CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-016

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

NDA#:	22-016
Sponsor:	Astellas, Inc
Drug:	Conivaptan hydrochloride (Vaprisol®)
Indication:	Treatment of hypervolemic hyponatremia
Date of Submission:	August 25, 2006
Primary Medical Reviewer:	Karen Murry Mahoney, M.D.

I. Introduction and Background

Astellas, Inc. has submitted this complete response seeking approval for conivaptan (Vaprisol) in the treatment of hypervolemic hyponatremia. Vaprisol is currently approved for the treatment of euvolemic hyponatremia (NDA 21-697) based on the June 2005 resubmission to the approvable action letter of November 30, 2004. Because of safety concerns regarding conivaptan use in hypervolemic, hyponatremic subjects with heart failure, the application was administratively unbundled and for the indication of treatment of hypervolemic hyponatremia, an approvable action letter was sent to Astellas (NDA 22-106). The action letter outlined the concerns regarding the imbalance seen in cardiac-related adverse events in patients with underlying congestive heart failure treated with conivaptan that may signal an unacceptable risk for use in this indication. Additional clinical trial data addressing risk versus benefit in patients with underlying congestive heart failure was requested. In addition, the Division requested exploration of the possibility of a lower effective dose, e.g. 10 mg/day, for hyponatremic patients with underlying heart failure.

Treatment of hyponatremia is mainly focused on the underlying disease process. The etiologies of hyponatremia are generally classified based on volume status – hypovolemic, euvolemic or hypervolemic. To specifically treat the euvolemic and hypervolemic hyponatremia, fluid restriction is generally required. Current therapies available specifically directed at the treatment of hyponatremia are limited. The drug development program for has focused on conivaptan in the treatment of euvolemic and hypervolemic hyponatremia. With both of these states, the amount of total body water exceeds the amount of salt. Sodium and water balance are, in part, regulated by vasopressin (AVP). Conivaptan acts as a vasopressin antagonist and blocks the effect of vasopressin at the kidney, causing a water diuresis. With the loss of excess body water, water and salt balance returns and sodium increases.

II. Clinical Efficacy

Issues raised during the first review cycle included lack of a clear minimum effective dose. Data submitted with the 2nd cycle response supported the efficacy of a 20mg dose of conivaptan, which led to the approval of the 20 mg i.v. loading dose, followed by 20 – 40 mg/day continuous infusion. In addition, during the second review cycle, there appeared to be a greater conivaptan exposure for heart failure patients than for patients without heart failure and the Division requested exploration of the possibility of a lower effective dose, 10 mg/day, for hyponatremic patients with underlying heart failure.

In order to provide the most current safety and efficacy data for conivaptan, the sponsor included data on an additional 136 subjects who completed previously ongoing studies. These data are from euvolemic and hypervolemic subjects treated with conivaptan. Data in this review and the primary clinical review by Dr. Mahoney, concentrate on the efficacy of conivaptan for treatment of hypervolemic hyponatremia. A total of 87 conivaptan treated subjects comprise the population presented. These subjects were enrolled in Studies 087-CL-027 (027) and 087-CL-080 (080) which have been previously reviewed in detail during the first and second review cycles. Study 027 is the pivotal placebo-controlled trial for the intravenous dosing regimen of conivaptan 20 mg IV loading dose followed by 20 - 80mg daily conivaptan by continuous infusion. Study 080 is an open-label, uncontrolled Phase III study which enrolled patients with both euvolemic and hypervolemic hyponatremia.

Throughout the conivaptan clinical development program, at least 112 subjects with hypervolemic hyponatremia have received intravenous conivaptan. A total of 87 subjects with hypervolemic hyponatremia received the marketed dose of a 20mg loading dose and 40 – 80mg daily by continuous infusion for up to 4 days.

The primary efficacy endpoint was change from baseline in area under the curve (AUC) for serum sodium. As outlined in the table below, conivaptan was effective in raising serum sodium AUC in the hypervolemic hyponatremic patient population. There appears to be a dose response. Similar effectiveness was seen in hypervolemic hyponatremic subjects regardless of whether heart failure was the etiology of the volume status.

Studies 027 & 080 Hypervolemic Population: Baseline-adjusted AUC Sodium Effect Curve				
	Placebo	**Coni 20mg**	**Coni 40mg**	**Coni 80mg**
All Subjects				
N	8	14	66	9
mean (SD)	-75 (134)	490 (384)	565 (438)	799 (246)
min , max	-227 , 125	48 , 1377	-303 , 1466	496 , 1162
median	-94	353	523	796
Subjects with Heart Failure				
N	4	8	43	5
mean (SD)	18 (117)	374 (340)	522 (443)	735 (208)
min , max	-124 , 125	48 , 915	-303 , 503	512 , 1050
median	36	287	503	667
Subjects without Heart Failure				
N	4	6	23	4
mean (SD)	-168 (72)	647 (413)	646 (425)	878 (298)
min , max	-227 , -64	303 , 1377	-90 , 1466	496 , 1162
median	-191	519	579	927

As outlined in the table below, only one subject in the placebo group achieved an increase in serum sodium of $\geq$ 4 mEq/L. In contrast, the 64 – 100% of the conivaptan-treated subjects achieved serum sodium levels $\geq$ 4 mEq/L over baseline. Similar ratios were seen in hypervolemic subjects with or without heart failure. The median event time from first dose of study medication to a confirmed sodium increase of $\geq$ 4 mEq/L was 58.5 hours for the 20 mg conivaptan group, 24.1 hours for the 40 mg conivaptan group, and 23.8 hours for the 80 mg conivaptan group.

Studies 027 & 080 Hypervolemic Population: Time to Increase in Sodium ≥ 4 mEq/L (hours)				
	Placebo	**Coni 20mg**	**Coni 40mg**	**Coni 80mg**
All Subjects				
N	8	14	66	9
n (%) with ≥ 4 mEq/L incr	1 (12)	9 (64)	53 (80)	9 (100)
median (95% CI)	NE	58.5 (NE)	24.1 (23.8,37.2)	23.8 (5.0,24.4)
Subjects with Heart Failure				
N	4	8	43	5
n (%) with ≥ 4 mEq/L incr	1 (25)	5 (62)	34 (79)	5 (100)
median (95% CI)	NE	53.8 (NE)	27.5 (24.0,57.7)	24.0 (23.5,48.1)
Subjects without Heart Failure				
N	4	6	23	4
n (%) with ≥ 4 mEq/L incr	0	4 (67)	19 (83)	4 (100)
median (95% CI)	NE	58.5 (NE)	24.0 (12.0,47.7)	4.5 (4.0,24.8)
NE = not estimated				

The total time subjects had sodium ≥ 4 mEq/L above baseline is presented in the table below. The mean number of hours with serum sodium ≥ 4 mEq/L over baseline was 3.6 ± 10.1 hours in the placebo group, 42.9 ± 36.2 hours in the 20 mg conivaptan group, 54.9 ± 35.6 hours in the 40 mg conivaptan group, and 81.0 ± 7.5 hours in the 80 mg conivaptan group. There was an apparent dose response. Similar results were seen in hypervolemic subjects with or without heart failure.

Studies 027 & 080 Hypervolemic Population: Time ≥ 4 mEq/L Increase in Sodium Maintained (hrs)				
	Placebo	**Coni 20mg**	**Coni 40mg**	**Coni 80mg**
All Subjects				
N	8	14	66	9
mean (SD)	3.6 (10.1)	42.9 (36.2)	54.9 (35.6)	81.0 (7.5)
min , max	0 , 29.1	0 , 93.3	0 , 93.5	72.2 , 93.0
median	0	37.7	69.9	80.0
Subjects with Heart Failure				
N	4	8	43	5
mean (SD)	7.3 (14.6)	40.3 (39.4)	53.9 (36.0)	77.6 (4.2)
min , max	0 , 29.1	0 , 93.3	0 , 93.5	72.2 , 82.2
median	0	21.0	69.4	79.4
Subjects without Heart Failure				
N	4	6	23	4
mean (SD)	0	46.2 (35.0)	56.7 (35.6)	85.2 (9.3)
min , max	0 , 0	0 , 93.0	0 , 74.8	73.0 , 93.0
median	0	53.6	74.8	87.3

As outlined in the table below, the mean change from baseline in serum sodium concentration was -0.8 ± 3.3 mEq/L in the placebo group, +7.1 ± 4.8 mEq/L in the 20 mg conivaptan group, +7.4 ± 5.4 mEq/L in the 40 mg conivaptan group, and +10.4 ± 2.8 mEq/L in the 80 mg conivaptan group.

Studies 027 & 080 Hypervolemic Population: Mean Change in Serum Sodium (mEq/L)				
	Placebo	**Coni 20mg**	**Coni 40mg**	**Coni 80mg**
All Subjects				
N	8	14	66	9
Baseline, mean (SD)	124.2 (4.6)	123.6 (4.6)	123.5 (4.9)	124.3 (4.0)
Day 4, n	8	12	62	9
mean (SD)	124.6 (1.0)	131.5 (2.8)	131.4 (5.3)	134.7 (1.7)
mean change (SD)	-0.4 (3.8)	7.6 (5.1)	7.7 (5.4)	10.4 (2.8)
End of Treatment, n	8	14	66	9
mean (SD)	123.3 (4.7)	130.7 (4.2)	131.0 (5.6)	134.7 (1.7)
mean change (SD)	-0.8 (3.3)	7.1 (4.8)	7.4 (5.4)	10.4 (2.8)
Subjects with Heart Failure				
N	4	8	43	5
Baseline, mean (SD)	124.9 (5.2)	123.7 (4.8)	123.7 (5.3)	124.1 (4.3)
Day 4, n	3	7	40	9
mean (SD)	124.8 (1.3)	130.3 (2.6)	131.7 (6.1)	134.4 (1.8)
mean change (SD)	1.0 (4.4)	5.3 (3.8)	7.8 (5.3)	10.3 (2.8)
End of Treatment, n	4	8	43	9
mean (SD)	125.8 (2.4)	128.9 (4.7)	131.1 (6.4)	134.4 (1.8)
mean change (SD)	0.9 (3.6)	5.2 (3.5)	7.4 (5.4)	10.3 (2.8)
Subjects without Heart Failure				
N	4	6	23	4
Baseline, mean (SD)	123.5 (4.7)	123.4 (4.7)	123.2 (4.3)	124.6 (4.3)
Day 4, n	2	5	22	4
mean (SD)	124.3 (0.7)	133.1 (2.2)	130.7 (3.6)	135.2 (1.7)
mean change (SD)	-2.5 (2.1)	10.8 (5.2)	7.5 (5.7)	10.6 (3.2)
End of Treatment, n	4	6	23	4
mean (SD)	120.9 (5.4)	133.0 (2.0)	130.9 (3.6)	135.2 (1.7)
mean change (SD)	-2.6 (1.9)	9.7 (5.4)	7.6 (5.6)	10.6 (3.2)

With regard to the exploration of a lower 10mg dose for treatment of hyponatremia in patients with congestive heart failure, the Sponsor opted not to perform additional studies. Data from the second cycle review suggested that a 10 mg/day dose might be effective for the treatment of hyponatremia in patients with underlying heart failure. However, this conclusion was based on what is now recognized as a flawed pharmacokinetic model. Upon review, pharmacokinetic data submitted with this application show no significant difference in conivaptan exposure between heart failure and non-heart-failure patients. In addition, there appears to be a clear dose response with the escalating doses of conivaptan. Although 20 mg/day produces a clinically meaningful increase in serum sodium in hypervolemic patients with underlying CHF, it does so more slowly compared to the higher doses of conivaptan with a median event time from first dose of study medication to a confirmed sodium increase of ≥ 4 mEq/L of 53.8 hours, compared to 27.8 hours and 24.0 hours with the higher conivaptan doses. Therefore, the Sponsor's interpretation, that based on the magnitude of change in serum sodium seen with the 20 mg/day dose, it is likely that a lower dose of 10 mg/day might not produce a prompt, reliable and clinically relevant improvement in serum sodium, appears reasonable.

Conclusions: Data from the hypervolemic subjects with hyponatremia from Studies 027 and 080 clearly support conivaptan's effectiveness at increasing serum sodium in both subjects with and

without heart failure. The results achieved are similar to the efficacy seen for the euvolemic population.

III. Clinical Safety

At the time of Vaprisol's approval for treatment of hyponatremia in euvolemic patients in December 2005, the data were inadequate to establish safety for the treatment of patients with hypervolemic hyponatremia. Safety concerns included an increased incidence of exacerbations of heart failure, and an apparent signal for an increased risk of death among patients with heart failure who received conivaptan, compared to heart failure patients who received placebo. This safety review concentrates on hypervolemic subjects with hyponatremia. Three studies of iv conivaptan provide the basis for the review. Study 027 is the pivotal placebo-controlled trial for the intravenous dosing regimen of conivaptan 20 mg IV loading dose followed by 20 - 80mg daily conivaptan by continuous infusion. Study 080 is an open-label, uncontrolled Phase III study which enrolled patients with both euvolemic and hypervolemic hyponatremia. Twenty-six subjects had hypervolemia without heart failure. Study 087-CL-071 (071) is a placebo-controlled trial for the intravenous dosing regimen of conivaptan 20 mg IV loading dose followed by 40 – 120 mg daily conivaptan by continuous infusion for 2 days, evaluating the safety and efficacy of conivaptan in patients with acutely decompensated heart failure. Overall, 126 subjects with hypervolemic hyponatremia (14 received placebo, 112 received conivaptan) received at least one dose of study drug and are included in these analyses.

Deaths: As outlined in the table below, in Studies 027, 071 and 080, death did not occur more frequently for hypervolemic hyponatremic subjects treated with conivaptan when compared to placebo. In the 2nd cycle review, the data suggested a correlation between dose of conivaptan and incidence of death. Although minimal new data was presented for this population, the previous signals of an increased risk of death for conivaptan versus placebo, and for dose-dependence of risk of death for heart failure patients, are no longer apparent. However, given that no new placebo-controlled data are presented, these findings should be considered with caution.

Pooled Safety Database: Subjects Who Died						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
Hypervolemic Subjects with Hyponatremia, Studies 027 and 080						
N	14	14	73	15	10	112
n (%)	1 (7)	2 (14)	6 (8)	1 (7)	1 (10)	10 (9)
All Phase 2/3 Heart Failure Studies						
N	103	32	89	47	42	
n (%)	4 (4)	1 (3)	3 (3)	0 (0)	4 (10)	

Serious adverse events: As outlined in the table below, serious adverse events did not occur more commonly among conivaptan-treated subjects when compared to placebo-treated subjects in the pooled safety database of hypervolemic hyponatremic subjects from Studies 027, 071 and 080. Safety signals in the overall conivaptan program were unchanged.

Pooled Safety Database: Serious Adverse Events						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
Hypervolemic Subjects with Hyponatremia, Studies 027, 080 and 071						
N	14	14	73	15	10	112

Pooled Safety Database: Serious Adverse Events						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
Any SAE	4 (29)	0	19 (26)	4 (27)	5 (50)	28 (25)
General	1 (7.1)	0	5 (6.8)	0	1 (10.0)	6 (5.4)
Cardiac	3 (21.4)	0	7 (9.6)	1 (6.7)	3 (30.0)	11 (9.8)
Gastrointestinal	1 (7.1)	0	1 (1.4)	0	0	1 (0.9)
Hepatobiliary	0	0	1 (1.4)	0	0	1 (0.9)
Nervous	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
Respiratory	0	0	1 (1.4)	2 (13.3)	0	3 (2.7)
Endocrine/Metabolic	3 (21.4)	0	3 (4.1)	0	0	3 (2.7)
Musculoskeletal	0	0	1 (1.4)	0	0	1 (0.9)
Infectious	0	0	5 (6.8)	1 (6.7)	1 (10.0)	7 (6.3)
Renal	1 (7.1)	0	0	1 (6.7)	1 (10.0)	2 (1.8)
Vascular Disorders	1 (7.1)	0	0	0	0	0
Vision Disorders	0	0	1 (1.4)	0	0	1 (0.9)
Psychiatric	0	0	2 (2.7)	0	0	1 (1.8)

Adverse events leading to withdrawal: In the pooled database of subjects with hypervolemic hypernatremia, discontinuations due to adverse events occurred in 3 (21%) subjects in the placebo group and 12 (11%) conivaptan-treated subjects. The most common adverse event resulting in discontinuation was infusion-site reactions which occurred in 4 conivaptan treated subjects.

Adverse events: As outlined in the table below, in the hypervolemic hyponatremic population, adverse events occurred more commonly among conivaptan-treated subjects than placebo-treated subjects. Infusion site reactions among conivaptan-treated subjects was the predominant reason for the difference. Other events which occurred with greater frequency in conivaptan-treated subjects include constipation, pyrexia, sepsis NOS, headache, and orthostatic hypotension. When evaluated by baseline volume status, events that occurred more frequently among hypervolemic subjects than euvolemic subjects were similar.

Pooled Safety Database: Adverse Events by System Organ Class						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
Hypervolemic Subjects with Hyponatremia, Studies 027, 080 and 071						
N	14	14	73	15	10	112
Any AE	11 (79)	13 (93)	69 (94)	14 (93)	10 (100)	106 (95)
General	7 (50)	8 (57)	53 (73)	9 (60)	7 (70)	77 (69)
Cardiac	5 (36)	3 (21)	19 (26)	3 (20)	3 (30)	28 (25)
Gastrointestinal	5 (36)	3 (21)	30 (41)	5 (33)	2 (20)	40 (36)
Hepatobiliary	0	0	4 (6)	0	0	4 (4)
Nervous	1 (7)	3 (21)	14 (19)	3 (20)	1 (10)	21 (19)
Respiratory	6 (43)	5 (36)	20 (27)	4 (27)	2 (20)	31 (28)
Endocrine/Metabolic	7 (50)	8 (57)	28 (38)	5 (33)	3 (30)	44 (39)
Musculoskeletal	1 (7)	0	7 (10)	2 (13)	3 (30)	12 (11)
Infectious	5 (36)	3 (21)	19 (26)	5 (33)	3 (30)	30 (27)
Renal	3 (21)	4 (29)	15 (20)	3 (20)	2 (20)	24 (21)
Skin	1 (7)	1 (7)	7 (10)	0	1 (10)	9 (8)
Blood and Lymphatic	2 (14)	4 (29)	6 (8)	2 (13)	3 (30)	15 (13)
Injury	0	2 (14)	6 (8)	0	0	8 (7)
Investigations	2 (14)	2 (14)	12 (16)	6 (40)	2 (20)	22 (20)
Neoplasm	0	2 (14)	2 (3)	0	0	4 (4)
Vascular Disorders	2 (14)	4 (29)	21 (29)	7 (47)	2 (20)	34 (30)

Pooled Safety Database: Adverse Events by System Organ Class						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
Eye Disorders	0	0	4 (6)	0	0	4 (4)
Psychiatric	3 (21)	1 (7)	11 (15)	3 (20)	1 (10)	16 (14)

When adverse events evaluated based on the etiology of the hypervolemia, subjects with underlying heart failure treated with conivaptan reported adverse events more frequently than those treated with placebo (90% of placebo-treated subjects and 95% of conivaptan-treated subjects). Events which occurred with greater frequency in conivaptan-treated subjects include infusion site reactions, anemia NOS, nausea, and sepsis NOS. In hypervolemic subjects without heart failure adverse events were reported in 50% of placebo-treated subjects and 94% of conivaptan-treated subjects. Infusion site reactions predominantly accounted for the difference between treatment groups. Orthostatic hypotension was the only adverse events which occurred more frequently in the conivaptan-treated group.

Adverse events of special interest

Atrial Arrhythmia: In the 2nd conivaptan review cycle, concerns arose regarding a signal for a higher rate of atrial arrhythmia events for conivaptan-treated subjects compared to the placebo group. In the pooled hypervolemic hyponatremic subjects database presented with this current application, atrial arrhythmias occurred in no placebo-treated subjects and 4 (4%) conivaptan-treated subjects. As outlined in the table below, all atrial arrhythmia events occurred in subjects with underlying heart failure. Overall, it continues to appear that atrial arrhythmia events occur more commonly among conivaptan-treated subjects. 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.

Pooled Safety Database: Atrial Arrhythmia Events in Hypervolemic, Hyponatremic Subjects						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
All Subjects						
N	14	14	73	15	10	112
Atrial Arrhythmia	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
Subjects with Heart Failure						
N	10	8	50	11	10	79
Atrial Arrhythmia	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
Subjects without Heart Failure						
N	4	6	23	4	NA	33
Atrial Arrhythmia	0	0	0	0	NA	0

Cardiac Failure: In the 2nd cycle review, concerns arose regarding a signal for a higher rate of heart failure events in the conivaptan group compared to the placebo group. Three different terms are used to describe heart failure events. Cardiac Failure Events include event terms used by Dr. Mahoney in prior reviews and include the terms cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy NOS, congestive cardiac failure aggravated, congestive cardiomyopathy, right ventricular failure and ventricular dysfunction. Cardiac Failure, Standardized Medical Query (SMQ) include cardiac failure events defined by standard MedDRA Query and included 44 terms but only 6 of the 9 terms identified by Dr. Mahoney. Missing terms included cardiomyopathy NOS, congestive cardiac failure aggravated, and congestive cardiomyopathy. Cardiac Failure, augmented standardized

Medical Query (aSMQ) events included all terms from the SMQ, the missing 3 terms from Dr. Mahoney's review, as well as dyspnea and exacerbation of dyspnea.

As outlined in the table below, in the pooled hypervolemic hyponatremic subjects database presented with this current application, cardiac failure events occurred in one (7%) placebo-treated subject and 12 (11%) conivaptan-treated subjects. Cardiac failure, SMQ events occurred in one (7%) placebo-treated subject and 11 (9.8%) conivaptan-treated subjects. Cardiac failure, aSMQ events occurred in 3 (21%) placebo-treated subjects and 28 (25%) conivaptan-treated subjects. These events predominantly occurred in subjects with heart failure. 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 remains consistent across multiple populations of heart failure patients who were considered by sodium status, development program, baseline volume status and route of administration.

Pooled Safety Database: Cardiac Failure Events in Hypervolemic, Hyponatremic Subjects						
	Pbo	**20 mg**	**40 mg**	**80 mg**	**120 mg**	**All Coni**
All Subjects						
N	14	14	73	15	10	112
Cardiac Failure Events	1 (7.1)	0	11 (15.1)	1 (6.7)	0	12 (10.7)
Cardiac Failure (SMQ)	1 (7.1)	0	9 (12.3)	1 (6.7)	1 (10.0)	11 (9.8)
Cardiac Failure (aSMQ)	3 (21.4)	1 (7.1)	22 (30.1)	4 (26.7)	1 (10.0)	28 (25.0)
Subjects with Heart Failure						
N	10	8	50	11	10	79
Cardiac Failure Events	0	0	11 (22)	1 (9.1)	0	12 (15.2)
Cardiac Failure (SMQ)	1 (10.0)	0	8 (16.0)	1 (9.1)	1 (10.0)	10 (12.7)
Cardiac Failure (aSMQ)	2 (20.0)	0	20 (40.0)	4 (36.4)	1 (10.0)	25 (31.6)
Subjects without Heart Failure						
N	4	6	23	4	NA	33
Cardiac Failure Events	1 (25.0)	0	0	0	NA	0
Cardiac Failure (SMQ)	0	0	1 (4.3)	0	NA	1 (3.0)
Cardiac Failure (aSMQ)	1 (25.0)	1 (16.7)	2 (8.7)	0	NA	3 (9.1)

Overly rapid rise in serum sodium: One potentially dangerous side-effect of hyponatremia treatment is an overly rapid rise in serum sodium. Rapid correction of serum sodium is associated with increased risk for central pontine myelinolysis, a rare neurologic complication with potentially devastating consequences. In the entire clinical development program, 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.

