascular Disorders	a	a	a
SOC Cardiac Disorders		a	
SOC Renal and Urinary Disorders		a	

Source: Tables 7.1.5.1-7.1.5.3 above; Applicant's Tables 6.1, 6.2, and 6.3, response document
 1: a = met criterion as an event which occurred in at least 3 patients, and occurred with a frequency at least 1% higher in the majority of the conivaptan dose groups compared to placebo
 b = met criterion as an event which did not occur in the placebo group, but occurred in at least 5 conivaptan patients.

To the limited extent one can use these observations to attribute potential causality to conivaptan, it appears that there are some attributable events which met criteria in the heart failure population, but did not meet criteria in the overall population or in the population without heart failure events. These events which may be more of a concern in the heart failure population than in the overall hypervolemic population, or the hypervolemic population without heart failure, include anemia NOS, congestive cardiac failure aggravated, dyspnea exacerbated, diarrhea NOS and nausea. Sepsis NOS may also be a concern for the heart failure population, as it met both criteria for potential attribution for the heart failure population and the overall hypervolemic population, but not for the hypervolemic population without heart failure.

For the hypervolemic hyponatremic population without heart failure, there were no unique events which met a criterion, but did not also meet a criterion in one of the other populations. However, the small size of the placebo group and some of the dose groups for this population limits the interpretability of this observation.

7.1.5.5 Updated Common Adverse Events for all Conivaptan Studies

The applicant also provided an updated listing of adverse events which have occurred in all conivaptan studies to date. The following table lists those events which occurred with a frequency at least 1% greater in the overall conivaptan group than in the placebo group.

Table 7.1.5.5: Updated Treatment-emergent Adverse Events, Events Which Occurred At a Frequency at Least 1% Higher in the Overall Conivaptan Group than in the Overall Placebo Group, All Conivaptan Studies

MedDRA System Organ Class	Preferred Term	Coni N=1284 n(%)	Pbo N=372 n(%)	
Blood and lymphatic system disorders	Any	78 (6)	17 (5)	
	Anemia NOS	49 (4)	8 (2)	
Cardiac disorders	Any	199 (15)	58 (16)	
	Atrial fibrillation	23 (2)	2 (<1)	
	Congestive cardiac failure aggravated	52 (4)	9 (2)	
Gastrointestinal disorders	Any	265 (20)	60 (16)	
	Constipation	60 (5)	15 (4)	
	Diarrhea NOS	50 (4)	8 (2)	
	Dry mouth	25 (2)	1 (<1)	
	Nausea	61 (5)	15 (4)	
	Vomiting NOS	39 (3)	8 (2)	
General disorders and administration site conditions	Any	499 (39)	65 (17)	
	Aesthenia	40 (3)	4 (1)	
	Chest pain	48 (4)	12 (3)	
	Edema peripheral	42 (3)	4 (1)	
	Infusion site erythema	19 (1)	0	
	Infusion site phlebitis	158 (12)	3 (<1)	
	Infusion site reaction	75 (6)	0	
	Pyrexia	39 (3)	6 (2)	
	Thirst	55 (4)	8 (2)	
	Infections and infestations	Any	217 (17)	52 (14)
		Upper respiratory tract infection NOS	20 (2)	4 (1)
Injury, poisoning and procedural complications	Any	55 (4)	10 (3)	
Investigations	Any	174 (13)	32 (9)	
Metabolism and nutrition disorders	Any	229 (18)	46 (12)	
	Hyperkalemia	34 (3)	5 (1)	
	Hypokalemia	66 (5)	14 (4)	
	Hyponatremia	35 (3)	2 (<1)	
Musculoskeletal and connective tissue disorders	Any	124 (10)	23 (6)	
	Back pain	22 (2)	4 (1)	
	Pain in extremity	28 (2)	4 (1)	
Neoplasms	Any	20 (2)	1 (<1)	
Nervous system disorders	Any	177 (14)	37 (10)	
	Dizziness	64 (5)	11 (3)	
Psychiatric disorders	Any	112 (9)	23 (6)	
	Confusional state	25 (2)	3 (<1)	
Renal and urinary disorders	Any	148 (11)	27 (7)	
	Polyuria	22 (2)	0	
	Renal failure NOS	40 (3)	5 (1)	
Respiratory, thoracic and mediastinal disorders	Any	198 (15)	57 (15)	
	Cough	34 (3)	8 (2)	
Skin and subcutaneous tissue disorders	Any	70 (5)	14 (4)	
Vascular disorders	Any	162 (13)	32 (9)	
	Hypertension NOS	31 (2)	1 (<1)	
	Orthostatic hypotension	31 (2)	4 (1)	

Source: Applicant's Table 1, beg pg 70, ISS

The relative frequency of events from the updated safety population does not differ substantially from that seen in the overall population from the 2nd review cycle.

7.1.5.6 Common Adverse Events Among Patients in IV Phase 2/3 Heart Failure Studies

The applicant also provided a summary of all adverse events (serious and nonserious) which occurred among patients treated with intravenous conivaptan in the heart failure development program, which was not limited to patients with hyponatremia. The following table includes those events which occurred in at least 3 patients in any group, and which occurred at a frequency at least 1% greater in a conivaptan group than in the placebo group.

Table 7.1.5.6: Number and Percentage of Heart Failure Patients with Treatment-emergent Events (Serious and Nonserious) Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group¹, All Phase 2/3 Heart Failure Studies² with Intravenous Conivaptan

Organ System Class	Event	Pbo N=103 n(%)	10 mg N=37 n(%)	20 mg N=32 n(%)	40 mg N=89 n(%)	80 mg N=53 n(%)	120 mg N=42 n(%)	Any IV Coni N=253 n(%)
Any system	Any AE	71 (68.9)	23 (62.2)	20 (62.5)	60 (67.4)	46 (86.8)	39 (92.9)	188 (74.3)
Blood and lymphatic	Any AE	5 (4.9)	0	0	1 (1.1)	5 (9.4)	3 (7.1)	9 (3.6)
	Anemia NOS	1 (1.0)	0	0	0	3 (5.7)	3 (7.1)	6 (2.4)
Cardiac	Any AE	22 (21.4)	2 (5.4)	4 (12.5)	14 (15.7)	12 (22.6)	13 (31.0)	45 (17.8)
	Atrial fibrillation	0	0	0	3 (3.4)	2 (3.8)	1 (2.4)	6 (2.4)
	Atrial flutter	0	0	1 (3.1)	0	1 (1.9)	3 (7.1)	5 (2.0)
	Cardiomyopathy NOS	0	0	0	2 (2.2)	0	1 (2.4)	3 (1.2)
	Ventricular tachycardia	10 (9.7)	1 (2.7)	0	3 (3.4)	6 (11.3)	4 (9.5)	14 (5.5)
Eye	Any AE	1 (1.0)	0	0	3 (3.4)	0	1 (2.4)	4 (1.6)
Gastrointestinal	Any AE	19 (18.4)	1 (2.7)	4 (12.5)	14 (15.7)	11 (20.8)	8 (19.0)	38 (15.0)
	Constipation	8 (7.8)	0	0	5 (5.6)	6 (11.3)	5 (11.9)	16 (6.3)
	Vomiting	2 (1.9)	1 (2.7)	0	3 (3.4)	1 (1.9)	0	5 (2.0)
General and administration site	Any AE	20 (19.4)	5 (13.5)	3 (9.4)	27 (30.3)	28 (52.8)	29 (69.0)	92 (36.3)
	Aesthenia	0	0	0	2 (2.2)	2 (3.8)	3 (7.1)	7 (2.8)
	Edema NOS	0	1 (2.7)	0	2 (2.2)	0	0	3 (1.2)
	Edema peripheral	0	0	0	2 (2.2)	1 (1.9)	0	3 (1.2)
	Infusion site edema	0	0	0	2 (2.2)	1 (1.9)	0	3 (1.2)
	Infusion site erythema	0	0	0	0	3 (5.7)	1 (2.4)	4 (1.6)
	Infusion site pain	0	0	0	2 (2.2)	2 (3.8)	1 (2.4)	5 (2.0)
	Infusion site phlebitis	2 (1.9)	0	0	7 (7.9)	13 (24.5)	14 (33.3)	34 (13.4)
	Infusion site tenderness	0	0	0	0	3 (5.7)	0	3 (1.2)
	Injection site cellulitis	0	0	0	4 (4.5)	2 (3.8)	3 (7.1)	9 (3.6)
	Injection site pain	1 (1.0)	2 (5.4)	1 (3.1)	0	0	2 (4.8)	5 (2.0)
	Injection site reaction NOS	2 (1.9)	0	1 (3.1)	4 (4.5)	4 (7.5)	3 (7.1)	12 (4.7)
	Injection site thrombosis	0	0	0	0	2 (3.8)	1 (2.4)	3 (1.2)
	Pyrexia	5 (4.9)	0	0	5 (5.6)	0	4 (9.5)	9 (3.6)
	Thirst	0	0	1 (3.1)	1 (1.1)	2 (3.8)	3 (7.1)	7 (2.8)
Immune	Any AE	0	0	0	2 (2.2)	0	2 (4.8)	4 (1.6)
Infections and infestations	Any AE	13 (12.6)	8 (21.6)	3 (9.4)	11 (12.4)	9 (17.0)	10 (23.8)	41 (16.2)
	Pneumonia NOS	4 (3.9)	0	0	1 (1.1)	2 (3.8)	5 (11.9)	8 (3.2)
	Urinary tract infection NOS	6 (5.8)	4 (10.8)	2 (6.3)	3 (3.4)	2 (3.8)	1 (2.4)	12 (4.7)

Table 7.1.5.6: Number and Percentage of Heart Failure Patients with Treatment-emergent Events (Serious and Nonserious) Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group¹, All Phase 2/3 Heart Failure Studies² with Intravenous Conivaptan

Organ System Class	Event	Pbo N=103 n(%)	10 mg N=37 n(%)	20 mg N=32 n(%)	40 mg N=89 n(%)	80 mg N=53 n(%)	120 mg N=42 n(%)	Any IV Coni N=253 n(%)
Injury, poisoning and procedural complications	Any AE	3 (2.9)	0	0	3 (3.4)	2 (3.8)	2 (4.8)	7 (2.8)
Investigations	Any AE	7 (6.8)	5 (13.5)	0	16 (18.0)	14 (26.4)	9 (21.4)	44 (17.4)
	Blood creatinine increased	2 (1.9)	0	0	0	2 (3.8)	1 (2.4)	3 (1.2)
	Blood magnesium decreased	0	0	0	1 (1.1)	3 (5.7)	0	4 (1.6)
	Blood potassium decreased	0	1 (2.7)	0	1 (1.1)	1 (1.9)	0	3 (1.2)
	Body temperature increased	2 (1.9)	0	0	0	2 (3.8)	1 (2.4)	3 (1.2)
	Heart rate increased	0	1 (2.7)	0	2 (2.2)	0	0	3 (1.2)
	Heart sounds abnormal	0	0	0	2 (2.2)	0	1 (2.4)	3 (1.2)
	Urine output decreased	1 (1.0)	0	0	1 (1.1)	1 (1.9)	1 (2.4)	3 (1.2)
	Urine sodium decreased	0	0	0	1 (1.1)	3 (5.7)	0	4 (1.6)
	White blood cell count increased	0	0	0	0	2 (3.8)	1 (2.4)	3 (1.2)
Metabolism and nutrition	Any AE	15 (14.6)	4 (10.8)	0	19 (21.3)	14 (26.4)	14 (33.3)	51 (20.2)
	Hyperglycemia NOS	0	0	0	2 (2.2)	1 (1.9)	3 (7.1)	6 (2.4)
	Hyperkalemia	2 (1.9)	2 (5.4)	0	5 (5.6)	2 (3.8)	1 (2.4)	10 (4.0)
	Hyponatremia	0	0	0	2 (2.2)	3 (5.7)	2 (4.8)	7 (2.8)
	Hypokalemia	9 (8.7)	0	0	6 (6.7)	8 (15.1)	4 (9.5)	18 (7.1)
	Hyponatremia	1 (1.0)	0	0	1 (1.1)	2 (3.8)	1 (2.4)	4 (1.6)
Musculoskeletal and connective tissue	Any AE	7 (6.8)	4 (10.8)	0	8 (9.0)	7 (13.2)	8 (19.0)	27 (10.7)
	Arthralgia	1 (1.0)	0	0	1 (1.1)	1 (1.9)	1 (2.4)	3 (1.2)
	Back pain	1 (1.0)	4 (10.8)	0	4 (4.6)	2 (3.8)	1 (2.4)	11 (4.3)
	Muscle cramp	2 (1.9)	0	0	1 (1.1)	2 (3.8)	0	3 (1.2)
	Pain in extremity	1 (1.0)	0	0	3 (3.4)	2 (3.8)	4 (9.5)	9 (3.6)
Nervous system	Any AE	12 (11.7)	3 (8.1)	5 (15.6)	14 (15.7)	4 (7.5)	6 (14.3)	32 (12.6)
	Dizziness	3 (2.9)	2 (5.4)	1 (3.1)	5 (5.6)	1 (1.9)	1 (2.4)	10 (4.0)
	Headache	6 (5.8)	0	3 (9.4)	6 (6.7)	1 (1.9)	4 (9.5)	14 (5.5)
	Syncope	0	0	0	3 (3.4)	0	1 (2.4)	4 (1.6)
Psychiatric	Any AE	8 (7.8)	1 (2.7)	3 (9.4)	13 (14.6)	3 (5.7)	4 (9.5)	24 (9.5)
	Agitation	0	0	0	2 (2.2)	0	2 (4.8)	4 (1.6)
	Anxiety	1 (1.0)	0	2 (6.3)	1 (1.1)	1 (1.9)	0	4 (1.6)
	Restlessness	0	1 (2.7)	0	3 (3.4)	0	0	4 (1.6)
Renal and urinary disorders	Any AE	7 (6.8)	1 (2.7)	1 (3.1)	11 (12.4)	8 (15.1)	5 (11.9)	26 (10.3)
	Hematuria	2 (1.9)	0	0	3 (3.4)	3 (5.7)	0	6 (2.4)
	Leukocyturia	0	0	0	1 (1.1)	2 (3.8)	0	3 (1.2)
	Renal failure NOS	1 (1.0)	0	0	3 (3.4)	1 (1.9)	2 (4.8)	6 (2.4)
Respiratory, thoracic and mediastinal	Any AE	20 (19.4)	3 (8.1)	1 (3.1)	14 (15.7)	20 (37.7)	14 (33.3)	52 (20.6)
	Bronchitis NOS	0	1 (2.7)	1 (3.1)	0	1 (1.9)	0	3 (1.2)
	Cough	3 (2.9)	0	0	4 (4.5)	2 (3.8)	1 (2.4)	7 (2.8)
	Dyspnea	8 (7.8)	0	0	8 (9.0)	10 (18.9)	8 (19.0)	26 (10.3)

Table 7.1.5.6: Number and Percentage of Heart Failure Patients with Treatment-emergent Events (Serious and Nonserious) Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group¹, All Phase 2/3 Heart Failure Studies² with Intravenous Conivaptan

Organ System Class	Event	Pbo N=103 n(%)	10 mg N=37 n(%)	20 mg N=32 n(%)	40 mg N=89 n(%)	80 mg N=53 n(%)	120 mg N=42 n(%)	Any IV Coni N=253 n(%)
	exacerbated							
	Pulmonary congestion	2 (1.9)	0	0	1 (1.1)	2 (3.8)	2 (4.8)	5 (2.0)
Skin and subcutaneous tissue	Any AE	3 (2.9)	2 (5.4)	0	4 (4.5)	6 (11.3)	4 (9.5)	16 (6.3)
	Erythema	0	0	0	0	2 (3.8)	1 (2.4)	3 (1.2)
	Pruritus	2 (1.9)	1 (2.7)	0	1 (1.1)	0	2 (4.8)	4 (1.6)
	Rash NOS	1 (1.0)	0	0	3 (3.4)	1 (1.9)	0	4 (1.6)
Vascular disorders	Any AE	9 (8.7)	0	2 (6.1)	9 (10.1)	5 (9.4)	6 (14.3)	22 (8.7)
	Hypertension NOS	0	0	0	2 (2.2)	2 (3.8)	0	4 (1.6)
	Hypotension NOS	0	0	0	2 (2.2)	2 (3.8)	0	4 (1.0)

Source: Applicant's Table 15, beg pg 94, response document

¹ Events which occurred in at least 3 patients in any treatment group, and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group

² Studies 016, 017, 020, 024, 032, 033, 034, 038, 044, 071; these were heart failure studies and not all patients were hyponatremic

In the overall population of heart failure intravenous study patients, which included patients both with and without hyponatremia, adverse events occurred more commonly among IV conivaptan-treated patients than among IV placebo-treated patients. This difference was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. Other events which occurred more frequently in the overall IV conivaptan-treated heart failure population than in the IV placebo-treated population, and which occurred more frequently in the majority of the conivaptan groups than in the placebo group, included anemia NOS, atrial fibrillation, atrial flutter, aesthenia, hyperglycemia NOS, hyperkalemia, hypernatremia, back pain, pain in extremity, dizziness, renal failure NOS and dyspnea exacerbated. For the System Organ Classes "General Disorders and Administration Site Conditions", "Infections and Infestations", "Investigations", "Metabolism and Nutrition Disorders", "Musculoskeletal and Connective Tissue Disorders", "Nervous System Disorders", "Psychiatric Disorders", "Renal and Urinary Disorders" and "Skin and Subcutaneous Tissue Disorders", events within the SOC were more common among conivaptan patients than among placebo patients, and occurred more frequently in the majority of conivaptan groups. Events which did not occur in any placebo group patients, and which occurred in ≥5 conivaptan group patients, included atrial fibrillation, atrial flutter, aesthenia, thirst, hyperglycemia NOS and hypernatremia.

7.1.5.7 Common Adverse Events Among Patients in Oral Phase 2/3 Heart Failure Studies

The following table examines the orally-treated heart failure study population (with and without hyponatremia), and includes those events (serious and nonserious) which occurred in at least 3 patients in any group, and which occurred at a frequency at least 1% greater in a conivaptan

group than in the placebo group. As previously mentioned, all oral doses used in studies had lower mean exposure than the proposed intravenous dose.

Table 7.1.5.7 Number and Percentage of Heart Failure Patients with Treatment-emergent Events Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group¹, All Phase 2/3 Heart Failure Studies² with Oral Conivaptan

Organ System Class	Event	Pbo N=187 n(%)	5 mg N=4 n(%)	10 mg N=80 n(%)	20 mg N=187 n(%)	40 mg N=192 n(%)	80 mg N=102 n(%)	Any Oral Coni N=565 n(%)
Any system	Any AE	119 (63.6)	3 (75.0)	51 (63.8)	122 (65.2)	121 (63.0)	67 (65.7)	364 (64.4)
Blood and lymphatic	Any AE	7 (3.7)	0	4 (5.0)	5 (2.7)	6 (3.1)	4 (3.9)	19 (3.4)
	Anemia NOS	2 (1.1)	0	3 (3.8)	2 (1.1)	3 (1.6)	3 (2.9)	11 (1.9)
Cardiac	Any AE	26 (13.9)	1 (25.0)	15 (18.8)	25 (13.4)	22 (11.5)	10 (9.8)	73 (12.9)
	Angina pectoris	2 (1.1)	0	4 (5.0)	6 (3.2)	1 (0.5)	1 (1.0)	12 (2.1)
	Atrial fibrillation	1 (0.5)	0	0	4 (2.1)	4 (2.1)	0	8 (1.4)
	Atrial flutter	0	0	1 (1.3)	0	3 (1.6)	0	4 (0.7)
	Bradycardia	2 (1.1)	0	3 (3.8)	1 (0.5)	3 (1.6)	1 (1.0)	8 (1.4)
	Cardiac arrest	0	0	1 (1.3)	0	2 (1.0)	1 (1.0)	4 (0.7)
	Congestive cardiac failure aggravated	7 (3.7)	1 (25.0)	3 (3.8)	8 (4.3)	7 (3.6)	3 (2.9)	22 (3.9)
Eye	Any AE	3 (1.6)	0	3 (3.8)	1 (0.5)	2 (1.0)	2 (2.0)	8 (1.4)
Gastrointestinal	Any AE	25 (13.4)	0	6 (7.5)	29 (15.5)	28 (14.6)	17 (16.7)	80 (14.2)
	Abdominal distension	0	0	0	2 (1.1)	2 (1.0)	2 (2.0)	6 (1.1)
	Diarrhea NOS	3 (1.6)	0	1 (1.3)	5 (2.7)	4 (2.1)	4 (3.9)	14 (2.5)
	Dry mouth	1 (0.5)	0	0	4 (2.1)	4 (2.1)	4 (3.9)	12 (2.1)
	Nausea	3 (1.6)	0	1 (1.3)	5 (2.7)	3 (1.6)	6 (5.9)	15 (2.7)
General and administration site	Any AE	34 (18.2)	3 (75.0)	16 (20.0)	40 (21.4)	45 (23.4)	32 (31.4)	136 (24.1)
	Aesthenia	2 (1.1)	0	1 (1.2)	3 (1.6)	5 (2.6)	3 (2.9)	12 (2.1)
	Chest discomfort	1 (0.5)	0	1 (1.3)	3 (1.6)	1 (0.5)	1 (1.0)	6 (1.1)
	Chest pain	9 (4.8)	0	8 (10.0)	8 (4.3)	9 (4.7)	8 (7.8)	33 (5.8)
	Edema peripheral	2 (1.1)	1 (25.0)	1 (1.3)	4 (2.1)	2 (1.0)	1 (1.0)	9 (1.6)
	Fatigue	14 (7.5)	1 (25.0)	1 (1.3)	10 (5.3)	15 (7.8)	11 (10.8)	38 (6.7)
	Influenza like illness	1 (0.5)	0	0	0	4 (2.1)	3 (2.9)	7 (1.2)
	Lethargy	0	0	2 (2.5)	0	1 (0.5)	1 (1.0)	4 (0.7)
	Thirst	7 (3.7)	1 (25.0)	1 (1.3)	13 (7.0)	15 (7.8)	10 (9.8)	40 (7.1)
Infections and infestations	Any AE	32 (17.1)	0	11 (13.8)	26 (13.9)	33 (17.2)	12 (11.8)	82 (14.5)
	Gastroenteritis	0	0	1 (1.3)	2 (1.1)	1 (0.5)	0	4 (0.7)
	Influenza	2 (1.1)	0	1 (1.3)	6 (3.2)	3 (1.6)	0	10 (1.8)
	Pneumonia NOS	2 (1.1)	0	2 (2.5)	0	1 (0.5)	1 (1.0)	4 (0.7)
	Sinusitis NOS	0	0	0	3 (1.6)	5 (2.6)	0	8 (1.4)
	Upper respiratory tract infection NOS	3 (1.6)	0	0	6 (3.2)	8 (4.2)	3 (2.9)	17 (3.0)
Injury, poisoning and procedural complications	Any AE	6 (3.2)	0	2 (2.5)	3 (1.6)	5 (2.6)	5 (4.9)	15 (2.7)
Investigations	Any AE	20 (10.7)	0	13 (16.3)	25 (13.4)	25 (13.0)	13 (12.7)	76 (13.5)
	Aspartate aminotransferase increased	0	0	0	2 (1.1)	1 (0.5)	1 (1.0)	4 (0.7)
	Blood creatine phosphokinase increased	0	0	0	0	3 (1.6)	1 (1.0)	4 (0.7)