Infusion Site Reactions: In prior reviews, infusion site reactions and infusion site phlebitis occur at a higher rate in conivaptan-treated subjects compared to placebo-treated subjects. Infusion site reactions also account for the majority of discontinuations due to adverse events. In the updated safety database for all iv conivaptan studies, infusion site reactions occurred in 8/132 (6%) placebo-treated subjects and 305/581 (52%) conivaptan-treated subjects. Vascular disorders, including deep venous thrombosis, phlebitis and thrombophlebitis, occurred in 1/132 (<1%) placebo-treated subjects and 23/581 (4%) conivaptan-treated subjects. The Sponsor is conducting a study to explore methods of decreasing the incidence of infusion site reactions.

Bone Marrow Events: A safety signal for anemia has previously been identified. In the updated safety database for all iv conivaptan studies, bone marrow adverse events occurred in 7/132 (5%)

placebo-treated subjects and 35/581 (6%) conivaptan-treated subjects. Anemia occurred more frequently in conivaptan-treated subjects (5/132 (4%) placebo-treated subjects and 33/581 (6%) conivaptan-treated subjects.

Hepatobiliary Events: In the updated safety database for all iv conivaptan studies, hepatobiliary adverse events occurred more frequently in conivaptan-treated subjects (1/132 (<1%) placebo-treated subjects and 20/581 (3%) conivaptan-treated subjects).

Laboratory evaluations:
One marked laboratory abnormality of potential concern is creatine kinase. Conivaptan is a potent inhibitor of CYP3A4. In prior reviews it was noted that two subjects taking oral conivaptan and concomitant statins developed rhabdomyolysis. In this updated database, a total of 4 subjects, all receiving intravenous conivaptan, developed marked elevations of creatine kinase. In all cases, there were other etiologies for the increases observed. There has been no data to suggest that conivaptan itself causes rhabdomyolysis..

In the updated safety databases, there are no clinically significant differences between conivaptan-treated subjects and placebo-treated subjects in mean change in hematology parameters. Greater mean changes (increases) in serum chemistry parameters were seen in conivaptan-treated subjects, which can be attributed to increased effective water clearance in these subjects. Mean random and fasting plasma glucose increased for conivaptan-treated subjects, and declined for placebo-treated subjects. This may be related to the D5W diluent used for conivaptan administration. I agree with Dr. Mahoney that this finding is unlikely to have clinical consequences over the proposed administration duration of 2-4 days.

In the updated conivaptan safety database, laboratory shifts occurred slightly more in conivaptan-treated subjects for fasting plasma glucose and serum creatinine.

Conclusions: The Sponsor has submitted an updated conivaptan database, rather than new data from placebo-controlled trials, to address the safety concerns raised in the approvable letter. They present data for 136 additional subjects from a non-placebo-controlled trial which included both euvolemic and hypervolemic subjects with and without heart failure. With regard to the apparent signal for an increased risk of death among patients with heart failure who received conivaptan, data reviewed did not demonstrate an increased rate of death or a dose response in conivaptan-treated subjects with hypervolemic hyponatremia. Serious adverse events did not occur more commonly among conivaptan-treated subjects when compared to placebo-treated subjects in the pooled safety database of hypervolemic hyponatremic subjects The only individual serious adverse event which occurred more frequently in the conivaptan group was sepsis NOS. Adverse events occurred more commonly among conivaptan-treated subjects than placebo-treated subjects. Infusion site reactions among conivaptan-treated subjects were the predominant reason for the difference. Other events which occurred with greater frequency in conivaptan-treated subjects include constipation, pyrexia, sepsis NOS, headache, and orthostatic hypotension.

Prior review cycles revealed an increased incidence of exacerbations of heart failure. Three different terms are used to describe cardiac failure events. Regardless of which term is used, 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 remains consistent across multiple populations of heart failure patients who were considered by sodium status, development program, baseline volume status and route of administration.

In addition, there continues to be a signal suggesting that atrial arrhythmia events occur more commonly among conivaptan-treated subjects. In the pooled hypervolemic hyponatremic subjects database presented with this current application, atrial arrhythmias occurred in no placebo-treated subjects and 4 (4%) conivaptan-treated subjects. All atrial arrhythmia events occurred in subjects with underlying heart failure.

Other safety signals recognized with conivaptan use remain unchanged in the hypervolemic hyponatremic population. These include infusion site reactions, anemia, and hepatobiliary events. Laboratory safety events of concern include marked elevations in creatine kinase (CK), which has been seen in 4 subjects treated with conivaptan.

IV. Cardio-Renal Consultation

[redacted] b(4)

While conivaptan did not result in improvement in heart failure outcomes in these studies, it was also not associated with a worsening of heart failure when evaluated using several objective measures, including hemodynamics, exercise tolerance, heart failure signs, structural heart changes, length of hospital/ICU stay and adjudicated heart failure hospitalizations/ER visits. Using symptom measures, conivaptan also was not worse than placebo. However, it is worth recognizing that the majority of subjects in the heart failure development program did not have hyponatremia. Hyponatremia is a marker of severity in heart failure. Therefore, heart failure patients who would receive conivaptan for the proposed indication would all be hyponatremic and therefore have more severe heart failure than those in whom no concerning safety signal was seen.

The Division of Cardiovascular and Renal Products was consulted regarding 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.

V. Pharmacology/Toxicology

There are no new Pharmacology / Toxicology data were submitted in this NDA.

VI. Clinical Pharmacology

The sponsor conducted a study of conivaptan systemic exposure comparability across sub-patient populations with volume (i.e., euvolemic vs. hypervolemic) and CHF (with and without) status to support their conclusion that the effect of CHF on hypervolemic hyponatremia treatment is insignificant. The new pharmacokinetic data from study 087 CL-080 was formally reviewed by Dr. Sang Chung. A total of 58 subjects with heart failure had PK sampling and it was concluded that conivaptan pharmacokinetics in patients with CHF were comparable to those of patients without CHF. In addition, there was no significant difference in parameters between euvolemic and hypervolemic patients with two conivaptan doses. Therefore, Dr. Chung has concluded that there is no significant difference in conivaptan pharmacokinetics between the euvolemic and

hypervolemic populations and conivaptan pharmacokinetics was not significantly different in geriatrics compared to that of patients' age less than 65 years.

VII. CMC

No new CMC data was submitted.

VIII. Other Regulatory Requirements

VIIIa. Financial Disclosure

No new studies are submitted for review. Therefore, there is no new financial disclosure information.

VIIIb. Pediatrics

Pediatric study requirements have previously been waived for ages 0-6 years. Studies in pediatric subjects aged 6 - 18 years are deferred until 10/31/2010

VIIIc. Clinical Audits/Inspections

A DSI audit was not conducted for this submission.

IX. Conclusions and Recommendations

IX.a. Conclusions

Data from the hypervolemic subjects with hyponatremia from Studies 027 and 080 clearly support conivaptan's effectiveness at increasing serum sodium in both subjects with and without heart failure. The results achieved are similar to the efficacy seen for the euvolemic population. Newly submitted pharmacokinetic data show no significant difference in conivaptan exposure between heart failure and non-heart-failure subjects. In addition, there appears to be a clear dose response with the escalating doses of conivaptan and while the 20 mg/day dose produces a clinically meaningful increase in serum sodium in hypervolemic patients with underlying CHF, it does so more slowly compared to the higher doses of conivaptan. Therefore, I agree with Dr. Mahoney that the Sponsor's conclusion that it is likely that a lower dose of 10 mg/day might not produce a prompt, reliable and clinically relevant improvement in serum sodium, appears reasonable.

The Sponsor has submitted a safety update that reveals that death and serious adverse events did not occur more frequently among conivaptan-treated subjects when compared to placebo-treated subjects in the pooled safety database of hypervolemic hyponatremic subjects. Adverse events occurred more commonly among conivaptan-treated subjects than placebo-treated subjects. Infusion site reactions among conivaptan-treated subjects was the predominant reason for the difference.

There continues to be a signal suggesting that atrial arrhythmia events and cardiac failure events occur more commonly among conivaptan-treated hypervolemic heart failure subjects. While, it is reassuring that in the heart failure development program, conivaptan was not associated with a worsening of heart failure when evaluated using multiple objective measures, I agree with Dr. Mahoney and our cardiology consultants that the very small size of the relevant population do not provide sufficient evidence to support that conivaptan is safe in heart failure patients with

hypervolemic hyponatremia. Therefore, language regarding this limitation of the data should remain in the label.

IXb. Recommendation

Approve, with the agreed-upon labeling changes

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/s/

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2/26/2007 11:08:19 AM
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CLINICAL REVIEW

Application Type	NDA 22016
Submission Number	000
Submission Code	AZ
Letter Date	25 Aug 06
Stamp Date	25 Aug 06
PDUFA Goal Date	20 Feb 07
Reviewer Name	Karen Murry Mahoney, MD, FACE
Review Completion Date	28 Jan 07
Established Name	Conivaptan hydrochloride
(Proposed) Trade Name	Vaprisol®
Therapeutic Class	Vasopressin receptor antagonist, "aquaretic"
Applicant	Astellas
Priority Designation	S
Formulation	Intravenous injection
Dosing Regimen	20 mg intravenous loading dose followed by 20-40 mg/day by continuous intravenous infusion for 2-4 days
Indication	Treatment of hypervolemic hyponatremia
Intended Population	Adults with hypervolemic hyponatremia

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends the approval of Vaprisol® for the treatment of hyponatremia in hospitalized patients with hypervolemic hyponatremia. 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.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In addition to routine postmarketing surveillance, the applicant proposes to include special analyses of heart failure-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 includes 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.

1.2.2 Required Phase 4 Commitments

The applicant agreed to several Phase 4 commitments at the time of the approval of Vaprisol® for the treatment of hyponatremia in euvolemic patients. The clinical reviewer has no recommendations for new commitments.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vaprisol® (conivaptan hydrochloride) is a V2/V1a vasopressin receptor antagonist, which is approved for the treatment of hyponatremia in euvolemic patients. In its first review cycle, Vaprisol® received an approvable action because the number of patients who had received conivaptan at the relevant clinical exposure was inadequate. More patients were accrued, and after a second cycle review, Vaprisol® received its approval for the treatment of euvolemic hyponatremia in hospitalized patients. At the time of this approval 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. An approvable action was taken for the indication for treatment of hypervolemic hyponatremia. The approvable letter requested additional clinical trial data addressing risk vs benefit in patients with underlying heart failure. Astellas now submits its response to that approvable action.

Please see the two previous clinical reviews of conivaptan for the first and second cycle New Drug Application (NDA) submissions under NDA 21697. These reviews are in the Division File System electronic archive.

1.3.2 Efficacy

The applicant presented efficacy data for the treatment of patients with hypervolemic hyponatremia, and for subpopulations of patients with and without underlying heart failure. Vaprisol®'s efficacy in the treatment of hyponatremia in the overall hypervolemic hyponatremic population was similar to that previously seen for the euvolemic population. Vaprisol® was also effective in the treatment of hyponatremia in each of the two hypervolemic hyponatremic subpopulations; those patients with and without underlying heart failure. Efficacy endpoints included:

- Change from baseline in area under the serum sodium effect curve
- Change from baseline in absolute serum sodium
- Percentages of patients achieving such goals as serum sodium ≥4 mEq/L over baseline, serum sodium ≥6 mEq/L over baseline, or achievement of a normal serum sodium
- Time to achievement of serum sodium ≥4 mEq/L over baseline

For the overall hypervolemic hyponatremic population, and for the subpopulation with heart failure, these effects exhibited dose-dependency.

Vaprisol® appears to be effective for the treatment of hypervolemic hyponatremia in hospitalized patients.

1.3.3 Safety

The question of greatest significance in this application was whether the applicant has submitted sufficient new information to alleviate safety concerns that were identified in the second cycle review for heart failure patients. The applicant did not submit any data from new trials, and did not submit any new placebo-controlled data for hypervolemic hyponatremic patients. The applicant presented non-placebo-controlled data for 136 previously unreported patients from a hyponatremia trial that had been ongoing at the time of the second cycle review. Not all of these patients were hypervolemic. The number of patients who had hypervolemic hyponatremia (serum sodium <130 mEq/L) and underlying heart failure who were treated with the proposed doses of intravenous conivaptan was very small. The applicant presented a total of 51 such patients from two intravenous hyponatremia trials, one of which was placebo-controlled and one of which was not. All patients from the placebo-controlled trial had already been presented in the first and second cycle reviews. Thus the size of the relevant safety population was very small, and even this small population did not contain many new patients.

The clinical reviewer also examined information from other populations in order to evaluate safety. This included heart failure [redacted] data from the applicant's heart failure development program, [redacted] Updated safety data for the entire conivaptan program were also reviewed as a whole, and were divided into subpopulations by route of administration, presence of underlying heart failure, presence of hyponatremia and volume status. b(4)

When including the new data, the previous signals of an increased risk of death for conivaptan versus placebo, and for dose-dependence of risk of death for heart failure patients, were no longer apparent. However, no new placebo-controlled data were presented.

For the overall hypervolemic hyponatremic population, and for the updated total safety population, the profile of serious and nonserious adverse events was very similar to that seen in the second cycle review. Infusion site-related events, hypokalemia, orthostatic hypotension and overly rapid correction of serum sodium continue to be important adverse events associated with conivaptan. No events of central pontine myelinolysis have been reported in either of the conivaptan development programs. When separately examining the population of hypervolemic hyponatremic patients without underlying heart failure who were treated intravenously, the only events which occurred with greater frequency among conivaptan-treated patients than among placebo-treated patients were orthostatic hypotension and infusion site-related events.

However, questions remain about the safety of conivaptan when administered to patients with underlying heart failure. The following list highlights some of those concerns:

- Hypervolemic hyponatremic patients with underlying heart failure who were treated with intravenous conivaptan had a higher incidence (compared to placebo) of cardiac failure events by three different methods of identifying events; two of these methods were those proposed by the applicant. This was also true for heart failure patients who were treated with intravenous conivaptan in the heart failure development program.

- Hypervolemic hyponatremic patients with underlying heart failure had a higher incidence (compared to placebo) of events of sepsis and anemia. This was not true for hypervolemic hyponatremic patients without heart failure.
- Among patients with underlying heart failure, intravenous conivaptan was associated with an increased risk for atrial arrhythmia events when compared to placebo. 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 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.
- Conivaptan demonstrated no benefit for heart failure patients on the vast majority of a wide array of heart failure

  This lack of superiority to placebo was demonstrated for 22 different endpoints, including such measures as length of hospital stay, categorized physical findings of heart failure, hemodynamic measurements, structural and functional changes on imaging, exercise tolerance and mortality.
- Patients from the applicant's heart failure program who received conivaptan had a higher incidence of discontinuations from treatment due to adverse events than did heart failure patients who received placebo.
- Cardiac failure patients usually take multiple medications, many of which are metabolized by cytochrome P450 3A4 (CYP3A4).

  b(4)

  intravenous form of the drug, to be used only in hospitalized patients. However, in previous reviews of conivaptan, the clinical reviewer noted that even in the highly controlled clinical trial environment, there were multiple protocol violations related to concomitant administration of prohibited CYP3A4-metabolized drugs.
- 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 per se would have any beneficial effect for these patients;

  b(4)

  If the drug is not known to benefit these vulnerable patients, *primum non nocere*.

The Division of Cardiovascular and Renal Products was consulted for that Division's opinion regarding the safety of conivaptan when administered to patients with underlying heart failure. They concluded that the data were inadequate to establish safety, particularly since no significant benefit other than increase in serum sodium was demonstrated for heart failure patients.

This clinical reviewer's overall conclusion regarding the safety of conivaptan for patients with underlying heart failure is there are simply not enough data for patients in the relevant hypervolemic hyponatremic heart failure population, and therefore safety cannot be established. Safety signals persist when comparing conivaptan-treated heart failure patients to placebo-treated

heart failure patients, and when comparing hypervolemic hyponatremic patients with underlying heart failure to hypervolemic hyponatremic patients without heart failure.

However, the safety profile for hypervolemic hyponatremic patients without heart failure who were treated with conivaptan appears to be similar to that for euvolemic hyponatremic patients.

1.3.4 Dosing Regimen and Administration

The applicant proposes no change in the dosing regimen, which consists of a 20 mg intravenous loading dose followed by 20-40 mg/day by continuous intravenous infusion for 2-4 days.

Data from the second cycle review suggested that a 10 mg/day dose might be effective for the treatment of hyponatremia in patients with underlying heart failure. This question is moot if one concurs that conivaptan has not been shown to be safe for heart failure patients. However, two types of data suggest that a 10 mg dose is not likely to be effective in raising serum sodium for heart failure patients. Previous data had suggested a much higher conivaptan exposure for heart failure patients than for patients without heart failure, which prompted the discussions of the possibility of a lower effective dose. However, those data came from a flawed pharmacokinetic model; direct pharmacokinetic data submitted with this application show no significant difference between heart failure and non-heart-failure patients for conivaptan exposure. Also, there is a clear dose response for the proportion of hyponatremic heart failure patients achieving serum sodium goals, and at the lowest approved dose (20 mg/day), only about 1/3 of patients achieved these goals. Patients in the lower dose group also had a slower rise in serum sodium. A 10 mg/day dose will probably be less likely to achieve the desired effect on serum sodium in a timely fashion.

1.3.5 Drug-Drug Interactions

No new drug-drug interaction data were submitted.

1.3.6 Special Populations

No new data for special populations were submitted.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vaprisol® (conivaptan hydrochloride) is a V2/V1a vasopressin receptor antagonist, which is approved for the treatment of hyponatremia in euvolemic patients. At the time of the original approval in December 2005, the data were inadequate to establish safety for the treatment of patients with hyponatremia who were hypervolemic. An approvable action was taken for this indication. Astellas now submits its response to that approvable action.

The applicant proposes the same dosing regimen for hypervolemic hyponatremia as that approved for euvolemic hyponatremia, i.e. a 20 mg intravenous loading dose administered over 30 minutes, followed by 20-40 mg/day given intravenously by continuous infusion, for a total duration of administration of 2-4 days. Use is limited to hospitalized patients.

2.2 Currently Available Treatment for Indications

At this time, there are no approved products for the treatment of hyponatremia in hypervolemic patients. Vaprisol® is now commercially available for euvolemic hyponatremia, and therefore may be in off-label use for hypervolemic hyponatremia. Traditional treatments for hypervolemic hyponatremia have included fluid restriction, diuretics, and treatment of the underlying cause of the hypervolemic hyponatremic state; less commonly, hypertonic saline or demeclocycline have been used.

2.3 Availability of Proposed Active Ingredient in the United States

Vaprisol® is approved and has been commercially launched in the United States.

2.5 Presubmission Regulatory Activity

On 29 Dec 05, an approvable letter was issued for Vaprisol® for the treatment of hypervolemic hyponatremia in hospitalized patients. 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 (pbo). The approvable letter requested additional clinical trial data addressing risk vs benefit in patients with underlying heart failure.

Please see the two previous clinical reviews of conivaptan for the first (1^{st}) and second (2^{nd}) cycle NDA submissions under NDA 21697. These reviews are in the Division File System electronic archive.

On 3 May 06, an End-of-Review conference was held with Astellas, in order for Astellas to discuss its plans for a response to the approvable action. In that conference, concern was

expressed that Astellas did not plan to submit any additional data on previously unpresented patients from placebo-controlled studies. The Division requested submission of efficacy and safety data from all trials in heart failure patients, [redacted] in the Division of Cardiovascular and Renal Products for [redacted] heart failure. Information regarding the efficacy of a 10 mg/day dose in heart failure patients was also requested. b(4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In the 2nd cycle review, data for a total of 1148 conivaptan-treated patients were received; this included patients from both the hyponatremia and heart failure development programs, from both oral and intravenous (IV) studies, and from both euvolemic and hypervolemic patients. In this submission, the applicant presents data from an additional 136 patients who received intravenous conivaptan in a non-placebo-controlled hyponatremia trial that was ongoing during the last review cycle; this trial included both hypervolemic and euvolemic patients. Across the entire development program (previously presented + newly presented patients) the applicant presented a total of 112 hypervolemic hyponatremic patients who received intravenous conivaptan in any dose. Of these patients, 79 had heart failure. Among the presented hypervolemic hyponatremic patients, a total of 87 received one of the proposed doses for marketing; a total of 58 heart failure patients with hypervolemic hyponatremia received one of the proposed doses.

For this 3rd cycle review, the applicant submits a response document, a safety update, and an updated study report for Study 080 which includes non-placebo-controlled data for some patients not presented in the 2nd cycle review materials.

4.2 Tables of Clinical Studies

No new studies were included in this NDA resubmission.

4.6 Financial Disclosures

No new studies were included in this NDA, and no new financial disclosure information was submitted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of hypervolemic hyponatremia in hospitalized patients

6.1.1 Methods

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. Please see the 1st and 2nd cycle reviews for descriptions of the study designs for Studies 027 and 080. Study 027 was the only placebo-controlled hyponatremia efficacy trial that was performed with intravenous conivaptan. Study 080 was an open-label trial conducted in hyponatremic patients, intended to gain more safety information for the intravenous use of conivaptan in hyponatremic patients. Both trials included both euvolemic and hypervolemic patients, but only efficacy information for hypervolemic patients is presented below.

Because major concerns for the 2nd cycle review centered around safety in patients with underlying heart failure, efficacy data are presented for all hypervolemic hyponatremic patients in these trials, followed by separate safety data for the subpopulations with and without heart failure.

6.1.4 Efficacy Findings

6.1.4.1 Efficacy in Combined Study Groups of Patients With Hypervolemic Hyponatremia With and Without Heart Failure

6.1.4.1.1 Primary Endpoint: Change from Baseline in Area Under the Serum Sodium Effect Curve

The following table summarizes the findings for the primary endpoint (change from baseline in area under the serum sodium effect curve), for all patients in Studies 027 and 080 with hypervolemic hyponatremia, including patients both with and without heart failure. For this overall group of hypervolemic hyponatremic patients, conivaptan was effective in raising serum sodium AUC at all doses tested. There was an apparent dose response.