Table 7.1.5.7 Number and Percentage of Heart Failure Patients with Treatment-emergent Events Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group¹, All Phase 2/3 Heart Failure Studies² with Oral Conivaptan

Organ System Class	Event	Pbo	5 mg	10 mg	20 mg	40 mg	80 mg	Any Oral Coni
		N=187 n(%)	N=4 n(%)	N=80 n(%)	N=187 n(%)	N=192 n(%)	N=102 n(%)	N=565 n(%)
	Blood glucose increased	4 (2.1)	0	5 (6.3)	2 (1.1)	3 (1.6)	2 (2.0)	12 (2.1)
	Blood lactate dehydrogenase increased	0	0	1 (1.3)	4 (2.1)	2 (1.0)	0	7 (1.2)
	Blood uric acid increased	2 (1.1)	0	2 (2.5)	0	1 (0.5)	0	3 (0.5)
	Gamma glutamyl transferase increased	1 (0.5)	0	1 (1.3)	3 (1.6)	1 (0.9)	0	5 (0.9)
	Hemoglobin decreased	0	0	2 (2.5)	2 (1.1)	0	0	4 (0.7)
	Red blood cell count decreased	0	0	2 (2.5)	2 (1.1)	0	0	4 (0.7)
	Venous jugular pressure increased	1 (0.5)	0	0	3 (1.6)	2 (1.0)	0	5 (0.9)
	Weight increased	2 (1.1)	0	1 (1.3)	4 (2.1)	4 (2.1)	3 (2.9)	12 (2.1)
Metabolism and nutrition	Any AE	20 (10.7)	0	14 (17.5)	18 (9.6)	17 (8.9)	12 (11.8)	61 (10.8)
	Anorexia	0	0	1 (1.3)	2 (1.1)	0	1 (1.0)	4 (0.7)
	Dehydration	0	0	0	1 (0.5)	1 (0.5)	4 (3.9)	6 (1.1)
	Diabetes mellitus NOS	2 (1.1)	0	2 (2.5)	1 (0.5)	1 (0.5)	0	4 (0.7)
	Hyperkalemia	1 (0.5)	0	1 (1.3)	5 (2.7)	2 (1.0)	0	8 (1.4)
Musculoskeletal and connective tissue	Any AE	14 (7.5)	1 (25.0)	10 (12.5)	17 (9.1)	16 (8.3)	14 (13.7)	58 (10.3)
	Pain in extremity	3 (1.6)	1 (25.0)	4 (5.0)	3 (1.6)	4 (2.1)	2 (2.0)	14 (2.5)
Neoplasms, benign, malignant and unspecified	Any AE	0	0	1 (1.3)	1 (0.5)	3 (1.6)	1 (1.0)	6 (1.1)
Nervous system	Any AE	16 (8.6)	0	8 (10.0)	23 (12.3)	17 (8.9)	14 (13.7)	62 (11.0)
	Dizziness	6 (3.2)	0	3 (3.8)	11 (5.9)	8 (4.2)	6 (5.9)	28 (5.0)
	Syncope	1 (0.5)	0	0	2 (1.1)	3 (1.6)	2 (2.0)	7 (1.2)
Psychiatric	Any AE	9 (4.8)	1 (25.0)	3 (3.8)	7 (3.7)	6 (3.1)	5 (4.9)	22 (3.9)
	Confusional state	0	0	1 (1.3)	0	1 (0.5)	2 (2.0)	4 (0.7)
Renal and urinary disorders	Any AE	11 (5.9)	0	8 (10.0)	9 (4.8)	18 (9.4)	8 (7.8)	43 (7.6)
	Pollakiuria	2 (1.1)	0	0	2 (1.1)	2 (1.0)	3 (2.9)	7 (1.2)
	Polyuria	0	0	0	2 (1.1)	5 (2.6)	0	7 (1.2)
Vascular disorders	Any AE	13 (7.0)	1 (25.0)	6 (7.5)	7 (3.7)	5 (2.6)	5 (4.9)	24 (4.2)

Source: Applicant's Table 15, beg pg 105, response document

¹ Events which occurred in at least 3 patients in any treatment group, and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group

² Studies 016, 017, 020, 024, 032, 033, 034, 038, 044, 071; these were heart failure studies and not all patients were hyponatremic

In heart failure studies where patients were treated with oral conivaptan, adverse events overall occurred with similar frequency in placebo and conivaptan groups. Adverse events which occurred with greater frequency in the overall population of orally-treated conivaptan group patients than among placebo-treated patients, and which occurred with greater frequency in the

majority of the conivaptan groups than in the placebo group, included anemia NOS, congestive cardiac failure aggravated, abdominal distension, diarrhea NOS, dry mouth, aesthenia, thirst, influenza, upper respiratory tract infection, weight increased, pain in extremity, dizziness and syncope. For the System Organ Classes "Gastrointestinal Disorders", "General Disorders and Administration Site Conditions", "Investigations", "Musculoskeletal and Connective Tissue Disorders", "Nervous System Disorders" and "Renal and Urinary Tract Disorders", events within the SOC were more common among conivaptan group patients overall than among placebo group patients, and occurred more frequently in the majority of the individual conivaptan dose groups than in the placebo group. Events which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan group patients, included abdominal distension, sinusitis, blood lactate dehydrogenase increased, dehydration and polyuria.

7.1.5.8 Comparison of Frequency of Adverse Events for Euvolemic and Hypervolemic Populations

The following tables list those events which occurred with a difference in frequency of at least 2% between hypervolemic and euvolemic patients, or for which the two volume status categories differed in relative incidence to their respective placebo incidence. The overall IV population is listed first (all IV conivaptan studies from both hyponatremia and heart failure programs), followed by the full conivaptan population (IV + oral, hyponatremia + heart failure programs). Only those studies for which baseline volume status was documented are included.

Among IV-treated patients who had baseline assessments of volume status, events which occurred more frequently among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and also occurred more commonly among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included cardiac failure NOS, ear pain, abdominal distension, abdominal pain NOS, dyspepsia, vomiting NOS, aesthenia, anasarca, catheter site pain, edema NOS, infusion site erythema, infusion site swelling, pyrexia, thirst, hepatic failure, sepsis NOS, septic shock, blood creatinine increased, blood urea increased, weight decreased, dehydration, hypokalemia, hypomagnesemia, asterixis, renal failure acute, dyspnea exacerbated, pulmonary congestion, decubitus ulcer, orthostatic hypotension, and phlebitis NOS. When narrowing this list to only those events which occurred at a rate at least 3% higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, events include cardiac failure NOS, abdominal pain NOS, dyspepsia, vomiting NOS, aesthenia, infusion site erythema, pyrexia, sepsis NOS, blood creatinine increased, weight decreased, hypokalemia, renal failure acute, decubitus ulcer and orthostatic hypotension. Only vomiting NOS, aesthenia, pyrexia and hypokalemia occurred at a rate that was $\geq 5\%$ higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and at a higher rate among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients.

Table 7.1.5.8.1: Comparison^a of Incidence of Treatment-emergent Adverse Events Between Hypervolemic and Euvolemic Patients, All IV Studies

System Organ Class	Preferred Term	Coni Hypervolemic N ^b =89 n(%)	Coni Euvolemic N ^b =217 n(%)	Pbo Hypervolemic N ^b =8 n(%)	Pbo Euvolemic N ^b =21 n(%)
Any SOC	Any Event	84 (94)	208 (96)	5 (63)	16 (76)
Blood and Lymphatic System Disorders	Any Event	10 (11)	21 (10)	0	2 (10)
	Anemia NOS	5 (6)	15 (7)	0	2 (10)
	Neutrophilia	2 (2)	0	0	0
Cardiac disorders	Any Event	21 (24)	22 (10)	2 (25)	3 (14)
	Cardiac failure NOS	3 (3)	0	0	0
	Congestive cardiac failure aggravated	7 (8)	5 (2)	1 (13)	0
	Myocardial infarction	0	4 (2)	0	0
Ear and labyrinth disorders	Any Event	2 (2)	2 (<1)	0	0
	Ear pain	2 (2)	0	0	0
Gastrointestinal disorders	Any Event	32 (36)	71 (33)	1 (13)	6 (29)
	Abdominal distension	3 (3)	1 (<1)	0	0
	Abdominal pain NOS	6 (7)	6 (3)	0	2 (10)
	Constipation	7 (8)	16 (7)	0	2 (10)
	Diarrhea NOS	5 (6)	20 (9)	0	0
	Dry mouth	1 (1)	8 (4)	0	0
	Dyspepsia	4 (4)	3 (1)	0	0
	Nausea	5 (6)	13 (6)	1 (13)	1 (5)
	Vomiting NOS	11 (12)	15 (7)	0	0
General disorders and administration site conditions	Any Event	62 (70)	171 (79)	2 (25)	1 (5)
	Aesthenia	6 (7)	5 (2)	0	0
	Anasarca	2 (2)	0	0	0
	Catheter site pain	2 (2)	0	0	0
	Chest pain	3 (3)	6 (3)	0	0
	Edema NOS	3 (3)	1 (<1)	0	0
	Edema peripheral	7 (8)	16 (7)	0	1 (5)
	Infusion site erythema	7 (8)	8 (4)	0	0
	Infusion site phlebitis	30 (34)	94 (43)	1 (13)	0
	Infusion site reaction	12 (13)	58 (27)	0	0
	Infusion site swelling	3 (3)	2 (<1)	0	0
	Injection site phlebitis	0	4 (2)	0	0
	Pyrexia	9 (10)	11 (5)	0	0
	Thirst	3 (3)	3 (1)	0	0
	Venipuncture site hemorrhage	0	3 (1)	0	0
	Hepatobiliary disorders	Any Event	4 (4)	4 (2)	0
Hepatic failure		2 (2)	0	0	0
Infections and infestations	Any Event	23 (26)	41 (19)	3 (38)	1 (5)

Table 7.1.5.8.1: Comparison^a of Incidence of Treatment-emergent Adverse Events Between Hypervolemic and Euvolemic Patients, All IV Studies

System Organ Class	Preferred Term	Coni Hypervolemic N ^b =89 n(%)	Coni Euvolemic N ^b =217 n(%)	Pbo Hypervolemic N ^b =8 n(%)	Pbo Euvolemic N ^b =21 n(%)
	Sepsis NOS	6 (7)	1 (<1)	0	0
	Septic shock	2 (2)	0	0	0
Injury, poisoning and procedural complications	Any Event	7 (8)	10 (5)	0	0
Investigations	Any Event	14 (16)	27 (12)	0	0
	Blood creatinine increased	4 (4)	2 (<1)	0	0
	Blood urea increased	3 (3)	3 (1)	0	0
	Weight decreased	3 (3)	3 (1)	0	0
Metabolism and nutrition disorders	Any Event	34 (38)	55 (25)	3 (38)	3 (14)
	Dehydration	3 (3)	3 (1)	0	0
	Hypokalemia	16 (18)	22 (10)	1 (13)	1 (5)
	Hypomagnesemia	4 (4)	4 (2)	0	0
Musculoskeletal and connective tissue disorders	Any Event	5 (6)	15 (7)	0	1 (5)
	Arthralgia	1 (1)	6 (3)	0	0
Neoplasms	Any Event	4 (4)	5 (2)	0	0
Nervous system disorders	Any Event	17 (19)	38 (18)	0	5 (24)
	Asterixis	2 (2)	0	0	0
	Headache	4 (4)	18 (8)	0	2 (10)
Psychiatric disorders	Any Event	13 (15)	32 (15)	2 (25)	1 (5)
	Confusional state	8 (9)	9 (4)	1 (13)	1 (5)
	Restlessness	1 (1)	6 (3)	0	0
Renal and urinary disorders	Any Event	19 (21)	44 (20)	2 (25)	2 (10)
	Renal failure acute	5 (6)	4 (2)	0	0
	Urinary retention	0	6 (3)	0	0
Respiratory, thoracic and mediastinal disorders	Any Event	21 (24)	26 (12)	2 (25)	4 (19)
	Dyspnea	7 (8)	5 (2)	1 (13)	0
	Dyspnea exacerbated	2 (2)	0	0	0
	Pulmonary congestion	3 (3)	1 (<1)	0	0
Skin and subcutaneous tissue disorders	Any Event	7 (8)	15 (7)	1 (13)	0
	Decubitus ulcer	3 (3)	0	0	0
Vascular disorders	Any Event	28 (31)	61 (28)	1 (13)	3 (14)
	Hypertension NOS	2 (2)	21 (10)	0	0
	Hypotension NOS	10 (11)	14 (6)	1 (13)	1 (5)
	Orthostatic hypotension	9 (10)	15 (7)	0	0
	Phlebitis NOS	5 (6)	8 (4)	0	1 (5)

Source: Applicant's Table 2, beg pg 96, ISS

^a Above table includes those events which occurred with a frequency difference $\geq 2\%$ between hypervolemic and euvolemic conivaptan-treated patients. Also includes events for which the relationship of conivaptan group incidence to placebo group incidence differed

Table 7.1.5.8.1: Comparison^a of Incidence of Treatment-emergent Adverse Events Between Hypervolemic and Euvolemic Patients, All IV Studies

System Organ Class	Preferred Term	Coni Hypervolemic N ^b =89 n(%)	Coni Euvolemic N ^b =217 n(%)	Pbo Hypervolemic N ^b =8 n(%)	Pbo Euvolemic N ^b =21 n(%)
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between hypervolemic and euvolemic groups

b N = number of patients with a volume status measurement at study entry; volume status collected only for Studies 026, 027, 031, 043 and 080

Table 7.1.5.8.2: Comparison^a of Incidence of Treatment-emergent Adverse Events Between Hypervolemic and Euvolemic Patients, All Conivaptan Studies

System Organ Class	Preferred Term	Coni Hypervolemic N ^b =129 n(%)	Coni Euvolemic N ^b =296 n(%)	Pbo Hypervolemic N ^b =23 n(%)	Pbo Euvolemic N ^b =59 n(%)
Any SOC	Any Event	114 (88)	259 (88)	14 (61)	39 (66)
Blood and Lymphatic System Disorders	Any Event	15 (12)	31 (10)	1 (4)	4 (7)
	Anemia NOS	9 (7)	22 (7)	1 (4)	4 (7)
	Neutrophilia	2 (2)	0	0	0
Cardiac disorders	Any Event	34 (26)	34 (11)	3 (13)	7 (12)
	Cardiac failure NOS	6 (5)	0	0	0
	Congestive cardiac failure aggravated	14 (11)	13 (4)	1 (4)	1 (2)
Ear and labyrinth disorders	Any Event	2 (2)	3 (1)	0	0
	Ear pain	2 (2)	0	0	0
Gastrointestinal disorders	Any Event	45 (35)	91 (31)	2 (9)	14 (24)
	Abdominal pain NOS	7 (5)	10 (3)	0	2 (3)
	Constipation	11 (9)	25 (8)	0	4 (7)
	Diarrhea NOS	7 (5)	22 (7)	0	1 (2)
	Dry mouth	1 (<1)	9 (3)	0	0
	Dyspepsia	5 (4)	5 (2)	0	0
	Vomiting NOS	12 (9)	18 (6)	0	2 (3)
	Any Event	73 (57)	186 (63)	3 (13)	8 (14)
General disorders and administration site conditions	Aesthenia	9 (7)	10 (3)	0	2 (3)
	Anasarca	2 (2)	0	0	0
	Catheter site pain	2 (2)	0	0	0
	Edema NOS	7 (5)	1 (<1)	0	0
	Infusion site erythema	7 (5)	8 (3)	0	0
	Infusion site phlebitis	30 (23)	94 (32)	1 (4)	0
	Infusion site reaction	12 (9)	58 (20)	0	0
	Pyrexia	12 (9)	16 (5)	0	1 (2)
Hepatobiliary disorders	Any Event	5 (4)	5 (2)	0	1 (2)
	Hepatic failure	2 (2)	0	0	0
Infections and	Any Event	30 (23)	58 (20)	3 (13)	4 (7)

Table 7.1.5.8.2: Comparison^a of Incidence of Treatment-emergent Adverse Events Between Hypervolemic and Euvolemic Patients, All Conivaptan Studies

System Organ Class	Preferred Term	Coni Hypervolemic N ^b =129 n(%)	Coni Euvolemic N ^b =296 n(%)	Pbo Hypervolemic N ^b =23 n(%)	Pbo Euvolemic N ^b =59 n(%)
	infestations				
	Sepsis NOS	6 (5)	1 (<1)	0	0
	Septic shock	2 (2)	0	0	0
Investigations	Any Event	18 (14)	34 (11)	1 (4)	4 (7)
	Blood creatinine increased	5 (4)	2 (<1)		
Metabolism and nutrition disorders	Any Event	40 (31)	72 (24)	4 (17)	7 (12)
	Hypokalemia	18 (14)	24 (8)	1 (4)	2 (3)
	Hypomagnesemia	5 (4)	5 (2)	0	0
Musculoskeletal and connective tissue disorders	Any Event	9 (7)	25 (8)	0	3 (5)
	Back pain	0	5 (2)	0	1 (2)
Nervous system disorders	Any Event	26 (20)	54 (18)	0	9 (15)
	Asterixis	2 (2)	0	0	0
	Dizziness	5 (4)	19 (6)	0	2 (3)
	Headache	10 (8)	26 (9)	0	4 (7)
	Somnolence	2 (2)	0	0	0
Psychiatric disorders	Any Event	16 (12)	45 (15)	3 (13)	3 (5)
	Confusional state	9 (7)	11 (4)	1 (4)	2 (3)
	Insomnia	6 (5)	18 (6)	1 (4)	1 (2)
Renal and urinary disorders	Any Event	26 (20)	49 (17)	2 (9)	5 (8)
	Renal failure NOS	10 (8)	8 (3)	1 (4)	0
	Renal failure acute	6 (5)	5 (2)	0	0
	Urinary retention	0	8 (3)	0	0
Respiratory, thoracic and mediastinal disorders	Any Event	26 (20)	38 (13)	2 (9)	8 (14)
	Dyspnea	5 (4)	10 (3)	0	1 (2)
Skin and subcutaneous tissue disorders	Any Event	11 (9)	19 (6)	1 (4)	1 (2)
	Decubitus ulcer	3 (2)	0	0	0
Surgical and medical procedures	Any Event	2 (2)	0	0	1 (2)
Vascular disorders	Any Event	34 (26)	71 (24)	3 (13)	7 (12)
	Flushing	0	5 (2)	0	1 (2)
	Hypertension NOS	3 (2)	23 (8)	0	1 (2)
	Hypotension NOS	13 (10)	18 (6)	2 (9)	3 (5)
	Orthostatic hypotension	10 (8)	18 (6)	1 (4)	1 (2)
	Phlebitis NOS	5 (4)	8 (3)	0	1 (2)

Source: Applicant's Table 2, beg pg 192, ISS

^a Above table includes those events which occurred with a frequency difference $\geq 2\%$ between hypervolemic and euvolemic conivaptan-treated patients. Also includes events for which the relationship of conivaptan group incidence to placebo group incidence differed between hypervolemic and euvolemic groups

^b N = number of patients with a volume status measurement at study entry; volume status collected only for Studies 026, 027, 031, 043 and 080

For the population of all studies with baseline volume assessments, in general, the types of events which occurred more frequently among hypervolemic patients than among euvoletic patients were similar to those for the IV population who had baseline volume assessments. However, in the overall population (IV + oral, all patients with baseline volume assessments), additional events which occurred at a rate $\geq 5\%$ higher among hypervolemic conivaptan-treated patients than among euvoletic conivaptan-treated patients, and at a higher rate among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included cardiac failure NOS, congestive cardiac failure aggravated, and renal failure NOS. Additional events which occurred at a rate $\geq 3\%$ higher among hypervolemic conivaptan-treated patients than among euvoletic conivaptan-treated patients, and at a higher rate among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included edema NOS and confusional state.

In a hypervolemic population, which would consist largely of patients with cardiac and hepatic failure, it is unsurprising to find a higher incidence of cardiac-failure-related and hepatic-failure-related events than one would find in a euvoletic population. Renal failure might also be expected to be higher in a hypervolemic population, as patients with cardiac and hepatic failure have a higher incidence of renal failure than persons without these conditions. However, the above events not only occurred more commonly among hypervolemic conivaptan-treated patients than among euvoletic conivaptan-treated patients, but also occurred more commonly among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients. Thus, underlying disease state cannot fully explain these differences. Additionally, the higher incidences of sepsis, pyrexia, hypokalemia and vomiting for hypervolemic vs euvoletic patients are unexplained by underlying disease state.

7.1.7 Laboratory Findings

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The applicant provided updated data for mean change from baseline for hematology and chemistry values. The following tables summarize these data for all IV studies, and for all conivaptan studies. The applicant did not provide standard deviations for mean change values.

Table 7.1.7.3.1.1: Mean Change¹ from Baseline to End of Treatment, Hematology Laboratory, All IV Studies			
Test	Units	Coni N=581 Mean Change	Pbo N=132 Mean Change
Basophils	%	0.05	0.05
Eosinophils	%	0.42	0.50
Hematocrit	%	-0.27	-0.46

Table 7.1.7.3.1.1: Mean Change¹ from Baseline to End of Treatment, Hematology Laboratory, All IV Studies

Test	Units	Coni N=581 Mean Change	Pbo N=132 Mean Change
Hemoglobin	g/dL	-0.16	-0.15
Lymphocytes	%	-0.76	-1.11
Mean corpuscular volume	fL	0.59	0.14
Monocytes	%	-0.42	0.54
Neutrophils	%	0.91	-0.11
Platelets	plt. $\cdot 10^3/\mu\text{L}$	0.05	0.05
Red blood cells	cells. $\cdot 10^6/\mu\text{L}$	-0.05	-0.05
White blood cells	cells. $\cdot 10^3/\mu\text{L}$	0.74	-0.17

Source: Applicant's Table 19, beg pg 349, ISS

¹ Applicant did not provide standard deviations for mean change

Table 7.1.7.3.1.2: Mean Change¹ from Baseline to End of Treatment, Hematology Laboratory, All Conivaptan Studies

Test	Units	Coni N=1284 Mean Change	Pbo N=372 Mean Change
Basophils	%	0.05	0.07
Eosinophils	%	0.33	0.19
Hematocrit	%	-0.30	-0.57
Hemoglobin	g/dL	-0.17	-0.21
Lymphocytes	%	0.02	0.54
Mean corpuscular volume	fL	0.51	0.10
Monocytes	%	-0.31	-0.37
Neutrophils	%	-0.05	-0.31
Platelets	plt. $\cdot 10^3/\mu\text{L}$	2.10	0.40
Red blood cells	cells. $\cdot 10^6/\mu\text{L}$	-0.06	-0.06
White blood cells	cells. $\cdot 10^3/\mu\text{L}$	0.45	-0.24

Source: Applicant's Table 19, beg pg 385, ISS.

¹ Applicant did not provide standard deviations for mean change

For these updated overall populations, there are no clinically meaningful differences between conivaptan and placebo for mean change from baseline in hematology parameters.