Table 6.1.4.1.1 Baseline-adjusted Area Under the Serum Sodium Effect Curve, All Hypervolemic Hyponatremic Patients, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	8	14	66	9
Mean (SD)	-74.8 (134.3)	490.0 (383.8)	565.3 (437.7)	798.6 (245.7)
Min	-226.6	48.0	-302.8	495.7
Median	-93.8	352.8	522.8	796.5
Max	125.0	1377.4	1466.3	1162.0

Source: Applicant's Table 1.1, pg 12, response document

6.1.4.1.2 Secondary Endpoints

6.1.4.1.2.1 Time from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase from Baseline in Serum Sodium

The percentage of patients achieving a 4 mEq/L increase from baseline in serum sodium increased in a dose-dependent fashion.

Table 6.1.4.1.2.1 Time (Hours) from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase from Baseline in Serum Sodium, All Hypervolemic Hyponatremic Patients, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N[a]	8	14	66	9
n (%)[b]	1 (12.5)	9 (64.3)	53 (80.3)	9 (100.0)
Median Event Time[c] (95% CI)	NE[d] (NE)	58.5 (NE)	24.1 (23.8, 37.2)	23.8 (5.0, 24.4)

Source: Applicant's Table 2.1, pg 15, response document
a Number of treated patients
b Number of patients who had a confirmed ≥4 mEq/L increase from baseline in serum sodium during the treatment phase; % = n*100/N
c Time from first dose of study medication to a confirmed ≥4 mEq/L increase from baseline in serum sodium.
d Not estimable

6.1.4.1.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients had a ≥4 mEq/L Increase from Baseline in Serum Sodium

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.

Table 6.1.4.1.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients Had ≥4 mEq/L Increase from Baseline in Serum Sodium, All Hypervolemic Hyponatremic Patients, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	8	14	66	9
Mean (SD)	3.6 (10.3)	42.9 (36.2)	54.9 (35.6)	81.0 (7.5)
Min	0	0	0	72.2

Table 6.1.4.1.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients Had ≥4 mEq/L Increase from Baseline in Serum Sodium, All Hypervolemic Hyponatremic Patients, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
Median	0	37.7	69.9	80.0
Max	29.1	93.3	93.5	93.0

Source: Applicant's Table 3.1, pg 18, response document

6.1.4.1.2.3 Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment

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. There was not a clear dose response.

Table 6.1.4.1.2.3.1: Mean and Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment, All Patients with Hypervolemic Hyponatremia, Studies 027 and 080

Measure	Pbo N = 8 Mean (SD)	20 mg N = 14[a] Mean (SD)	40 mg N = 66[b] Mean (SD)	80 mg N = 9 Mean (SD)
Mean Serum Sodium at Baseline[c]	124.2 (4.6)	123.6 (4.6)	123.5 (4.9)	124.3 (4.0)
Mean Serum Sodium at Day 4[a,b]	124.6 (1.0)	131.5 (2.8)	131.4 (5.3)	134.7 (1.7)
Mean Serum Sodium at End of Treatment	123.3 (4.7)	130.7 (4.2)	131.0 (5.6)	134.7 (1.7)
Mean Change in Serum Sodium from Baseline to Day 4	-0.4 (3.8)	7.6 (5.1)	7.7 (5.4)	10.4 (2.8)
Mean Change in Serum Sodium from Baseline to End of Treatment	-0.8 (3.3)	7.1 (4.8)	7.4 (5.4)	10.4 (2.8)

Source: Applicant's Table 4.1.1, pg 21, response document
a At Day 4 of treatment, N = 12
b At Day 4 of treatment, N = 62
c Baseline = average of nonmissing serum sodium measurements obtained predose

When examining at each day of treatment, there appears to be a dose response at 24 hours, and possibly at 48 and 96 hours. The baseline serum sodium values in this table differ slightly from those in Table 6.1.4.1.2.3.1 above, because in the above table, the applicant used the average of nonmissing predose serum sodium measurements, and in the table below, used the last nonmissing predose serum sodium measurement.

Table 6.1.4.1.2.3.2: Mean and Mean Change in Serum Sodium from Baseline to Hours 24, 48, 72 and 96, All Patients with Hypervolemic Hyponatremia, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N at Baseline	8	14	66	9
N at Hour 24	8	13	63	9
N at Hour 48	6	12	63	9
N at Hour 72	5	12	59	9
N at Hour 96	5	12	59	9
Mean Serum Sodium at Baseline[1] (SD)	124.5 (4.8)	124.1 (4.8)	124.4 (5.2)	125.9 (4.3)

Table 6.1.4.1.2.3.2: Mean and Mean Change in Serum Sodium from Baseline to Hours 24, 48, 72 and 96, All Patients with Hypervolemic Hyponatremia, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
Mean Serum Sodium at Hour 24 (SD)	123.6 (5.3)	127.5 (4.7)	129.7 (6.3)	134.4 (6.3)
Mean Serum Sodium at Hour 48 (SD)	120.8 (7.0)	129.5 (2.9)	130.3 (5.7)	133.7 (3.2)
Mean Serum Sodium at Hour 72 (SD)	125.4 (2.6)	131.0 (3.6)	130.9 (5.8)	133.9 (2.1)
Mean Serum Sodium at Hour 96 (SD)	126.0 (1.0)	131.8 (3.4)	132.3 (5.2)	136.8 (3.0)
Mean Change from Baseline in Serum Sodium at Hour 24 (SD)	-0.9 (1.3)	3.7 (3.2)	5.1 (5.0)	8.5 (6.0)
Mean Change from Baseline in Serum Sodium at Hour 48 (SD)	-2.8 (3.5)	5.0 (4.8)	5.8 (5.2)	7.8 (3.6)
Mean Change from Baseline in Serum Sodium at Hour 72 (SD)	0.8 (2.7)	6.6 (5.3)	6.5 (5.4)	8.0 (3.3)
Mean Change from Baseline in Serum Sodium at Hour 96 (SD)	1.4 (4.3)	7.4 (5.2)	7.5 (5.4)	11.0 (2.9)

Source: Applicant's Table 4.1.2, pg 22, response document
1 Baseline = last nonmissing serum sodium measurement before treatment phase

6.1.4.1.2.4 Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment

Among all patients with hypervolemic hyponatremia, no patients in the placebo group achieved one of these goals, while most patients in the conivaptan groups did. There was an apparent dose response.

Table 6.1.4.1.2.4: Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment, All Patients with Hypervolemic Hyponatremia, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N	8	14	66	9
n	0	7	43	9
%	0	50.0	65.2	100.0

Source: Applicant's Table 5.1, pg 30, response document

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6.1.4.2 Efficacy in Patients With Hypervolemic Hyponatremia With Heart Failure

6.1.4.2.1 Primary Endpoint

The following table summarizes the findings for the primary endpoint (change from baseline in area under the serum sodium effect curve), for patients in Studies 027 and 080 who had both hypervolemic hyponatremia and congestive heart failure (CHF). For this group of hypervolemic hyponatremic patients with heart failure, conivaptan was effective in raising serum sodium AUC at all doses tested. There was an apparent dose response.

Table 6.1.4.2.1 Baseline-adjusted Area Under the Serum Sodium Effect Curve, Hypervolemic Hyponatremic Patients with Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	4	8	43	5
Mean (SD)	18.4 (117.0)	374.2 (339.8)	522.1 (443.2)	735.3 (207.6)
Min	-123.9	48.0	-302.8	512.1
Median	36.3	287.3	502.9	667.0
Max	125.0	915.0	1361.9	1050.0

Source: Applicant's Table 1.2, pg 13, response document

6.1.4.2.2 Secondary Endpoints

6.1.4.2.2.1 Time from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase from Baseline in Serum Sodium

The percentage of patients achieving a 4 mEq/L increase from baseline in serum sodium increased in a dose-dependent fashion; there was a suggestion of a dose-dependent decrease in time to this event.

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Table 6.1.4.2.2.1 Time (Hours) from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase from Baseline in Serum Sodium, Hypervolemic Hyponatremic Patients with Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N[a]	4	8	43	5
n (%)[b]	1 (25.0)	5 (62.5)	34 (79.1)	5 (100.0)
Median Event Time[c] (95% CI)	NE[d] (NE)	53.8 (NE)	27.5 (24.0, 57.7)	24.0 (23.5, 48.1)

Source: Applicant's Table 2.2, pg 16, response document
a Number of treated patients
b Number of patients who had a confirmed ≥4 mEq/L increase from baseline in serum sodium during the treatment phase; % = n*100/N
c Time from first dose of study medication to a confirmed ≥4 mEq/L increase from baseline in serum sodium.
d Not estimable

6.1.4.2.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients had ≥4 mEq/L Increase from Baseline in Serum Sodium

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.

Table 6.1.4.2.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients Had ≥4 mEq/L Increase from Baseline in Serum Sodium, Hypervolemic Hyponatremic Patients With Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	4	8	43	5
Mean (SD)	7.3 (14.6)	40.3 (39.4)	53.9 (36.0)	77.6 (4.2)
Min	0	0	0	72.2
Median	0	21.0	69.4	79.4
Max	29.1	93.3	93.5	82.2

Source: Applicant's Table 3.2, pg 19, response document

6.1.4.2.2.3 Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment

Absolute serum sodium increased significantly from baseline to Day 4 and to end of treatment in all conivaptan dose groups. There was a suggestion of a dose response.

Table 6.1.4.2.2.3.1: Mean and Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment, All Patients with Hypervolemic Hyponatremia and CHF, Studies 027 and 080

Measure	Pbo N = 4[a] Mean (SD)	20 mg N = 8[b] Mean (SD)	40 mg N = 43[c] Mean (SD)	80 mg N = 5 Mean (SD)
Mean Serum Sodium at Baseline[d]	124.9 (5.2)	123.7 (4.8)	123.7 (5.3)	124.1 (4.3)
Mean Serum Sodium at Day 4[a,b,c]	124.8 (1.3)	130.3 (2.6)	131.7 (6.1)	134.4 (1.8)
Mean Serum Sodium at End of Treatment	125.8 (2.4)	128.9 (4.7)	131.1 (6.4)	134.4 (1.8)

Table 6.1.4.2.2.3.1: Mean and Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment, All Patients with Hypervolemic Hyponatremia and CHF, Studies 027 and 080

Measure	Pbo N = 4[a] Mean (SD)	20 mg N = 8[b] Mean (SD)	40 mg N = 43[c] Mean (SD)	80 mg N = 5 Mean (SD)
Mean Change in Serum Sodium from Baseline to Day 4	1.0 (4.4)	5.3 (3.8)	7.8 (5.3)	10.3 (2.8)
Mean Change in Serum Sodium from Baseline to End of Treatment	0.9 (3.6)	5.2 (3.5)	7.4 (5.4)	10.3 (2.8)

Source: Applicant's Table 4.2.1, pg 24, response document
a At Day 4 of treatment, N = 3
b At Day 4 of treatment, N = 7
c At Day 4 of treatment, N = 40
d Baseline = average of nonmissing serum sodium measurements obtained predose

When examining at each day of treatment, there appears to be a dose response at each of the examined time points. The baseline serum sodium values in this table differ slightly from those in Table 6.1.4.2.2.3.1 above, because in the above table, the applicant used the average of nonmissing predose serum sodium measurements, and in the table below, used the last nonmissing predose serum sodium measurement.

Table 6.1.4.2.2.3.2: Mean and Mean Change in Serum Sodium from Baseline to Hours 24, 48, 72 and 96, All Patients with Hypervolemic Hyponatremia and CHF, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N at Baseline	4	8	43	5
N at Hour 24	4	8	40	5
N at Hour 48	3	7	40	5
N at Hour 72	3	7	38	5
N at Hour 96	3	7	39	5
Mean Serum Sodium at Baseline[1] (SD)	125.8 (6.1)	123.6 (4.7)	124.2 (5.6)	124.6 (4.3)
Mean Serum Sodium at Hour 24 (SD)	125.3 (5.9)	127.6 (4.1)	129.7 (7.1)	135.1 (7.8)
Mean Serum Sodium at Hour 48 (SD)	122.7 (5.9)	129.0 (3.2)	130.0 (6.7)	132.1 (2.5)
Mean Serum Sodium at Hour 72 (SD)	124.7 (2.3)	129.3 (3.5)	131.1 (6.4)	134.1 (2.5)
Mean Serum Sodium at Hour 96 (SD)	126.3 (1.2)	130.6 (3.6)	132.8 (3.6)	135.9 (3.1)
Mean Change from Baseline in Serum Sodium at Hour 24 (SD)	-0.5 (0.6)	4.0 (2.8)	5.3 (5.1)	10.5 (7.3)
Mean Change from Baseline in Serum Sodium at Hour 48 (SD)	-1.3 (0.6)	5.8 (-2.0)	5.6 (5.5)	7.5 (4.0)
Mean Change from Baseline in Serum Sodium at Hour 72 (SD)	0.7 (3.8)	4.6 (5.1)	6.8 (5.2)	9.5 (2.7)
Mean Change from Baseline in Serum Sodium at Hour 96 (SD)	2.3 (4.9)	5.9 (4.8)	8.3 (5.4)	11.3 (2.9)

Source: Applicant's Table 4.2.2, pg 25, response document
1 Baseline = last nonmissing serum sodium measurement before treatment phase

6.1.4.2.2.4 Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment

Among patients with hypervolemic hyponatremia and heart failure, no patients in the placebo group achieved one of these goals. A percentage of patients in each of the conivaptan groups achieved one of these goals. There was an apparent dose response.

Table 6.1.4.2.2.4: Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment, Patients with Hypervolemic Hyponatremia and CHF, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N	4	8	43	5
n	0	3	28	5
%	0	37.5	65.1	100.0

Source: Applicant's Table 5.2, pg 31, response document

6.1.4.3 Efficacy in Patients With Hypervolemic Hyponatremia Without Heart Failure

6.1.4.3.1 Primary Endpoint: Change from Baseline in Area Under the Serum Sodium Effect Curve

The following table summarizes the findings for the primary endpoint (change from baseline in area under the serum sodium effect curve), for patients in Studies 027 and 080 who had hypervolemic hyponatremia but did not have heart failure. For this group of hypervolemic hyponatremic patients without heart failure, conivaptan was effective in raising serum sodium AUC at all doses tested. There was not a clear dose response, although patients at the highest dose (80 mg) had the highest baseline-adjusted serum sodium AUC.

Table 6.1.4.3.1 Baseline-adjusted Area Under the Serum Sodium Effect Curve, Hypervolemic Hyponatremic Patients Without Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	4	6	23	4
Mean (SD)	-168.0 (72.3)	646.6 (413.0)	646.1 (425.0)	877.8 (297.5)
Min	-226.6	302.7	-90.1	495.7
Median	-190.9	518.7	579.4	926.7
Max	-63.6	1377.4	1466.3	1162.0

Source: Applicant's Table 1.3, pg 14, response document

6.1.4.3.2 Secondary Endpoints

6.1.4.3.2.1 Time from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase From Baseline in Serum Sodium

The percentage of patients achieving a 4 mEq/L increase from baseline in serum sodium increased in a dose-dependent fashion; there was a dose-dependent decrease in time to this event.

Table 6.1.4.3.2.1 Time (Hours) from First Dose of Study Medication to a Confirmed ≥4 mEq/L Increase from Baseline in Serum Sodium, Hypervolemic Hyponatremic Patients Without Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N[a]	4	6	23	4
n (%)[b]	0	4 (66.7)	19 (82.6)	4 (100.0)
Median Event Time[c] (95% CI)	NE[d] (NE)	58.5 (NE)	24.0 (12.0, 47.7)	4.5 (4.0, 24.8)

Source: Applicant's Table 2.3, pg 17, response document
a Number of treated patients
b Number of patients who had a confirmed ≥4 mEq/L increase from baseline in serum sodium during the treatment phase; % = n*100/N
c Time from first dose of study medication to a confirmed ≥4 mEq/L increase from baseline in serum sodium.
d Not estimable

6.1.4.3.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients had ≥4 mEq/L Increase from Baseline in Serum Sodium

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.

Table 6.1.4.3.2.2 Time from First Dose of Study Medication to End of Treatment During Which Patients Had ≥4 mEq/L Increase from Baseline in Serum Sodium, Hypervolemic Hyponatremic Patients Without Heart Failure, Intravenous Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
n	4	6	23	4
Mean (SD)	0	46.2 (35.0)	56.7 (35.6)	85.2 (9.3)
Min	0	0	0	73.0
Median	0	53.6	74.8	87.3
Max	0	93.0	93.5	93.0

Source: Applicant's Table 3.3, pg 20, response document

6.1.4.3.2.3 Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment

Absolute serum sodium increased significantly from baseline to Day 4 and to end of treatment in all conivaptan dose groups. There was not a clear dose response.

Table 6.1.4.3.2.3.1: Mean and Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment, All Patients with Hypervolemic Hyponatremia and Without CHF, Studies 027 and 080

Measure	Pbo N = 4[a] Mean (SD)	20 mg N = 6[b] Mean (SD)	40 mg N = 23[c] Mean (SD)	80 mg N = 4 Mean (SD)
Mean Serum Sodium at Baseline[d]	123.5 (4.7)	123.4 (4.7)	123.2 (4.3)	124.6 (4.3)
Mean Serum Sodium at Day 4[a,b,c]	124.3 (0.7)	133.1 (2.2)	130.7 (3.6)	135.2 (1.7)
Mean Serum Sodium at End of Treatment	120.9 (5.4)	133.0 (2.0)	130.9 (3.6)	135.2 (1.7)

Table 6.1.4.3.2.3.1: Mean and Mean Change in Serum Sodium from Baseline to Day 4 and to End of Treatment, All Patients with Hypervolemic Hyponatremia and Without CHF, Studies 027 and 080

Measure	Pbo N = 4[a] Mean (SD)	20 mg N = 6[b] Mean (SD)	40 mg N = 23[c] Mean (SD)	80 mg N = 4 Mean (SD)
Mean Change in Serum Sodium from Baseline to Day 4	-2.5 (2.1)	10.8 (5.2)	7.5 (5.7)	10.6 (3.2)
Mean Change in Serum Sodium from Baseline to End of Treatment	-2.6 (1.9)	9.7 (5.4)	7.6 (5.6)	10.6 (3.2)

Source: Applicant's Table 4.3.1, pg 27, response document
a At Day 4 of treatment, N = 2
b At Day 4 of treatment, N = 5
c At Day 4 of treatment, N = 22
d Baseline = average of nonmissing serum sodium measurements obtained predose

When examining at each day of treatment, there was a suggestion of a dose response for change in mean serum sodium at hours 24 and 48, but not at the other examined time points. The baseline serum sodium values in this table differ slightly from those in Table 6.1.4.3.2.3.1 above, because in the above table, the applicant used the average of nonmissing predose serum sodium measurements, and in the table below, used the last nonmissing predose serum sodium measurement.

Table 6.1.4.3.2.3.2: Mean and Mean Change in Serum Sodium from Baseline to Hours 24, 48, 72 and 96, All Patients with Hypervolemic Hyponatremia and Without CHF, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N at Baseline	4	6	23	4
N at Hour 24	4	5	23	4
N at Hour 48	3	5	23	4
N at Hour 72	2	5	21	4
N at Hour 96	2	5	20	4
Mean Serum Sodium at Baseline[1] (SD)	123.3 (3.7)	124.9 (5.2)	124.8 (4.5)	127.5 (4.4)
Mean Serum Sodium at Hour 24 (SD)	122.0 (4.8)	127.4 (6.2)	129.6 (4.6)	133.5 (5.0)
Mean Serum Sodium at Hour 48 (SD)	119.0 (8.9)	130.1 (2.6)	130.8 (3.5)	135.8 (3.0)
Mean Serum Sodium at Hour 72 (SD)	126.5 (3.5)	133.4 (2.3)	130.6 (4.5)	133.9 (1.7)
Mean Serum Sodium at Hour 96 (SD)	125.5 (0.7)	133.4 (2.7)	131.3 (3.1)	138.0 (2.7)
Mean Change from Baseline in Serum Sodium at Hour 24 (SD)	-1.3 (1.7)	3.2 (4.1)	4.8 (4.9)	6.0 (3.3)
Mean Change from Baseline in Serum Sodium at Hour 48 (SD)	-4.3 (4.9)	5.9 (3.4)	6.1 (4.6)	8.3 (3.6)
Mean Change from Baseline in Serum Sodium at Hour 72 (SD)	1.0 (0)	9.5 (4.5)	5.9 (5.9)	6.3 (3.3)
Mean Change from Baseline in Serum Sodium at Hour 96 (SD)	0.0 (4.2)	9.5 (5.4)	6.1 (5.3)	10.5 (3.3)

Source: Applicant's Table 4.3.2, pg 28, response document
1 Baseline = last nonmissing serum sodium measurement before treatment phase

6.1.4.3.2.4 Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment

Among patients with hypervolemic hyponatremia and without heart failure, no patients in the placebo group achieved one of these goals, while most patients in the conivaptan groups did. There was not a clear dose response.

Table 6.1.4.3.2.4: Number and Percentage of Patients Who Attained a Confirmed ≥6 mEq/L Increase From Baseline in Serum Sodium or a Normal Serum Sodium (≥135 mEq/L) During Treatment, All Patients with Hypervolemic Hyponatremia, Studies 027 and 080

Measure	Pbo	20 mg	40 mg	80 mg
N	4	6	23	4
n	0	4	15	4
%	0	66.7	65.2	100.0

Source: Applicant's Table 5.3, pg 32, response document

6.1.6 Efficacy Conclusions

By multiple efficacy measures, intravenous conivaptan appeared to be effective in the treatment of hypervolemic hyponatremia. This was true for the overall hypervolemic hyponatremic population, and for the subpopulations with and without heart failure.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated review of safety concentrates on the safety of conivaptan when used in the treatment of hypervolemic hyponatremia. The key population of safety concern was that containing hypervolemic hyponatremic patients who also had underlying heart failure. However, this population represents only a fraction of the total population exposed to conivaptan in clinical studies. In the 2nd cycle review, data for 1148 patients exposed to conivaptan had been received. In this submission, there are data for 1284 patients exposed to conivaptan; all of the additional patients received intravenous conivaptan. To date, 581 patients have received IV conivaptan in clinical studies. In this submission, the applicant presents data from an additional 136 patients who received intravenous conivaptan in a non-placebo-controlled hyponatremia trial which had been ongoing at the time of the 2nd cycle review; this trial included both hypervolemic and euvolemic patients. Across the development program (previously presented + newly presented patients) the applicant presented a total of 112 hypervolemic hyponatremic patients who received intravenous conivaptan in any dose. Of these patients, 79 had heart failure. Among the presented hypervolemic hyponatremic patients, a total of 87 received one of the proposed doses for marketing; a total of 58 heart failure patients with hypervolemic hyponatremia 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). Thus, the number of IV conivaptan-treated

hypervolemic hyponatremic heart failure patients with clinically significant hyponatremia is very low. Although the Division of Metabolism and Endocrinology Products (DMEP) had requested additional data from placebo-controlled trials of intravenous conivaptan in the treatment of hypervolemic hyponatremia, none of the new data submitted by the applicant were from placebo-controlled studies. The clinical reviewer has had to examine data from other types of patients in order to attempt to assess the safety of conivaptan for the intended population, and for the subpopulation of concern (heart failure patients with hypervolemic hyponatremia).