Table 7.1.7.3.1.3: Mean Change^{1,2} from Baseline to End of Treatment, Serum Chemistry Laboratory, All IV Studies

Test	Units	Coni N=581 Mean Change	Pbo N=132 Mean Change
Albumin	g/dL	-0.13	-0.15
Alkaline phosphatase	U/L	-0.8	-2.9
Alanine aminotransferase	U/L	2.1	-3.7
Aspartate aminotransferase	U/L	0.6	-3.4
Bilirubin, total	mg/dL	-0.01	0.03
Blood urea nitrogen	mg/dL	0.29	-0.58
Calcium	mg/dL	0.28	0
Carbon dioxide	mEq/L	0.32	0.13

Table 7.1.7.3.1.3: Mean Change^{1,2} from Baseline to End of Treatment, Serum Chemistry Laboratory, All IV Studies

Test	Units	Coni N=581 Mean Change	Pbo N=132 Mean Change
Chloride	mEq/L	4.49	0.06
Creatine kinase	U/L	-58.4	-14.9
Creatinine	mg/dL	0.12	-0.04
Gamma glutamyl transferase	U/L	2.7	2.3
Glucose, random	mg/dL	7.2	-12.1
Glucose, fasting	mg/dL	7.6	-9.5
International normalized ratio	n/a	0.01	0.06
Lactate dehydrogenase	U/L	2.8	-24.8
Potassium	mEq/L	0.120	0.003
Protein, total	g/dL	-0.11	-0.22
Prothrombin time	sec	0.08	0.41
Sodium	mEq/L	5.2	-0.5
Uric acid	μmol/L	7.24	-24.97

Source: Applicant's Table 20, beg pg 403, ISS
 1 Applicant did not provide standard deviations for mean change from baseline
 2 Applicant provided different numbers of significant digits for different laboratory tests

Table 7.1.7.3.1.4: Mean Change^{1,2} from Baseline to End of Treatment, Serum Chemistry Laboratory, All Conivaptan Studies

Test	Units	Coni N=1284 Mean Change	Pbo N=372 Mean Change
Albumin	g/dL	-0.08	-0.09
Alkaline phosphatase	U/L	-1.0	-2.1
Alanine aminotransferase	U/L	2.1	-1.3
Aspartate aminotransferase	U/L	1.2	-1.1
Bilirubin, total	mg/dL	-0.026	-0.002
Blood urca nitrogen	mg/dL	0.38	-0.32
Calcium	mg/dL	-0.02	-0.13
Carbon dioxide	mEq/L	0.16	-0.15
Chloride	mEq/L	2.46	0.39
Creatine kinase	U/L	-22.0	-3.9
Creatinine	mg/dL	0.10	-0.02
Gamma glutamyl transferase	U/L	1.2	4.9
Glucose, random	mg/dL	2.2	-6.8
Glucose, fasting	mg/dL	3.5	-2.5
International normalized ratio	n/a	-0.07	-0.09
Lactate dehydrogenase	U/L	-3.5	-6.5
Potassium	mEq/L	0.07	0.02
Protein, total	g/dL	-0.05	-0.11
Prothrombin time	sec	-0.67	-1.01
Sodium	mEq/L	2.9	0.1
Uric acid	μmol/L	14.97	-14.74

Source: Applicant's Table 20, beg pg 403, ISS
 1 Applicant did not provide standard deviations for mean change from baseline
 2 Applicant provided different numbers of significant digits for different laboratory tests

Because the effective water clearance of patients who received conivaptan increased more than that of patients who received placebo, slightly greater mean increases in serum chemistry parameters might be expected due to hemoconcentration. In general, the differences between

conivaptan-treated patients and placebo-treated patients were not clinically significant. However, mean random and fasting plasma glucose increased for conivaptan-treated patients, but declined for placebo-treated patients. This may be related to the fact that conivaptan is diluted in D5W. If conivaptan were to be administered chronically, this might have clinical significance, but the small differences between treatment groups are unlikely to have clinical consequences over the proposed administration duration of 2-4 days.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following tables present the number and percentage of patients who had shifts from normal to abnormal in laboratory values, for all IV conivaptan studies, and for all conivaptan studies (IV + oral, hyponatremia + heart failure development programs).

Table 7.1.7.3.2.1: Number and Percentage of Patients Who Shifted^a from Normal to Abnormal Values, Hematology Laboratory, All IV Studies

Test	Units	Coni n(%) ^b	Pbo n(%) ^b
Basophils	%	23 (5.3)	9 (12.9)
Eosinophils	%	42 (9.6)	10 (14.3)
Hematocrit	%	232 (40.9)	76 (59.4)
Hemoglobin	g/dL	253 (45.3)	72 (56.3)
Lymphocytes	%	209 (47.8)	34 (48.6)
Mean corpuscular volume	fL	10 (5.0)	4 (4.6)
Monocytes	%	19 (4.4)	2 (2.9)
Neutrophils	%	1 (0.3)	0
Platelets	plt.10 ³ /μL	58 (10.3)	25 (19.8)
Red blood cells	cells.10 ⁹ /μL	212 (45.6)	67 (52.3)
White blood cells	cells.10 ³ /μL	12 (2.1)	6 (4.7)

Source: Applicant's Table 13, beg pg 322, ISS

^a Treatment-emergent abnormality defined as lab measurement taken after first administered dose where the lab value is outside of specified criteria, for a patient with a baseline value that was either normal or missing.

^b Percentages based on number of patients with at least one post-baseline measurement

Table 7.1.7.3.2.2: Number and Percentage of Patients Who Shifted^a from Normal to Abnormal Values, Hematology Laboratory, All Conivaptan Studies

Test	Units	Coni n(%) ^b	Pbo n(%) ^b
Basophils	%	50 (6.9)	18 (11.2)
Eosinophils	%	88 (12.1)	21 (12.8)
Hematocrit	%	534 (42.6)	172 (42.7)
Hemoglobin	g/dL	606 (49.0)	189 (52.8)
Lymphocytes	%	355 (48.4)	84 (51.2)
Mean corpuscular volume	fL	36 (6.1)	14 (6.3)
Monocytes	%	34 (4.6)	10 (6.1)
Neutrophils	%	55 (8.9)	11 (8.9)
Platelets	plt.10 ³ /μL	179 (14.3)	55 (15.4)
Red blood cells	cells.10 ⁹ /μL	441 (50.7)	145 (56.9)
White blood cells	cells.10 ³ /μL	40 (4.1)	14 (5.5)

Source: Applicant's Table 13, beg pg 326, ISS

^a Treatment-emergent abnormality defined as lab measurement taken after first administered dose where the lab value is outside of specified criteria, for a patient with a baseline value that was either normal or missing.

^b Percentages based on number of patients with at least one post-baseline measurement

For hematology laboratory, shifts from normal to abnormal did not occur substantially more frequently among conivaptan-treated patients than among placebo-treated patients.

Table 7.1.7.3.2.3: Number and Percentage of Patients Who Shifted^a from Normal to Abnormal Values, Serum Chemistry Laboratory, All IV Studies

Test	Units	Coni n (%) ^b	Pbo n (%) ^b
Albumin	g/dL	192 (34.3)	53 (42.1)
Alkaline phosphatase	U/L	108 (19.1)	15 (12.0)
Alanine aminotransferase	U/L	48 (8.6)	22 (17.6)
Aspartate aminotransferase	U/L	71 (12.6)	25 (19.7)
Bilirubin, total	mg/dL	99 (17.7)	25 (19.8)
Blood urea nitrogen	mg/dL	180 (31.3)	59 (45.0)
Calcium	mg/dL	28 (24.1)	9 (22.5)
Carbon dioxide	mEq/L	69 (34.5)	29 (33.0)
Chloride	mEq/L	185 (32.7)	46 (36.2)
Creatine kinase	U/L	51 (9.2)	12 (10.0)
Creatinine	mg/dL	177 (30.8)	46 (35.1)
Gamma glutamyl transferase	U/L	26 (29.9)	15 (44.1)
Glucose, random	mg/dL	317 (58.4)	78 (62.9)
Glucose, fasting	mg/dL	52 (45.6)	13 (46.4)
International normalized ratio	n/a	11 (3.9)	6 (31.6)
Lactate dehydrogenase	U/L	86 (19.4)	23 (27.1)
Potassium	mEq/L	159 (27.7)	47 (36.7)
Protein, total	g/dL	162 (28.9)	41 (32.3)
Prothrombin time	sec	50 (20.1)	5 (27.8)
Sodium	mEq/L	217 (37.9)	73 (56.6)
Uric acid	µmol/L	148 (31.4)	51 (41.1)

Source: Applicant's Table 14, beg pg 328, ISS

^a Treatment-emergent abnormality defined as lab measurement taken after first administered dose where the lab value is outside of specified criteria, for a patient with a baseline value that was either normal or missing.

^b Percentages based on number of patients with at least one post-baseline measurement

Table 7.1.7.3.2.4: Number and Percentage of Patients Who Shifted^a from Normal to Abnormal Values, Serum Chemistry Laboratory, All Conivaptan Studies

Test	Units	Coni n (%) ^b	Pbo n (%) ^b
Albumin	g/dL	256 (20.6)	78 (22.0)
Alkaline phosphatase	U/L	238 (19.3)	49 (14.2)
Alanine aminotransferase	U/L	196 (16.0)	68 (19.7)
Aspartate aminotransferase	U/L	239 (19.4)	81 (23.3)
Bilirubin, total	mg/dL	186 (15.0)	60 (16.9)
Blood urea nitrogen	mg/dL	369 (36.5)	114 (40.1)
Calcium	mg/dL	39 (10.6)	15 (12.5)
Carbon dioxide	mEq/L	297 (48.6)	99 (43.2)
Chloride	mEq/L	416 (33.5)	124 (34.7)
Creatine kinase	U/L	155 (12.8)	54 (16.1)
Creatinine	mg/dL	547 (43.3)	147 (40.6)
Gamma glutamyl transferase	U/L	116 (34.1)	44 (38.6)
Glucose, random	mg/dL	754 (64.8)	212 (67.5)
Glucose, fasting	mg/dL	116 (49.4)	30 (44.8)
International normalized ratio	n/a	21 (5.3)	7 (11.1)
Lactate dehydrogenase	U/L	238 (21.7)	71 (23.6)
Potassium	mEq/L	356 (28.2)	122 (34.1)

Table 7.1.7.3.2.4: Number and Percentage of Patients Who Shifted^a from Normal to Abnormal Values, Serum Chemistry Laboratory, All Conivaptan Studies

Test	Units	Coni n (%) ^b	Pbo n (%) ^b
Protein, total	g/dL	263 (21.1)	72 (20.2)
Prothrombin time	sec	115 (29.2)	26 (37.7)
Sodium	mEq/L	415 (32.9)	137 (38.2)
Uric acid	μmol/L	539 (46.8)	165 (47.0)

Source: Applicant's Table 14, beg pg 334, ISS

^a Treatment-emergent abnormality defined as lab measurement taken after first administered dose where the lab value is outside of specified criteria, for a patient with a baseline value that was either normal or missing.

^b Percentages based on number of patients with at least one post-baseline measurement

Across all IV studies, conivaptan-treated patients did not develop shifts from normal to abnormal chemistry values more often than did placebo-treated patients. Across the entire conivaptan development program, conivaptan-treated patients developed shifts from normal to abnormal slightly more often (compared to placebo-treated patients) for fasting plasma glucose and serum creatinine.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The following table gives the ranges of clinical concern which were used by the applicant for identification of marked laboratory abnormalities.

Table 7.1.7.3.3.1 Applicant's Ranges of Clinical Concern for Identification of Marked Abnormalities of Hematology and Serum Chemistry Parameters

Parameter	Women	Men	Units
<i>Hematology Parameters</i>			
Hematocrit	<33	<37	%
Hemoglobin	<11	<12.5	g/dL
Neutrophils	<1.5	<1.5	%
Platelets	<130	<130	10 ³ cells/μL
Red Blood Cells	<3.8	<4	10 ⁶ cells/μL
White Blood Cells	<3.8	<3.8	10 ³ cells/μL
<i>Clinical Chemistry Parameters</i>			
Alkaline Phosphatase	>220	>220	IU/L
Blood Urea Nitrogen	>35	>35	mg/dL
Creatine kinase	>1450	>1450	IU/L
Creatinine	>1.6	>1.6	mg/dL
International Normalized Ratio	>1.5	>1.5	Ration
SGOT (AST)	>50	>50	IU/L
SGPT (ALT)	>50	>50	IU/L
Total Bilirubin	>1.2	>1.2	mg/dL

Source: Applicant's Appendix 1, pg 481, ISS

The following tables summarize the number and percentage of patients who developed laboratory abnormalities that met the above criteria.

Table 7.1.7.3.3.2: Number and Percentage of Patients Who Developed Clinically Significant^a Laboratory Abnormalities, All IV Studies

Test ^a	Coni n(%) ^b	Pbo n(%) ^b
Hematocrit	199 (35.1)	54 (42.2)
Hemoglobin	213 (38.2)	55 (43.0)
Neutrophils	0	0
Platelets	47 (8.3)	17 (13.5)
Red blood cells	169 (36.3)	50 (39.1)
White blood cells	6 (1.1)	3 (2.3)
Alanine aminotransferase	36 (6.4)	11 (8.8)
Alkaline phosphatase	28 (5.0)	34 (26.0)
Aspartate aminotransferase	58 (10.3)	12 (9.4)
Bilirubin, total	89 (15.9)	21 (16.7)
Blood urea nitrogen	105 (18.3)	34 (26.0)
Creatine kinase	4 (0.7)	0
Creatinine	123 (21.4)	30 (22.9)
International normalized ratio	3 (1.1)	4 (21.1)

Sources: Applicant's Table 16, pg 340, ISS and Table 17, pg 343, ISS

a For definitions of ranges of clinical concern, and for units of measurement, see Table 7.1.7.3.3.1

b Percentages are based on the number of patients with at least one post-baseline measurement for the given parameter

Table 7.1.7.3.3.3: Number and Percentage of Patients Who Developed Clinically Significant^a Laboratory Abnormalities, All Conivaptan Studies

Test ^a	Coni n(%) ^b	Pbo n(%) ^b
Hematocrit	409 (32.6)	121 (33.8)
Hemoglobin	409 (33.1)	125 (34.9)
Neutrophils	14 (15.4)	7 (22.6)
Platelets	109 (8.7)	29 (8.1)
Red blood cells	304 (35.0)	98 (38.4)
White blood cells	20 (2.1)	6 (2.4)
Alanine aminotransferase	122 (10.0)	44 (12.8)
Alkaline phosphatase	130 (10.6)	31 (9.0)
Aspartate aminotransferase	118 (9.6)	29 (8.4)
Bilirubin, total	163 (13.2)	53 (14.9)
Blood urea nitrogen	211 (20.9)	66 (23.2)
Creatine kinase	8 (0.7)	0
Creatinine	335 (26.5)	80 (22.1)
International normalized ratio	6 (1.5)	4 (6.3)

Sources: Applicant's Table 16, pg 342, ISS and Table 17, pg 345, ISS

a For definitions of ranges of clinical concern, and for units of measurement, see Table 7.1.7.3.3.1

b Percentages are based on the number of patients with at least one post-baseline measurement for the given parameter

Of potential clinical concern is the fact that all marked abnormalities of creatine kinase (>1450 IU/L) occurred among conivaptan patients. This was noted as a concern prior to the 1st cycle submission; conivaptan is a potent inhibitor of CYP3A4, and two patients who were taking concomitant statins developed rhabdomyolysis. This led to the applicant's decision to pursue only an IV formulation. At the time of the 2nd cycle review, only one case of marked elevation of creatine kinase (CK) had occurred in a patient who received IV conivaptan. Since then, 3 out

of the additional 136 patients who received IV conivaptan between the 2nd and 3rd cycle submissions were reported to have marked abnormalities of CK. Case report forms for these events were not included in the submitted materials. The clinical reviewer requested them from Dr. Donald Raineri, Regulatory Affairs contact for Astellas, on 19 Jan 07. On 29 Jan 07, the applicant provided information regarding these patients.

Patient 10410 was a 79 year old woman who had an elevated baseline CK of 5316 IU/L prior to study drug dosing; this elevated CK was attributed to a viral illness. The patient's CK declined to 598 IU/L on Study Day 2; the next value was normal (71 IU/L) on Study Day 11. The patient was not taking a concomitant statin at the time of study entry. Patient 11238 was an 81 year old woman who had a baseline CK of 746 IU/L. The patient had ST segment changes on ECG, and an elevated troponin, and was diagnosed with a myocardial infarction. The patient's CK peaked at 1777 IU/L on Study Day 2, and had declined to 732 IU/L by Study Day 4; the patient died of ventricular fibrillation on Study Day 5. This patient's CK elevation could reasonably be attributed to a myocardial infarction, although the applicant reports that CK-MB was not obtained. Patient 20707 was a 59 year old woman who experience two seizures on Study Day 1, prior to receiving any conivaptan; the patient was not receiving a statin. This patient's elevated CK can reasonably be attributed to seizures..

Each of these patients appears to have had an underlying condition which caused baseline CK elevation; none were taking concomitant statins at entry. At this time, there does not appear to be a significant signal for risk of rhabdomyolysis with intravenous conivaptan.

7.1.17 Postmarketing Experience

As of 24 Jan 07, there are no reports of adverse events with conivaptan as a suspect drug in the Adverse Event Reporting System (AERS) database. Through periodic safety updates for NDA 21697, there have been no reports (as of 24 Jan 07) of adverse events which are not already described in the product label.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The following table enumerates patients across both conivaptan clinical development programs.

Table 7.2.1.1:

Enumeration of Subjects in the Conivaptan Development Program		
Cutoff Date: May 31, 2006		
Study Groups	Treatment Groups	
	Conivaptan	Placebo
Completed Phase 1		
Single Dose	251	33
Multiple Dose	308	58
Phase 1 Subtotal	559	91
Completed Phase 2 and Phase 3		
Placebo-controlled	942	374
<i>Short Term (< 4 days)</i>	308	134
<i>Long Term (≥ 4 days)</i>	634	240
Uncontrolled†	342	0
<i>Short Term (< 4 days)</i>	105	0
<i>Long Term (≥ 4 days)</i>	237	0
Completed Phase 2 and Phase 3 Subtotal	1284	374
Single Dose Subtotal	394	96
Multiple Dose Subtotal	1449	369
Grand Total	1843	465

† Patients from Study 087-CL-026 or 087-CL-027 could roll over into the open-label extension study 087-CL-031. Only patients who received placebo in 087-CL-026 or -027 were counted as "new patients" for Study -031. Patients from Study 087-CL-043 could roll over into Study 087-CL-047. Only patients who received placebo in 087-CL-043 were counted as "new patients" for Study -047.

Source: Applicant's Appendix 2, pg 482, ISS

7.2.1.2 Demographics

The following table presents updated demographic data for all conivaptan studies. No new placebo patients were treated between the 2nd and 3rd review cycles. Conivaptan-treated patients were generally similar to patients in the 2nd cycle review population, although they were slightly older and slightly more likely to be women in this review cycle.

Table 7.2.1.2.1: Updated Demographics, All Conivaptan Studies

Demographic	Coni 2 nd Cycle Review Submission N=1148	Coni 3 rd (Current) Cycle Review Submission N=1284	Pbo N=372
Mean age (years) ± SD	63.2 (13.1)	64.2 (13.4)	63.4 (13.9)
n (%) <65 years	603 (52.5)	632 (49.2)	191 (51.3)
n (%) ≥65 years	545 (47.5)	652 (50.8)	181 (48.7)
n (%) ≥75 years	255 (22.2)	326 (25.4)	80 (21.5)
n (%) male gender	776 (67.6)	823 (64.1)	261 (70.2)
n (%) Caucasian	916 (79.8)	1037 (80.8)	286 (76.9)
n (%) Black	179 (15.6)	189 (14.7)	71 (19.1)
n (%) Hispanic	36 (3.1)	36 (2.8)	10 (2.7)
n (%) Asian	6 (0.5)	8 (0.6)	1 (0.3)
n (%) other racial group	11 (1.0)	14 (1.1)	4 (1.1)

Source: Table 9, pg 292, ISS

The following table presents a summary of age and gender for all intravenous studies. Mean age of placebo group patients was somewhat younger than that for conivaptan patients; this was due to the higher mean age of patients in Study 080, which did not have a placebo control. A younger placebo group would not be expected to favor conivaptan in terms of risk for adverse events. The applicant did not provide racial demographics broken down by dose. However, the overall IV population (all conivaptan doses) had a similar distribution between conivaptan and pbo (Table 9, pg 290, ISS). This table includes only those doses proposed for labeling. There was no significant imbalance in groups which would suggest a problem with randomization.

Table 7.2.1.2.2: Age and Gender Demographics, All IV Studies¹

Demographic	IV Pbo N=69	Coni 20 mg N=37	Coni 40 mg N=315
Mean age (years) ± SD	50.9 ± 23.2	73.5 ± 13.2	63.6 ± 20.1
n (%) <65 years	43 (62.3)	4 (10.8)	126 (40.0)
n (%) ≥65 years	26 (37.7)	33 (89.2)	189 (60.0)
n (%) ≥75 years	15 (21.7)	22 (35.1)	127 (40.3)
n (%) male gender	33 (47.8)	13 (35.1)	128 (40.6)

Source: Applicant's Table "Label Table 2", pg 192, response document
¹ Studies 027, 074, 079, 080, 083

The following table summarizes demographics for all patients in Phase 2/3 heart failure studies. Of the 818 heart failure patients who were exposed to conivaptan, 253 received intravenous conivaptan. Demographics were similar, and do not suggest problems with randomization.

Table 7.2.1.2.3: Demographics, All Phase 2/3 Heart Failure Studies¹

Demographic	Coni N=818	Pbo N=290
Mean age (years) ± SD	60.9 ± 12.01	61.0 ± 13.22
n (%) <65 years	493 (60.3)	170 (58.6)
n (%) ≥65 years	325 (39.7)	120 (41.4)
n (%) ≥75 years	122 (14.9)	40 (13.8)
n (%) male gender	617 (75.4)	218 (75.2)
n (%) Caucasian	624 (76.3)	208 (71.7)
n (%) Black	152 (18.6)	68 (23.4)
n (%) Hispanic	33 (4.0)	10 (3.4)
n (%) Asian	4 (0.5)	1 (0.3)
n (%) other racial group	5 (0.6)	3 (1.0)

Source: Applicant's Table 12.1, pg 86, response document
 1 Studies 016, 017, 020, 024, 032, 033, 034, 038, 044, 071

7.2.1.3 Extent of exposure (dose/duration)

The following table details exposure to any dose of conivaptan in all conivaptan studies. The extent of exposure from the 2nd and 3rd cycle review submissions are presented for conivaptan; there were no additional placebo exposures for the 3rd cycle.

Table 7.2.1.3.1: Updated Summary of Exposure to Oral and Intravenous Conivaptan, All Studies

Measure	Coni, 2 nd Cycle Review Submission N=1148	Coni, 3 rd (Current) Cycle Review Submission N=1284	Pbo N=372
Mean duration of exposure, days (SD)	51.4 (72.5)	46.4 (70.1)	43.3 (47.3)
Median duration of exposure, days	22	5	7
Minimum and maximum exposure, days	1, 771	1, 771	1, 229
# patients with exposure ≥ 1 day, n (%)	1148 (100)	1284 (100)	372 (100)
# patients with exposure ≥ 2 days, n (%)	971 (84.6)	1099 (85.6)	303 (81.5)
# patients with exposure ≥ 3 days, n (%)	833 (72.6)	951 (74.1)	256 (68.8)
# patients with exposure ≥ 4 days, n (%)	800 (69.7)	912 (71.0)	251 (67.5)
# patients with exposure ≥ 6 days, n (%)	606 (52.8)	606 (47.2)	183 (49.2)
# patients with exposure ≥ 7 days, n (%)	604 (52.6)	604 (47.0)	183 (49.2)
# patients with exposure ≥ 14 days, n (%)	582 (50.7)	582 (45.2)	174 (46.8)
# patients with exposure ≥ 28 days, n (%)	568 (49.5)	568 (44.2)	172 (46.2)
# patients with exposure ≥ 84 days, n (%)	319 (27.8)	319 (24.8)	96 (25.8)
# patients with exposure ≥ 182 days, n (%)	42 (3.7)	42 (3.3)	10 (2.7)

Source: Applicant's Table 11, pg 298, ISS

The vast majority of exposure, in terms of patient-days, was from oral conivaptan studies. All new data were uncontrolled data from IV Study 080, with duration of conivaptan administration ≤ 4 days.

The following table updates the exposure to IV conivaptan from all studies. Mean IV duration was much shorter than mean oral duration.

Table 7.2.1.3.2: Updated Summary of Exposure to Intravenous Conivaptan, All Studies

Measure	Coni, 2 nd Cycle Review Submission N=445	Coni, 3 rd (Current) Cycle Review Submission N=581	Pbo N=132
Mean duration of exposure, days (SD)	2.3 (1.3)	2.6 (1.3)	1.9 (1.1)
Median duration of exposure, days	2	2	2
Minimum and maximum exposure, days	1, 4	1, 4	1, 4
# patients with exposure ≥ 1 day, n (%)	445 (100)	581 (100)	132 (100)
# patients with exposure ≥ 2 days, n (%)	284 (63.8)	412 (70.9)	67 (50.8)
# patients with exposure ≥ 3 days, n (%)	147 (33.0)	265 (45.6)	26 (19.7)
# patients with exposure ≥ 4 days, n (%)	139 (31.2)	251 (43.2)	22 (16.7)
# patients with exposure ≥ 5 days, n	0	0	0

Source: Applicant's Table 11, pg 296, ISS

The following table details exposure to any dose of conivaptan, oral or intravenous, in all Phase 2/3 heart failure studies. All exposure of >2 days duration was to oral conivaptan, which is associated with approximately 1/3 the conivaptan exposure of intravenous conivaptan.

Table 7.2.1.3.3: Summary of Exposure to Oral and Intravenous Conivaptan, All Phase 2/3 Heart Failure Studies¹

Measure	Coni N=818	Pbo N=290
Mean duration of exposure, days (SD)	55.7 (48.8)	53.9 (48.5)
Median duration of exposure, days	78	78
Minimum and maximum exposure, days	1, 267	1, 229
# patients with exposure ≥ 1 day, n (%)	818 (100)	290 (100)
# patients with exposure ≥ 2 days, n (%)	666 (81.4)	223 (76.9)
# patients with exposure ≥ 3 days, n (%)	553 (67.6)	183 (63.1)
# patients with exposure ≥ 4 days, n (%)	530 (64.8)	183 (63.1)
# patients with exposure ≥ 6 days, n (%)	529 (64.7)	183 (63.1)
# patients with exposure ≥ 7 days, n (%)	528 (64.5)	183 (63.1)
# patients with exposure ≥ 14 days, n (%)	509 (62.2)	174 (60.0)
# patients with exposure ≥ 28 days, n (%)	502 (61.4)	172 (59.3)
# patients with exposure ≥ 84 days, n (%)	278 (34.0)	96 (33.1)
# patients with exposure ≥ 182 days, n (%)	25 (3.1)	10 (3.4)

Source: Applicant's Table 13.1, pg 89, response document

Total patient-year exposure to conivaptan in Phase 2/3 heart failure studies, for oral and intravenous combined, was 124.8 patient-years. However, as illustrated below, <1 patient-year of this exposure was to intravenous conivaptan. None of the patients who received oral

conivaptan had single-dose exposure equivalent to the exposure from the proposed intravenous dose.

The following table includes exposure information for intravenous conivaptan in heart failure studies.

Table 7.2.1.3.4: Summary of Exposure to Intravenous Conivaptan, All Phase 2/3 Heart Failure Studies¹

Measure	Pbo N=103	10 mg N=37	20 mg N=32	40 mg N=89	80 mg N=53	120 mg N=42	Any Coni N=253
Mean duration of exposure, days (SD)	1.4 (0.49)	1.0 (0)	1.0 (0)	1.4 (0.50)	1.7 (0.45)	1.9 (0.33)	1.4 (0.50)
Median duration of exposure, days	1.0	1.0	1.0	1.0	2.0	2.0	1.0
Minimum and maximum exposure, days	1, 2	1, 1	1, 1	1, 2	1, 2	1, 2	1, 2
# patients with exposure ≥ 1 day, n (%)	103 (100)	37 (100)	32 (100)	89 (100)	53 (100)	42 (100)	253 (100)
# patients with exposure ≥ 2 days, n (%)	39 (37.9)	0	0	37 (41.6)	39 (73.6)	37 (88.1)	113 (44.7)
# patients with exposure ≥ 3 days, n (%)	0	0	0	0	0	0	0

Source: Applicant's Table 13.2, pg 90, response document

Total duration of exposure to intravenous conivaptan in Phase 2/3 heart failure studies was very low. Among all patients and all doses, total duration of intravenous exposure for the sum of all patients was <1 patient-year (354.2 patient-days across the entire Phase 2/3 heart failure program).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.2 Explorations for Predictive Factors

7.4.2.4 Explorations for drug-disease interactions

The potential drug-disease interaction that was of most concern in the previous cycle review was that of heart failure and conivaptan. The 2nd cycle review raised questions of an increased risk of cardiac failure events, and a signal for a dose-related increase in mortality for this population. Because the majority of hypervolemic hyponatremic patients had heart failure, this led to approval of conivaptan for euvolemic hyponatremia, but not for hypervolemic hyponatremia. Heart failure was also of special concern because there is considerable interest in the medical

literature regarding the potential usefulness of vasopressin receptor antagonists in the treatment of heart failure per se, independent of serum sodium status. The potential for off-label use exists, and the general heart failure population is much larger than the population of patients who are hospitalized with significant hyponatremia.

Please see Sections 7.1.2, 7.1.3.3, and 7.1.5 for information regarding adverse events which occurred specifically among patients with hyponatremia. Specific tables of adverse events for the overall hypervolemic hyponatremic population, the population of hypervolemic hyponatremic patients with heart failure, the population of hypervolemic hyponatremic patients without heart failure, and overall heart failure populations, are presented in these sections.

The applicant was also asked to present ([REDACTED]) data from all patients who were studied in the applicant's heart failure development program ([REDACTED]) in the Division of Cardiovascular and Renal Products. Most of these patients did not have hyponatremia, but may provide additional relevant safety information for the specific population of heart failure patients.

b(4)

[REDACTED]

However, the applicant asserts that conivaptan did not worsen underlying CHF by various efficacy and safety assessments.

The heart failure development program consisted of 12 studies. Two of these studies were conducted in Japan, and have Japanese databases. Therefore, the applicant provided translated study reports for these studies, but did not include the data in an integrated database with the 10 other studies' data. The 12 studies included a total of 818 heart failure patients, and are described in the following table.

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Table 7.4.2.4.1: Conivaptan Heart Failure Studies

Study Number	Objective	Dose and Duration	Number of Subjects
<i>Studies with IV conivaptan</i>			
087-CL-071	Evaluate efficacy and safety of IV YM087 in patients with acutely decompensated chronic heart failure	IV conivaptan 20 mg loading dose followed by 40, 80, or 120 mg/day for 2 days	162
087-CL-032	Determine safety and efficacy of 3 doses of acute IV administration of conivaptan, in patients with NYHA class III/IV CHF	Single dose of IV conivaptan, 10, 20, or 40 mg	143
087-CL-038	Determine effectiveness of IV administered conivaptan on the relief of pulmonary congestion symptoms in patients with acute decompensated heart failure	2 single IV conivaptan 20 mg infusions over 30 mins, 8 hours apart	26
087-CL-044	Explore effectiveness of IV-administered conivaptan on relief of pulmonary congestion in patients admitted for acute CHF exacerbation	2 single IV conivaptan 40 mg infusions over 30 mins, 8 hours apart	26
087-CL-019†‡	Investigate safety, effect on hemodynamics, and water diuretic action of IV administered conivaptan in acute heart failure or acute exacerbation of chronic heart failure	Single IV dose of 2, 10, 25, 50, 125, 250 mcg/kg	42
<i>Studies with Oral Conivaptan</i>			
087-CL-034	Determine the dose-dependent effects of conivaptan on patients with Class II to IV CHF	12 weeks of oral conivaptan 10, 20, or 40 mg twice daily	343
087-CL-020	Investigate the effect of oral conivaptan on exercise capacity in NYHA Class II-III CHF	12 weeks of oral conivaptan, 5, 10, or 20 mg twice daily	304
087-CL-033	Evaluate 3 doses of conivaptan in patients with severe NYHA class II-IV CHF	26 weeks of oral conivaptan, 10, 20, or 40 mg twice daily	47
087-CL-017	Investigate safety and tolerability of oral conivaptan in patients with CHF NYHA class III/IV	7 days of oral conivaptan, 5, 10, 20 or 40 mg twice daily	24
087-CL-024	Determine the safety and efficacy of concomitant treatment with oral conivaptan and furosemide in patients with CHF	3 days of oral conivaptan in combination with furosemide, 20 or 40 mg	24
087-CL-016†	Study the PK and safety of single doses of oral conivaptan in patients with severe CHF	Single dose of oral conivaptan, 5, 10 or 20 mg	12
087-CL-018†‡	Study the water diuresis effect and safety of oral conivaptan in patients with edematous diseases due to cardiac, renal or hepatic diseases	1, 5, 10, 20, 30 mg dose escalation over 5 days	30 (n=10 with underlying CHF)

† The study included a small number of patients and/or a single-dose dosing regimen and is not discussed in text; the study report is included in the submission.

‡ Study databases are in Japanese and are not included in the integrated safety analyses

Source: Applicant's Table 1, pg 212, response document

These studies included a variety of efficacy endpoints. The following tables summarize efficacy outcomes of these studies. Outcomes from Study 071 are presented separately and in some detail, since this was the main controlled IV heart failure study. In that study, there were no significant differences between treatment groups for heart failure efficacy outcomes. In general, for other studies, efficacy outcomes were also not statistically significantly different between placebo and conivaptan. For other studies, if efficacy endpoints were identical to those used in

Study 071 and were also not significantly different, results are not repeated; only other unique endpoints and significantly different outcomes are shown.

In Study 071, patients with acutely decompensated congestive heart failure were randomized to receive either IV pbo, or one of 3 doses of conivaptan, for 48 hours. All conivaptan groups received a 20 mg IV bolus, followed by either 40, 80, or 120 mg/day, administered by continuous intravenous infusion for 48 hours. There was no significant difference between placebo and any conivaptan dose for any of these outcomes.

Table 7.4.2.4.2: Summary of Heart Failure Efficacy Outcomes for Study 071

Outcome	Pbo N=40	Coni 40 mg N=40	Coni 80 mg N=40	Coni 120 mg N=42	p-value (if any)
AUC change from baseline to hour 48 in Respiratory Visual Analog Scale (Patient Assessment), mean ± SD ^a (primary efficacy outcome)	2138 ± 1187	2199 ± 949	2165 ± 1044	2036 ± 890	0.643 ^b
Mean change from baseline to hour 48 in respiratory rate, breaths/min ± SD ^c	-4.1 ± 3.7	-3.4 ± 4.6	-4.9 ± 4.3	-3.0 ± 5.5	0.293 ^d
Mean change from baseline to hour 72 in body weight, kg ± SD ^e	-2.5 ± 6.3	-3.2 ± 3.6	-3.3 ± 3.3	-1.8 ± 5.3	0.742 ^d
Mean duration of index hospitalization, days ± SD ^f	9.2 ± 14.1	12.9 ± 19.5	9.4 ± 14.2	14.1 ± 22.7	0.554 ^d
Mean number of hospital days over 90 days of study, days ± SD ^g	15.0 ± 18.4	17.0 ± 21.8	14.2 ± 16.8	23.1 ± 29.7	0.870 ^d
# deaths (%) ^h	5 (12.5)	3 (7.5)	3 (7.5)	7 (16.7)	0.214 ⁱ
Mean change in categorical jugular venous pressure score (0-3) at 72 hours, ± SD ^{j,k}	-1.0 ± 0.9	-0.6 ± 0.7	-0.9 ± 0.8	-0.7 ± 0.7	ND ^l
Mean change in categorical pulmonary rales score (0-4) at 72 hours, ± SD ^{m,n}	-1.2 ± 0.9	-1.2 ± 1.3	-1.7 ± 1.1	-1.5 ± 0.8	ND
Mean change in categorical pulmonary effusion score (0-1) at 72 hours, ± SD ^{o,p}	0 ± 0	-0.1 ± 0.4	-0.2 ± 0.4	-0.1 ± 0.3	ND
Mean change in categorical third heart sound score (0-1) at 72 hours, ± SD ^{q,r}	-0.2 ± 0.5	-0.2 ± 0.5	-0.2 ± 0.5	-0.1 ± 0.4	ND
Mean change in categorical ascites score (0-3) at 72 hours, ± SD ^{s,t}	-0.3 ± 0.6	-0.4 ± 0.8	-0.1 ± 0.4	-0.1 ± 0.3	ND
Mean change in categorical leg edema score (0-4) at 72 hours, ± SD ^{u,v}	-0.7 ± 1.3	-0.8 ± 1.4	-1.1 ± 1.0	-0.7 ± 0.8	ND

a Source: Applicant's Table 11-3, pg 75, Study 071 report
 b Dose-response p-value based on logistic regression model with dose as a covariate
 c Source: Applicant's Table 14.2.7.1, pg 229, Study 071 report
 d Pairwise p-value vs pbo for 40 mg/day grp (proposed dose for indication), based on analysis of covariance model with fixed effects for treatment and analysis center with baseline as covariate
 e Source: Applicant's Table 11-6, pg 82, Study 071 report
 f Source: Applicant's Table 14.2.19.1, pg 252, Study 071 report
 g Source: Applicant's Table 14.2.20.1, pg 253, Study 071 report
 h Source: Applicant's Table 14.2.21.1, pg 254, Study 071 report
 i Pairwise p-value for 40 mg vs pbo, based on COX PH model with incremental effects, stratified by analysis center
 j JVP categories: 0 = none, 1 = <8 cm water, 2 = ≥8 cm water, 3 = above angle of jaw
 k Source: Applicant's Table T1.2.1, pg 643, Study 071 report
 l Not done
 m Pulmonary rales categories: 0 = none, 1 = at bases only, 2 = 1/3 way up lung field, 3 = ½ way up, 4 = >1/2 way up
 n Source: Applicant's Table T1.2.2, pg 644, Study 071 report
 o Pleural effusion categories: 0 = not present, 1 = present
 p Source: Applicant's Table T1.2.3, pg 645, Study 071 report
 q Third heart sound categories: 0 = not present, 1 = present
 r Source: Applicant's Table T1.2.4, pg 646, Study 071 report
 s Ascites categories: 0 = none, 1 = mild, 2 = moderate, 3 = marked distension
 t Source: Applicant's Table T1.2.7, pg 649, Study 071 report
 u Leg edema categories: 0 = none, 1 = trace, 2 = ankle only, 3 = pretibial, 4 = above knee
 v Source: Applicant's Table T1.2.8, pg 650, Study 071 report

In Study 032, patients with NYHA FC III/IV heart failure, who all had pulmonary capillary wedge pressures (PCWP) of ≥ 16 mmHg at entry, were randomized to receive single doses of pbo or conivaptan (10, 20, or 40 mg) IV. Efficacy outcomes were hemodynamic measures. Conivaptan was associated with a statistically significantly greater decline in PCWP than was placebo. There was no difference between conivaptan and placebo for other hemodynamic measures.

Table 7.4.2.4.3: Summary of Hemodynamic Efficacy Outcomes for Heart Failure Single IV Dose Study 032

Outcome	Pbo N=37	Coni 10 mg N=37	Coni 20 mg N=32	Coni 40 mg N=35	p-value (if any)
Least squares mean peak change in PCWP from baseline to 3-6 hrs, mmHg \pm SE ^a (primary efficacy outcome)	-2.6 (0.77)	-3.7 (0.7)	-5.4 (0.7)	-4.3 (0.3)	0.044 ^b
Least squares mean change in baseline-corrected AUC for PCWP, mmHg-hr ^c	-3.9 (7.2)	-22.9 (7.3)	-29.8 (7.6)	-26.8 (7.4)	0.029 ^b
Least squares mean change in baseline-corrected AUC for cardiac index, L/min/m ² -hr ^d	1.2 (0.5)	1.5 (0.6)	2.6 (0.6)	1.5 (0.6)	0.740 ^b
Least squares mean change in baseline-corrected AUC for pulmonary vascular resistance, dynes-sec-cm ⁻⁵ -hr ^e	-150.4 (151.2)	164.8 (153.0)	-97.9 (162.4)	35.4 (155.4)	0.393 ^b
Least squares mean change in baseline-corrected AUC for systemic vascular resistance, dynes-sec-cm ⁻⁵ -hr ^f	-1043 (463)	-727 (470)	-1589 (497)	-538 (475)	0.448 ^b
a Source: Applicant's Table 11, pg 62, Study 032 report b LS mean for 40 mg vs pbo c Source: Applicant's Table 13, pg 66, Study 032 report d Source: Applicant's Table 14, pg 69, Study 032 report e Source: Applicant's Table 15, pg 71, Study 032 report f Source: Applicant's Table 16, pg 73, Study 032 report					

In Studies 038 and 044, patients with acutely decompensated NYHA FC II-IV heart failure received either IV pbo or IV conivaptan 20 mg (Study 038) or 40 mg (Study 044). In both studies, conivaptan or pbo was given as a 30 minute infusion on 2 occasions 8 hours apart. There was no clear difference between treatment groups for change in respiratory rate or a total heart failure score. This total heart failure score consisted of a total of categorical scores for clinical findings; types of clinical findings and categories were similar to those detailed above in Table 7.4.2.4.2 from Study 071. Reduction in alveolar-arterial (A-a) gradient was numerically greater for conivaptan than for placebo. Length of hospital stay and length of stay in a monitored unit were numerically shorter for 20 mg conivaptan than for pbo, but numerically longer for 40 mg conivaptan than for pbo. These were exploratory studies, and the applicant did not perform statistical tests.

Table 7.4.2.4.4: Summary of Efficacy Outcomes for Heart Failure, IV Studies 038 and 044

Endpoint	Study 038		Study 044	
	Pbo N=12	Coni 20 mg N=14	Pbo N=13	Coni 40 mg N=13
Change from baseline to 12 hours in mean respiratory rate, breaths/min \pm SD ^a	-2.4 \pm 1.0	-1.5 \pm 1.5	-2.3 \pm 1.2	-5.0 \pm 0.9
Change from baseline to 3 hours in mean A-a gradient, mmHg \pm SE ^a	44.1 \pm 28.6	-14.7 \pm 33.0	-39.3 \pm 49.1	-60.9 \pm 99.3
Change from baseline in categorical total acute heart failure score ^b (possible range 0-26) to hour 12, mean score \pm SE ^a	-4.2 \pm 0.9	-4.6 \pm 1.2	-2.5 \pm 0.8	-3.1 \pm 1.0
Mean length of hospital stay, days \pm SE ^c	6.5 (2.4)	7.6 (1.7)	15.8 (1.7)	12.1 (2.3)
Mean length of stay in a monitored unit, days \pm SE ^c	4.5 (1.5)	5.5 (1.3)	5.0 (1.3)	3.2 (0.7)

a Source: Applicant's Table 5, pg 222, response document
 b Total heart failure score consisted of a total of categorical scores for clinical findings; types of clinical findings and categories were similar to those detailed above in Table 7.4.2.4.2 from Study 071.
 c Source: Applicant's Table 7, pg 223, response document

Study 033 was a 26-week oral study in which patients with NYHA FC II-IV chronic heart failure were randomized to placebo or conivaptan (10, 20 or 40 mg BID). There were no clinically meaningful differences between placebo and conivaptan for multiple efficacy endpoints; the most pertinent endpoints are presented below.

Table 7.4.2.4.5: Summary of Efficacy Outcomes in Oral Heart Failure Study 033 (26 Weeks)

Outcome	Pbo N=11	Coni 20 mg/day N=14	Coni 40 mg/day N=11	Coni 80 mg/day N=10	p-value
Least squares mean change from baseline to final evaluation in left ventricular end-diastolic volume index by MRI, mL/m ² \pm SE ^a (primary efficacy outcome)	-6.4 \pm 7.3	-7.7 \pm 7.3	-5.4 \pm 7.6	-10.7 \pm 7.1	0.6716 ^b
Mean change from baseline to final evaluation in left ventricular end-systolic volume index by MRI, mL/m ² \pm SE ^c	-2.6 (5.8)	-1.5 (5.2)	0.5 (5.1)	-8.2 (6.0)	0.6179 ^b
Mean change from baseline to final evaluation in left ventricular mass index by MRI, g/m ² \pm SE ^d	1.6 (5.3)	5.6 (3.8)	-2.0 (4.3)	0.5 (5.5)	0.4758 ^b
Least squares mean change from baseline to final evaluation in left ventricular ejection fraction by echocardiography, % \pm SE ^e	-0.02 (2.60)	0.05 (2.60)	-2.07 (2.85)	5.25 (2.52)	0.1460 ^b
Number and percentage of patients with improvement in NYHA FC score at final evaluation, n(%) ^f	4 (36.2)	4 (28.6)	1 (9.1)	5 (50.0)	ND ^g

a Source: Applicant's Table 10, pg 55, Study 033 report
 b p-value for comparison of least squares means for 80 mg/day vs pbo. 80 mg/day presented because this dose is the closest to the proposed IV dose in terms of conivaptan exposure
 c Source: Applicant's Table 11, pg 57, Study 033 report
 d Source: Applicant's Table 12, pg 58, Study 033 report
 e Source: Applicant's Table 13, pg 59, Study 033 report
 f Source: Applicant's Table 15, pg 61, Study 033 report
 g Not done

In Study 034, patients with chronic NYHA FC II-IV heart failure received 12 weeks of pbo or conivaptan (10, 20 or 40 mg BID). Effects on functional and exercise capacity were assessed. There were no statistically significant differences between conivaptan and placebo.