Presentation of an organized and coherent safety review presented a challenge, as data for several populations needed separate consideration. These included populations separated by volume status, presence of underlying heart failure, and route of study drug administration. Where data for multiple populations were available, they have been arranged within each section of the safety review in the following order:

- All hypervolemic hyponatremic patients who were treated intravenously
- All hypervolemic hyponatremic patients with underlying heart failure, who were treated intravenously
- All hypervolemic hyponatremic patients without underlying heart failure, who were treated intravenously
- All patients, regardless of volume status or heart failure status, who were treated intravenously
- All patients, regardless of volume status, heart failure status, or route of administration
- All patients with underlying heart failure, regardless of baseline sodium, who were treated intravenously
- All patients with underlying heart failure, regardless of baseline sodium and route of administration

General safety information, and the majority of safety information for heart failure patients, are presented in Sections 7.1-7.5. The Division asked that, in addition to submission of information from the safety findings of its studies, the applicant also submit efficacy data from its heart failure program. These data are presented separately in Section 7.4.2.4.

7.1.1 Deaths

Among hypervolemic hyponatremic patients in intravenous Studies 027, 071 and 080, death did not occur more frequently for conivaptan-treated patients than for placebo-treated patients.

Table 7.1.1.1: Number and Percentage of Hypervolemic Hyponatremic Patients Who Died During Treatment or Within 30 Days After Cessation of Treatment, Studies 027, 071 and 080

Pbo N=14	20 mg N=14	40 mg N=73	80 mg N=15	120 mg N=10	All Coni N=112
1 (7.1)	2 (14.3)	6 (8.2)	1 (6.7)	1 (10.0)	10 (8.9)

Source: Applicant's Table 8.3, pg 66, response document

The following table examines crude mortality for all hypervolemic hyponatremic patients in IV Studies 027 and 080, and all patients in Phase 2/3 heart failure studies. This provides additional information regarding conivaptan and risk of death among hypervolemic patients. Crude mortality was not significantly higher for conivaptan group patients than for placebo group patients. Dose dependence was not demonstrated, although the highest mortality rate was in the highest dose group.

Table 7.1.1.2: Number and Percentage of Patients Who Died, All Patients in Phase 2/3 IV Heart Failure Studies, and Hypervolemic Hyponatremic Patients in IV Hyponatremia Studies 027 and 080

IV Dose	# Deaths/# Patients	Crude Mortality
Pbo	5/111	4.5%
20 mg	3/46	6.5%
40 mg	9/155	5.8%
80 mg	1/62	1.6%
120 mg	4/42	9.5%
Any Coni	17/305	5.6%

Source: Applicant's Table 24, pg 250, response document
Deaths during study drug treatment or within 30 days of cessation of study drug

In the 2nd cycle review, the data suggested a correlation between dose of conivaptan and incidence of death. This signal was of most concern for heart failure patients.

The following table lists the incidence of death for each dose group across all Phase 2/3 studies (oral and IV, hyponatremia and heart failure development programs).

Table 7.1.1.3: Crude Mortality by Dose, All Phase 2/3 Studies[1] (IV and Oral, Hyponatremia and Heart Failure Programs), Oral and IV Doses Presented Separately

Dose Grp	# Deaths/ # Subjects	Crude Mortality[2] (%)
IV Pbo	7/132	5.3
IV 20 mg	3/72	4.2
IV 40 mg	22/340	6.5
IV 80 mg	3/86	3.5
IV 120 mg	4/43	9.3
Oral Pbo	5/240	2.1
Oral 10 mg	1/82	1.2
Oral 20 mg	4/213	1.9

Table 7.1.1.3: Crude Mortality by Dose, All Phase 2/3 Studies[1] (IV and Oral, Hyponatremia and Heart Failure Programs), Oral and IV Doses Presented Separately

Dose Grp	# Deaths/ # Subjects	Crude Mortality[2] (%)
Oral 40 mg	16/274	5.8
Oral 80 mg	5/167	3.0

Source: Applicant's Table 20.1, pg 163, response document
1 Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 071, 080
2 Deaths occurring during study drug treatment or within 30 days after cessation of study drug treatment

The following table includes the same data, but the doses are arranged in order of estimated exposure. On direct comparison, the conivaptan exposure associated with the oral form was approximately 1/3 that associated with the IV form.

Table 7.1.1.4: Crude Mortality by Dose, All Phase 2/3 Studies[1] (IV and Oral, Hyponatremia and Heart Failure Programs), Doses Presented in Order of Approximate Daily Conivaptan Exposure

Dose Grp	Approximate IV-equivalent Exposure (mg)	# Deaths/ # Subjects	Crude Mortality[2] (%)
Oral Pbo	0	5/240	2.1
IV Pbo	0	7/132	5.3
Oral 10 mg	3	1/82	1.2
Oral 20 mg	7	4/213	1.9
Oral 40 mg	13	16/274	5.8
IV 20 mg	20	3/72	4.2
Oral 80 mg	27	5/167	3.0
IV 40 mg	40	22/340	6.5
IV 80 mg	80	3/86	3.5
IV 120 mg	120	4/43	9.3

Source: Applicant's Table 20.2, pg 164, response document
1 Studies 016, 017, 020, 021, 022, 023, 024, 025, 026, 027, 031, 032, 033, 034, 038, 043, 044, 071, 080
2 Deaths occurring during study drug treatment or within 30 days after cessation of study drug treatment

Neither of these tables now suggest an association between conivaptan dose and risk of death.

Death was not more common among heart failure patients who were treated with IV conivaptan than among those who were treated with placebo. In oral conivaptan studies in heart failure patients, there were no placebo group deaths, and there was a total of 7 deaths among conivaptan patients (1.2%). There was no apparent dose response. The following table lists mortality by dose group; doses are listed in order of expected conivaptan exposure (oral ≈ 1/3 IV).

Table 7.1.1.5: Crude Mortality[1] by Dose, All Phase 2/3 Heart Failure Studies

Oral or IV	Dose[2]	#deaths/# patients (%)
Oral	Pbo	0
Combined oral + IV	Pbo	4/290 (1.4)
IV	Pbo	4/103 (3.9)
Oral	5 mg	0

Table 7.1.1.5: Crude Mortality[1] by Dose, All Phase 2/3 Heart Failure Studies

Oral or IV	Dose[2]	#deaths/# patients (%)
Oral	10 mg	1/80 (1.3)
Oral	20 mg	2/187 (1.1)
IV	10 mg	0
Oral	40 mg	2/192 (1.0)
IV	20 mg	1/32 (3.1)
Oral	80 mg	2/102 (2.0)
IV	40 mg	3/89 (3.4)
IV	80 mg	0
IV	120 mg	4 (9.5)
Oral	Any	7/565 (1.2)
Combined oral + IV	Any	15/818 (1.8)
IV	Any	8/253 (3.2)

Source: Applicant's Tables 18 and 19, pgs 161 and 162, response document
1 Deaths which occurred during study drug treatment or within 30 days after cessation of study drug treatment
2 Doses presented in order of expected daily conivaptan exposure (oral ≈ 1/3 IV)

The following table lists the causes of deaths for hypervolemic patients in the IV hyponatremia program studies, and for all patients in heart failure studies.

Table 7.1.1.6: Deaths Listing, Hypervolemic Patients in IV Hyponatremia Studies, and All Patients in Heart Failure Studies

Study	Trtmnt	Pt ID	Age	Gender	Study Day of Death	Preferred Term	Investigator Term
027	IV Pbo	027-0077208	71	m	9	Congestive cardiac failure aggravated	Worsening congestive heart failure
027	IV 40 mg	027-0075806	81	f	3	Hepatic failure, sepsis NOS	Liver failure, gram negative sepsis
027	IV 80 mg	027-0071602	91	m	22	Congestive cardiac failure aggravated, pneumonia NOS	CHF exacerbation, bilateral pneumonia
071	IV 40 mg	071-0070002	69	m	6	Congestive cardiomyopathy	Worsening dilated cardiomyopathy
071	IV 40 mg	071-0070004	78	m	28	Cardiomyopathy NOS	Worsening cardiomyopathy
071	IV 80 mg	071-0040003	47	m	18	Dyspnea exacerbated	Worsening shortness of breath (pt also had end-stage HIV infxn and CHF)
071	IV 80 mg	071-0240008	25	f	5	Sudden cardiac death	Sudden cardiac death, postpartum cardiomyopathy, anomalous left coronary artery
071	IV 80 mg	071-0260002	62	f	2	Ventricular fibrillation	Ventricular fibrillation
071	IV 80 mg	071-0320001	49	m	26	Cardiorespiratory arrest	Cardiopulmonary arrest
080	IV 20 mg	080-0010110	80	f	22	Gastric cancer stage IV with metastases	Progression of metastatic carcinoma of stomach
080	IV 20 mg	080-0010203	76	m	5	Cerebrovascular accident	Suspected CVA
080	IV 40 mg	080-0010003	42	f	27	Multiorgan failure	Multiorgan failure
080	IV 40 mg	080-0010020	57	m	33	Hepatic failure	Hepatic failure

Table 7.1.1.6: Deaths Listing, Hypervolemic Patients in IV Hyponatremia Studies, and All Patients in Heart Failure Studies

Study	Trtmnt	Pt ID	Age	Gender	Study Day of Death	Preferred Term	Investigator Term
080	IV 40 mg	080-0010307	63	m	18	Septic shock	Septic shock
080	IV 40 mg	080-0010501	76	m	13	Multiorgan failure	Multiorgan failure
080	IV 40 mg	080-0020401	67	f	25	Cerebrovascular accident	Unconfirmed cerebrovascular accident
016	Oral 20 mg	016-0000110	81	m	4	Cardiogenic shock	Cardiogenic shock due to ischemia
017	Oral 10 mg	017-0001001	47	f	15	Cardiac arrest	Cardiac arrest
020	Oral 40 mg	020-0021002	58	m	54	Cardiac arrest	Cardiac arrest
020	Oral 40 mg	020-0032008	64	m	60	Cardiac failure NOS	Cardiac failure
032	IV pbo	032-0021004	82	m	6	Ventricular fibrillation	Ventricular fibrillation
032	IV pbo	032-0027003	73	m	23	Cardiac failure chronic	Exacerbation chronic heart failure
032	IV 20 mg	032-0010011	51	m	20	Ischemic cardiomyopathy	Ischemic cardiomyopathy
032	IV 40 mg	032-0010009	54	m	3	Cardiac arrest	Cardiac arrest
034	Oral 20 mg	034-0049020	60	m	50	Sudden death	Sudden death
034	Oral 80 mg	034-0024005	69	m	57	Cerebrovascular accident	Cerebral vascular accident
034	Oral 80 mg	034-0032018	74	m	48	Cardiac arrest	Cardiac arrest
038	IV pbo	038-0002007	44	m	24	Cardiorespiratory arrest	Cardiorespiratory arrest
038	IV pbo	038-0002011	83	f	19	Cardiac failure NOS	Decompensated CHF

Source: Applicant's Listing ADV4LLA.LST, pg 177 and ADV5LA.LST, pg 188, response document

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.

Summaries of narratives for all but one of these patients may be found in the 1st and 2nd cycle clinical reviews. At the end of the 2nd cycle review, Study 080 was still ongoing; one further death occurred. This was a 57 year old man (ID 10020) with hepatocellular carcinoma, hepatic cirrhosis, a history of hepatitis B infection, and diabetes. While hospitalized for cirrhosis, he received 4 days of IV conivaptan, 40 mg/day. Three days after his last dose of conivaptan, he was readmitted to the hospital with abdominal pain and worsening ascites. After multiple

paracenteses, he was released on Study Day 16. He was readmitted on Study Day 25, 21 days after his last dose of conivaptan, for worsening ascites. He was found to have severe hypercalcemia and hyponatremia (serum sodium 120 mEq/L); he died of hepatic failure on Study Day 26, which was 22 days after his last dose of conivaptan. In the clinical reviewer's opinion, the patient's death was likely due to the patient's underlying hepatocellular carcinoma and hepatic failure, and was not due to his conivaptan exposure.

Overall, in these updated data, the incidence of death does not appear to be higher for conivaptan-treated patients than for placebo-treated patients. The signal for a dose-dependent increase in risk of death among conivaptan-treated patients with underlying heart failure is not apparent when including these updated data. However, 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.

7.1.2 Other Serious Adverse Events

Overall, among patients with hypervolemic hyponatremia in Studies 027, 071 and 080, serious adverse events did not occur more commonly among conivaptan-treated patients than among placebo-treated patients.

The following table lists the number and percentage of patients who experienced serious adverse events in those trials.

Table 7.1.2.1 Number and Percentage of Patients with Serious Adverse Events, Patients with Hypervolemic Hyponatremia in IV Studies 027, 071, 080

System Organ Class	Preferred Term	Pbo N=14 n(%)	20 mg N=14 n(%)	40 mg N=73 n(%)	80 mg N=15 n(%)	120 mg N=10 n(%)	Any Coni N=112 n(%)
All Systems	Any AE	4 (28.6)	0	19 (26.0)	4 (26.7)	5 (50.0)	28 (25.0)
Cardiac disorders	Any AE	3 (21.4)	0	7 (9.6)	1 (6.7)	3 (30.0)	11 (9.8)
	Atrial fibrillation	0	0	0	0	1 (10.0)	1 (0.9)
	Atrioventricular block NOS	0	0	1 (1.4)	0	0	1 (0.9)
	Bradyarrhythmia	0	0	1 (1.4)	0	0	1 (0.9)
	Cardiac failure congestive	0	0	1 (1.4)	0	0	1 (0.9)
	Cardiopulmonary failure	1 (7.1)	0	0	0	0	0
	Congestive cardiac failure aggravated	1 (7.1)	0	4 (5.5)	1 (6.7)	0	5 (4.5)
	Ischemic cardiomyopathy	0	0	0	0	1 (10.0)	1 (0.9)
	Myocardial infarction	1 (7.1)	0	0	0	0	0
	Supraventricular arrhythmia NOS	1 (7.1)	0	0	0	0	0
	Ventricular fibrillation	0	0	0	0	1 (10.0)	1 (0.9)
	Ventricular tachycardia	0	0	0	0	1 (10.0)	1 (0.9)
Eye disorders	Any AE	0	0	1 (1.4)	0	0	1 (0.9)
	Glaucoma NOS	0	0	1 (1.4)	0	0	1 (0.9)
Gastrointestinal disorders	Any AE	1 (7.1)	0	1 (1.4)	0	0	1 (0.9)
	Colon gangrene	0	0	1 (1.4)	0	0	1 (0.9)

Table 7.1.2.1 Number and Percentage of Patients with Serious Adverse Events, Patients with Hypervolemic Hyponatremia in IV Studies 027, 071, 080

System Organ Class	Preferred Term	Pbo N=14 n(%)	20 mg N=14 n(%)	40 mg N=73 n(%)	80 mg N=15 n(%)	120 mg N=10 n(%)	Any Coni N=112 n(%)
	Mesenteric occlusion	0	0	1 (1.4)	0	0	1 (0.9)
	Peritonitis	0	0	1 (1.4)	0	0	1 (0.9)
	Upper gastrointestinal hemorrhage	1 (7.1)	0	0	0	0	0
General disorders and administration site conditions	Any AE	1 (7.1)	0	5 (6.8)	0	1 (10.0)	6 (5.4)
	Anasarca	0	0	1 (1.4)	0	0	1 (0.9)
	Asthenia	0	0	2 (2.7)	0	0	2 (1.8)
	Edema NOS	0	0	1 (1.4)	0	0	1 (0.9)
	Impaired healing	0	0	1 (1.4)	0	0	1 (0.9)
	Infusion site phlebitis	0	0	0	0	1 (10.0)	1 (0.9)
	Multiorgan failure	1 (7.1)	0	2 (2.7)	0	0	2 (1.8)
	Systemic inflammatory response syndrome	1 (7.1)	0	0	0	0	0
Hepatobiliary disorders	Any AE	0	0	1 (1.4)	0	0	1 (0.9)
	Hepatic failure	0	0	1 (1.4)	0	0	1 (0.9)
Infections and infestations	Any AE	0	0	5 (6.8)	1 (6.7)	1 (10.0)	7 (6.3)
	Cellulitis	0	0	1 (1.4)	0	0	1 (1.9)
	Pneumonia NOS	0	0	0	1 (6.7)	0	1 (0.9)
	Sepsis NOS	0	0	3 (4.1)	0	1 (10.0)	4 (3.6)
	Urinary tract infection	0	0	1 (1.4)	0	0	1 (0.9)
	Urosepsis	0	0	1 (1.4)	0	0	1 (0.9)
Metabolism and nutrition disorders	Any AE	3 (21.4)	0	3 (4.1)	0	0	3 (2.7)
	Dehydration	0	0	1 (1.4)	0	0	1 (0.9)
	Hyperkalemia	1 (7.1)	0	0	0	0	0
	Hyponatremia	2 (14.3)	0	2 (2.7)	0	0	2 (1.8)
	Hypovolemia	0	0	1 (1.4)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	Any AE	0	0	1 (1.4)	0	0	1 (0.9)
	Musculoskeletal chest pain	0	0	1 (1.4)	0	0	1 (0.9)
Nervous system disorders	Any AE	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
	Cerebrovascular accident	0	0	1 (1.4)	0	1 (10.0)	2 (1.8)
	Epilepsy NOS	0	0	1 (1.4)	0	0	1 (0.9)
Psychiatric disorders	Any AE	0	0	2 (2.7)	0	0	1 (1.8)
	Confusional state	0	0	2 (2.7)	0	0	1 (1.8)
Renal and urinary disorders	Any AE	1 (7.1)	0	0	1 (6.7)	1 (10.0)	2 (1.8)
	Renal failure NOS	1 (7.1)	0	0	0	1 (10.0)	1 (0.9)
	Renal failure acute on chronic	0	0	0	1 (6.7)	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	Any AE	0	0	1 (1.4)	2 (13.3)	0	3 (2.7)
	Pulmonary congestion	0	0	1 (1.4)	1 (6.7)	0	2 (1.8)
	Respiratory failure	0	0	0	1 (6.7)	0	1 (0.9)
Vascular disorders	Any AE	1 (7.1)	0	0	0	0	0
	Hypotension NOS	1 (7.1)	0	0	0	0	0

Source: Applicant's Table 8.2, pg 63, response document

There were few events which occurred in >2 patients, and which occurred more frequently in the conivaptan groups than in the placebo group. The following table summarizes the organ systems and the individual event which met these criteria:

Table 7.1.2.2: Organ Systems and Serious Adverse Events for Which There Were at Least Three Conivaptan Group Patients With Events, and for Which Events Occurred More Frequently Among Conivaptan-treated Patients than Among Placebo-treated Patients, Patients with Hypervolemic Hyponatremia in IV Studies 027, 071, 080

System Organ Class	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=10 n (%)	Any Coni N=112 n (%)
Infections and infestations	Any AE	0	0	5 (6.8)	1 (6.7)	1 (10.0)	7 (6.3)
	Sepsis NOS	0	0	3 (4.1)	0	1 (10.0)	4 (3.6)
Nervous system disorders	Any AE	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
Respiratory, thoracic and mediastinal disorders	Any AE	0	0	1 (1.4)	2 (13.3)	0	3 (2.7)

Source: Applicant's Table 8.2, pg 63, response document

The only individual event which met these criteria was "sepsis NOS". Overall, conivaptan was not associated with an increased risk for serious adverse events compared to placebo.

The applicant also provided an updated summary of all serious adverse events that occurred in all conivaptan trials (hyponatremia and heart failure programs, IV and oral). The types of serious adverse events which occurred with higher frequency among conivaptan-treated patients than among placebo-treated patients were similar to those seen in the 2nd cycle review. A full listing may be found beginning on page 262 of the applicant's Integrated Summary of Safety. The table below includes only those events which occurred with a frequency at least 1% higher in the conivaptan group than in the placebo group.

Table 7.1.2.3: Serious Adverse Events Which Occurred with a Frequency at Least 1% Higher among Conivaptan-treated Patients than among Placebo-treated Patients, All Conivaptan Trials (Hyponatremia and Heart Failure Programs, IV and Oral)

System Organ Class	Preferred Term	Coni N=1284 n(%)	Pbo N=372 n(%)
Any SOC	Any SAE	281 (22)	51 (14)
Cardiac disorders	Any	93 (7)	21 (6)
	Congestive cardiac failure aggravated	26 (2)	3 (<1)
General disorders and administration site conditions	Any	36 (3)	6 (2)
Infections and infestations	Any	52 (4)	7 (2)
Metabolism and nutrition disorders	Any	38 (3)	4 (1)
	Hyponatremia	20 (2)	2 (<1)
Nervous system disorders	Any	29 (2)	1 (<1)
Renal and urinary disorders	Any	26 (2)	4 (1)
Respiratory, thoracic and mediastinal disorders	Any	40 (3)	9 (2)

Source: Applicant's Table 8, beg pg 263, ISS

Overall, 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 ≥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. 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 7.1.2.4: Number and Percentage of Heart Failure Patients with Serious Treatment-emergent Events Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group[1], All Phase 2/3 Heart Failure Studies[2] with Intravenous Conivaptan

System Organ 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 SOC	Any AE	27 (26.2)	5 (13.5)	2 (6.3)	17 (19.1)	15 (28.3)	18 (42.9)	57 (22.5)
Cardiac disorders	Any AE	10 (9.7)	1 (2.7)	1 (3.1)	8 (9.0)	4 (7.5)	9 (21.4)	23 (9.1)
	Cardiomyopathy NOS	0	0	0	2 (2.2)	0	1 (2.4)	3 (1.2)
	Ventricular tachycardia	3 (2.9)	0	0	2 (2.2)	1 (1.9)	2 (4.8)	5 (2.0)
General and administration site conditions	Any AE	4 (3.9)	0	0	3 (3.4)	0	5 (11.9)	8 (3.2)
Infections and infestations	Any AE	6 (5.8)	4 (10.8)	1 (3.1)	2 (2.2)	4 (7.5)	5 (11.9)	16 (6.3)
	Pneumonia NOS	2 (1.9)	0	0	0	1 (1.9)	2 (4.8)	3 (1.2)
	Urinary tract infection NOS	0	1 (2.7)	1 (3.1)	1 (1.1)	1 (1.9)	0	4 (1.6)
Nervous system	Any AE	1 (1.0)	1 (2.7)	0	2 (2.2)	0	1 (2.4)	4 (1.6)
Renal and urinary tract	Any AE	3 (2.9)	0	0	2 (2.2)	1 (1.9)	2 (4.8)	5 (2.0)
Respiratory, mediastinal and thoracic	Any AE	6 (5.8)	1 (2.7)	0	1 (1.1)	8 (15.1)	5 (11.9)	15 (5.9)
	Dyspnea exacerbated	5 (4.9)	0	0	0	3 (5.7)	3 (7.1)	6 (2.4)

Source: Applicant's Table 18, pg 152, response document
1 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
2 Studies 032, 038, 044, 071

For the intravenous heart failure development program 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 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 7.1.2.5: Number and Percentage of Heart Failure Patients with Serious Treatment-emergent Events Which Occurred More Commonly Among Patients in a Conivaptan Group than in the Placebo Group[1], All Phase 2/3 Heart Failure Studies[2] with Oral Conivaptan

System Organ 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 SOC	Any AE	16 (8.6)	0	10 (12.5)	29 (15.5)	18 (9.4)	18 (17.6)	75 (13.3)
Cardiac	Any AE	9 (4.8)	0	5 (6.3)	12 (6.4)	4 (2.1)	2 (2.0)	23 (4.1)
	Angina pectoris	1 (0.5)	0	1 (1.3)	3 (1.6)	0	0	4 (0.7)
	Angina unstable	0	0	2 (2.5)	1 (0.5)	0	0	3 (0.5)
	Cardiac arrest	0	0	1 (1.3)	0	2 (1.0)	1 (1.0)	4 (0.7)
	Congestive cardiac failure aggravated	2 (1.1)	0	1 (1.3)	4 (2.1)	0	0	5 (0.9)
Gastrointestinal	Any AE	0	0	0	4 (2.1)	2 (1.0)	0	6 (1.1)
General and administration site conditions	Any AE	0	0	3 (3.8)	6 (3.2)	1 (0.5)	4 (3.9)	14 (2.5)
	Chest pain	0	0	2 (2.5)	4 (2.1)	1 (0.5)	1 (1.0)	8 (1.4)
Infections and infestations	Any AE	1 (0.5)	0	0	2 (1.1)	3 (1.6)	3 (2.9)	8 (1.4)
Investigations	Any AE	0	0	0	1 (0.5)	2 (1.0)	1 (1.0)	4 (0.7)
Metabolism and nutrition	Any AE	1 (0.5)	0	1 (1.3)	3 (1.6)	1 (0.5)	3 (2.9)	8 (1.4)
	Dehydration	0	0	0	1 (0.5)	0	3 (2.9)	4 (0.7)
Nervous system	Any AE	0	0	0	1 (0.5)	5 (2.6)	4 (3.9)	10 (1.8)
	Syncope	0	0	0	1 (0.5)	3 (1.6)	1 (1.0)	5 (0.9)
Renal and urinary tract	Any AE	0	0	2 (2.5)	1 (0.5)	4 (2.1)	0	7 (1.2)
	Renal failure NOS	0	0	1 (1.3)	1 (0.5)	2 (1.0)	0	4 (0.7)

Source: Applicant's Table 18, pg 155, response document
1 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
2 Studies 016, 017, 020, 024, 033, 034

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.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

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.

Table 7.1.3.1.1: Updated Disposition of Patients and Reasons for Discontinuation, All Conivaptan Studies (Hyponatremia and Heart Failure Programs, Euvolemic and Hypervolemic Patients, Hyponatremia and Eunatremic Patients)

	Reason for Discontinuation	Coni		Pbo	
Patients treated	**n/a**	1148	1284	372	372
Number and percentage of patients who completed treatment	**n/a**	1040 (90.6)	1151 (89.6)	341 (91.7)	341 (91.7)
Number and percentage of patients who discontinued study medication prematurely	**n/a**	147 (12.8)	172 (13.4)	31 (8.3)	31 (8.3)
	Adverse event	68 (5.9)	82 (6.4)	16 (4.3)	16. (4.3)
	Lack of efficacy	13 (1.1)	13 (1.0)	3 (0.8)	3 (0.8)
	Withdrawal of consent	9 (0.8)	14 (1.1)	1 (0.3)	1 (0.3)
	Lost to follow-up	0	0	0	0
	Protocol violation	4 (0.3)	4 (0.3)	2 (0.5)	2 (0.5)
	Lack of compliance	14 (1.2)	14 (1.1)	0	0
	Other/Admin	35 (3.0)	41 (3.2)	9 (2.4)	9 (2.4)
	Satisfactory response	1 (0.1)	1 (0.1)	0	0

Source: Applicant's Table 10, pg 295, ISS

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. All premature discontinuations due to death occurred in conivaptan group patients.

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Table 7.1.3.1.2: Reasons for Discontinuation, All Phase 2/3 Heart Failure Studies[1]

Reason for Discontinuation	Coni (Any Dose) N=818 n (%)	Pbo N=290 n (%)
Any premature discontinuation	68 (8.3)	17 (5.9)
Adverse event	36 (4.4)	10 (3.4)
Lack of efficacy	5 (0.6)	1 (0.3)
Withdrawal of consent	3 (0.4)	1 (0.3)
Lost to follow-up	0	0
Protocol violation	4 (0.5)	2 (0.7)
Patient died	3 (0.4)	0
Lack of compliance	11 (1.3)	0
Other/administrative reasons	6 (0.7)	3 (1.0)
Satisfactory response	0	0

Source: Applicant's Table 11.1, pg 83, response document
1 Includes all patients, regardless of baseline serum sodium status, from Studies 016, 017, 020, 024, 032, 033, 034, 038, 044 and 071; includes both intravenous and oral studies

There is 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.

Table 7.1.3.1.3: Reasons for Discontinuation by Dose Group, All Intravenous Phase 2/3 Heart Failure Studies

Reason for Discontinuation	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 Coni N=253 n (%)
Any premature discontinuation	3 (2.9)	2 (5.4)	0	5 (5.6)	4 (7.5)	9 (21.4)	20 (7.9)
Adverse event	2 (1.9)	0	0	1 (1.1)	3 (5.7)	5 (11.9)	9 (3.6)
Lack of efficacy	1 (1.0)	2 (5.4)	0	1 (1.1)	1 (1.9)	1 (2.4)	5 (2.0)
Withdrawal of consent	0	0	0	1 (1.1)	0	0	1 (0.4)
Lost to follow-up	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Patient died	0	0	0	0	0	0	0
Lack of compliance	0	0	0	1 (1.1)	0	2 (4.8)	3 (1.2)
Other/administrative reason	0	0	0	1 (1.1)	0	2 (4.8)	2 (0.8)
Satisfactory response	0	0	0	0	0	0	0

Source: Applicant's Table 11.2, pg 84, response document

Table 7.1.3.1.4: Reasons for Discontinuation by Dose Group, All Oral Phase 2/3 Heart Failure Studies

Reason for Discontinuation	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 Coni N=565 n (%)
Any premature discontinuation	14 (7.5)	0	4 (5.0)	15 (8.0)	18 (9.4)	11 (10.8)	48 (8.5)
Adverse event	8 (4.3)	0	2 (2.5)	7 (3.7)	12 (6.3)	6 (5.9)	27 (4.8)
Lack of efficacy	0	0	0	0	0	0	0
Withdrawal of consent	1 (0.5)	0	0	2 (1.1)	0	0	2 (0.4)
Lost to follow-up	0	0	0	0	0	0	0

Table 7.1.3.1.4: Reasons for Discontinuation by Dose Group, All Oral Phase 2/3 Heart Failure Studies

Reason for Discontinuation	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 Coni N=565 n (%)
Protocol violation	2 (1.1)	0	1 (1.1)	2 (1.1)	1 (0.5)	0	4 (0.7)
Patient died	0	0	1 (1.3)	0	2 (1.0)	0	3 (0.5)
Lack of compliance	0	0	0	4 (2.1)	2 (1.0)	2 (2.0)	8 (1.4)
Other/administrative reason	3 (1.6)	0	0	0	1 (0.5)	3 (2.9)	4 (0.7)
Satisfactory response	0	0	0	0	0	0	0
Source: Applicant's Table 11.2, pg 85, response document							

7.1.3.2 Adverse events associated with dropouts

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.

Table 7.1.3.2.1: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Withdrawal Among Patients with Hypervolemic Hyponatremia in IV Studies 027, 071, and 080

System Organ Class	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=10 n (%)	All Coni N=112 n (%)
All Systems	Any AE	3 (21.4)	1 (7.1)	4 (5.5)	4 (26.7)	3 (30.0)	12 (10.7)
Cardiac disorders	Any AE	1 (7.1)	0	0	0	1 (10.0)	1 (0.9)
	Congestive cardiac failure aggravated	1 (7.1)	0	0	0	0	0
	Ventricular tachycardia	0	0	0	0	1 (10.0)	1 (0.9)
Gastrointestinal Disorders	Any AE	1 (7.1)	0	0	0	0	0
	Upper gastrointestinal hemorrhage	1 (7.1)	0	0	0	0	0
General disorders and administration site conditions	Any AE	0	0	1 (1.4)	1 (6.7)	2 (20.0)	4 (3.6)
	Infusion related reaction	0	0	0	0	1 (10.0)	1 (0.9)
	Infusion site phlebitis	0	0	1 (1.4)	1 (6.7)	1 (10.0)	3 (2.7)
	Injection site reaction NOS	0	0	0	0	1 (10.0)	1 (0.9)
Infections and infestations	Any AE	0	0	1 (1.4)	0	0	1 (0.9)
	Sepsis NOS	0	0	1 (1.4)	0	0	1 (1.4)
Investigations	Any AE	0	0	0	1 (6.7)	0	1 (0.9)
	Blood creatinine increased	0	0	0	1 (6.7)	0	1 (0.9)
Metabolism and nutrition disorders	Any AE	1 (7.1)	0	1 (1.4)	0	0	1 (0.9)
	Hyponatremia	1 (7.1)	0	1 (1.4)	0	0	1 (0.9)
Nervous system disorders	Any AE	0	1 (7.1)	1 (1.4)	0	0	2 (1.8)

Table 7.1.3.2.1: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Withdrawal Among Patients with Hypervolemic Hyponatremia in IV Studies 027, 071, and 080

System Organ Class	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=10 n (%)	All Coni N=112 n (%)
	Cerebrovascular event	0	1 (7.1)	0	0	0	1 (0.9)
	Epilepsy NOS	0	0	1 (1.4)	0	0	1 (0.9)
Renal and urinary disorders	Any AE	1 (7.1)	0	0	1 (6.7)	0	1 (0.9)
	Renal failure NOS	1 (7.1)	0	0	0	0	0
	Renal failure acute on chronic	0	0	0	1 (6.7)	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	Any AE	0	0	0	1 (6.7)	0	1 (0.9)
	Respiratory failure	0	0	0	1 (6.7)	0	1 (0.9)
Vascular disorders	Any AE	1 (7.1)	1 (7.1)	0	1 (6.7)	0	2 (1.8)
	Hypotension NOS	1 (7.1)	1 (7.1)	0	1 (6.7)	0	2 (1.8)

Source: Applicant's Table 8.1, pg 61, response document

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.

Table 7.1.3.2.2: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Discontinuation, Heart Failure Studies[1] with Intravenous Conivaptan

System Organ Class	Event Leading to D/C	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 SOC	Any AE	3 (2.9)	0	0	3 (3.4)	3 (5.7)	6 (14.3)	12 (4.7)
Cardiac	Any AE	0	0	0	0	0	1 (2.4)	1 (0.4)
	Ventricular tachycardia	0	0	0	0	0	1 (2.4)	1 (0.4)
Gastrointestinal	Any AE	1 (1.0)	0	0	0	0	0	0
	Upper gastrointestinal hemorrhage	1 (1.0)	0	0	0	0	0	0
General and administration site	Any AE	0	0	0	1 (1.1)	0	3 (7.1)	4 (1.6)
	Infusion related reaction	0	0	0	0	0	1 (2.4)	1 (0.4)
	Infusion site phlebitis	0	0	0	1 (1.1)	0	2 (4.8)	3 (1.2)
	Injection site reaction NOS	0	0	0	0	0	1 (2.4)	1 (0.4)
Investigations	Any AE	0	0	0	1 (1.1)	1 (1.9)	0	2 (0.8)
	Blood creatinine increased	0	0	0	0	1 (1.9)	0	1 (0.4)
	Heart rate increased	0	0	0	1 (1.1)	0	0	1 (0.4)
Metabolism and nutrition	Any AE	0	0	0	1 (1.1)	0	2 (4.8)	3 (1.2)

Table 7.1.3.2.2: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Discontinuation, Heart Failure Studies[1] with Intravenous Conivaptan

System Organ Class	Event Leading to D/C	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(%)
	Hypernatremia	0	0	0	1 (1.1)	0	2 (4.8)	3 (1.2)
Renal and urinary	Any AE	0	0	0	0	1 (1.9)	0	1 (0.4)
	Renal failure acute on chronic	0	0	0	0	1 (1.9)	0	1 (0.4)
Respiratory, thoracic and mediastinal	Any AE	0	0	0	0	1 (1.9)	0	1 (0.4)
	Respiratory failure	0	0	0	0	1 (1.9)	0	1 (0.4)
Vascular	Any AE	1 (1.0)	0	0	0	1 (1.9)	0	1 (0.4)
	Hypotension NOS	1 (1.0)	0	0	0	1 (1.9)	0	1 (0.4)

Source: Applicant's Table 16, pg 118, response document

Among all heart failure patients treated orally in Phase 2/3 heart failure studies, discontinuations due to adverse events were more common among conivaptan group patients than among placebo group patients. Those events which led more frequently to discontinuation for conivaptan-treated patients than for placebo-treated patients were somewhat clustered in the cardiac, gastrointestinal, general disorders, and nervous system disorders classes; 20 events in these System Organ Classes (SOCs) led to conivaptan discontinuations, while only 1 event within these SOCs led to a placebo discontinuation. There were also 3 discontinuations due to renal events in the conivaptan groups, and none in the placebo group.

Table 7.1.3.2.3: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Discontinuation, Heart Failure Studies[1] with Oral Conivaptan

System Organ Class	Event Leading to D/C	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 SOC	Any AE	5 (2.7)	0	2 (2.5)	7 (3.7)	11 (5.7)	6 (5.9)	26 (4.6)
Cardiac	Any AE	1 (0.5)	0	1 (1.3)	3 (1.6)	1 (0.5)	1 (1.0)	6 (1.1)
	Angina pectoris	0	0	1 (1.3)	0	0	0	1 (0.2)
	Arrhythmia NOS	0	0	0	1 (0.5)	0	0	1 (0.2)
	Cardiac arrest	0	0	0	0	0	1 (1.0)	1 (0.2)
	Cardiac failure NOS	1 (0.5)	0	0	0	1 (0.5)	0	1 (0.2)
	Congestive cardiac failure aggravated	0	0	0	1 (0.5)	0	0	1 (0.2)
	Ventricular tachycardia	0	0	0	1 (0.5)	0	0	1 (0.2)
Ear and labyrinth	Any AE	1 (0.5)	0	0	0	0	0	0
	Vertigo	1 (0.5)	0	0	0	0	0	0
Gastrointestinal	Any AE	0	0	0	1 (0.5)	2 (1.0)	1 (1.0)	4 (0.7)
	Abdominal pain NOS	0	0	0	1 (0.5)	1 (0.5)	0	2 (0.4)
	Abdominal pain upper	0	0	0	1 (0.5)	0	0	1 (0.2)

Table 7.1.3.2.3: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Discontinuation, Heart Failure Studies[1] with Oral Conivaptan

System Organ Class	Event Leading to D/C	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(%)
	Dyspepsia	0	0	0	0	0	1 (1.0)	1 (0.2)
	Fecal abnormality NOS	0	0	0	0	1 (0.5)	0	1 (0.2)
	Flatulence	0	0	0	0	1 (0.5)	0	1 (0.2)
	Small intestinal obstruction NOS	0	0	0	0	1 (0.5)	0	1 (0.2)
General and administration site	Any AE	0	0	1 (1.3)	2 (1.1)	3 (1.6)	0	6 (1.1)
	Chest pain	0	0	0	1 (0.5)	0	0	1 (0.2)
	Feeling abnormal	0	0	0	0	1 (0.5)	0	1 (0.2)
	Malaise	0	0	0	0	1 (0.5)	0	1 (0.2)
	Mass NOS	0	0	1 (1.3)	0	0	0	1 (0.2)
	Sudden death	0	0	0	1 (0.5)	0	0	1 (0.2)
	Thirst	0	0	0	0	1 (0.5)	0	1 (0.2)
Immune system	Any AE	1 (0.5)	0	0	0	1 (0.5)	0	1 (0.2)
	Drug hypersensitivity	1 (0.5)	0	0	0	0	0	0
	Hypersensitivity NOS	0	0	0	0	1 (0.5)	0	1 (0.2)
Injury, poisoning and procedural complications	Any AE	0	0	0	0	0	1 (1.0)	1 (0.2)
	Head injury	0	0	0	0	0	1 (1.0)	1 (0.2)
Investigations	Any AE	1 (0.5)	0	0	0	0	0	0
	Liver function test abnormal	1 (0.5)	0	0	0	0	0	0
Metabolism and nutrition	Any AE	0	0	0	1 (0.5)	1 (0.5)	0	2 (0.4)
	Appetite decreased NOS	0	0	0	1 (0.5)	0	0	1 (0.2)
	Hyperkalemia	0	0	0	0	1 (0.5)	0	1 (0.2)
Musculoskeletal and connective tissue	Any AE	0	0	0	0	0	1 (1.0)	1 (0.2)
	Myalgia	0	0	0	0	0	1 (1.0)	1 (0.2)
Nervous	Any AE	0	0	0	0	2 (1.0)	2 (2.0)	4 (0.7)
	Cerebrovascular accident	0	0	0	0	0	1 (1.0)	1 (0.2)
	Dizziness	0	0	0	0	1 (0.5)	0	1 (0.2)
	Grand mal convulsion	0	0	0	0	0	1 (1.0)	1 (0.2)
	Headache	0	0	0	0	1 (0.5)	0	1 (0.2)
	Syncope	0	0	0	0	1 (0.5)	0	1 (0.2)
Psychiatric	Any AE	1 (0.5)	0	0	0	0	0	0
	Insomnia	1 (0.5)	0	0	0	0	0	0
Renal and urinary	Any AE	0	0	1 (1.3)	1 (0.5)	1 (0.5)	0	3 (0.5)
	Renal failure NOS	0	0	1 (1.3)	0	1 (0.5)	0	2 (0.4)
	Renal impairment NOS	0	0	0	1 (0.5)	0	0	1 (0.2)
Reproductive and breast	Any AE	0	0	0	0	0	1 (1.0)	1 (0.2)
	Erectile dysfunction NOS	0	0	0	0	0	1 (1.0)	1 (0.2)
Respiratory,	Any AE	0	0	0	0	2 (1.0)	0	2 (0.4)

Table 7.1.3.2.3: Number and Percentage of Patients with Treatment-emergent Adverse Events Leading to Discontinuation, Heart Failure Studies[1] with Oral Conivaptan

System Organ Class	Event Leading to D/C	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(%)
thoracic and mediastinal								
	Dyspnea exacerbated	0	0	0	0	1 (0.5)	0	1 (0.2)
	Nocturnal dyspnea	0	0	0	0	1 (0.5)	0	1 (0.2)
Skin and subcutaneous tissue	Any AE	0	0	0	0	0	1 (1.0)	1 (0.2)
	Rash NOS	0	0	0	0	0	1 (1.0)	1 (0.2)
Vascular	Any AE	0	0	1 (1.3)	0	0	0	1 (0.2)
	Hypotension NOS	0	0	1 (1.3)	0	0	0	1 (0.2)

Source: Applicant's Table 16, pg 120, response document

The following table lists adverse events which led to discontinuation for all conivaptan studies in both development programs. Only events which led to discontinuation for ≥3 conivaptan group patients are included in this summary table. 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.

Table 7.1.3.2.4: Adverse Events Leading to Discontinuation, All Conivaptan Studies (Hyponatremia and Heart Failure Programs, IV and Oral)[1]

System Organ Class	Preferred Term	Coni N=1284 n(%)	Pbo N=372 n(%)
Cardiac disorders	Any	12 (<1)	3 (<1)
	Cardiac failure NOS	3 (<1)	1 (<1)
	Congestive cardiac failure aggravated	3 (<1)	1 (<1)
Gastrointestinal disorders	Any	5 (<1)	2 (<1)
General disorders and administration site conditions	Any	22 (2)	0
	Infusion site phlebitis	12 (<1)	0
Infections and infestations	Any	4 (<1)	0
Investigations	Any	5 (<1)	1 (<1)
Metabolism and nutrition disorders	Any	6 (<1)	1 (<1)
Nervous system disorders	Any	9 (<1)	1 (<1)
	Headache	3 (<1)	0
Renal and urinary disorders	Any	6 (<1)	1 (<1)
	Renal failure NOS	3 (<1)	1 (<1)
Respiratory, thoracic and mediastinal disorders	Any	6 (<1)	0
Vascular disorders	Any	6 (<1)	2 (<1)

Source: Applicant's Table 3, beginning pg 248, ISS
1 Includes events which led to discontinuation for ≥3 conivaptan group patients

7.1.3.3 Other significant adverse events

Included in this section are a series of analyses related to findings in the 2nd cycle review regarding atrial arrhythmia events and heart failure events. Also included and discussed separately are evaluations of prior signals of infusion site reactions, overly rapid rise in serum sodium, bone marrow events and hepatobiliary events.

7.1.3.3.1 Analyses of Atrial Arrhythmia and Cardiac Failure Event Signals Identified in the Second Cycle Review of Conivaptan

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 studies did not include adjudication of heart failure events, and that some 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 its own "Augmented SMQ" which included dyspnea terms.

The following series of tables includes atrial arrhythmia events, and each of the groupings of events potentially related to heart failure. For the category which the applicant calls "Cardiac Failure Events", event selection should be explained. In the 2nd cycle review, the clinical reviewer examined all adverse events that had been reported up to that point, and selected those events which appeared to be specific cardiac failure events, with the objective of more closely examining these types of events for which there was a previous signal. This event listing would not have included all possible MedDRA preferred terms for specific cardiac failure events; it only included terms for events which had already been reported in the conivaptan development program up to that point. For the 3rd cycle review, the applicant has taken that same list for the category "Cardiac Failure Events". If new events had occurred which were classified by a MedDRA term that had not been used in the 2nd cycle review, those events would not appear in these tables. Thus, this may not be a comprehensive group of specific cardiac failure terms. However, the clinical reviewer examined all adverse events which have been reported with this 3rd cycle update, and it does not appear that a significant number of new MedDRA specific cardiac failure terms were used to report new events.

Tables for all hypervolemic hyponatremic patients from IV Studies 027, 071 and 080 are presented first, followed by the heart failure and non-heart-failure subpopulations of hypervolemic hyponatremic patients from these studies.