Table: Summary of Efficacy Outcomes in Oral Heart Failure Study 034 (12 Weeks)

Outcome	Pbo N=93	Coni 20 mg/day N=76	Coni 40 mg/day N=85	Coni 80 mg/day N=89	p- value
Least squares mean change from baseline to final evaluation in VO ₂ (oxygen consumption per minute) measured at 70% of peak workload on exercise testing ^a , mL/kg/min ± SE	7.8 (9.0)	9.5 (9.6)	-6.5 (9.2)	9.8 (9.3)	1.0 ^b
Least squares mean change from baseline to final evaluation in exercise time to peak VO ₂ , seconds ± SE ^c	10.7 (11.6)	13.4 (12.5)	3.5 (12.1)	12.6 (12.1)	1.0 ^d
Number and percentage of patients with improvement in NYHA FC score from baseline to final evaluation, n (%) ^{e,f}	20.0 (21.5)	9 (11.8)	8 (9.4)	14 (15.7)	ND ^g

a Source: Applicant's Table 13, pg 65, Study 034 report
 b Least squares means comparison for 80 mg/day vs pbo (Dunnett's). 80 mg/day chosen because this dose is closest to proposed IV dose in terms of exposure
 c Source: Applicant's Table 16, pg 69, Study 034 report
 d Least squares means comparison for 80 mg/day vs pbo (Dunnett's). 80 mg/day chosen because this dose is closest to proposed IV dose in terms of exposure. Adjusted for multiple comparisons
 e Source: Applicant's Table 20, pg 73, Study 034 report
 f Percentages in reviewer's table are ITT and differ slightly from applicant's table
 g Not done

Study 020 was also a 12-week study, involving 225 patients, which used oral conivaptan and examined exercise capacity; maximum conivaptan dose in this study was 20 mg BID. Results were similar to those in Study 034.

In six of the heart failure studies, which included a total of 641 conivaptan-treated patients, there was an Endpoint Classification Committee which adjudicated events related to heart failure hospitalizations and/or emergency room (ER) visits. Across these studies, the incidence of heart failure hospitalizations or ER visits secondary to worsening of heart failure was 6.3% (15/240) for the placebo groups and 4.5% (29/641) for the conivaptan groups. The incidence of all-cause mortality across these 6 studies was 1.7% (4/240) for the placebo groups and 1.7% (11/641) for the conivaptan dose groups.

While conivaptan did not result in improvement of heart failure outcomes in heart failure studies, conivaptan was also not associated with a worsening of heart failure on several fairly objective measures, including hemodynamics, exercise tolerance, heart failure signs, structural heart changes, length of hospital/ICU stay and adjudicated heart failure hospitalizations/ER visits. In possibly less objective measures of heart failure symptoms, conivaptan also was not worse than placebo. However, the majority of patients in these studies did not have hyponatremia, which is a marker of severity of heart failure, and heart failure patients who would receive conivaptan for the proposed indication would all be hyponatremic.

The Division of Metabolism and Endocrinology Products consulted the Division of Cardiovascular and Renal Products for that Division's specific comments on the safety of

conivaptan when given to patients with underlying heart failure. They concluded that, although the updated data do not demonstrate a grossly increased safety risk for patients with underlying heart failure, the very small size of the relevant population was inadequate to permit a definitive statement. In the absence of a clear clinical benefit (other than a change in serum sodium) for heart failure patients, their tolerance for uncertainty regarding risk is low. Overall, their conclusion was that they do not have enough data to support that the drug is either effective or safe to treat heart failure patients with hypervolemic hyponatremia.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the 1st cycle review, it was noted that a lower dose of conivaptan than the proposed 40 mg/day dose could potentially be effective. Data submitted with the 2nd cycle response supported that conclusion. In the 2nd cycle review, it was noted that data submitted thus far indicated a greater conivaptan exposure for heart failure patients than for patients without heart failure. This was based on a pharmacokinetic model which had proved inaccurate for an IV:oral exposure comparison in the 1st cycle review. Safety concerns for patients with underlying heart failure also arose in the 2nd cycle review. The Division requested exploration of the possibility of a lower effective dose, e.g. 10 mg/day, for hyponatremic patients with underlying heart failure. The applicant did not submit data for efficacy evaluation of a 10 mg/day dose for heart failure patients. Rather, the applicant submitted pharmacokinetic data from Study 080 to support equal exposure for heart failure patients compared to patients without heart failure. Although these data are somewhat limited, the clinical pharmacology reviewer (Dr. Chung) agrees that there is not a significant difference in exposure for hypervolemic vs euvolemic patients.

Additionally, the applicant submits dose-response data to support a less robust and slower response to the 20 mg/day dose than to the 40 mg/day dose, based on the efficacy results from hypervolemic hyponatremic heart failure patients in IV hyponatremia Studies 027 and 080. These summary data are presented in the following table.

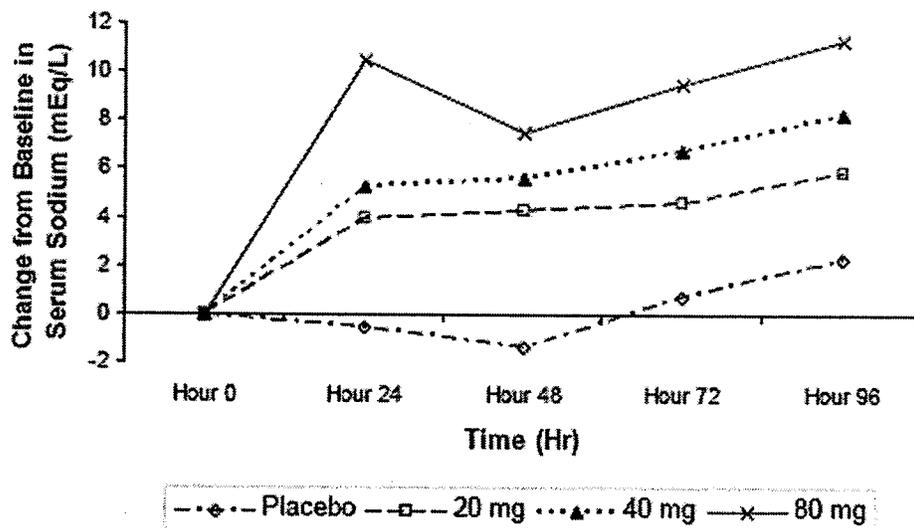
Table 8.1: Dose-response Efficacy Results for Hypervolemic Hyponatremia Patients with Underlying Heart Failure, IV Hyponatremia Studies 027 and 080

Endpoint	Pbo N=4	Coni 20 mg N=8	Coni 40 mg N=43	Coni 80 mg N=5
Mean baseline-adjusted serum sodium AUC over duration of treatment, mEq-hr/L (SD)	18.4 (117.0)	374.2 (339.8)	522.1 (443.2)	735.3 (207.6)
Number and percentage of patients with a confirmed ≥ 4 mEq/L increase from baseline in serum sodium, n (%)	1 (25.0)	5 (62.5)	34 (79.1)	5 (100.0)
Mean time to confirmed ≥ 4 mEq/L increase in serum sodium, hrs (95% CI)	NE ¹	53.8 (NE)	27.5 (24.0, 57.7)	24.0 (23.5, 48.1)
Mean total time from first dose of study medication to end of treatment during which patients had confirmed ≥ 4 mEq/L increase from baseline in serum sodium, hrs (SD)	7.3 (14.6)	40.3 (39.4)	53.9 (36.0)	77.6 (4.2)
Mean change from baseline to end of treatment in absolute serum sodium, mEq/L (SD)	0.9 (3.6)	5.2 (3.5)	7.4 (5.4)	10.3 (2.8)
Number and percentage of patients with a confirmed ≥ 6 mEq/L increase from baseline in serum sodium or a normal serum sodium concentration (≥ 135 mEq/L) during treatment, n (%)	0	3 (37.5)	28 (65.1)	5 (100.0)

Source: Applicant's Table 1, pg 284, response document

This dose response is illustrated in the following figure for change from baseline in absolute serum sodium. Mean change in this figure will differ slightly from that in the above table, because the figure uses mean change to specified time points, and the table uses mean change to end of treatment.

Figure 8.1: Mean Change from Baseline in Absolute Serum Sodium Concentration, Hypervolemic Hyponatremic Patients with Underlying Heart Failure, IV Hyponatremia Studies 027 and 080



Source: Applicant's Figure 1, pg 285, response document

The applicant asserts that, although a conivaptan dose of 20 mg/day produces a clinically meaningful increase in serum sodium concentration, it does so more slowly than higher doses, and there is a dose response. Based on the magnitude of change in serum sodium seen at 20 mg/day, the applicant asserts that 10 mg/day might not produce a prompt, "reliable" and clinically relevant increase in serum sodium concentration.

The clinical reviewer concurs that it no longer appears necessary for the applicant to explore a 10 mg/day dose.

8.7 Postmarketing Risk Management Plan

In addition to routine postmarketing surveillance, the applicant proposes to include special analyses of CHF-related events in the applicant's Periodic Adverse Drug Experience Reports and Annual Reports. The applicant will use its "Augmented" Standard MedDRA Query for heart failure events, which included 49 MedDRA preferred terms related to heart failure. The applicant also proposes to submit expedited (15 day) reports of events related to cardiac failure.

9 OVERALL ASSESSMENT

9.1 Conclusions

At the time of the original approval of Vaprisol® in December 2005, the data were inadequate to establish safety for the treatment of patients with hyponatremia who were hypervolemic. Safety concerns had included a possible increased incidence of exacerbations of heart failure, and a possible signal for an increased risk of death among patients with heart failure who received conivaptan compared to heart failure patients who received placebo. The approvable letter requested additional clinical trial data addressing risk vs benefit in patients with underlying heart failure.

In this response, the applicant did not submit new data from placebo-controlled trials of conivaptan in hypervolemic hyponatremia. Instead, they presented additional data for 136 patients from a non-placebo-controlled hyponatremia trial that had been ongoing at the time of the last review cycle. This trial included both hypervolemic and euvolemic patients, and included patients with and without heart failure.

Across the development program, including data from patients who were previously presented and data from the new patients mentioned above, the applicant presented data for a total of 112 patients with hypervolemic hyponatremia who were treated received intravenous conivaptan in any dose. Of these 112 patients, 79 had heart failure. Among the 112 presented hypervolemic hyponatremic patients, a total of 87 received one of the doses proposed for this application. Of these 87 patients, there were 58 heart failure patients with hypervolemic hyponatremia who received one of the proposed doses. Of these 58 patients, 51 were from Studies 027 and 080, where hyponatremia was defined as a serum sodium of <130 mEq/L (in Study 071,

hyponatremia was defined as a serum sodium ≤ 134 mEq/L). The Division has considered a serum sodium of < 130 mEq/L to be a clinically significant degree of hyponatremia. Thus, the number of IV conivaptan-treated hypervolemic hyponatremic heart failure patients with clinically significant hyponatremia presented by the applicant is very low. This low number of relevant patients complicated the safety review, and necessitated the consideration of safety information from other types of patients who received conivaptan.

9.1.1 Efficacy Conclusions

In order to assess the efficacy of conivaptan for the treatment of hypervolemic hyponatremia, the applicant examined hypervolemic patients from its two hyponatremia trials of intravenous conivaptan. This group included a total of 89 conivaptan-exposed patients, 56 of whom had underlying heart failure. Efficacy data were considered for this entire population of hypervolemic hyponatremic patients, and for the subpopulations with and without heart failure.

For the overall hypervolemic hyponatremic population that was treated with intravenous conivaptan, conivaptan appeared to be effective in the treatment of hyponatremia by several parameters. For the primary endpoint (change from baseline in area under the serum sodium effect curve), conivaptan was effective in raising serum sodium AUC at all doses tested, with an apparent dose response. Several secondary endpoints also demonstrated greater effectiveness for conivaptan than for placebo. The percentage of patients achieving a 4 mEq/L increase from baseline in serum sodium increased in a dose-dependent fashion. The mean number of hours during which patients had a serum sodium that was ≥ 4 mEq/L above their baseline increased in a dose-dependent fashion. Absolute serum sodium increased significantly from baseline to Day 4 and to end of treatment in all dose groups, while decreasing slightly in the placebo group. For this endpoint, however, there was not a clear dose response. For treatment to goal (≥ 6 mEq/L increase in serum sodium from baseline, or serum sodium ≥ 135 mEq/L), no placebo group patients achieved either of these goals, while most conivaptan-treated patients did, with an apparent dose response. For the 3 conivaptan doses studied (20, 40 and 80 mg/day), the respective percentages of patients who achieved one of these goals were 50%, 65% and 100%.

When considering the subpopulation of hypervolemic hyponatremia patients with heart failure, efficacy results were very similar to those seen in the overall hypervolemic hyponatremic population. For treatment to goal, the pattern of dose response was more clearly demonstrated for the subpopulation of hypervolemic hyponatremic patients with heart failure than for the overall hypervolemic hyponatremic population. In the lowest dose group (20 mg/day), which is also the lowest dose proposed by the applicant, 38% of patients achieved one of these goals, compared to 65% and 100% of patients in the 40 and 80 mg/day dose groups, respectively.

For the subgroup of hypervolemic hyponatremic patients without heart failure, efficacy results were similar. However, for most endpoints, a dose response was not evident.

Overall, by multiple measures, conivaptan appears to be effective in treating hyponatremia in hypervolemic patients. This is also true when one considers subpopulations with and without heart failure.

9.1.2 Safety Conclusions

The population identified from the 2nd cycle review as the safety population of greatest interest was that of hypervolemic hyponatremic patients with underlying heart failure. As mentioned above, the actual number of hypervolemic hyponatremic patients who were treated with IV conivaptan was very low; fewer still had underlying heart failure. Assessment of safety required expansion of the review to include other types of conivaptan-exposed patients.

The vast majority of exposure, in terms of patient-days, was from oral conivaptan studies. All new data were uncontrolled data from IV Study 080, with duration of conivaptan administration ≤ 4 days.

In the group of all Phase 2/3 heart failure studies, all exposure of >2 days duration was to oral conivaptan, which is associated with approximately 1/3 the conivaptan exposure of intravenous conivaptan. Total patient-year exposure to conivaptan in Phase 2/3 heart failure studies, for oral and intravenous combined, was 124.8 patient-years. However, <1 total patient-year of this exposure was to intravenous conivaptan. None of the patients who received oral conivaptan had single-dose exposure equivalent to the exposure from the proposed intravenous dose.

In the 2nd cycle review, the data had suggested a correlation between dose of conivaptan and incidence of death. This signal was of most concern for heart failure patients. For the data presented with this submission, death did not occur more frequently for conivaptan-treated patients than for placebo-treated patients for the hypervolemic hyponatremic population, or for the IV-treated heart failure population. Examination of the relationship between conivaptan and risk of death did not reveal a dose response when considering hypervolemic hyponatremic patients, and all patients in Phase 2/3 heart failure studies. There was also no evident dose response for risk of death when considering updated safety data for all patients across both development programs.

The majority of the patients who died had underlying decompensated heart failure, and died of progression or complications of heart failure. Heart failure has a high mortality rate; in the COPERNICUS trial of the effect of carvedilol on mortality in heart failure, the annual mortality in the placebo + usual care group was 19.7% (Fowler 2004). For all conivaptan heart failure program studies, the annual rate of death in conivaptan groups was 11.2%. For IV heart failure studies, no patient received >2 days of study medication, making estimations of annual mortality inaccurate. Only one conivaptan group patient in an IV heart failure study died during study drug administration. Additionally, the total exposure of heart failure patients to IV conivaptan was very small, at less than one total year of exposure for the entire population in the heart failure development program. Thus, firm conclusions cannot be reached regarding the risk of death for heart failure patients who receive intravenous conivaptan.

Overall, among patients with hypervolemic hyponatremia treated with IV conivaptan, serious adverse events did not occur more commonly among conivaptan-treated patients than among

placebo-treated patients. The only individual serious adverse event occurred more frequently for conivaptan group patients than for placebo group patients was "sepsis NOS".

When considering updated information from all conivaptan trials (hyponatremia and heart failure programs, IV and oral), serious adverse events occurred more frequently among conivaptan-treated patients than among placebo-treated patients. This was not due to an excess of a particular type or types of events, but rather to a slightly higher frequency of multiple events in several organ systems. The only individual serious adverse events which occurred at a frequency $\geq 1\%$ higher among conivaptan-treated patients than among placebo-treated patients were congestive cardiac failure aggravated and hyponatremia.

The applicant also provided a summary of all serious adverse events which occurred among patients treated with intravenous conivaptan in the heart failure development program, which was not limited to patients with hyponatremia. In these studies, serious adverse events in general did not occur more frequently among conivaptan group patients than among placebo group patients. The applicant also provided a summary of all serious adverse events which occurred among patients treated with oral conivaptan in the heart failure development program, which was also not limited to patients with hyponatremia. Angina, chest pain and syncope occurred more commonly among conivaptan group patients than among placebo group patients. All cases of renal failure (4 renal failure NOS, 1 renal failure acute) occurred among conivaptan group patients.

Among all patients with hypervolemic hyponatremia in IV studies, dropouts due to adverse events were not more common among conivaptan-treated patients than among placebo-treated patients. Of the 12 patients who withdrew from conivaptan treatment due to an adverse event, 4 withdrew due to an infusion-site-related event. Otherwise, there was no predominant type of event leading to withdrawal in either group.

In the overall updated conivaptan safety population (hyponatremia and heart failure programs, euvolemic and hypervolemic), the percentage of patients who completed treatment, and those who discontinued due to adverse events, was similar to that in the 2nd cycle review. As in that review, discontinuations due to adverse events occurred more commonly among conivaptan-treated patients than among placebo-treated patients.

Among all heart failure patients treated intravenously in Phase 2/3 heart failure studies, discontinuations due to adverse events were more common among conivaptan group patients than among placebo group patients. Of the 12 discontinuations in the conivaptan groups, 4 were due to infusion site adverse events, and three patients discontinued due to hypernatremia. Otherwise, no single type of event predominated as a cause of discontinuation.

Among all patients in Phase 2/3 heart failure studies (including both euvolemic and hypervolemic patients), discontinuations due to adverse events, or to "lack of compliance", were more common among conivaptan-treated patients than among placebo-treated patients. There was an apparent dose response for overall discontinuation, and discontinuation due to adverse events, for conivaptan-treated patients in both the IV and oral heart failure study groups.

Across the conivaptan development program, infusion site phlebitis was the only individual event which led to discontinuation for a higher percentage of conivaptan group patients than for placebo group patients.

In the 2nd cycle review, concerns arose regarding a signal for a higher rate of heart failure events and atrial arrhythmia events for conivaptan group patients compared to placebo group patients. For heart failure events, this signal was noted for specific heart failure event terms. The applicant argued that some of its studies did not include adjudication of heart failure events, and that for some studies, investigators received no instruction on how to report heart failure events, i.e. whether to use heart failure terms per se, or whether to use terms for individual symptoms such as dyspnea. The applicant performed additional analyses using a Standard MedDRA Query (SMQ) for heart failure; the applicant further devised an "Augmented SMQ" which included dyspnea terms.

When considering the hypervolemic hyponatremic population that was treated with IV conivaptan, for these adverse event term groupings of interest, conivaptan-treated patients had a higher numerical frequency of events within each of the heart failure groupings than did placebo patients, but conivaptan-treated patients did not have a higher frequency within the overall cardiac event grouping than did placebo-treated patients. The vast majority of patients who had any event within any of these groupings were patients who had baseline heart failure (34/39 conivaptan-treated patients with any event). When considering only those hypervolemic hyponatremic patients with baseline heart failure, conivaptan-treated patients had a higher numerical frequency of events within each of the heart failure groupings, and also within the overall cardiac events grouping. When examining the frequency of heart failure events among hypervolemic hyponatremic patients with baseline heart failure, each of three different grouping methods (two proposed by the applicant) for examining the overall occurrence of heart failure events showed a higher numerical frequency of heart failure events among conivaptan-treated patients than among placebo-treated patients. There were no atrial arrhythmia events among placebo patients; all 4 events occurred among conivaptan-treated patients with baseline heart failure.

Among hypervolemic hyponatremic patients without heart failure, there were no atrial arrhythmia or heart failure events or event groupings which occurred more frequently for conivaptan group patients than for placebo group patients.

Heart failure and atrial arrhythmia events were also examined for all patients with underlying heart failure in all Phase 2/3 IV studies (both the hyponatremia and heart failure programs). These studies include patients with and without hyponatremia. Conivaptan-treated patients (compared to placebo-treated patients) had a higher numerical frequency of events within each of the three cardiac failure event groupings. A dose response was suggested for the MedDRA Cardiac Failure SMQ and the applicant's "Augmented Cardiac Failure SMQ". Conivaptan-treated patients did not have a higher numerical frequency of events within the overall cardiac disorders SOC. All these intravenous studies were placebo-controlled. All 10 atrial arrhythmia events occurred in conivaptan-treated patients, with none in the placebo group.

When considering only hyponatremic patients from intravenous heart failure studies, there was no difference between groups for specific heart failure events, the MedDRA Cardiac Failure SMQ, or overall cardiac events. There was a higher incidence of events in the applicant's "augmented" cardiac failure SMQ for conivaptan vs placebo, due to more dyspnea events in the conivaptan group. Only 45/253 (18%) of patients in the heart failure development program IV studies had hyponatremia. This small sample size prevents clear conclusions.

When considering only hyponatremic patients from oral heart failure studies, specific cardiac failure events and events from the applicant's "augmented" cardiac failure SMQ occurred more commonly among conivaptan-treated patients than among placebo-treated patients. However, only 49/565 (9%) of patients in the heart failure program oral studies had hyponatremia; this small sample sizes limits the interpretability of this observation.

The incidence of heart failure and atrial arrhythmia events was also compared by baseline sodium status (eunatremic vs hyponatremic), for the population of patients in all Phase 2/3 studies. This population included all heart failure patients in the hyponatremia and heart failure development programs. Among heart failure patients who were also hyponatremic, specific heart failure events and events in the applicant's "augmented" heart failure SMQ occurred more commonly among conivaptan group patients than among placebo group patients. This difference between conivaptan and placebo was not noted for eunatremic heart failure patients.

Overall, it appears that atrial arrhythmia events and cardiac failure events occurred more commonly among hypervolemic heart failure patients who were treated with intravenous conivaptan than among hypervolemic heart failure patients who were treated with placebo. This signal is consistent across multiple populations of heart failure patients who were considered by sodium status, development program, baseline volume status and route of administration.

In the treatment of hyponatremia, an overly rapid rise in serum sodium is undesirable, as it is associated with increased risk for a rare neurologic complication, central pontine myelinolysis. All hyponatremia studies had defined criteria and responses for rapid rise in serum sodium. The incidence of overly rapid correction of serum sodium was higher for conivaptan-treated patients than for placebo-treated patients. There were no cases of central pontine myelinolysis. One patient had a delayed seizure without apparent sequelae. The current Vaprisol® label contains cautionary language regarding the risks of overly rapid correction of serum sodium.

In the 1st and 2nd cycle reviews, infusion site reactions accounted for the majority of the difference in the incidence of adverse events for conivaptan patients vs placebo patients. Per the approval letter for the euvolemic indication, the applicant is conducting a study to explore methods of decreasing the incidence of infusion site reactions. In the updated safety information submitted for this cycle, infusion site reactions again occurred much more frequently for conivaptan group patients than for placebo group patients.

For this cycle, the applicant devised a classification system for infusion site reactions, and asserts that the majority of reactions were mild in nature. However, this post hoc assignment of event

severity must be interpreted cautiously. When one considers adverse events that met the criteria for the *regulatory* definition of a serious adverse event, the incidence of serious infusion site-related adverse events was higher for the conivaptan groups than for the placebo group. Furthermore, discontinuations from study due to infusion site-related events were more common among conivaptan-treated patients than among placebo-treated patients.

In previous reviews of conivaptan, there was a safety signal for anemia. In this submission, for both the IV and total populations, anemia occurred slightly, but not significantly, more frequently among conivaptan-treated patients than among placebo-treated patients.

Across all conivaptan studies (IV + oral, hyponatremia + heart failure studies), and across all IV conivaptan studies, hepatobiliary adverse events occurred slightly, but not significantly, more commonly among conivaptan-treated patients than among placebo-treated patients.

When considering all adverse events (serious and nonserious), in the overall IV-treated hypervolemic hyponatremic population, adverse events occurred more commonly among conivaptan patients than among placebo patients. This difference was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. Other events which occurred with greater frequency in the overall conivaptan-treated population than in the placebo population, and which occurred with greater frequency in the majority of the conivaptan groups than in the placebo group, included constipation, pyrexia, sepsis NOS, headache, and orthostatic hypotension. Events which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan patients, included aesthenia, peripheral edema, sepsis NOS, blood creatinine increased, dizziness, headache, polyuria, acute renal failure and orthostatic hypotension.

In the population of IV-treated hypervolemic hyponatremic patients who also had CHF, adverse events occurred more commonly among conivaptan patients than among placebo patients. This difference was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. Other events which occurred with greater frequency in the overall conivaptan-treated population than in the placebo population, and which occurred with greater frequency in the majority of the conivaptan groups than in the placebo group, included anemia NOS, nausea and sepsis NOS. Events which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan patients, included "congestive cardiac failure aggravated", diarrhea NOS, nausea, peripheral edema, sepsis NOS, blood creatinine increased, and "dyspnea exacerbated".

For IV-treated hypervolemic hyponatremic patients without heart failure, adverse events did not occur more frequently for conivaptan-treated patients than for placebo-treated patients. The only individual type of adverse event which occurred with greater frequency for conivaptan-treated patients was orthostatic hypotension.

Those individual (by preferred event term) events which may be more of a concern in the hypervolemic hyponatremic heart failure population than in the overall hypervolemic hyponatremic population, or the hypervolemic hyponatremic population without heart failure,

include anemia NOS, congestive cardiac failure aggravated, dyspnea exacerbated, diarrhea NOS, nausea and sepsis NOS.

In the overall population of heart failure intravenous study patients, which included patients both with and without hyponatremia, adverse events occurred more commonly among IV conivaptan-treated patients than among IV placebo-treated patients. This difference was largely attributable to the increased rate of infusion site-related adverse events among conivaptan patients. Other events which occurred more frequently in the overall IV conivaptan-treated heart failure population than in the IV placebo-treated population, and which occurred more frequently in the majority of the conivaptan groups than in the placebo group, included anemia NOS, atrial fibrillation, atrial flutter, aesthenia, hyperglycemia NOS, hyperkalemia, hypernatremia, back pain, pain in extremity, dizziness, renal failure NOS and dyspnea exacerbated. Events which did not occur in any placebo group patients, and which occurred in ≥ 5 conivaptan group patients, included atrial fibrillation, atrial flutter, aesthenia, thirst, hyperglycemia NOS and hypernatremia.

Among IV-treated patients who had baseline assessments of volume status, events which occurred more frequently among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and also occurred more commonly among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included cardiac failure NOS, ear pain, abdominal distension, abdominal pain NOS, dyspepsia, vomiting NOS, aesthenia, anasarca, catheter site pain, edema NOS, infusion site erythema, infusion site swelling, pyrexia, thirst, hepatic failure, sepsis NOS, septic shock, blood creatinine increased, blood urea increased, weight decreased, dehydration, hypokalemia, hypomagnesemia, asterixis, renal failure acute, dyspnea exacerbated, pulmonary congestion, decubitus ulcer, orthostatic hypotension, and phlebitis NOS. When narrowing this list to only those events which occurred at a rate at least 3% higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, events include cardiac failure NOS, abdominal pain NOS, dyspepsia, vomiting NOS, aesthenia, infusion site erythema, pyrexia, sepsis NOS, blood creatinine increased, weight decreased, hypokalemia, renal failure acute, decubitus ulcer and orthostatic hypotension. Only vomiting NOS, aesthenia, pyrexia and hypokalemia occurred at a rate that was $\geq 5\%$ higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and at a higher rate among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients.

For the population of all studies with baseline volume assessments, in general, the types of events which occurred more frequently among hypervolemic patients than among euvolemic patients were similar to those for the IV population who had baseline volume assessments. However, in the overall population (IV + oral, all patients with baseline volume assessments), additional events which occurred at a rate $\geq 5\%$ higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and at a higher rate among hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included cardiac failure NOS, congestive cardiac failure aggravated, and renal failure NOS. Additional events which occurred at a rate $\geq 3\%$ higher among hypervolemic conivaptan-treated patients than among euvolemic conivaptan-treated patients, and at a higher rate among

hypervolemic conivaptan-treated patients than among hypervolemic placebo-treated patients, included edema NOS and confusional state.

In a hypervolemic population, which would consist largely of patients with cardiac and hepatic failure, it is unsurprising to find a higher incidence of cardiac-failure-related and hepatic-failure-related events than one would find in a euvolemic population. Renal failure might also be expected to be higher in a hypervolemic population, as patients with cardiac and hepatic failure have a higher incidence of renal failure than persons without these conditions. However, the higher incidences of sepsis, pyrexia, hypokalemia and vomiting are unexplained by underlying disease state.

In support of safety for the heart failure population, the applicant was also asked to present [REDACTED] data from all patients who were studied in the applicant's heart failure development program [REDACTED] in the Division of Cardiovascular and Renal Products. Most of these patients did not have hyponatremia, but may provide additional relevant safety information for the specific population of heart failure patients. [REDACTED]

[REDACTED] However, the applicant asserts that conivaptan did not worsen underlying CHF by various efficacy and safety assessments.

The heart failure development program consisted of 12 studies, which included a total of 818 heart failure patients. These studies included a wide variety of efficacy endpoints; for the vast majority of these endpoints, there was no difference between conivaptan and placebo. Endpoints for which this was true included:

- Mean change from baseline to hour 48 in AUC for Respiratory Visual Analog Scale (Patient Assessment)
- Mean change from baseline to hour 48 in respiratory rate
- Mean change from baseline to hour 72 in body weight
- Mean duration of index hospitalization
- Mean number of hospital days over 90 days of study
- Number of deaths
- Mean change in categorical jugular venous pressure score (0-3) at 72 hours
- Mean change in categorical pulmonary rales score (0-4) at 72 hours
- Mean change in categorical pulmonary effusion score (0-1) at 72 hours
- Mean change in categorical third heart sound score (0-1) at 72 hours
- Mean change in categorical ascites score (0-3) at 72 hours
- Mean change in categorical leg edema score (0-4) at 72 hours
- Mean change in baseline-corrected AUC for cardiac index
- Mean change in baseline-corrected AUC for pulmonary vascular resistance
- Mean change in baseline-corrected AUC for systemic vascular resistance
- Mean change in left ventricular end-diastolic volume index by MRI
- Mean change in left ventricular end-systolic volume index by MRI
- Mean change in left ventricular mass index by MRI
- Mean change in left ventricular ejection fraction by echocardiography

- Number and percentage of patients with improvement in NYHA FC
- Mean change in VO_2 on exercise testing
- Mean change in exercise time to peak VO_2

For the following two endpoints, conivaptan was statistically superior to placebo in one heart failure study for each:

- Reduction in PCWP
- Reduction in A-a gradient

In six of the heart failure studies, which included a total of 641 conivaptan-treated patients, there was an Endpoint Classification Committee which adjudicated events related to heart failure hospitalizations and/or emergency room visits. Across these studies, the incidence of heart failure hospitalizations or ER visits secondary to worsening of heart failure was 6.3% (15/240) for the placebo groups and 4.5% (29/641) for the conivaptan groups. The incidence of all-cause mortality across these 6 studies was 1.7% (4/240) for the placebo groups and 1.7% (11/641) for the conivaptan dose groups.

While conivaptan did not result in improvement of heart failure outcomes in heart failure studies, conivaptan also was not associated with a worsening of heart failure on several fairly objective measures, including hemodynamics, exercise tolerance, heart failure signs, structural heart changes, length of hospital/ICU stay and adjudicated heart failure hospitalizations/ER visits. In possibly less objective measures of heart failure symptoms, conivaptan also was not worse than placebo. However, the majority of patients in these studies did not have hyponatremia, which is a marker of severity of heart failure, and heart failure patients who would receive conivaptan for the proposed indication would all have hyponatremia.

The Division of Metabolism and Endocrinology Products consulted the Division of Cardiovascular and Renal Products for that Division's specific comments on the safety of conivaptan when given to patients with underlying heart failure. They concluded that, although the updated data do not demonstrate a grossly increased safety risk for patients with underlying heart failure, the very small size of the relevant population was inadequate to permit a definitive statement. In the absence of a clear clinical benefit (other than a change in serum sodium) for heart failure patients, their tolerance for uncertainty regarding risk is low. Overall, their conclusion was that they do not have enough data to support that the drug is either effective or safe to treat heart failure patients with hypervolemic hyponatremia.

Safety in patients with underlying heart failure remains a thorny question. The following table summarizes points in favor of and against use of conivaptan in patients with underlying heart failure.

Table 9.1.2: Clinical Reviewer's List of Pros and Cons Regarding the Use of Conivaptan in Patients With Underlying Heart Failure

Pros	Cons
Conivaptan is effective in raising serum sodium in hypervolemic hyponatremic heart failure patients with underlying heart failure.	When considering hypervolemic hyponatremic patients with underlying heart failure, patients treated with conivaptan had a higher rate of specific cardiac failure events, events within the MedDRA Standard Query for heart failure, and events within the applicant's "augmented" MedDRA Standard Query. This was also true for heart failure patients treated with IV conivaptan in the applicant's heart failure development program.
Previous concerns regarding an increased risk of death, and a dose-related increase in risk of death, are not apparent with newly submitted data, although the amount of newly submitted data is small.	No new placebo-controlled data were submitted for hypervolemic hyponatremic patients with underlying heart failure, limiting the ability of the clinical reviewer to reevaluate the previous signals.
Across six heart failure studies in the heart failure development program which had adjudication of cardiovascular events and involved a total of 641 conivaptan-treated patients, conivaptan was not associated with higher overall mortality, or a higher incidence of hospitalizations or emergency room visits for heart failure.	The number of hypervolemic hyponatremic heart failure patients who have received conivaptan is very small.
Conivaptan was no worse than placebo for a wide array of heart failure efficacy outcomes from the heart failure development program, although most of these patients were not hyponatremic.	The Division of Cardiovascular and Renal Products states that, in the absence of clinical benefit(s) other than raising serum sodium, the number of patients in the relevant population is inadequate for a firm assessment of the safety of conivaptan when used in patients with heart failure.
Patients who are acutely ill and hospitalized with heart failure often require multiple intravenous medications. Treatment of hyponatremia by fluid restriction is often very difficult for these patients, given the minimum volume of fluids that must often be given with intravenous medications. The availability of an effective medication for hyponatremia could simplify fluid management for these patients; in clinical trials, Vaprisol® appeared to be effective even when patients did not adhere to fluid restriction.	Conivaptan showed no benefit for heart failure patients on a wide array of heart failure efficacy outcomes from the twelve studies in its heart failure development program.
Previous concerns have been allayed regarding the possibility of a much higher exposure of conivaptan for heart failure patients compared to patients without heart failure.	Among patients with underlying heart failure, IV conivaptan was associated with an increased risk for atrial dysrhythmia events, when compared to placebo. This was not true for hypervolemic hyponatremic patients without heart failure.
	Among hypervolemic hyponatremic patients with underlying heart failure, IV conivaptan-treated patients had a higher incidence of events of sepsis and anemia. This was not true for hypervolemic hyponatremic patients without heart failure.
	In the applicant's heart failure development program, patients treated with oral conivaptan had a higher

Table 9.1.2: Clinical Reviewer's List of Pros and Cons Regarding the Use of Conivaptan in Patients With Underlying Heart Failure

Pros	Cons
	incidence (compared to placebo) of serious adverse events of angina, chest pain and syncope. All cases of acute renal failure (5 events) occurred in conivaptan-treated patients.
	Among all patients, and among all IV-treated patients, in the applicant's heart failure program, conivaptan groups had a higher incidence than placebo of discontinuations due to adverse events. This differed from the finding for hypervolemic hyponatremic patients in general, where conivaptan group dropout incidence did not exceed placebo group dropout incidence.
	Cardiac failure patients take a wide array of CYP3A4-metabolized drugs; conivaptan inhibits CYP3A4 metabolism. Although the label discusses this important interaction, patients may still receive these drugs. Even in the highly controlled setting of the clinical trials of conivaptan, there were numerous protocol violations regarding administration of prohibited CYP3A4-metabolized drugs.
	The potential for off-label use for the treatment of heart failure <i>per se</i> exists if providers are not made aware that conivaptan is ineffective for the treatment of heart failure.
	Hyponatremia is a marker of severity of cardiac failure, and therefore hypervolemic hyponatremic patients with heart failure represent a very ill and medically fragile population. It is unknown if raising serum sodium <i>per se</i> would have any beneficial effect for these patients. If the drug is not known to benefit these vulnerable patients, <i>primum non nocere</i> .

On balance, in the clinical reviewer's opinion, the small amount of uncontrolled safety data submitted for the current review cycle is insufficient to allay previous concerns for the safety of conivaptan in heart failure patients. Additionally, across the entire development program, the number of hypervolemic heart failure patients with clinically meaningful hyponatremia was very small; there were only 51 such conivaptan-exposed patients from the controlled hyponatremia IV Study 027, and the non-placebo-controlled hyponatremia IV Study 080. Signals of increased risk for multiple adverse events persist. In the clinical reviewer's opinion, conivaptan should not be administered to patients with underlying heart failure. If the applicant wishes to pursue use in heart failure patients, new placebo-controlled safety data are needed for hypervolemic hyponatremic heart failure patients.

For laboratory findings, in general, the differences between conivaptan-treated patients and placebo-treated patients were not clinically significant. However, mean random and fasting plasma glucose increased for conivaptan-treated patients, but declined for placebo-treated

patients. This may be related to the fact that conivaptan is diluted in D5W. If conivaptan were to be administered chronically, this might have clinical significance, but the small differences between treatment groups are unlikely to have clinical consequences over the proposed administration duration of 2-4 days.

Across all IV studies, conivaptan-treated patients did not develop shifts from normal to abnormal chemistry values more often than did placebo-treated patients. Across the entire conivaptan development program, conivaptan-treated patients developed shifts from normal to abnormal slightly more often (compared to placebo-treated patients) for fasting plasma glucose and serum creatinine.

9.1.3 Conclusions Regarding Exploration of a 10 mg/day Dose for Heart Failure Patients

In the 1st cycle review, it was noted that a lower dose of conivaptan than the proposed 40 mg/day dose could potentially be effective. Data submitted with the 2nd cycle response supported that conclusion, and a dose of 20 mg/day was approved for the treatment of euvolemic hyponatremia. In the 2nd cycle review, it was noted that data submitted thusfar indicated a greater conivaptan exposure for heart failure patients than for patients without heart failure. This was based on a pharmacokinetic model which had proved inaccurate for an IV:oral exposure comparison in the 1st cycle review. Safety concerns for patients with underlying heart failure also arose in the 2nd cycle review. In the post-review conference for the hypervolemic hyponatremia indication, DMEP requested exploration of the possibility of a lower effective dose, e.g. 10 mg/day, for hyponatremic patients with underlying heart failure. The applicant did not submit data for efficacy evaluation of a 10 mg/day dose for heart failure patients. Rather, the applicant submitted pharmacokinetic data from Study 080 to support equal exposure for heart failure patients compared to patients without heart failure. Although these data are somewhat limited, the clinical pharmacology reviewer (Dr. Chung) agrees that there is not a significant difference in exposure for hypervolemic vs euvolemic patients.

Additionally, the applicant submits dose-response data to support a less robust and slower response to the 20 mg/day dose than to the 40 mg/day dose, based on the efficacy results from hypervolemic hyponatremic heart failure patients in IV hyponatremia Studies 027 and 080, as described above. The applicant asserts that, although a conivaptan dose of 20 mg/day produces a clinically meaningful increase in serum sodium concentration, it does so more slowly than higher doses, and there is a dose response. Based on the magnitude of change in serum sodium seen at 20 mg/day, the applicant asserts that 10 mg/day might not produce a prompt, "reliable" and clinically relevant increase in serum sodium concentration. After consideration of the new pharmacokinetic data indicating no difference in conivaptan exposure for hypervolemic patients compared to euvolemic patients, and the demonstration of somewhat lower and slower effectiveness of the 20 mg/day dose (compared to higher doses), the clinical reviewer concurs that it no longer appears necessary for the applicant to explore a 10 mg/day dose.

9.1.4 Overall Conclusions

Conivaptan appears to be effective for the treatment of hypervolemic hyponatremia. However, the data are inadequate to establish safety for the population of hypervolemic hyponatremic patients who have underlying heart failure. The subpopulation of hypervolemic hyponatremic patients without heart failure is also small. However, this population shows little in the way of risk compared to placebo, other than the well-described risk of infusion site reactions and other risks that are described in the current label for euvolemic hyponatremia.

9.2 Recommendation on Regulatory Action

The clinical reviewer recommends approval of conivaptan for treatment of hyponatremia in hypervolemic patients. However, the clinical reviewer recommends retention of language in the product label stating that the safety of conivaptan has not been established for patients with underlying heart failure.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

In addition to routine postmarketing surveillance, the applicant proposes to include special analyses of CHF-related events in the applicant's Periodic Adverse Drug Experience Reports and Annual Reports. The applicant will use its "Augmented" Standard MedDRA Query for heart failure events, which included 49 MedDRA preferred terms related to heart failure. The applicant also proposes to submit expedited (15 day) reports of events related to cardiac failure.

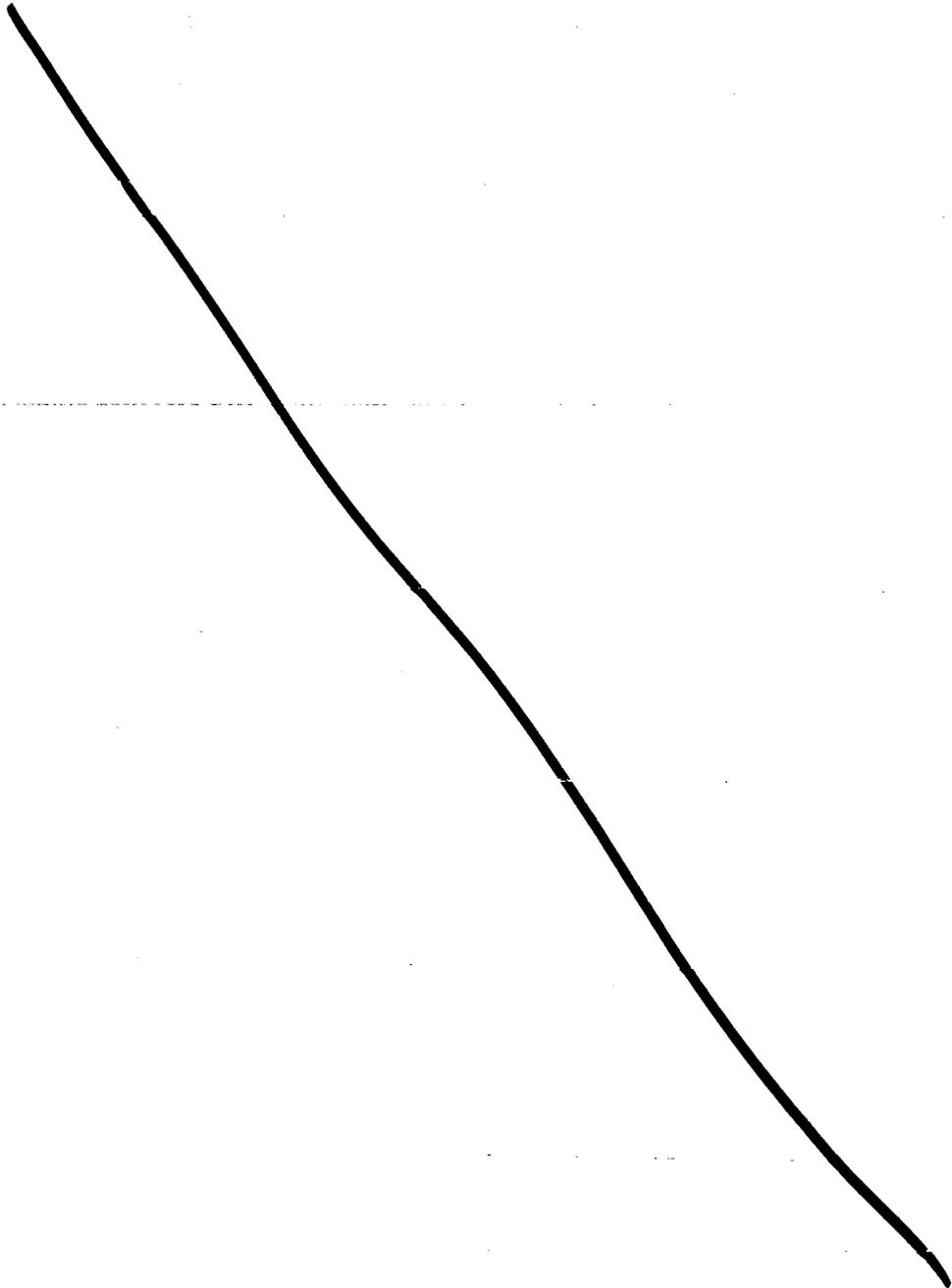
Although the applicant's assumption was that the approval for hypervolemic hyponatremia would not recommend against use in heart failure patients, the clinical reviewer still feels that the applicant's proposal is an appropriate risk management activity. It will give information regarding whether Vaprisol® is being used in heart failure despite the label's precaution against such use, and will also provide some information on adverse events that are occurring for these patients. The clinical reviewer recommends that the scope of the plan be augmented to include reporting not only of all events within the applicant's "Augmented" Standard MedDRA Query for heart failure, but also other events that occur in patients with underlying heart failure.