Table 7.1.3.3.1.1: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Hypervolemic Hyponatremic Patients (IV Studies 027, 071, and 080)

		TREATMENT GROUP (1)					
CLASS	PREFERRED TERM	IV PLACEBO (N=14)	IV 20MG (N=14)	IV 40MG (N=73)	IV 80MG (N=15)	IV 120MG (N=10)	ALL YM087 (N=112)
ALL SYSTEMS	ANY AE	6 (42.9%)	3 (21.4%)	27 (37.0%)	6 (40.0%)	3 (30.0%)	39 (34.8%)
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	1 (7.1%)	2 (2.7%)	0 (0.0%)	1 (10.0%)	4 (3.6%)
	Atrial fibrillation	0 (0.0%)	1 (7.1%)	2 (2.7%)	0 (0.0%)	1 (10.0%)	4 (3.6%)
Cardiac Failure Events	ANY AE	1 (7.1%)	0 (0.0%)	11 (15.1%)	1 (6.7%)	0 (0.0%)	12 (10.7%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (4.1%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Congestive cardiac failure aggravated	1 (7.1%)	0 (0.0%)	6 (8.2%)	1 (6.7%)	0 (0.0%)	7 (6.3%)
Cardiac disorders	ANY AE	5 (35.7%)	3 (21.4%)	19 (26.0%)	3 (20.0%)	3 (30.0%)	28 (25.0%)
	Angina pectoris	1 (7.1%)	0 (0.0%)	1 (1.4%)	1 (6.7%)	0 (0.0%)	2 (1.8%)
	Angina unstable	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Atrial fibrillation	0 (0.0%)	1 (7.1%)	2 (2.7%)	0 (0.0%)	1 (10.0%)	4 (3.6%)
	Atrioventricular block NOS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Atrioventricular block complete	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Atrioventricular block second degree	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Bradyarrhythmia	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Bradycardia NOS	2 (14.3%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (10.0%)	2 (1.8%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (4.1%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiopulmonary failure	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	1 (7.1%)	0 (0.0%)	6 (8.2%)	1 (6.7%)	0 (0.0%)	7 (6.3%)
	Coronary artery occlusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (0.9%)
	Hepatojugular reflux	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Ischaemic cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (0.9%)
	Mitral valve incompetence	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Myocardial infarction	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Myocardial ischaemia	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Palpitations	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Sinus tachycardia	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Supraventricular arrhythmia NOS	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular bigeminy	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	2 (2.7%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
	Ventricular fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (0.9%)
	Ventricular tachycardia	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (6.7%)	1 (10.0%)	3 (2.7%)

(1)Percentage is number of patients with any event per 100 patients in group.
*In 071 Hypervolemic Hyponatremia is defined as baseline serum sodium < 135 mEq/L

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Table 7.1.3.3.1.1 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Hypervolemic Hyponatremic Patients (IV Studies 027, 071, and 080)

CLASS	PREFERRED TERM	TREATMENT GROUP (1) IV PLACEBO (N=14)	IV 20MG (N=14)	IV 40MG (N=73)	IV 80MG (N=15)	IV 120MG (N=10)	ALL YM087 (N=112)
Cardiac failure (SMQ)	ANY AE	1 (7.1%)	0 (0.0%)	9 (12.3%)	1 (6.7%)	1 (10.0%)	11 (9.8%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (4.1%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiopulmonary failure	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (0.9%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	4 (5.5%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	3 (4.1%)	1 (6.7%)	0 (0.0%)	4 (3.6%)
Cardiac failure (Augmented SMQ)	ANY AE	3 (21.4%)	1 (7.1%)	22 (30.1%)	4 (26.7%)	1 (10.0%)	28 (25.0%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (4.1%)	0 (0.0%)	0 (0.0%)	3 (2.7%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
	Cardiopulmonary failure	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	1 (7.1%)	0 (0.0%)	6 (8.2%)	1 (6.7%)	0 (0.0%)	7 (6.3%)
	Dyspnoea	2 (14.3%)	0 (0.0%)	7 (9.6%)	1 (6.7%)	0 (0.0%)	8 (7.1%)
	Dyspnoea exacerbated	0 (0.0%)	1 (7.1%)	4 (5.5%)	1 (6.7%)	0 (0.0%)	6 (5.4%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (0.9%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	4 (5.5%)	0 (0.0%)	0 (0.0%)	4 (3.6%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	3 (4.1%)	1 (6.7%)	0 (0.0%)	4 (3.6%)

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(1) Percentage is number of patients with any event per 100 patients in group.
*In 071 Hypervolemic Hyponatremia is defined as baseline serum sodium < 135 mEq/L

Source: Applicant's Table 7.1, pg 54, response document

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Table 7.1.3.3.1.2: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hypervolemic Hyponatremic Patients With Heart Failure (IV Studies 027, 071, and 080)

(027, 071*, 080)

CLASS	PREFERRED TERM	TREATMENT GROUP (1) IV PLACEBO (N=10)	IV 20MG (N=8)	IV 40MG (N=50)	IV 80MG (N=11)	IV 120MG (N=10)	ALL YM087 (N=79)
ALL SYSTEMS	ANY AE	4 (40.0%)	2 (25.0%)	23 (46.0%)	6 (54.5%)	3 (30.0%)	34 (43.0%)
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	1 (12.5%)	2 (4.0%)	0 (0.0%)	1 (10.0%)	4 (5.1%)
	Atrial fibrillation	0 (0.0%)	1 (12.5%)	2 (4.0%)	0 (0.0%)	1 (10.0%)	4 (5.1%)
Cardiac Failure Events	ANY AE	0 (0.0%)	0 (0.0%)	11 (22.0%)	1 (9.1%)	0 (0.0%)	12 (15.2%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Congestive cardiac failure aggravated	0 (0.0%)	0 (0.0%)	6 (12.0%)	1 (9.1%)	0 (0.0%)	7 (8.9%)
Cardiac disorders	ANY AE	3 (30.0%)	2 (25.0%)	17 (34.0%)	3 (27.3%)	3 (30.0%)	25 (31.6%)
	Angina pectoris	1 (10.0%)	0 (0.0%)	1 (2.0%)	1 (9.1%)	0 (0.0%)	2 (2.5%)
	Angina unstable	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Atrial fibrillation	0 (0.0%)	1 (12.5%)	2 (4.0%)	0 (0.0%)	1 (10.0%)	4 (5.1%)
	Atrioventricular block complete	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Atrioventricular block second degree	2 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Bradyarrhythmia	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Bradycardia NOS	2 (20.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	1 (10.0%)	2 (2.5%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Cardiopulmonary failure	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	0 (0.0%)	0 (0.0%)	6 (12.0%)	1 (9.1%)	0 (0.0%)	7 (8.9%)
	Coronary artery occlusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (1.3%)
	Hepatojugular reflux	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Ischaemic cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (1.3%)
	Myocardial infarction	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Palpitations	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Sinus tachycardia	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Ventricular bigeminy	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Ventricular fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (1.3%)
	Ventricular tachycardia	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (9.1%)	1 (10.0%)	3 (3.8%)
Cardiac failure (SMQ)	ANY AE	1 (10.0%)	0 (0.0%)	8 (16.0%)	1 (9.1%)	1 (10.0%)	10 (12.7%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

(1)Percentage is number of patients with any event per 100 patients in group.
*In 071 Hypervolemic Hyponatremia is defined as baseline serum sodium < 135 mEq/L

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Table 7.1.3.3.1.2 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hypervolemic Hyponatremic Patients With Heart Failure (IV Studies 027, 071, and 080)

		TREATMENT GROUP (1)					
CLASS	PREFERRED TERM	IV PLACEBO (N=10)	IV 20MG (N=8)	IV 40MG (N=50)	IV 80MG (N=11)	IV 120MG (N=10)	ALL YM087 (N=79)
Cardiac failure (SMQ)	Cardiopulmonary failure	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (1.3%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	3 (6.0%)	1 (9.1%)	0 (0.0%)	4 (5.1%)
Cardiac failure (Augmented SMQ)	ANY AE	2 (20.0%)	0 (0.0%)	20 (40.0%)	4 (36.4%)	1 (10.0%)	25 (31.6%)
	Cardiac failure NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Cardiac failure congestive	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Cardiomyopathy NOS	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	Cardiopulmonary failure	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	0 (0.0%)	0 (0.0%)	6 (12.0%)	1 (9.1%)	0 (0.0%)	7 (8.9%)
	Dyspnoea	2 (20.0%)	0 (0.0%)	6 (12.0%)	1 (9.1%)	0 (0.0%)	7 (8.9%)
	Dyspnoea exacerbated	0 (0.0%)	0 (0.0%)	4 (8.0%)	1 (9.1%)	0 (0.0%)	5 (6.3%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (1.3%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	3 (6.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	3 (6.0%)	1 (9.1%)	0 (0.0%)	4 (5.1%)

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(1)Percentage is number of patients with any event per 100 patients in group.
*In 071 Hypervolemic Hyponatremia is defined as baseline serum sodium < 135 mEq/L

Source: Applicant's Table 7.2, pg 56, response document

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Table 7.1.3.3.1.3: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hypervolemic Hyponatremic Patients Without Heart Failure (IV Studies 027, 071, and 080)

CLASS	PREFERRED TERM	TREATMENT GROUP (1) IV PLACEBO (N=4)	IV 20MG (N=6)	IV 40MG (N=23)	IV 80MG (N=4)	ALL YM087 (N=33)
ALL SYSTEMS	ANY AE	2 (50.0%)	1 (16.7%)	4 (17.4%)	0 (0.0%)	5 (15.2%)
Cardiac Failure Events	ANY AE	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	ANY AE	2 (50.0%)	1 (16.7%)	2 (8.7%)	0 (0.0%)	3 (9.1%)
	Atrioventricular block NOS	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
	Congestive cardiac failure aggravated	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mitral valve incompetence	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
	Myocardial ischaemia	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
	Palpitations	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
	Supraventricular arrhythmia NOS	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
Cardiac failure (SMQ)	ANY AE	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
Cardiac failure (Augmented SMQ)	ANY AE	1 (25.0%)	1 (16.7%)	2 (8.7%)	0 (0.0%)	3 (9.1%)
	Congestive cardiac failure aggravated	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Dyspnoea	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)
	Dyspnoea exacerbated	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	1 (3.0%)

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(1) Percentage is number of patients with any event per 100 patients in group.
*In 071 Hypervolemic Hyponatremia is defined as baseline serum sodium < 135 mEq/L

Source: Applicant's Table 7.3, pg 58, response document

The following tables present only those events or term groupings which occurred in at least 3 patients in a treatment group, and occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group. Some terms appear more than once, because they were part of more than one grouping.

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Table 7.1.3.3.1.4: Number and Percentage of Hypervolemic Hyponatremic Patients with Events Within Atrial Arrhythmia and Cardiac Failure Event Term Groupings; Events Which Occurred in at Least 3 Patients in Any Group, and Which Occurred with a Frequency at Least 1% Greater in a Conivaptan Group than in the Placebo Group; Intravenous Studies 027, 071, and 080

Event Term Grouping	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=10 n (%)	Any Coni Dose N=112 n (%)
Atrial arrhythmia events	Any AE	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
	Atrial fibrillation	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
Specific cardiac failure event terms	Any AE	1 (7.1)	0	11 (15.1)	1 (6.7)	0	12 (10.7)
	Cardiac failure NOS	0	0	3 (4.1)	0	0	3 (2.7)
	Congestive cardiac failure aggravated	1 (7.1)	0	6 (8.2)	1 (6.7)	0	7 (6.3)
Cardiac disorders SOC	Any AE	5 (35.7)	3 (21.4)	19 (26.0)	3 (20.0)	3 (30.0)	28 (25.0)
	Atrial fibrillation	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
	Cardiac failure NOS	0	0	3 (4.1)	0	0	3 (2.7)
	Congestive cardiac failure aggravated	1 (7.1)	0	6 (8.2)	1 (6.7)	0	7 (6.3)
	Ventricular tachycardia	0	0	1 (1.4)	1 (6.7)	1 (10.0)	3 (2.7)
Cardiac failure SMQ	Any AE	1 (7.1)	0	9 (12.3)	1 (6.7)	1 (10.0)	11 (9.8)
	Cardiac failure NOS	0	0	3 (4.1)	0	0	3 (2.7)
	Edema NOS	0	0	4 (5.5)	0	0	4 (3.6)
	Pulmonary congestion	0	0	3 (4.1)	1 (6.7)	0	4 (3.6)
Cardiac failure "augmented" SMQ	Any AE	3 (21.4)	1 (7.1)	22 (30.1)	4 (26.7)	1 (10.0)	28 (25.0)
	Cardiac failure NOS	0	0	3 (4.1)	0	0	3 (2.7)
	Congestive cardiac failure aggravated	1 (7.1)	0	6 (8.2)	1 (6.7)	0	7 (6.3)
	Dyspnea exacerbated	0	1 (7.1)	4 (5.5)	1 (6.7)	0	6 (5.4)
	Edema NOS	0	0	4 (5.5)	0	0	4 (3.6)
	Pulmonary congestion	0	0	3 (4.1)	1 (6.7)	0	4 (3.6)

Source: Applicant's Table 7.1, pg 54, response document

Table 7.1.3.3.1.5: Number and Percentage of Hypervolemic Hyponatremic Heart Failure Patients with Events Within Atrial Arrhythmia and Cardiac Failure Event Term Groupings; Events Which Occurred in at Least 3 Patients in Any Group, and Which Occurred with a Frequency at Least 1% Greater in a Conivaptan Group than in the Placebo Group; Intravenous Studies 027, 071, and 080

Event Term Grouping	Preferred Term	Pbo N=10 n (%)	20mg N=8 n (%)	40mg N=50 n (%)	80mg N=11 n (%)	120mg N=10 n (%)	Any Coni Dose N=79 n (%)
Atrial arrhythmia events	Any AE	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
	Atrial fibrillation	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
Specific cardiac failure event terms	Any AE	0	0	11 (22.0)	1 (9.1)	0	12 (15.2)
	Cardiac failure NOS	0	0	3 (6.0)	0	0	3 (3.8)

Table 7.1.3.3.1.5: Number and Percentage of Hypervolemic Hyponatremic Heart Failure Patients with Events Within Atrial Arrhythmia and Cardiac Failure Event Term Groupings; Events Which Occurred in at Least 3 Patients in Any Group, and Which Occurred with a Frequency at Least 1% Greater in a Conivaptan Group than in the Placebo Group; Intravenous Studies 027, 071, and 080

Event Term Grouping	Preferred Term	Pbo N=10 n (%)	20mg N=8 n (%)	40mg N=50 n (%)	80mg N=11 n (%)	120mg N=10 n (%)	Any Coni Dose N=79 n (%)
	Congestive cardiac failure aggravated	0	0	6 (12.0)	1 (9.1)	0	7 (8.9)
Cardiac disorders SOC	Any AE	3 (10.0)	2 (25.0)	17 (34.0)	3 (27.3)	3 (30.0)	25 (31.6)
	Atrial fibrillation	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
	Cardiac failure NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Congestive cardiac failure aggravated	0	0	6 (12.0)	1 (9.1)	0	7 (8.9)
	Ventricular tachycardia	0	0	1 (2.0)	1 (9.1)	1 (10.0)	3 (3.8)
Cardiac failure SMQ	Any AE	1 (10.0)	0	8 (16.0)	1 (9.1)	1 (10.0)	10 (12.7)
	Cardiac failure NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Edema NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Pulmonary congestion	0	0	3 (6.0)	1 (9.1)	0	4 (5.1)
Cardiac failure "augmented" SMQ	Any AE	2 (20.0)	0	20 (40.0)	4 (36.4)	1 (10.0)	25 (31.6)
	Cardiac failure NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Congestive cardiac failure aggravated	0	0	6 (12.0)	1 (9.1)	0	7 (8.9)
	Dyspnea exacerbated	0	0	4 (8.0)	1 (9.1)	0	5 (6.3)
	Edema NOS	0	0	3 (6.0)	0	0	3 (6.8)
	Pulmonary congestion	0	0	3 (6.0)	1 (9.1)	0	4 (5.1)

Source: Applicant's Table 7.2, pg 56, response document

Among hypervolemic hyponatremic patients without heart failure, there were no atrial arrhythmia or heart failure events or event groupings which met the criteria of occurring in at least 3 patients in any conivaptan group and at a frequency at least 1% greater for a conivaptan group than for the placebo group.

When considering all hypervolemic hyponatremic patients in these studies, 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 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.

The applicant also provided tables for heart failure events for all patients with underlying heart failure in all Phase 2/3 studies (both the hyponatremia and heart failure programs). These studies include patients with and without hyponatremia. Tables for IV and oral studies are presented separately.

Table 7.1.3.3.1.6: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 IV Studies (Hyponatremia and Heart Failure Programs)

		TREATMENT GROUP (1)															
		IV PLACEBO (N=103)		IV 10MG (N=37)		IV 20MG (N=32)		IV 40MG (N=89)		IV 80MG (N=53)		IV 120MG (N=42)		ALL IV YHOST (N=253)	
CLASS	PREFERRED TERM														
Atrial Arrhythmia Events	ANY AE	0	0.0%	0	0.0%	1	3.1%	3	3.4%	2	3.8%	4	9.5%	10	4.0%
	Atrial fibrillation	0	0.0%	0	0.0%	0	0.0%	3	3.4%	2	3.8%	1	2.4%	6	2.4%
	Atrial flutter	0	0.0%	0	0.0%	1	3.1%	0	0.0%	1	1.9%	3	7.1%	5	2.0%
Cardiac Failure Events	ANY AE	2	1.9%	1	2.7%	1	3.1%	4	4.5%	1	1.9%	1	2.4%	8	3.2%
	Cardiac failure NOS	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Cardiac failure acute	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Cardiac failure chronic	1	1.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	2.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	2	2.2%	0	0.0%	1	2.4%	3	1.2%
	Congestive cardiac failure aggravated	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
Cardiac disorders	ANY AE	22	21.4%	2	5.4%	4	12.5%	14	15.7%	12	22.6%	13	31.0%	45	17.8%
	Angina pectoris	2	1.9%	0	0.0%	0	0.0%	2	2.2%	1	1.9%	1	2.4%	4	1.6%
	Angina unstable	2	1.9%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Atrial fibrillation	0	0.0%	0	0.0%	0	0.0%	3	3.4%	2	3.8%	1	2.4%	6	2.4%
	Atrial flutter	0	0.0%	0	0.0%	1	3.1%	0	0.0%	1	1.9%	3	7.1%	5	2.0%
	Atrial thrombosis	0	0.0%	0	0.0%	0	0.0%	2	2.2%	0	0.0%	0	0.0%	2	0.8%
	Atrioventricular block complete	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Atrioventricular block second degree	2	1.9%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Bradycardia NOS	6	5.8%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Cardiac arrest	0	0.0%	0	0.0%	0	0.0%	2	2.2%	0	0.0%	0	0.0%	2	0.8%
	Cardiac failure NOS	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Cardiac failure acute	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Cardiac failure chronic	1	1.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	2.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Cardio-respiratory arrest	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	2	2.2%	0	0.0%	1	2.4%	3	1.2%
	Cardiopulmonary failure	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Congestive cardiac failure aggravated	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%

(1)Percentage is number of patients with any event per 100 patients in group.

Table 7.1.3.3.1.6 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 IV Studies (Hyponatremia and Heart Failure Programs)

		TREATMENT GROUP (1)											
		IV PLACEBO (N=103)		IV 10MG (N=37)		IV 20MG (N=32)		IV 40MG (N=89)		IV 80MG (N=53)		IV 120MG (N=42)		ALL IV YM087 (N=253)	
CLASS	PREFERRED TERM														
Cardiac disorders	Coronary artery disease aggravated	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Coronary artery occlusion	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Ischaemic cardiomyopathy	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	1	2.4%	2	0.8%
	Mitral valve incompetence	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Myocardial infarction	1	1.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Palpitations	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Sick sinus syndrome	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Sinus bradycardia	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Sinus tachycardia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Ventricular bigeminy	1	1.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Ventricular extrasystoles	0	0.0%	0	0.0%	0	0.0%	1	1.1%	1	1.9%	0	0.0%	2	0.8%
	Ventricular fibrillation	1	1.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	1	2.4%	2	0.8%
	Ventricular tachycardia	10	9.7%	1	2.7%	0	0.0%	3	3.4%	6	11.3%	4	9.5%	14	5.5%
Cardiac failure (SMQ)	ANY AE	5	4.9%	2	5.4%	0	0.0%	5	5.6%	4	7.5%	5	11.9%	16	6.3%
	Cardiac failure NOS	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Cardiac failure acute	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Cardiac failure chronic	1	1.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	2.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Cardiac index decreased	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiopulmonary failure	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Heart transplant rejection	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Oedema NOS	0	0.0%	1	2.7%	0	0.0%	2	2.2%	0	0.0%	0	0.0%	3	1.2%
	Pulmonary congestion	2	1.9%	0	0.0%	0	0.0%	1	1.1%	2	3.8%	2	4.8%	5	2.0%
	Pulmonary oedema NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	2	4.8%	3	1.2%
Cardiac failure (Augmented SMQ)	ANY AE	15	14.6%	2	5.4%	1	3.1%	15	16.9%	15	28.3%	13	31.0%	46	18.2%
	Cardiac failure NOS	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Cardiac failure acute	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	0	0.0%	1	0.4%
	Cardiac failure chronic	1	1.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiac failure congestive	0	0.0%	1	2.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Cardiac index decreased	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Cardiomyopathy NOS	0	0.0%	0	0.0%	0	0.0%	2	2.2%	0	0.0%	1	2.4%	3	1.2%
	Cardiopulmonary failure	1	1.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

(1)Percentage is number of patients with any event per 100 patients in group.