9.3.2 Required Phase 4 Commitments

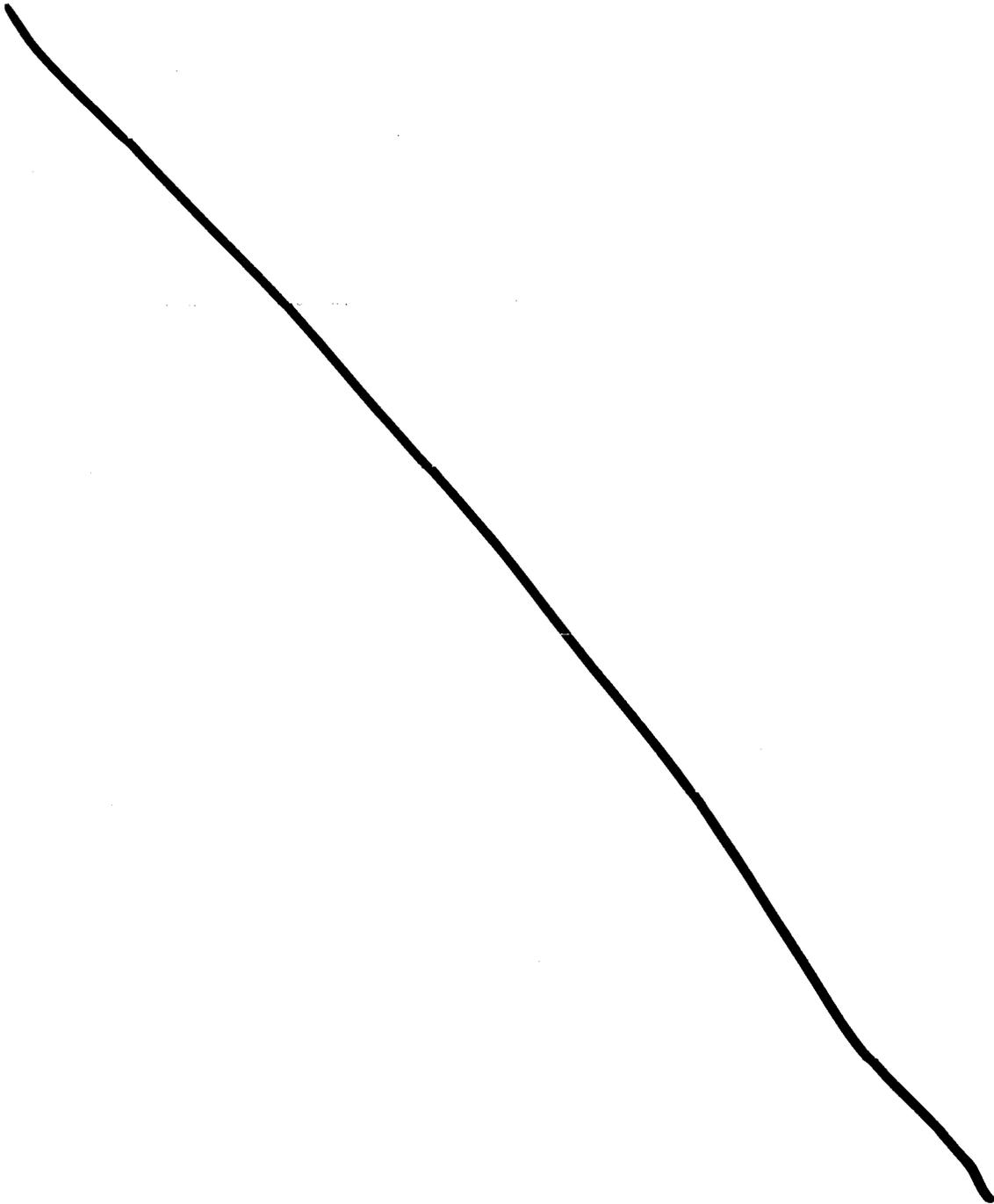
The applicant has ongoing Phase 4 commitments under NDA 21697. The clinical reviewer does not have recommendations for new Phase 4 commitments. If the applicant decides to pursue removal of language regarding the recommendation that conivaptan not be used in heart failure patients, the design and scope of required study can be discussed at a post-approval conference.

9.3.3 Other Phase 4 Requests

9.4 Labeling Review



b(4)



b(4)

References

Fowler M 2004. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial: Carvedilol in Severe Heart Failure. Am J Cardiol 93(Suppl):35B-39B

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Karen Mahoney
2/6/2007 09:56:10 PM
MEDICAL OFFICER

Theresa Kehoe
2/7/2007 08:21:50 AM
MEDICAL OFFICER

**Division of Cardio-Renal Drug Products
Consultation for Division of Antiviral Products**

From: Shen Xiao, M.D., Ph.D. Medical Officer
Division of Cardiovascular and Renal Products
Through: Norman Stockbridge, M.D., Ph.D. Division Director
Division of Cardiovascular and Renal Products
To: Jennifer Johnson, RPM
Division of Metabolism and Endocrine Products (DMEP)

Subject: NDA 22-016

Name of Drug: Vaprisol (Conivaptan Hydrochloride)

Formulation: Intravenous Injection

Related Applications: IND [REDACTED] NDA 21-697

Approved Indications: 20 mg IV loading dose followed by 40 mg/24 hrs by continuous IV infusion for 2-4 days for the treatment of euvolemic hyponatremia

Proposed Indication: Same dosage for the treatment of hypervolemic hyponatremia

Sponsor: Astellas Pharma US, Inc, Three Parkway North, Deerfield, IL 60015-2537,
Tel: 847-405-1604

Documents Used for Review: Original NDA submissions, sponsor's final complete response to the approvable letter and Dr. Mahoney's original reviews.

Date Consult assigned: November 27, 2006

Date Consult completed: December 18, 2006

Background Information:

Conivaptan hydrochloride (Vaprisol™) is a nonpeptide vasopressin receptor antagonist. The vasopressin 2 (V2) receptors located in the distal collecting tubules of the kidney. Vasopressin is a neurohypophyseal hormone; its primary function via V2 receptors is to permit conservation of free water by the kidney. Activation of vasopressin V2 receptors results in the insertion of water channels, or aquaporins, in the collecting tubule, allowing for passive reabsorption of water. The sponsor proposes intravenous use of conivaptan to block the V2 receptors in patients with euvolemic and hypervolemic hyponatremia, to increase the elimination of free water and thereby raise serum sodium concentration.

This product in NDA 21-697 was originally submitted on January 30, 2004, and originally received an approvable action on November 30, 2004. The firm submitted a complete response to the November 2004 approvable action letter. On December 29, 2005, the firm received an approval action for the euvolemic hyponatremia indication, and an approvable action for the hypervolemic hyponatremia indication. An administrative split of the NDA was required, and the approvable action was assigned to NDA 22-016, while the approved indication remained with NDA 21-697. The indication for the treatment of hypervolemic hyponatremia in NDA 22-016 received an approvable action, rather than an approval was due to an observation of an apparent increase in heart failure adverse events among heart failure patients receiving conivaptan compared to

heart failure patients receiving placebo. Heart failure patients comprised the majority of the hypervolemic hyponatremic population. There was also a question of a relationship between dose of conivaptan and risk of mortality among hypervolemic patients. Additional data were requested in the approvable letter to assist in the assessment of risk versus benefit for heart failure patients on December 29, 2005; the applicant has now provided its complete response to the approvable letter.

Brief summary of original safety concerns of conivaptan related to patients with heart failure reviewed by the original reviewer (Dr. Mahoney) in DMEP:

- The mortality rate was similar between conivaptan-treated subjects and placebo subjects in the overall safety population. However, in the congestive heart failure trials, death occurred slightly more frequently among conivaptan patients than among placebo patients.
- Among patients with underlying congestive heart failure, cardiac failure events, and atrial arrhythmia events occurred more frequently among conivaptan-treated patients than among placebo-treated patients. The incidence of these events within the 20-40 mg/day IV dosage range was also specifically considered (i.e. excluding lower and higher exposures).
- Total renal adverse events, and “nonserious” events of renal failure occurred more commonly numerically among conivaptan-treated patients than among placebo-treated patients in the “full dose” IV study population. This was not seen in the overall controlled (IV + oral) safety population, which included oral patients with lower exposure. Most patients who developed renal failure had an underlying diagnosis of congestive heart failure, which carries a high baseline risk of acute renal failure with best current treatment. Overall, it appears that conivaptan may be associated with a slightly greater risk of nonserious, reversible renal adverse events. Most events were reversible moderate increases in creatinine, which may have been associated with volume depletion due to conivaptan, or with the patients’ underlying diseases.

Overall comments: The indication of this NDA is to treat patients with hypervolemic hyponatremia due to various causes including cardiac failure. The proposed clinical dose is 20 mg IV loading dose followed by 40 mg/24 hrs by continuous IV infusion for 2-4 days. Safety issues were not evaluated adequately in patients with cardiac failure and were the primary concern in the original NDA.

To address the safety concern in patients with cardiac failure, the sponsor provided all of their studies of conivaptan in heart failure patients in this final complete response for review. There were a total of 818 patients with congestive heart failure who received conivaptan and 290 patients who received placebo. Of the patients in the conivaptan treatment group, 253 received IV conivaptan and 565 received oral conivaptan. In the heart failure patients treated with IV conivaptan, the proposed dose range was only tested in one clinical trial (study 087-CL-071) and there were only 23 patients with hyponatremia in this study (there are a few heart failure patients with hyponatremia in the combined studies). Therefore, the reviewer believes that the data were insufficient to evaluate the safety issues of conivaptan in heart failure patients with hyponatremia based

on the proposed clinical dose. The questions that were addressed below were based on the whole clinical data set regardless the dose that was proposed in the indication.

Questions addressed: By providing the sponsor's complete response and the original NDA reviews, DMEP has the following questions for consultation:

1. Is conivaptan associated with an increased risk of heart failure events in patients with underlying heart failure?

Although a slightly higher incidence rate of the heart failure events in patients underlying heart failure was observed in conivaptan IV treated groups than IV treated controls (18.2% vs 14.6%) in the whole IV study program (four clinical studies) as shown in attached table 12, the difference was almost certainly not even nominally statistically significant, and what difference there appears to be is probably an artifact of one neutral high-risk study (Study 087-CL-071) with unbalanced randomization to drug (Simpson's paradox) as shown in tables 12 and 13. All of the patients in this study are acute decompensated heart failure and shown a high mortality rate (table 13). The incidence rate of heart failure events in the study 087-CL-071 was similar between conivaptan treated groups and placebo group. The incidence rate and severity of nine clinical signs of heart failure including jugular venous pressure, pulmonary rales, pleural effusion, third heart sound, cardiac murmur, hepatomegaly, ascites, leg and presacral edema were also same between conivaptan and placebo treated groups. In addition, in the single IV study at dose up to 40 mg in patients with heart failure, a difference in cardiac hemodynamic parameters including cardiac index, pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) was not observed between conivaptan treated groups and placebo control.

Overall, the incidence of cardiac events is similar across dose groups for oral and IV studies. However, in the 4 reported IV studies, the proposed dose range and treatment duration were only tested in one study report (087-CL-071). There were even only 23 patients with hyponatremia and most of patients in this study were in the normal plasma level of sodium. Therefore, it is still not clear if conivaptan could increase the risk of heart failure events in heart failure patients with hyponatremia based on the sponsor's response, but the available evidence does not strongly support such a risk.

2. Is conivaptan associated with an increased risk of other cardiovascular events in patients with underlying heart failure?

The incidence rate of atrial fibrillation (2.4%) and flutter (2.0%) is higher in IV conivaptan group compared to IV placebo (0), but ventricular tachycardia was higher in the IV placebo group at 9.7% versus 5.5% in the IV conivaptan group. Since these arrhythmia events are not unusual in this patient population, it is not clear if the atrial fibrillation and flutter are related to the effects of conivaptan due to the change of body fluid and/or the plasma level of electrolytes. Sponsor needs to provide follow-up data in these patients. but we see no compelling association here. Differences in other

cardiovascular events between the conivaptan and placebo treated groups were not observed.

3. Is there evidence of a relationship between dose of conivaptan and risk of mortality in heart failure patients?

There is a significant increase of mortality rate in patients at dose of 120 mg as compared to the placebo in the study 087-CL-071. In the dose range of ≤ 80 mg, the relationship between dose of conivaptan and risk of mortality either in oral or IV route was not significant. Overall, the occurrence of death was similar across treatment groups based on the data provided by the sponsor in the final complete response.

4. Do you note other safety concerns regarding the administration of conivaptan to patients with underlying heart failure?

Acute renal failure and hyperkalemia are the major safety concerns other than the cardiovascular events based on the sponsor provided response data.

The increased incidence rate of reversible renal failure was observed in conivaptan treated patients. In patients with underlying cardiac failure, the decreased renal function may indicate a poor prognosis. The mechanism for progressive renal failure in patients who have persisting heart failure is complex and involves many factors. However, for reversible acute renal failure, decreased renal perfusion may be the major cause. The differential diagnosis of acute renal failure due to “pre-renal” (cardiac problem, etc) or renal factors can be determined by measuring sodium excretion, ratio of urea to creatinine, etc. If the “pre-renal” acute renal failure persists, non-reversible renal failure may occur.

No difference in hypokalemia between the conivaptan treated groups and placebo in heart failure patients was observed. However, a significant increased incidence of hyperkalemia in IV conivaptan treated groups was observed. Since hyperkalemia is also a significant adverse event of ACEI and ARB which are widely used in heart failure patients, the plasma level of potassium needs to be strictly monitored.

Rapid correction of the severe hyponatremia may cause cerebral pontine myelinolysis (CPM). Although the incidence of this severe complication was very low in the whole study program, it can not be predicted in heart failure patients with hyponatremia due to the insufficient size of this population in the trial.

5. Conivaptan is restricted to short-term intravenous use in hospitalized patients. If you note safety concerns in patients with heart failure, does this limitation in the setting of use ameliorate the safety concern? Do you suggest other risk management measures?

Monitoring vital signs, body fluid and electrolyte balance should be the key issues to ameliorate the safety concern. Hemodynamic parameters such as cardiac index, PCWP, etc, may also need to be monitored in some conditions. In addition, to minimize the risk

of CPM, in general, the correction rate of hyponatremia should be less than 0.5 mEq/L/hour or 12 mEq/L/day.

6. Do you have other comments regarding the use of conivaptan in hyponatremic heart failure patients?

Sodium and water retention in heart failure involves in a complex interplay of hemodynamic and neurohumoral factors. These factors at least include the sympathetic nervous system, the renin-angiotensin-aldosterone system, the vasopressin axis, and vasodilatory/natriuretic pathways. Hypervolemic hyponatremia (diluted hyponatremia) is much less common in mild to moderate heart failure but becomes more likely as cardiac output falls with more severe disease. The profound reduction in cardiac output in severe heart failure is an important mechanism for the development of hyponatremia.

Regarding the effect of vasopressin in heart failure patients, although the concentration of vasopressin is not uniformly elevated, even in the presence of hyponatremia, of equal importance is that concentrations of this water-retaining hormone are not totally suppressed as they should be in the setting of plasma hypo-osmolality. Vasopressin levels typically are not suppressed appropriately with a water load in heart failure; however, there exists a subset of patients with heart failure in whom water loading results in appropriate reduction in vasopressin. Therefore, conivaptan should be used to treat heart failure patients with elevated or "normal" levels of vasopressin in the presence of hyponatremia.

Based on the data provided by the sponsor, conivaptan did not show any significant clinical benefits to patients with heart failure except increasing the plasma level of sodium by 3 to 10 mEq/L. Since only very limit number of patients had hyponatremia and most of these heart failure patients are in the normal range for sodium in this whole study program, the indication of conivaptan for treating the heart failure patients with hyponatremia is not supported.

Summary of clinical studies of conivaptan in patients with heart failure with or without hyponatremia:

A total of 818 patients with congestive heart failure received conivaptan and 290 patients received placebo. Of the patients in the conivaptan treatment group, 253 received IV conivaptan and 565 received oral conivaptan. The majority of patients completed treatment in both the conivaptan and placebo treatment groups, 91.7% and 94.1%, respectively. The incidence of discontinuation of study drug was primarily due to adverse events (conivaptan: 36/818, 4.4%; placebo: 10/290, 3.4%). The incidence of discontinuation was comparable to placebo across all conivaptan doses in the oral studies and up to 80 mg/day in the IV studies. Studies were summarized in the following table 1.

Table 1: Conivaptan Clinical Studies in Patients with Heart Failure

Study Number	Objective	Dose and Duration	Number of Subjects
<i>Studies with IV conivaptan</i>			
087-CL-071	Evaluate efficacy and safety of IV YM087 in patients with acutely decompensated chronic heart failure	IV conivaptan 20 mg loading dose followed by 40, 80, or 120 mg/day for 2 days	162
087-CL-032	Determine safety and efficacy of 3 doses of acute IV administration of conivaptan, in patients with NYHA class III/IV CHF	Single dose of IV conivaptan, 10, 20, or 40 mg	143
087-CL-038	Determine effectiveness of IV administered conivaptan on the relief of pulmonary congestion symptoms in patients with acute decompensated heart failure	2 single IV conivaptan 20 mg infusions over 30 mins, 8 hours apart	26
087-CL-044	Explore effectiveness of IV-administered conivaptan on relief of pulmonary congestion in patients admitted for acute CHF exacerbation	2 single IV conivaptan 40 mg infusions over 30 mins, 8 hours apart	26
087-CL-019††	Investigate safety, effect on hemodynamics, and water diuretic action of IV administered conivaptan in acute heart failure or acute exacerbation of chronic heart failure	Single IV dose of 2, 10, 25, 50, 125, 250 mcg/kg	42
<i>Studies with Oral Conivaptan</i>			
087-CL-034	Determine the dose-dependent effects of conivaptan on patients with Class II to IV CHF	12 weeks of oral conivaptan 10, 20, or 40 mg twice daily	343
087-CL-020	Investigate the effect of oral conivaptan on exercise capacity in NHYA Class II-III CHF	12 weeks of oral conivaptan, 5, 10, or 20 mg twice daily	304
087-CL-033	Evaluate 3 doses of conivaptan in patients with severe NYHA class II-IV CHF	26 weeks of oral conivaptan, 10, 20, or 40 mg twice daily	47
087-CL-017	Investigate safety and tolerability of oral conivaptan in patients with CHF NYHA class III/IV	7 days of oral conivaptan, 5, 10, 20 or 40 mg twice daily	24
087-CL-024	Determine the safety and efficacy of concomitant treatment with oral conivaptan and furosemide in patients with CHF	3 days of oral conivaptan in combination with furosemide, 20 or 40 mg	24
087-CL-016†	Study the PK and safety of single doses of oral conivaptan in patients with severe CHF	Single dose of oral conivaptan, 5, 10 or 20 mg	12
087-CL-018††	Study the water diuresis effect and safety of oral conivaptan in patients with edematous diseases due to cardiac, renal or hepatic diseases	1, 5, 10, 20, 30 mg dose escalation over 5 days	30 (n=10 with underlying CHF)

† The study included a small number of patients and/or a single-dose dosing regimen and is not discussed in text; the study report is included in the submission.

†† Study databases are in Japanese and are not included in the integrated safety analyses

1. IV studies: there are 5 clinical studies of conivaptan receiving IV infusion including 087-CL-071, 032, 038, 044, and 019. Data for study 087-CL-019 were not submitted.

1) 087-CL-071 is a randomized, double-blind, placebo-controlled study of 3 doses of conivaptan in patients with acutely decompensated CHF. A total of 162 CHF patients (23 with underlying hyponatremia) were treated with a 20 mg loading dose of conivaptan or placebo followed by 2 days of continuous infusion with IV placebo or IV conivaptan at doses of 40, 80 or 120 mg per day. The patients were followed for the assessment of safety through 30 days after the start of infusion of study drug. Morbidity and mortality were followed up to 90 days. The number of patients who died during the entire study

including the follow-up period was highest in the 120 mg/day group (7/42, 16.7%), followed by the placebo group (5/40, 12.5%), and the 40 and 80 mg/day groups (3/40, 7.5% each). A total of 9 clinical signs of heart failure (jugular venous pressure, pulmonary rales, pleural effusion, third heart sound, cardiac murmur, hepatomegaly, ascites, leg and presacral edema) were evaluated at hour 24, 48 and 72 and day 30 after start of infusion. Over the observation period, improvement in heart failure signs was similar in magnitude as shown in the following table 2.

Table 2: Mean Change from Baseline to Day 30 for Heart Failure Signs (Study 087-CL-071)

Heart Failure Sign	Placebo	IV YM087		
		40 mg	80 mg	120 mg
Elevated Jugular Pressure	-1.0 (n=28)	-0.8 (n=24)	-0.9 (n=30)	-0.8 (n=32)
Pulmonary Rales	-1.4 (n=30)	-1.4 (n=25)	-1.8 (n=30)	-1.8 (n=32)
Pleural Effusion	0.0 (n=28)	-0.1 (n=21)	-0.2 (n=30)	-0.1 (n=32)
Third Heart Sound	-0.2 (n=30)	-0.3 (n=24)	-0.1 (n=30)	-0.2 (n=32)
Cardiac Murmur	-0.1 (n=30)	-0.2 (n=25)	-0.1 (n=29)	0.0 (n=32)
Hepatomegaly	-0.1 (n=28)	-0.6 (n=23)	-0.3 (n=30)	-0.1 (n=30)
Ascites	-0.4 (n=30)	-0.7 (n=23)	-0.3 (n=30)	-0.2 (n=32)
Leg Edema	-0.6 (n=30)	-1.0 (n=24)	-1.5 (n=29)	-1.0 (n=31)
Presacral Edema	-0.2 (n=30)	-0.2 (n=23)	-0.3 (n=29)	-0.1 (n=31)

Source: Study 087-CL-071 Tables T1.2.1, T1.2.2, T1.2.3, T1.2.4, T1.2.5, T1.2.6, T1.2.7, T1.2.8, T1.2.9

2) 087-CL-032 is a randomized, double-blind, placebo-controlled study to evaluate the effects of a single dose of IV conivaptan on cardiopulmonary hemodynamic parameters in patients with severe CHF (NYHA class III/IV). Cardiac index (CI) \leq 2.8 L/min and pulmonary capillary wedge pressure (PCWP) \geq 16 mmHg were required for admission into the study. Patients received either placebo or conivaptan (10, 20, or 40 mg) intravenously over 30 minutes. In the 30 days follow up after the treatment, the combined incidence of all-cause death and CHF-related hospitalization or ER visit was slightly higher in the placebo group (15.8%, 6/38) compared to the combined conivaptan-treated group (9.6%, 10/104) as shown in the following table 4. No clinically significant dose dependent findings were noted in the adverse event profile.

Table 4: Combined Incidence of All-Cause Deaths, CHF-Related Hospitalizations, and/or ER Visits, Study 087-CL-032

Patients with:	Placebo (n=38)	Conivaptan			All (n=104)
		10 mg (n=37)	20 mg (n=32)	40 mg (n=35)	
Combined event of all-cause death or CHF-related hospitalization or ER visit	6 (15.8%)	2 (5.4%)	4 (12.5%)	4 (11.4%)	10 (9.6%)
Cardiovascular-related death	1 (2.6%)	0	1 (3.1%)	2 (5.7%)	3 (2.9%)
Non-cardiovascular related death	1 (2.6%)	0	0	0	0
CHF-related hospitalization or ER visits	4 (10.5%)	2 (5.4%)	3 (9.4%)	2 (5.7%)	7 (6.7%)

Source: Study 087-CL-032 Appendix C.34

3)087-CL-038 and 087-CL-044 are studies to evaluate the effects of conivaptan on the relief of pulmonary congestion symptoms in patients with exacerbation of CHF. Patients included in the studies had symptomatic heart failure with a history of NYHA class II-IV functional impairment, admitted for exacerbation of CHF with pulmonary congestion. Patients received either IV conivaptan or placebo administered as a 30-minute infusion on 2 occasions 8 hours apart; the dose of IV conivaptan was 20 mg in Study 087-CL-038 and 40 mg in Study 087-CL-044. The results indicate that there were no deaths in the treated groups but 3 of 12 (25%) of patients in the placebo group in Study 087-CL-038 as shown in the following table 6. The incidence rate of adverse events was similar between the active and placebo groups. No clinically significant differences were observed between treatment groups in the adverse event profiles in either study. Total doses of 40-80 mg administered as 2 infusions at least 8 hours apart did not worsen heart failure as evidenced by efficacy assessments, lengths of hospital stay, deaths, and re-hospitalizations.

Table 6: Combined Incidence of All-Cause Deaths, CHF-Related Hospitalizations, and/or ER Visits, Studies 087-CL-038 and 087-CL-044

Patients with:	Study 087-CL-038		Study 087-CL-044	
	Placebo (n=12)	Conivaptan 20 mg (n=14)	Placebo (n=13)	Conivaptan 40 mg (n=13)
Combined event of all-cause death or CHF-related hospitalization or ER visit	3 (25.0%)†	0	0	0
Cardiovascular-related death	2 (16.7%)	0	0	0
Non-cardiovascular related death	0	0	0	0
CHF-related hospitalization or ER visits	2 (16.7%)	0	0	0

† One patient (2011) experienced 1 CHF-related hospitalization on day 12 and died on day 19

Source: Study 087-CL-038 Appendix B.12, Study 087-CL-044 Appendix B.15

2. Oral Studies: Although the administered route for the proposed indication is IV infusion, data for oral studies in patients with CHF were also requested to evaluate the adverse events of conivaptan in this population. Exposure after short-term oral conivaptan dosing is approximately one-third less than that after short term IV dosing. The duration of exposure in the CHF studies using the oral formulation ranged from single doses of 5 mg up to 40 mg BID for 26 weeks and would be equivalent to IV doses of 4 to 30 mg per day.

1) Study 087-CL-017 is study to evaluate escalating doses of conivaptan 5 mg BID (n=4), 10 mg BID (n=4), 20 mg BID (n=4), or 40 mg BID (n=4) or placebo (n=8) administered for 1 week in patients with chronic NYHA class III/IV CHF of at least 3 months duration and left ventricular ejection fraction (LVEF) of <0.40. There were no obvious changes in hemodynamic parameters including right arterial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and cardiac output from baseline to day 7 to suggest potential improvement or worsening in underlying CHF.

2) Study 087-CL-033 is a study to evaluate conivaptan 10 mg BID (n=14), 20 mg BID (n=11), or 40 mg BID (n=10) or placebo (n=12) for 26 weeks in patients with severe

CHF NYHA class II-IV. To be eligible for the study, patients were to have LVEF \leq 35% with enlarged left ventricular end diastolic diameter (LVEDD) \geq 5.7 cm, and were to be receiving current therapy for heart failure consisting of at least 2 months duration of an angiotensin converting enzyme inhibitor, loop diuretic, and optionally beta-blocker and/or digoxin. Dose-dependent effects on cardiac dimensions were determined. There were no clinically meaningful or statistically significant differences in all-cause deaths, CHF hospitalizations and/or emergency room visits for worsening heart failure between the conivaptan groups and placebo. No dose response was apparent and overall conivaptan events were similar to placebo as shown in the following table 8.

Table 8: Combined Incidence of All-Cause Deaths, CHF-Related Hospitalizations, and/or ER Visits for Worsening Heart Failure, Study 087-CL-033

Patients with:	Placebo (n=12)	Conivaptan			
		20 mg† (n=14)	40 mg‡ (n=11)	80 mg§ (n=10)	All (n=35)
Combined event of all-cause death or CHF-related hospitalization or ER visit	1 (8.3%)	1 (7.1%)	2 (18.2%)	0	3 (8.6%)
All-cause death	0	0	1 (9.1)	0	1 (2.9%)
CHF-related hospitalization or ER visits	1 (8.3%)	1 (7.1%)	2 (18.2%)	0	3 (8.6%)

† 10 mg BID

‡ 20 mg BID

§ 40 mg BID

3) Study 087-CL-034 is a study to evaluate the dose dependent effects of 12 weeks of conivaptan therapy in improving symptoms of heart failure and functional capacity during treadmill exercise after chronic oral administration in patients with NYHA class II-IV CHF. A total of 343 patients were enrolled in the study and received placebo (n=93), conivaptan 10 mg BID (n=76), 20 mg BID (n=85), or 40 mg BID (n=89) for 12 weeks. Most patients had NYHA class III CHF. There were no clinically meaningful or statistically significant differences in patient exercise or symptom assessments between any of the conivaptan treatment groups and the placebo group that would suggest either improvement or worsening of underlying CHF. Similarly, there was no meaningful difference in changes in NYHA class between conivaptan and placebo. The incidence of CHF hospitalizations and/or emergency room visits was similar in the conivaptan (4.4%, 11/250) and placebo (3.2%, 3/93) groups. Conivaptan-treated patients experienced a slightly higher mortality rate (2.0%, 5/250) compared with the placebo group (0/93). Of the 5 deaths, 4 occurred in the 80 mg (40 mg BID) dose group. Further evaluation of the 4 deaths indicated that 1 death occurred during the placebo phase of the study, 1 patient died of a cerebrovascular accident while 2 patients with significant medical histories including ischemic heart disease died of sudden cardiac arrest. Data were present in the following table 9.

Table 9: Combined Incidence of All-Cause Deaths, CHF-Related Hospitalizations, and/or ER Visits for Worsening Heart Failure, Study 087-CL-034

Patients with:	Placebo (n=93)	Conivaptan			
		20 mg† (n=76)	40 mg‡‡ (n=85)	80 mg§ (n=89)	All (n=250)
Combined event of all-cause death or CHF-related hospitalization or ER visit	3 (3.2%)	3 (3.9%)	5 (5.9%)	7 (7.9%)	15 (6.0%)
All-cause deaths	0	1 (1.3%)	0	4 (4.5%)	5 (2.0%)
CHF-related hospitalization or ER visits	3 (3.2%)	2 (2.6%)	5 (5.9%)	4 (4.5%)	11 (4.4%)

† 10 mg BID

‡‡ 20 mg BID

§ 40 mg BID

4) Study 087-CL-020 is a study to evaluate the effects of conivaptan on exercise capacity in patients with symptomatic chronic CHF NYHA class II-III known for at least 3 months and stable for at least 6 weeks. Patients received placebo (n=74) or conivaptan 5 mg BID (n=72), 10 mg BID (n=77), or 20 mg BID (n=81) for 12 weeks. There were no changes in LWHF or NYHA scores, or CHF hospitalizations to suggest potential worsening of underlying CHF. The incidence of CHF hospitalization and/or ER visits was similar in the conivaptan and placebo groups and there was no dose response. Of the 2 patients in the 40 mg dose group (20 mg BID) included in the cardiovascular deaths, 1 of the 2 patients died of pulmonary thrombosis post surgery. Data were summarized in the following table 10.

Table 10: Combined Incidence of Cardiovascular Deaths, CHF-Related Hospitalizations and/or ER Visits for Worsening Heart Failure, Study 087-CL-020

Patients with	Placebo (n=72)	Conivaptan			
		10 mg† (n=71)	20 mg‡‡ (n=74)	40 mg§ (n=80)	All (n=225)
Combined event of cardiovascular death or CHF-related hospitalization or ER visit	5 (6.9%)	4 (5.6%)	4 (5.4%)	2 (2.5%)	10 (4.4%)
Cardiovascular-related death	0	0	0	2 (2.5%)	2 (0.9%)
CHF-related hospitalization or ER visits	5 (6.9%)	4 (5.6%)	4 (5.4%)	0	8 (3.6%)

† 5 mg BID

‡‡ 10 mg BID

§ 20 mg BID

5) Study 087-CL-024 is a study to determine the safety and efficacy of concomitant treatment with oral conivaptan and furosemide in patients with NYHA class II/III CHF on current therapy with an angiotensin converting enzyme inhibitor and optionally a beta-blocker and digoxin. It was an open-label study with 4 phases: screening (1 day), furosemide balance (4 days), baseline (2 days), and treatment (3 days). A total of 24 patients were randomized 1:1:1:1 to furosemide 40 mg/conivaptan 20 mg, furosemide 40 mg/conivaptan 40 mg, furosemide 80 mg/conivaptan 20 mg, or furosemide 80 mg/conivaptan 40 mg. Patients received either furosemide 40 mg or 80 mg QD during the 4-day furosemide balance phase to allow sodium and fluid balance to be achieved. Data from this multi-center, randomized trial suggest that treatment with concomitant

conivaptan and furosemide produced a favorable aquaretic effect without adversely affecting blood pressure or serum electrolytes. Patients in this trial were clinically stable, had moderate to severe heart failure, and were on contemporary background therapy.

3. Summary of the adverse events of both IV and oral studies of conivaptan in patients with CHF:

1) Cardiac events: Overall, the incidence of cardiac events is similar across dose groups for oral and IV studies. However, a higher rate was observed in the conivaptan IV group versus the placebo IV group as shown in the following tables 12, 14. This difference is mainly due to the 80 mg and 120 mg groups in the study 087-CL-071. The cardiac failure adverse events rate in Study 087-CL-071 in the 80 mg and 120 mg dose groups was similar to placebo as shown table 13.

Table 12: Overall Summary of Cardiac Events in Patients with Congestive Heart Failure, All Phase 2/3 Studies (Pool 5C)

Criteria for Defining Cardiac Failure Events	IV		Oral	
	Conivaptan n=253	Placebo n=103	Conivaptan n=565	Placebo n=187
Cardiac Failure Events†	8 (3.2%)	2 (1.9%)	26 (4.6%)	11 (5.9%)
Cardiac Disorders (SOC)	45 (17.8%)	22 (21.4%)	73 (12.9%)	26 (13.9%)
Cardiac Failure (SMQ)	16 (6.3%)	5 (4.9%)	24 (4.2%)	7 (3.7%)
Cardiac Failure (Augmented SMQ)	46 (18.2%)	15 (14.6%)	77 (13.6%)	23 (12.3%)

SOC: System Organ Class; SMQ: Standard MedDRA Query.

† Based on MedDRA preferred terms identified by the Division.

Table 13: Incidence of Cardiac Adverse Events in Patients with Acute Decompensated Congestive Heart Failure (Study 087-CL-071)

Criteria for Defining Cardiac Failure Events	Placebo n=40	IV YM087			
		40 mg n=40	80 mg n=40	120 mg n=42	All Doses n=122
Cardiac Failure Events†	0	3 (7.5%)	0	1 (2.4%)	4 (3.3%)
Cardiac Disorders (SOC)	13 (32.5%)	9 (22.5%)	9 (22.5%)	13 (31.0%)	31 (25.4%)
Cardiac Failure (SMQ)	3 (7.5%)	2 (5.0%)	3 (7.5%)	5 (11.9%)	10 (8.2%)
Cardiac Failure (Augmented SMQ)	12 (30.0%)	11 (27.5%)	14 (35.0%)	13 (31.0%)	38 (31.1%)

SOC: System Organ Class; SMQ: Standard MedDRA Query.

† Based on MedDRA preferred terms identified by the Division.

Source: Appendix A Table 7.4

Table 14: Overall Summary of Cardiac Events in Patients with Congestive Heart Failure, All IV Phase 2/3 Studies (Pool 5A), by Dose Group

Criteria for Defining Cardiac Failure Events	Placebo n=103	IV Conivaptan				
		10 mg n=37	20 mg n=32	40 mg n=89	80 mg n=53	120 mg n=42
Cardiac Failure Events†	2 (1.9%)	1 (2.7%)	1 (3.1%)	4 (4.5%)	1 (1.9%)	1 (2.4%)
Cardiac Disorders (SOC)	22 (21.4%)	2 (5.4%)	4 (12.5%)	14 (15.7%)	12 (22.6%)	13 (31.0%)
Cardiac Failure (SMQ)	5 (4.9%)	2 (5.4%)	0	5 (5.6%)	4 (7.5%)	5 (11.9%)
Cardiac Failure (Augmented SMQ)	15 (14.6%)	2 (5.4%)	1 (3.1%)	15 (16.9%)	15 (28.3%)	13 (31.0%)

SOC: System Organ Class; SMQ: Standard MedDRA Query.

† Based on MedDRA preferred terms identified by the Division.

2) Mortality rate: There are small difference between active drug and placebo with oral conivaptan. Overall, the occurrence of death was comparable across treatment groups. No dose dependent findings were noted except a higher number of patients who received IV conivaptan 120 mg/day died during the study; this dose was evaluated only in the acute decompensated heart failure patients in Study 087-CL-071. According to the sponsor, this mortality rate of 9.5% is similar to that published in this patient population. Data were summarized in the following table 22.

Table 22: Deaths During Treatment or Within 30 Days of Last Dose of Study Drug in CHF Studies

	Placebo (n=103)	IV Conivaptan					
		10 mg (n=37)	20 mg (n=32)	40 mg (n=89)	80 mg (n=53)	120 mg (n=42)	All (n=253)
Deaths	4 (3.9%)	0	1 (3.1%)	3 (3.4%)	0	4 (9.5%)	8 (3.2%)

	Placebo (n=187)	Oral Conivaptan					
		5 mg (n=4)	10 mg (n=80)	20 mg (n=187)	40 mg (n=192)	80 mg (n=102)	All (n=565)
Deaths	0	0	1 (1.3%)	2 (1.1%)	2 (1.0%)	2 (2.0%)	7 (1.2%)

In patients with CHF, the deaths were mainly attributed to underlying cardiac disease. The causes of death in the IV conivaptan studies were similar in the active treatment and placebo groups, and represent underlying cardiac disease and the acute nature of the patients' conditions. Data were provided in the following table 23.

Table 23: Listing of Deaths During Treatment or Within 30 Days of Last Dose of Study Drug in CHF Studies

Treatment Group	Patient ID	Age (years)	Gender	MedDRA Preferred Term	Study Day of Death	Relationship to Study Drug
087-CL-032 (IV)						
Placebo	21004	82	Male	Ventricular fibrillation	6	Not related
Placebo	27003	73	Male	Sepsis NOS	23	Not related
20 mg	10011	51	Male	Ischemic cardiomyopathy	20	Not related
40 mg	10009	54	Male	Cardiac arrest	3	Not related
087-CL-038 (IV)						
Placebo	2007	44	Male	Cardiorespiratory arrest	24	Not related
Placebo	2011	83	Female	Cardiac failure NOS	19	Not related
087-CL-044 (IV)						
No patients died during treatment or within 30 days of last dose of study drug in Study 087-CL-044						
087-CL-071 (IV)						
Placebo	No patients in the placebo group died during treatment or within 30 days of last dose of study drug					
40 mg	70002	69	Male	Congestive cardiomyopathy	6	Not related
	70004	78	Male	Cardiomyopathy NOS	28	Not related
80 mg	No patients in the 80 mg group died during treatment or within 30 days of last dose of study drug					
120 mg	40003	47	Male	Dyspnoea exacerbated	18	Not related
	240008	25	Female	Sudden cardiac death	5	Not related
	260002	62	Female	Ventricular fibrillation	2	Possibly
	320001	49	Male	Cardio-respiratory arrest	26	Not related
087-CL-016 (Oral)						
20 mg	110	81	Male	Cardiogenic shock	4	Unlikely
087-CL-017 (Oral)						
10 mg	1001	47	Female	Cardiac arrest	15	Unlikely
087-CL-020 (Oral)						
40 mg	21002	58	Male	Cardiac arrest	54	Unlikely
40 mg	32008	64	Male	Cardiac failure NOS	60	Unlikely
<i>Table continued on next page</i>						

Treatment Group	Patient ID	Age (years)	Gender	MedDRA Preferred Term	Study Day of Death	Relationship to Study Drug
087-CL-033 (Oral)						
No patients died during treatment or within 30 days of last dose of study drug in Study 087-CL-033						
087-CL-034 (Oral)						
20 mg	49020	60	Male	Sudden death	50	Unlikely
80 mg	24005	69	Male	Cerebrovascular accident	57	Unknown
80 mg	32018	74	Male	Cardiac arrest	48	Unlikely

Source: Listing of deaths during treatment or within 30 days of last dose of study drug in CHF studies

In comparison of the mortality rate in patients with hypervolemic condition, the mortality rates in hypervolemic patients across the studies who received conivaptan were similar to placebo. No dose-dependent trend was observed, however, the mortality rate was highest in the 120 mg dose group as shown in the following table 24.

Table 24: Mortality† for All Phase 2/3 CHF IV Studies and Hypervolemic Patients from Studies 087-CL-027 and 087-CL-080

Dose	Number of Deaths	Number of Subjects	Crude Mortality
IV Placebo	5	111	4.5%
IV 20 mg	3	46	6.5%
IV 40 mg	9	155	5.8%
IV 80 mg	1	62	1.6%
IV 120 mg	4	42	9.5%

† deaths during treatment or within 30 days of last dose of study drug

3) Common adverse events: Generally, the adverse events observed in the conivaptan-treated patients were consistent with events observed in the placebo-treated patients. The incidence of aggravated congestive heart failure was 0.4% (1/253) higher with IV conivaptan as compare with the IV placebo, and was similar in conivaptan and placebo groups (3.7-3.9%) for oral studies.

The incidence of atrial fibrillation and flutter was higher in the IV conivaptan group compared to IV placebo but ventricular tachycardia was higher in the IV placebo group at 9.7% versus 5.5% in the IV conivaptan group. Since these arrhythmia events are not unusual in this patient population, it is not clear if the atrial fibrillation is related to the effect of conivaptan.

The incidence rate of reversible acute renal failure was higher in both IV and oral conivaptan treated groups in the placebo. In patients underlying the cardiac failure, the non-reversible decreased renal function may indicate a poor prognosis. The mechanism for progressive renal failure in patients who have persisting heart failure is complex and involve many factors. However, for reversible acute renal failure, decreased renal perfusion may be the major cause. The differential diagnosis of acute renal failure due to “pre-renal” (cardiac problem, etc) or renal factors can be determined by measuring sodium excretion, ratio of urea to creatinine, etc. If the “pre-renal” acute renal failure persists, the non-reversible renal failure may occur.

Drug-related hypokalemia that was found in some of non-heart failure patients study was not observed these studies. However, an increased incidence rate of hyperkalemia both in IV and oral conivaptan treated groups was observed as compared with the placebo control.

Data were summarized in the following table 11.

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Table 11: Summary of Common Treatment-Emergent Adverse Events in Patients with Congestive Heart Failure

Adverse Event Description MedDRA, v 6.0		IV		Oral	
SOC	Preferred Term	Conivaptan	Placebo	Conivaptan	Placebo
Number of Patients		253	103	565	187
Blood and lymphatic system disorders	Anemia NOS	6 (2.4%)	1 (1.0%)	11 (1.9%)	2 (1.1%)
Cardiac disorders	Angina pectoris	4 (1.6%)	2 (1.9%)	12 (2.1%)	2 (1.1%)
	Atrial fibrillation	6 (2.4%)	0	8 (1.4%)	1 (0.5%)
	Atrial flutter	5 (2.0%)	0	4 (0.7%)	0
	Congestive cardiac failure aggravated	1 (0.4%)	0	22 (3.9%)	7 (3.7%)
	Ventricular tachycardia	14 (5.5%)	10 (9.7%)	3 (0.5%)	2 (1.1%)
Gastrointestinal disorders	Constipation	16 (6.3%)	8 (7.8%)	5 (0.9%)	3 (1.6%)
	Diarhea NOS	5 (2.0%)	4 (3.9%)	14 (2.5%)	3 (1.6%)
	Dry mouth	2 (0.8%)	0	12 (2.1%)	1 (0.5%)
	Nausea	12 (4.7%)	8 (7.8%)	15 (2.7%)	3 (1.6%)
	Vomiting NOS	5 (2.0%)	2 (1.9%)	4 (0.7%)	4 (2.1%)
General disorders and administration site conditions	Asthenia	7 (2.8%)	0	12 (2.1%)	2 (1.1%)
	Chest pain	0	3 (2.9%)	33 (5.8%)	9 (4.8%)
	Fatigue	2 (0.8%)	1 (1.0%)	38 (6.7%)	14 (7.5%)
	Infusion site pain	5 (2.0%)	0	0	0
	Infusion site phlebitis	34 (13.4%)	2 (1.9%)	0	0
	Infusion site reaction	5 (2.0%)	0	0	0
	Injection site cellulitis	9 (3.6%)	0	0	0
	Injection site pain	5 (2.0%)	1 (1.0%)	0	0
	Injection site reaction NOS	12 (4.7%)	2 (1.9%)	0	0
	Pyrexia	9 (3.6%)	5 (4.9%)	2 (0.4%)	0
Infections and infestations	Thirst	7 (2.8%)	0	40 (7.1%)	7 (3.7%)
	Nasopharyngitis	1 (0.4%)	0	17 (3.0%)	7 (3.7%)
	Pneumonia NOS	8 (3.2%)	4 (3.9%)	4 (0.7%)	2 (1.1%)
	Upper respiratory tract infection NOS	2 (0.8%)	0	17 (3.0%)	3 (1.6%)
Investigations	Urinary tract infection NOS	12 (4.7%)	6 (5.8%)	12 (2.1%)	6 (3.2%)
	Blood glucose increased	2 (0.8%)	1 (1.0%)	12 (2.1%)	4 (2.1%)
Metabolism and nutrition disorders	Weight increased	2 (0.8%)	0	12 (2.1%)	2 (1.1%)
	Hyperglycemia NOS	6 (2.4%)	0	13 (2.3%)	6 (3.2%)
	Hyperkalemia	10 (4.0%)	2 (1.9%)	8 (1.4%)	1 (0.5%)
	Hypertremia	7 (2.8%)	0	0	0
	Hypoglycemia NOS	5 (2.0%)	1 (1.0%)	2 (0.4%)	1 (0.5%)
	Hypokalemia	18 (7.1%)	9 (8.7%)	6 (1.1%)	2 (1.1%)
	Hypomagnesemia	6 (2.4%)	4 (3.9%)	0	0
Musculoskeletal and connective tissue disorders	Back pain	11 (4.3%)	1 (1.0%)	6 (1.1%)	2 (1.1%)
	Pain in extremity	9 (3.6%)	1 (1.0%)	14 (2.5%)	3 (1.6%)
Nervous system disorders	Dizziness	10 (4.0%)	3 (2.9%)	28 (5.0%)	6 (3.2%)
	Headache	14 (5.5%)	6 (5.8%)	17 (3.0%)	9 (4.8%)

Table continued on next page

Adverse Event Description MedDRA, v 6.0		IV		Oral	
SOC	Preferred Term	Conivaptan	Placebo	Conivaptan	Placebo
Psychiatric Disorders	Insomnia	12 (4.7%)	7 (6.8%)	5 (0.9%)	4 (2.1%)
Renal and urinary disorders	Renal failure NOS	6 (2.4%)	1 (1.0%)	13 (2.3%)	3 (1.6%)
Respiratory, thoracic and mediastinal disorders	Cough	7 (2.8%)	3 (2.9%)	12 (2.1%)	4 (2.1%)
	Dyspnea	4 (1.6%)	6 (5.8%)	13 (2.3%)	3 (1.6%)
	Dyspnea exacerbated	26 (10.3%)	8 (7.8%)	23 (4.1%)	6 (3.2%)
	Pulmonary congestion	5 (2.0%)	2 (1.9%)	2 (0.4%)	1 (0.5%)
Vascular disorders	Hypotension NOS	15 (5.9%)	7 (6.8%)	18 (3.2%)	9 (4.8%)

Common TEAEs which occurred in $\geq 2\%$ of patients treated with either oral or IV conivaptan.

SOC: system organ class; NOS: not otherwise specified

Source: Appendix A Table 15

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this page is the manifestation of the electronic signature.**

/s/

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