Table 7.1.3.3.1.6 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 IV Studies (Hyponatremia and Heart Failure Programs)

		TREATMENT GROUP (1)											
		IV PLACEBO (N=103)		IV 10MG (N=37)		IV 20MG (N=32)		IV 40MG (N=89)		IV 80MG (N=53)		IV 120MG (N=42)		ALL IV YM087 (N=253)	
CLASS	PREFERRED TERM														
Cardiac failure (Augmented SMQ)	Congestive cardiac failure aggravated	0	0.0%	0	0.0%	1	3.1%	0	0.0%	0	0.0%	0	0.0%	1	0.4%
	Congestive cardiomyopathy	0	0.0%	0	0.0%	0	0.0%	1	1.1%	0	0.0%	0	0.0%	1	0.4%
	Dyspnoea	6	5.8%	0	0.0%	0	0.0%	2	2.2%	2	3.8%	0	0.0%	4	1.6%
	Dyspnoea exacerbated	8	7.8%	0	0.0%	0	0.0%	8	9.0%	10	18.9%	8	19.0%	26	10.3%
	Heart transplant rejection	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	2.4%	1	0.4%
	Oedema NOS	0	0.0%	1	2.7%	0	0.0%	2	2.2%	0	0.0%	0	0.0%	3	1.2%
	Pulmonary congestion	2	1.9%	0	0.0%	0	0.0%	1	1.1%	2	3.8%	2	4.8%	5	2.0%
	Pulmonary oedema NOS	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.9%	2	4.8%	3	1.2%

Source: Applicant's Table 17.1, beg pg 122, response document

Table 7.1.3.3.1.7: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 Oral Studies (Hyponatremia and Heart Failure Programs)

		TREATMENT GROUP (1)											
CLASS	PREFERRED TERM	ORAL PLACEBO (N=187)		ORAL 5MG (N=4)		ORAL 10MG (N=80)		ORAL 20MG (N=187)		ORAL 40MG (N=192)		ORAL 80MG (N=102)		ALL ORAL YM087 (N=565)	
Atrial Arrhythmia Events	ANY AE	1	0.5%	0	0.0%	1	1.3%	4	2.1%	6	3.1%	0	0.0%	11	1.9%
	Atrial fibrillation	1	0.5%	0	0.0%	0	0.0%	4	2.1%	4	2.1%	0	0.0%	8	1.4%
	Atrial flutter	0	0.0%	0	0.0%	1	1.3%	0	0.0%	3	1.6%	0	0.0%	4	0.7%
Cardiac Failure Events	ANY AE	11	5.9%	1	25.0%	4	5.0%	9	4.8%	8	4.2%	4	3.9%	26	4.6%
	Cardiac failure NOS	3	1.6%	0	0.0%	2	2.5%	1	0.5%	1	0.5%	0	0.0%	4	0.7%
	Cardiac failure congestive	1	0.5%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	1.0%	2	0.4%
	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%
Cardiac disorders	ANY AE	26	13.9%	1	25.0%	15	18.8%	25	13.4%	22	11.5%	10	9.8%	73	12.9%
	Acute coronary syndrome	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Angina pectoris	2	1.1%	0	0.0%	4	5.0%	6	3.2%	1	0.5%	1	1.0%	12	2.1%
	Angina unstable	0	0.0%	0	0.0%	2	2.5%	1	0.5%	0	0.0%	0	0.0%	3	0.5%
	Arrhythmia NOS	0	0.0%	0	0.0%	1	1.3%	1	0.5%	0	0.0%	1	1.0%	3	0.5%
	Atrial fibrillation	1	0.5%	0	0.0%	0	0.0%	4	2.1%	4	2.1%	0	0.0%	8	1.4%
	Atrial flutter	0	0.0%	0	0.0%	1	1.3%	0	0.0%	3	1.6%	0	0.0%	4	0.7%
	Atrioventricular block complete	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	0.2%
	Atrioventricular block first degree	3	1.6%	0	0.0%	1	1.3%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	Bradycardia NOS	2	1.1%	0	0.0%	3	3.8%	1	0.5%	3	1.6%	1	1.0%	8	1.4%
	Bundle branch block left	1	0.5%	0	0.0%	1	1.3%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
	Cardiac arrest	0	0.0%	0	0.0%	1	1.3%	0	0.0%	2	1.0%	1	1.0%	4	0.7%
	Cardiac failure NOS	3	1.6%	0	0.0%	2	2.5%	1	0.5%	1	0.5%	0	0.0%	4	0.7%
	Cardiac failure congestive	1	0.5%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	1.0%	2	0.4%
	Cardiogenic shock	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%	1	0.2%
	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%
	Coronary artery disease NOS	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	0	0.0%	1	0.2%
	Mitral valve incompetence	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Myocardial infarction	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Palpitations	2	1.1%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	1.0%	2	0.4%
	Sinus arrhythmia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	0.2%
	Sinus bradycardia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	0.2%

(1)Percentage is number of patients with any event per 100 patients in group.

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Table 7.1.3.3.1.7 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 Oral Studies (Hyponatremia and Heart Failure Programs)

GROUP=ORAL

CLASS	PREFERRED TERM	TREATMENT GROUP (1) ORAL PLACEBO (N=187)	ORAL 5MG (N=4)	ORAL 10MG (N=80)	ORAL 20MG (N=187)	ORAL 40MG (N=192)	ORAL 80MG (N=102)	ALL ORAL YM087 (N=565)
Cardiac disorders	Supraventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Supraventricular tachycardia	1 (0.5%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Tachycardia NOS	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	Ventricular arrhythmia NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Ventricular bigeminy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.2%)
	Ventricular extrasystoles	1 (0.5%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
	Ventricular fibrillation	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular tachycardia	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	3 (0.5%)
Cardiac failure (SMQ)	ANY AE	7 (3.7%)	0 (0.0%)	3 (3.8%)	8 (4.3%)	8 (4.2%)	5 (4.9%)	24 (4.2%)
	Acute pulmonary oedema	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiac failure NOS	3 (1.6%)	0 (0.0%)	2 (2.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	4 (0.7%)
	Cardiac failure congestive	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	Cardiogenic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Central venous pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Dyspnoea paroxysmal nocturnal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	Nocturnal dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Oedema NOS	1 (0.5%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (1.0%)	2 (2.0%)	5 (0.9%)
	Pulmonary congestion	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (1.0%)	2 (0.4%)
	Pulmonary oedema NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Venous pressure jugular increased	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (1.6%)	2 (1.0%)	0 (0.0%)	5 (0.9%)
Cardiac failure (Augmented SMQ)	ANY AE	23 (12.3%)	1 (25.0%)	10 (12.5%)	26 (13.9%)	27 (14.1%)	13 (12.7%)	77 (13.6%)
	Acute pulmonary oedema	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiac failure NOS	3 (1.6%)	0 (0.0%)	2 (2.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	4 (0.7%)
	Cardiac failure congestive	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	Cardiogenic shock	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Central venous pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	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%)

(1)Percentage is number of patients with any event per 100 patients in group.

Table 7.1.3.3.1.7 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, All Heart Failure Patients in all Phase 2/3 Oral Studies (Hyponatremia and Heart Failure Programs)

GROUP=ORAL

CLASS	PREFERRED TERM	TREATMENT GROUP (1) ORAL PLACEBO (N=187)	ORAL 5MG (N=4)	ORAL 10MG (N=80)	ORAL 20MG (N=187)	ORAL 40MG (N=192)	ORAL 80MG (N=102)	ALL ORAL YM087 (N=565)
Cardiac failure (Augmented SMQ)	Dyspnoea	3 (1.6%)	0 (0.0%)	4 (5.0%)	5 (2.7%)	2 (1.0%)	2 (2.0%)	13 (2.3%)
	Dyspnoea exacerbated	6 (3.2%)	0 (0.0%)	2 (2.5%)	7 (3.7%)	11 (5.7%)	3 (2.9%)	23 (4.1%)
	Dyspnoea paroxysmal nocturnal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	Nocturnal dyspnoea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Oedema NOS	1 (0.5%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	2 (1.0%)	2 (2.0%)	5 (0.9%)
	Pulmonary congestion	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (1.0%)	2 (0.4%)
	Pulmonary oedema NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
	Venous pressure jugular increased	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (1.6%)	2 (1.0%)	0 (0.0%)	5 (0.9%)

Source: Applicant's Table 17.2, beg pg 128, response document

The following tables, also for the heart failure IND studies, present only those events or term groupings which occurred in at least 3 patients in a treatment group, and which occurred with a

frequency at least 1% higher in a conivaptan group than in the placebo group. Some terms appear more than once, because they were part of more than one grouping. Intravenous and oral studies are presented separately.

Table 7.1.3.3.1.8: Number and Percentage of Heart Failure Patients with Events Within Atrial Arrhythmia and Cardiac Failure Event Term Groupings; Events Which Occurred in at Least 3 Patients in Any Group, and Which Occurred with a Frequency at Least 1% Greater in a Conivaptan Group than in the Placebo Group; Heart Failure Intravenous Studies 032, 038, 044 and 071

Event Term Grouping	Preferred Term	Pbo N=103 n(%)	10mg N=37 n(%)	20mg N=32 n(%)	40mg N=89 n(%)	80mg N=53 n(%)	120mg N=42 n(%)	Any Coni Dose N=253 n (%)
Atrial arrhythmia events	Any AE	0	0	1 (3.1)	3 (3.4)	2 (3.8)	4 (9.5)	10 (4.0)
	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)
Specific cardiac failure event terms	Any AE	2 (1.9)	1 (2.7)	1 (3.1)	4 (4.5)	1 (1.9)	1 (2.4)	8 (3.2)
	Cardiomyopathy NOS	0	0	0	2 (2.2)	0	1 (2.4)	3 (1.2)
Cardiac disorders SOC	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)
Cardiac failure SMQ	Any AE	5 (4.9)	2 (5.4)	0	5 (5.6)	4 (7.5)	5 (11.9)	16 (6.3)
	Edema NOS	0	1 (2.7)	0	2 (2.2)	0	0	3 (1.2)
	Pulmonary congestion	2 (1.9)	0	0	1 (1.1)	2 (3.8)	2 (4.8)	5 (2.0)
	Pulmonary edema NOS	0	0	0	0	1 (1.9)	2 (4.8)	3 (1.2)
Cardiac failure "augmented" SMQ	Any AE	15 (14.6)	2 (5.4)	1 (3.1)	15 (16.9)	15 (28.3)	13 (31.0)	46 (18.2)
	Cardiomyopathy NOS	0	0	0	2 (2.2)	0	1 (2.4)	3 (1.2)
	Dyspnea	6 (5.8)	0	0	2 (2.2)	2 (3.8)	0	4 (1.6)
	Dyspnea exacerbated	8 (7.8)	0	0	8 (9.0)	10 (18.9)	8 (19.0)	26 (10.3)
	Edema NOS	0	1 (2.7)	0	2 (2.2)	0	0	3 (1.2)
	Pulmonary congestion	2 (1.9)	0	0	1 (1.1)	2 (3.8)	2 (4.8)	5 (2.0)
	Pulmonary edema NOS	0	0	0	0	1 (1.9)	2 (4.8)	3 (1.2)

Source: Applicant's Table 17.1, pg 122, response document

When considering patients from intravenous studies in the heart failure development program, for these adverse event term groupings of interest, 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.

Table 7.1.3.3.1.9: Number and Percentage of Heart Failure Patients with Events Within Atrial Arrhythmia and Cardiac Failure Event Term Groupings; Events Which Occurred in at Least 3 Patients in Any Group, and Which Occurred with a Frequency at Least 1% Greater in a Conivaptan Group than in the Placebo Group; Heart Failure Oral Studies 016, 017, 020, 024, 033 and 034

Event Term Grouping	Preferred Term	Pbo N=187 n(%)	5mg N=4 n(%)	10mg N=80 n(%)	20mg N=187 n(%)	40mg N=192 n(%)	80mg N=102 n(%)	Any Coni Dose N=565 n(%)
Atrial arrhythmia events	Any AE	1 (0.5)	0	1 (1.3)	4 (2.1)	6 (3.1)	0	11 (1.9)
	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)
Specific cardiac failure event terms	Any AE	11 (5.9)	1 (25.0)	4 (5.0)	9 (4.8)	8 (4.2)	4 (3.9)	26 (4.6)
	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)
Cardiac disorders SOC	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)
	Angina unstable	0	0	2 (2.5)	1 (0.5)	0	0	3 (0.5)
	Arrhythmia NOS	0	0	1 (1.3)	1 (0.5)	0	1 (1.0)	3 (0.5)
	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 NOS	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)
Cardiac failure SMQ	Any AE	7 (3.7)	0	3 (3.8)	8 (4.3)	8 (4.2)	5 (4.2)	24 (4.2)
	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)
	Edema NOS	1 (0.5)	0	1 (1.3)	0	2 (1.0)	2 (2.0)	5 (0.9)
	Venous pressure jugular increased	1 (0.5)	0	0	3 (1.6)	2 (1.0)	0	5 (0.9)
Cardiac failure "augmented" SMQ	Any AE	23 (12.3)	1 (25.0)	10 (12.5)	26 (13.9)	27 (14.1)	13 (12.7)	77 (13.6)
	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)
	Dyspnea	3 (1.6)	0	4 (5.0)	5 (2.7)	2 (1.0)	2 (2.0)	13 (2.3)
	Dyspnea exacerbated	6 (3.2)	0	2 (2.5)	7 (3.7)	11 (5.7)	3 (2.9)	23 (4.1)
	Edema NOS	1 (0.5)	0	1 (1.3)	0	2 (1.0)	2 (2.0)	5 (0.9)
	Venous pressure jugular increased	1 (0.5)	0	0	3 (1.6)	2 (1.0)	0	5 (0.9)

Source: Applicant's Table 17.1, pg 122, response document

When considering patients from oral studies in the heart failure development program, for these adverse event term groupings of interest, conivaptan-treated patients (compared to placebo-treated patients) had a higher numerical frequency of events within the applicant's cardiac failure event "Augmented Cardiac Failure SMQ" grouping, but not in the specific cardiac failure events grouping or the MedDRA Cardiac Failure SMQ. Conivaptan-treated patients did not have a higher numerical frequency of events within the overall cardiac disorders SOC. A dose response was not suggested by the data. Of the 565 patients in oral heart failure studies, 530 (94%) were from placebo-controlled studies. When considering only controlled oral heart failure studies, results were very similar (Applicant's Table 17.4, pg 149, response document).

For atrial arrhythmia events, 11/12 events occurred in conivaptan-treated patients, with 1 event in the placebo group.

The higher frequency (conivaptan vs placebo) of cardiac failure events which is seen in heart failure patients treated with intravenous conivaptan, in the hyponatremia development program studies and separately in the heart failure development programs studies, is of clinical concern. It is of interest that this difference between conivaptan and placebo for heart failure events was less evident among heart failure patients treated with oral conivaptan in the heart failure development program. The reason for this difference is unknown, but could be related to the significantly lower conivaptan exposure for the oral drug. This possibility is also supported by the suggestion of a dose response for the "MedDRA Cardiac Failure SMQ" and the applicant's "Augment Cardiac Failure SMQ" for the intravenous studies in the heart failure development program.

The following table, also examining atrial arrhythmias and cardiac failure events, includes only hyponatremic patients from intravenous heart failure studies. It does not include data from hyponatremic patients with underlying heart failure who were in the hyponatremia development program intravenous Studies 027 and 080.

Table 7.1.3.3.1.10: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hyponatremic Patients From Heart Failure IND IV Studies (032, 038, 044, 071)

		TREATMENT GROUP (1)						
CLASS	PREFERRED TERM	IV PLACEBO (N=12)	IV 10MG (N=6)	IV 20MG (N=2)	IV 40MG (N=16)	IV 80MG (N=11)	IV 120MG (N=10)	ALL IV YM087 (N=45)
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Atrial fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
Cardiac Failure Events	ANY AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Cardiac failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
Cardiac disorders	ANY AE	3 (25.0%)	1 (16.7%)	0 (0.0%)	2 (12.5%)	4 (36.4%)	3 (30.0%)	10 (22.2%)
	Angina pectoris	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (9.1%)	0 (0.0%)	2 (4.4%)
	Atrial fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Atrioventricular block complete	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Atrioventricular block second degree	2 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Bradycardia NOS	2 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Cardiac failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Cardiopulmonary failure	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Coronary artery occlusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Ischaemic cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Myocardial infarction	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Palpitations	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular bigeminy	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
	Ventricular fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Ventricular tachycardia	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (10.0%)	3 (6.7%)
Cardiac failure (SMQ)	ANY AE	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	2 (18.2%)	1 (10.0%)	4 (8.9%)
	Cardiac failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Cardiopulmonary failure	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
Cardiac failure (Augmented SMQ)	ANY AE	1 (8.3%)	0 (0.0%)	0 (0.0%)	3 (18.8%)	4 (36.4%)	1 (10.0%)	8 (17.8%)
	Cardiac failure acute	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Cardiopulmonary failure	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

(1)Percentage is number of patients with any event per 100 patients in group.
* Hyponatremia is defined as baseline serum sodium < 135 mEq/L.

Table 7.1.3.3.1.10 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hyponatremic Patients From Heart Failure IND IV Studies (032, 038, 044, 071)

		TREATMENT GROUP (1)						
CLASS	PREFERRED TERM	IV PLACEBO (N=12)	IV 10MG (N=6)	IV 20MG (N=2)	IV 40MG (N=16)	IV 80MG (N=11)	IV 120MG (N=10)	ALL IV YM087 (N=45)
Cardiac failure (Augmented SMQ)	Dyspnoea	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)
	Dyspnoea exacerbated	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)	1 (9.1%)	0 (0.0%)	4 (8.9%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.2%)
	Oedema NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
	Pulmonary congestion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (2.2%)

Source: Applicant's Table 17.3.2, pg 135, response document

Only 45/253 (18%) of patients in the heart failure development program IV studies had hyponatremia. This small sample size prevents clear conclusions. 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.

The following table, also examining atrial arrhythmias and cardiac failure events, includes only hyponatremic patients from oral heart failure studies. It does not include data from hyponatremic patients with underlying heart failure who were in the hyponatremia development program.

Table 7.1.3.3.1.11: Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hyponatremic Patients From Heart Failure IND Oral Studies (016, 017, 020, 024, 033, 034)

		TREATMENT GROUP (1)					
CLASS	PREFERRED TERM	ORAL PLACEBO (N=13)	ORAL 10MG (N=8)	ORAL 20MG (N=16)	ORAL 40MG (N=18)	ORAL 80MG (N=7)	ALL ORAL YM087 (N=49)
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Atrial flutter	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Cardiac Failure Events	ANY AE	1 (7.7%)	1 (12.5%)	2 (12.5%)	2 (11.1%)	0 (0.0%)	5 (10.2%)
	Cardiac failure congestive	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiac failure aggravated	0 (0.0%)	1 (12.5%)	2 (12.5%)	2 (11.1%)	0 (0.0%)	5 (10.2%)
Cardiac disorders	ANY AE	2 (15.4%)	2 (25.0%)	3 (18.8%)	2 (11.1%)	0 (0.0%)	7 (14.3%)
	Angina unstable	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Atrial flutter	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Atrioventricular block first degree	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiac failure congestive	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiogenic shock	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Congestive cardiac failure aggravated	0 (0.0%)	1 (12.5%)	2 (12.5%)	2 (11.1%)	0 (0.0%)	5 (10.2%)
	Supraventricular extrasystoles	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Supraventricular tachycardia	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Cardiac failure (SMQ)	ANY AE	1 (7.7%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Cardiac failure congestive	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiogenic shock	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Cardiac failure (Augmented SMQ)	ANY AE	1 (7.7%)	1 (12.5%)	5 (31.3%)	2 (11.1%)	0 (0.0%)	8 (16.3%)
	Cardiac failure congestive	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Cardiogenic shock	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Congestive cardiac failure aggravated	0 (0.0%)	1 (12.5%)	2 (12.5%)	2 (11.1%)	0 (0.0%)	5 (10.2%)

(1)Percentage is number of patients with any event per 100 patients in group.
* Hyponatremia is defined as baseline serum sodium < 135 mEq/L.

Table 7.1.3.3.1.11 (cont): Number and Percentage of Patients with Atrial Arrhythmia Events and Cardiac Failure Events, Hyponatremic Patients From Heart Failure IND Oral Studies (016, 017, 020, 024, 033, 034)

		TREATMENT GROUP (1)					
CLASS	PREFERRED TERM	ORAL PLACEBO (N=13)	ORAL 10MG (N=8)	ORAL 20MG (N=16)	ORAL 40MG (N=18)	ORAL 80MG (N=7)	ALL ORAL YM087 (N=49)
Cardiac failure (Augmented SMQ)	Dyspnoea	0 (0.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)	0 (0.0%)	2 (4.1%)
	Dyspnoea exacerbated	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.0%)

Source: Applicant's Table 17.3.2, pg 137, response document

In the above table, 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 following table divides heart failure patients in all Phase 2/3 studies by baseline sodium status (eunatremic vs hyponatremic). This population includes 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.

Table 7.1.3.3.1.12: Summary of Atrial Arrhythmia and Cardiac Failure Events by Baseline Serum Sodium Status, Patients with Baseline Heart Failure in All Phase 2/3 Studies (Hyponatremia and Heart Failure Development Programs)

	Hyponatremic		Eunatremic	
Event Grouping[1]	**Coni N=94 n(%)**	**Pbo N=25 n(%)**	**Coni N=724 n(%)**	**Pbo N=265 n(%)**
Specific cardiac failure events	6 (6.4)	1 (4.0)	28 (3.9)	12 (4.5)
Cardiac disorders SOC	17 (18.1)	5 (20.0)	101 (14.0)	43 (16.2)
Cardiac failure SMQ	5 (5.3)	2 (8.0)	35 (4.8)	10 (3.8)
Applicant's "augmented" cardiac failure SMQ	16 (17.0)	2 (8.0)	107 (14.8)	36 (13.6)

Source: Applicant's Table 16, pg 239, response document
1 For events contained within each grouping, see Table 7.1.3.3.1.6 and 7.1.3.3.1.7

The following table presents information from Study 071 on adverse events that were determined to be of interest in the 2nd cycle review. Study 071 was a placebo-controlled study of the effects of different doses of intravenous conivaptan on heart failure outcomes in patients with New York Heart Association functional class (NYHA FC) III and IV heart failure. Not all patients in Study 071 were hyponatremic.

In this trial, atrial arrhythmia events occurred exclusively in conivaptan-treated patients, with 7.4% of conivaptan-treated patients experiencing an event. For specific heart failure terms, these again occurred only in conivaptan-treated patients, with 3.3% of conivaptan-treated patients experiencing an event. The incidence of any cardiac event was not higher among conivaptan-treated patients than among placebo-treated patients. For the Standard MedDRA Query for cardiac failure, 8.2% of conivaptan-treated patients had an event, while 7.5% of placebo-treated patients had an event. For the applicant's "augmented" cardiac failure SMQ, 31.1% of conivaptan-treated patients experienced an event, while 30% of placebo-treated patients had an event. The majority of events in both groups were dyspnea events, although the incidence of dyspnea events in the placebo group was higher than that in the conivaptan groups (pbo 13/16 events [81.2%], conivaptan 28/42 events [66.7%]). When one considers only non-dyspnea

events in this "augmented" SMQ, there were 3 events among 40 placebo group pts (7.5 events/100 patients), and 14 events among 122 conivaptan group patients (11.5 events/100 patients). Overall, it appears that cardiac failure events (apart from nonspecific reports of dyspnea) were more common among conivaptan-treated patients than among placebo-treated patients in the heart failure Study 071.

Table 7.1.3.3.1.13: Number and Percentage of Patients with Atrial Arrhythmia and Cardiac Failure Adverse Events, Study 071 (Intravenous Heart Failure Study)

		TREATMENT GROUP (1)				
CLASS	PREFERRED TERM	IV PLACEBO (N=40)	IV 40MG (N=40)	IV 80MG (N=40)	IV 120MG (N=42)	ALL YM087 (N=122)
Atrial Arrhythmia Events	ANY AE	0 (0.0%)	3 (7.5%)	2 (5.0%)	4 (9.5%)	9 (7.4%)
	Atrial fibrillation	0 (0.0%)	3 (7.5%)	2 (5.0%)	1 (2.4%)	6 (4.9%)
	Atrial flutter	0 (0.0%)	0 (0.0%)	1 (2.5%)	3 (7.1%)	4 (3.3%)
Cardiac Failure Events	ANY AE	0 (0.0%)	3 (7.5%)	0 (0.0%)	1 (2.4%)	4 (3.3%)
	Cardiomyopathy NOS	0 (0.0%)	2 (5.0%)	0 (0.0%)	1 (2.4%)	3 (2.5%)
	Congestive cardiomyopathy	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
Cardiac disorders	ANY AE	13 (32.5%)	9 (22.5%)	9 (22.5%)	13 (31.0%)	31 (25.4%)
	Angina pectoris	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.4%)	4 (3.3%)
	Angina unstable	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Atrial fibrillation	0 (0.0%)	3 (7.5%)	2 (5.0%)	1 (2.4%)	6 (4.9%)
	Atrial flutter	0 (0.0%)	0 (0.0%)	1 (2.5%)	3 (7.1%)	4 (3.3%)
	Atrial thrombosis	0 (0.0%)	2 (5.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
	Atrioventricular block complete	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Atrioventricular block second degree	2 (5.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (0.8%)
	Bradycardia NOS	4 (10.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Cardiac arrest	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Cardio-respiratory arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Cardiomyopathy NOS	0 (0.0%)	2 (5.0%)	0 (0.0%)	1 (2.4%)	3 (2.5%)
	Cardiopulmonary failure	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiomyopathy	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Coronary artery disease aggravated	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Coronary artery occlusion	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (0.8%)
	Ischaemic cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Mitral valve incompetence	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Myocardial infarction	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Palpitations	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Sick sinus syndrome	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (0.8%)
	Sinus bradycardia	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Sinus tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Ventricular bigeminy	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ventricular extrasystoles	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	2 (1.6%)
	Ventricular fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Ventricular tachycardia	7 (17.5%)	0 (0.0%)	5 (12.5%)	4 (9.5%)	9 (7.4%)
Cardiac failure (SMQ)	ANY AE	3 (7.5%)	2 (5.0%)	3 (7.5%)	5 (11.9%)	10 (8.2%)
	Cardiopulmonary failure	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Oedema NOS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Pulmonary congestion	2 (5.0%)	1 (2.5%)	2 (5.0%)	2 (4.8%)	5 (4.1%)
	Pulmonary oedema NOS	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (4.8%)	3 (2.5%)

		TREATMENT GROUP (1)				
CLASS	PREFERRED TERM	IV PLACEBO (N=40)	IV 40MG (N=40)	IV 80MG (N=40)	IV 120MG (N=42)	ALL YM087 (N=122)
Cardiac failure (Augmented SMQ)	ANY AE	12 (30.0%)	11 (27.5%)	14 (35.0%)	13 (31.0%)	38 (31.1%)
	Cardiomyopathy NOS	0 (0.0%)	2 (5.0%)	0 (0.0%)	1 (2.4%)	3 (2.5%)
	Cardiopulmonary failure	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Congestive cardiomyopathy	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Dyspnoea	5 (12.5%)	1 (2.5%)	2 (5.0%)	0 (0.0%)	3 (2.5%)
	Dyspnoea exacerbated	8 (20.0%)	7 (17.5%)	10 (25.0%)	8 (19.0%)	25 (20.5%)
	Heart transplant rejection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	1 (0.8%)
	Oedema NOS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
	Pulmonary congestion	2 (5.0%)	1 (2.5%)	2 (5.0%)	2 (4.8%)	5 (4.1%)
	Pulmonary oedema NOS	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (4.8%)	3 (2.5%)

Source: Applicant's Table 7.4, pg 59, response document

Please see Section 7.4.2.4 for further data regarding explorations for drug-disease interactions for patients with underlying heart failure; information regarding efficacy outcomes in heart failure studies is included in that section.

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.

7.1.3.3.2 Overly rapid rise in serum sodium

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. Patients with overly rapid rise in serum sodium were identified by the presence of any one of the following criteria:

- serum sodium increase >12 mEq in 1 day
- serum sodium increase >24 mEq/L total
- serum sodium exceeded 145 mEq/L
- study drug dose decreased or temporarily withheld by investigator because he or she believed serum sodium was correcting too quickly

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 following table details the numbers of patients who met one or more criteria for overly rapid correction of serum sodium; only the 20 and 40 mg/day IV, and the 80 mg/day oral groups are included, because these are doses which would be associated with exposures in the range expected for the proposed clinical dose.

Table 7.1.3.3.2 Number and Percentage of Patients Who Met a Criterion for Overly Rapid Rise in Serum Sodium, All Placebo-controlled Phase 2/3 Studies

Tx Grp	Total N in Group	n (%) with Overly Rapid Rise in Sodium
IV pbo	132	7 (5.3)
Oral pbo	240	8 (3.3)
All pbo	372	15 (4.0)
20 mg/day IV	32	15 (4.0)
80 mg/day oral	147	14 (9.5)
40 mg/day IV	118	10 (8.5)
All patients in above dose groups	297	27 (9.1)

Source: Applicant's Table "Label Table 1", pg 191, response document

Conivaptan is associated with risk for overly rapid correction of serum sodium, but to date has not been associated with permanent neurologic sequelae associated with rapid serum sodium correction. The current Vaprisol® label contains cautionary language regarding this risk.

7.1.3.3.3 Infusion Site Reactions

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.

The following table details the incidence of infusion site reactions for all IV conivaptan studies (both hyponatremia and heart failure programs). Infusion site reactions occurred much more frequently for conivaptan group patients than for placebo group patients.

Table 7.1.3.3.3.1 Number and Percentage of Patients with Adverse Infusion Site Events, All IV Conivaptan Studies (Hyponatremia and Heart Failure Programs)

System Organ Class	Preferred Term	Coni N=581 n(%)	Pbo N=132 n(%)
Any SOC	Any infusion site event	305 (52)	8 (6)
General disorders and administration site conditions	Any infusion site event	285 (49)	7 (5)
	Infusion related reaction	1 (<1)	0
	Infusion site erythema	19 (3)	0
	Infusion site induration	1 (<1)	0
	Infusion site inflammation	2 (<1)	0
	Infusion site edema	3 (<1)	0
	Infusion site pain	9 (2)	0
	Infusion site phlebitis	158 (27)	3 (2)
	Infusion site reaction	75 (13)	0
	Infusion site swelling	7 (1)	1 (<1)
	Infusion site tenderness	3 (<1)	0
	Infusion site warmth	1 (<1)	0
	Injection site bruising	1 (<1)	0
	Injection site cellulitis	12 (2)	0
	Injection site discomfort	1 (<1)	0
	Injection site erythema	2 (<1)	0
	Injection site hemorrhage	1 (<1)	0
	Injection site inflammation	2 (<1)	0
	Injection site pain	5 (<1)	1 (<1)
	Injection site phlebitis	5 (<1)	0
	Injection site pruritus	1 (<1)	0
	Injection site reaction NOS	18 (3)	2 (2)
	Injection site swelling	2 (<1)	0
	Injection site tenderness	1 (<1)	0
	Injection site thrombosis	3 (<1)	0
	Venipuncture site bruise	1 (<1)	0
Infections and infestations	Any infusion site event	2 (<1)	0
	Infusion site infection	1 (<1)	0
	Injection site infection	1 (<1)	0
Vascular disorders	Any infusion site event	24 (5)	1 (<1)
	Deep vein thrombosis	23 (4)	1 (<1)
	Phlebitis NOS	5 (<1)	0
	Phlebitis superficial	16 (4)	1 (<1)
	Thrombophlebitis	3 (<1)	0
	Thrombophlebitis superficial	2 (<1)	0

Source: Applicant's Table 4, pg 252, ISS

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 the response document, the applicant entitled the following table as a label table. However, it does not appear in the annotated Word version of the table provided by the applicant. The clinical reviewer would not recommend its inclusion in labeling. The table is somewhat misleading, as it implies prospectively defined severity classes. The choice of which adverse events to include in Classes >I is also somewhat arbitrary; one could argue that phlebitis or thrombophlebitis of any degree is a clinically concerning adverse event. In that case, a large percentage of patients in the conivaptan groups would move to a higher classification, indicating that the majority of patients who experienced an infusion site adverse event had a clinically significant event. Additionally, this classification omits at least one serious adverse infusion site event (a jugular venous thrombosis).

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Table 7.1.3.3.3.2 Applicant's Proposed Table for Classification (Post Hoc) of Infusion Site Reactions

Number and Percentage of Patients with TEAEs of Infusion Site Reaction by SOC and preferred term
Pool 6A: All Patients and Healthy Volunteers - IV Studies (Population: SAF)
(027, 074, 079, 080, 083)

		TREATMENT GROUP		
		PLACEBO (N=69)	YM087 20MG/DAY (N=37)	YM087 40MG/DAY (N=315)
SYSTEM ORGAN CLASS (1)	PREFERRED TERM			
ALL SYSTEMS	ANY AE	3 (4.3%)	27 (73.0%)	197 (62.5%)
Class I	ANY AE	3 (4.3%)	27 (73.0%)	190 (60.3%)
	INFUSION SITE ERYTHEMA	0 (0.0%)	0 (0.0%)	18 (5.7%)
	INFUSION SITE INFLAMMATION	0 (0.0%)	0 (0.0%)	1 (0.3%)
	INFUSION SITE PAIN	1 (1.4%)	0 (0.0%)	16 (5.1%)
	INFUSION SITE PHLEBITIS	1 (1.4%)	19 (51.4%)	102 (32.4%)
	INFUSION SITE REACTION	0 (0.0%)	8 (21.6%)	61 (19.4%)
	INFUSION SITE SWELLING	1 (1.4%)	0 (0.0%)	9 (2.9%)
	INJECTION SITE PHLEBITIS	0 (0.0%)	0 (0.0%)	3 (1.0%)
	INJECTION SITE SWELLING	0 (0.0%)	0 (0.0%)	2 (0.6%)
	PHLEBITIS NOS	1 (1.4%)	1 (2.7%)	8 (2.5%)
	THROMBOPHLEBITIS SUPERFICIAL	0 (0.0%)	0 (0.0%)	2 (0.6%)
Class II	ANY AE	0 (0.0%)	0 (0.0%)	3 (1.0%)
	THROMBOPHLEBITIS	0 (0.0%)	0 (0.0%)	3 (1.0%)
Class III	ANY AE	0 (0.0%)	2 (5.4%)	5 (1.6%)
	DEEP VEIN THROMBOSIS	0 (0.0%)	1 (2.7%)	3 (1.0%)
	INJECTION SITE CELLULITIS	0 (0.0%)	1 (2.7%)	2 (0.6%)

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(1) WITHIN A SYSTEM ORGAN CLASS, SUBJECTS MAY EXPERIENCE MORE THAN ONE ADVERSE EVENT. THE SUM OF TERMS BY SYSTEM ORGAN CLASS MAY EXCEED 100%.
Note: Class III - Cellulitis at infusion site/Cellulitis and Deep Vein Thrombosis, Class II - Thrombophlebitis (not superficial thrombophlebitis), Class I - All others.

Source: Applicant's "Label Table 3", pg 193, response document

Infusion site reactions remain an important adverse reaction associated with intravenous conivaptan.

7.1.3.3.4 Bone Marrow Events

In previous reviews of conivaptan, there was a safety signal for anemia. The following two tables update the incidence of adverse events related to the bone marrow, for all IV studies, and for all conivaptan studies. In both the IV and total populations, anemia occurred slightly more frequently among conivaptan-treated patients than among placebo-treated patients. These tables include both the data for the 2nd cycle review, and the updated data for this cycle.

Table 7.1.3.3.4.1: Bone Marrow Adverse Events, All IV Studies (Both Hyponatremia and Heart Failure Programs)

	YM087 Any Dose		Placebo	
System Organ Class MedDRA Term	NDA n(%) (N=445)	Updated n(%) (N=581)	NDA n(%) (N=132)	Updated n(%) (N=132)
Patients With at Least One Event	23 (5)	35 (6)	7 (5)	7 (5)
Blood and lymphatic system disorders	18 (4)	31 (5)	7 (5)	7 (5)
Anaemia NOS	13 (3)	26 (4)	3 (2)	3 (2)
Febrile neutropenia	1 (<1)	1 (<1)	0	0
Iron deficiency anaemia	1 (<1)	1 (<1)	0	0
Leukopenia NOS	1 (<1)	0	0	0
Microcytic anaemia	0	0	0	0
Neutropenia	0	0	0	0
Normochromic normocytic anaemia	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Secondary anaemia	0	0	1 (<1)	1 (<1)
Thrombocytopenia	3 (<1)	4 (<1)	2 (2)	2 (2)
Investigations	4 (<1)	3 (<1)	0	0
Haematocrit decreased	1 (<1)	1 (<1)	0	0
Haemoglobin decreased	3 (<1)	2 (<1)	0	0
Platelet count decreased	1 (<1)	1 (<1)	0	0
Red blood cell count decreased	0	0	0	0
White blood cell count decreased	0	0	0	0
Skin and subcutaneous tissue disorders	1 (<1)	1 (<1)	0	0
Purpura NOS	1 (<1)	1 (<1)	0	0

Source: Applicant's Table 5, pg 254, ISS

Table 7.1.3.3.4.2: Bone Marrow Adverse Events, All Conivaptan Studies (Both Hyponatremia and Heart Failure Programs, IV and Oral)

	YM087 Any Dose		Placebo	
System Organ Class MedDRA Term	NDA n(%) (N=1148)	Updated n(%) (N=1284)	NDA n(%) (N=372)	Updated n(%) (N=372)
Patients With at Least One Event	61 (5)	73 (6)	16 (4)	16 (4)
Blood and lymphatic system disorders	48 (4)	61 (5)	13 (3)	13 (3)
Anaemia NOS	36 (3)	49 (4)	8 (2)	8 (2)
Febrile neutropenia	1 (<1)	1 (<1)	0	0
Iron deficiency anaemia	1 (<1)	1 (<1)	0	0
Leukopenia NOS	3 (<1)	2 (<1)	1 (<1)	1 (<1)
Microcytic anaemia	1 (<1)	1 (<1)	0	0
Neutropenia	2 (<1)	2 (<1)	0	0
Normochromic normocytic anaemia	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Secondary anaemia	0	0	1 (<1)	1 (<1)
Thrombocytopenia	6 (<1)	7 (<1)	2 (<1)	2 (<1)
Investigations	12 (1)	11 (<1)	3 (<1)	3 (<1)
Haematocrit decreased	3 (<1)	3 (<1)	1 (<1)	1 (<1)
Haemoglobin decreased	8 (<1)	7 (<1)	0	0
Platelet count decreased	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Red blood cell count decreased	4 (<1)	4 (<1)	0	0
White blood cell count decreased	1 (<1)	1 (<1)	0	0
Skin and subcutaneous tissue disorders	1 (<1)	1 (<1)	0	0
Purpura NOS	1 (<1)	1 (<1)	0	0

Source: Applicant's Table 5, pg 256, ISS

7.1.3.3.5 Hepatobiliary Events

Across all conivaptan studies (IV + oral, hyponatremia + heart failure studies), and across all IV conivaptan studies, hepatobiliary adverse events occurred slightly more commonly among conivaptan-treated patients than among placebo-treated patients. The single case of hepatic failure occurred in a patient who had underlying hepatocellular carcinoma and hepatic failure at baseline.

Table 7.1.3.3.5.1: Hepatobiliary Adverse Events, All IV Conivaptan Studies

System Organ Class MedDRA Term	YM087 Any Dose NDA n(%) (N=445)	YM087 Any Dose Updated n(%) (N=581)	Placebo NDA n(%) (N=132)	Placebo Updated n(%) (N=132)
Patients With at Least One Event	13 (3)	20 (3)	1 (<1)	1 (<1)
Gastrointestinal disorders	0	2 (<1)	0	0
Ascites	0	2 (<1)	0	0
Hepatobiliary disorders	3 (<1)	6 (1)	0	0
Cholecystitis NOS	1 (<1)	1 (<1)	0	0
Cholestasis	0	0	0	0
Hepatic congestion	0	1 (<1)	0	0
Hepatic failure	1 (<1)	2 (<1)	0	0
Hepatitis NOS	0	0	0	0
Hepatomegaly	0	1 (<1)	0	0
Jaundice cholestatic	1 (<1)	1 (<1)	0	0
Investigations	9 (2)	12 (2)	1 (<1)	1 (<1)
Alanine aminotransferase increased	0	0	1 (<1)	1 (<1)
Aspartate aminotransferase increased	0	0	1 (<1)	1 (<1)
Blood alkaline phosphatase increased	3 (<1)	4 (<1)	0	0
Blood bilirubin increased	1 (<1)	1 (<1)	0	0
Gamma-glutamyltransferase increased	2 (<1)	2 (<1)	1 (<1)	1 (<1)
International normalised ratio increased	1 (<1)	2 (<1)	0	0
Liver function test abnormal	3 (<1)	3 (<1)	0	0
Prothrombin time abnormal NOS	0	0	0	0
Prothrombin time prolonged	1 (<1)	2 (<1)	0	0
Metabolism and nutrition disorders	1 (<1)	1 (<1)	0	0
Hypoalbuminaemia	1 (<1)	1 (<1)	0	0
Hypoproteinaemia	1 (<1)	1 (<1)	0	0
Nervous system disorders	0	1 (<1)	0	0
Hepatic encephalopathy	0	1 (<1)	0	0

Source: Applicant's Table 6, pg 257, ISS

Table 7.1.3.3.5.2: Hepatobiliary Adverse Events, All Conivaptan Studies (IV + Oral, Hyponatremia + Heart Failure Programs)

System Organ Class MedDRA Term	YM087 Any Dose NDA n(%) (N=1148)	YM087 Any Dose Updated n(%) (N=1284)	Placebo NDA n(%) (N=372)	Placebo Updated n(%) (N=372)
Patients With at Least One Event	36 (3)	43 (3)	6 (2)	6 (2)
Gastrointestinal disorders	2 (<1)	4 (<1)	0	0
Ascites	2 (<1)	4 (<1)	0	0
Hepatobiliary disorders	6 (<1)	9 (<1)	0	0
Cholecystitis NOS	1 (<1)	1 (<1)	0	0
Cholestasis	1 (<1)	1 (<1)	0	0
Hepatic congestion	0	1 (<1)	0	0
Hepatic failure	1 (<1)	2 (<1)	0	0
Hepatitis NOS	1 (<1)	1 (<1)	0	0
Hepatomegaly	1 (<1)	2 (<1)	0	0
Jaundice cholestatic	1 (<1)	1 (<1)	0	0
Investigations	29 (3)	32 (2)	6 (2)	6 (2)
Alanine aminotransferase increased	5 (<1)	5 (<1)	1 (<1)	1 (<1)
Aspartate aminotransferase increased	6 (<1)	6 (<1)	1 (<1)	1 (<1)
Blood alkaline phosphatase increased	4 (<1)	5 (<1)	1 (<1)	1 (<1)
Blood bilirubin increased	3 (<1)	3 (<1)	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	7 (<1)	7 (<1)	2 (<1)	2 (<1)
International normalised ratio increased	3 (<1)	4 (<1)	1 (<1)	1 (<1)
Liver function test abnormal	11 (<1)	11 (<1)	2 (<1)	2 (<1)
Prothrombin time abnormal NOS	1 (<1)	1 (<1)	0	0
Prothrombin time prolonged	2 (<1)	3 (<1)	0	0
Metabolism and nutrition disorders	2 (<1)	2 (<1)	0	0
Hypoalbuminaemia	2 (<1)	2 (<1)	0	0
Hypoproteinaemia	1 (<1)	1 (<1)	0	0
Nervous system disorders	0	1 (<1)	0	0
Hepatic encephalopathy	0	1 (<1)	0	0

Source: Applicant's Table 6, pg 259, ISS

7.1.5 Common Adverse Events

7.1.5.1 Common Adverse Events Among All Patients With Hypervolemic Hyponatremia Who Were Treated with Intravenous Conivaptan

The following tables list 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.

Table 7.1.5.1 Number and Percentage of Hypervolemic Hyponatremic Patients Who Had Treatment-emergent Adverse Events[1], Intravenous Studies 027, 071, 080

System Organ Class (SOC)	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=15 n (%)	Any Coni Dose N=112 n (%)
All SOCs	Any AE	11 (78.6)	13 (92.9)	69 (94.5)	14 (93.3)	10 (100.0)	106 (94.6)
Blood and lymphatic system disorders	Any AE	2 (14.3)	4 (28.6)	6 (8.2)	2 (13.3)	3 (30.0)	15 (13.4)
	Anemia NOS	1 (7.1)	2 (14.3)	3 (4.1)	2 (13.3)	3 (30.0)	10 (8.9)
Cardiac disorders	Any AE	5 (35.7)	3 (21.4)	19 (26.0)	3 (20.0)	3 (30.0)	28 (25.0)
	Atrial fibrillation	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
	Cardiac failure NOS	0	0	3 (4.1)	0	0	3 (2.7)
	Congestive cardiac failure aggravated	1 (7.1)	0	6 (8.2)	1 (6.7)	0	7 (6.3)
	Ventricular tachycardia	0	0	1 (1.4)	1 (6.7)	1 (10.0)	3 (2.7)
Eye disorders	Any AE	0	0	4 (5.5)	0	0	4 (3.6)
Gastrointestinal disorders	Any AE	5 (35.7)	3 (21.4)	30 (41.1)	5 (33.3)	2 (20.0)	40 (35.7)
	Abdominal pain NOS	1 (7.1)	0	6 (8.2)	1 (6.7)	0	7 (6.3)
	Constipation	1 (7.1)	2 (14.3)	6 (8.2)	4 (26.7)	1 (10.0)	13 (11.6)
	Diarrhea NOS	0	0	5 (6.8)	0	1 (10.0)	6 (5.4)
	Dyspepsia	0	0	4 (5.5)	0	0	4 (3.6)
	Nausea	1 (7.1)	1 (7.1)	5 (6.8)	2 (13.3)	0	8 (7.1)
	Vomiting NOS	1 (7.1)	1 (7.1)	10 (13.7)	1 (6.7)	0	12 (10.7)
General disorders and administration site conditions	Any AE	7 (50.0)	8 (57.1)	53 (72.6)	9 (60.0)	7 (70.0)	77 (68.8)
	Anasarca	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
	Aesthenia	0	0	6 (8.2)	0	1 (10.0)	7 (6.3)
	Chest pain	0	0	3 (4.1)	0	0	3 (2.7)
	Edema NOS	0	0	4 (5.5)	0	0	4 (3.6)
	Edema peripheral	0	0	7 (9.6)	0	0	7 (6.3)
	Fatigue	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
	Infusion site pain	0	0	2 (2.7)	1 (6.7)	0	3 (2.7)
	Infusion site phlebitis	2 (14.3)	4 (28.6)	28 (38.4)	3 (20.0)	4 (40.0)	39 (34.8)
	Infusion site reaction	0	3 (21.4)	8 (11.0)	1 (6.7)	0	12 (10.7)
	Pain NOS	0	1 (7.1)	2 (2.7)	1 (6.7)	0	4 (3.6)
	Pyrexia	1 (7.1)	2 (14.3)	6 (8.2)	1 (6.7)	1 (10.0)	10 (8.9)
	Thirst	0	1 (7.1)	2 (2.7)	0	0	3 (2.7)
Hepatobiliary disorders	Any AE	0	0	4 (5.5)	0	0	4 (3.6)
Infections and infestations	Any AE	5 (35.7)	3 (21.4)	19 (26.0)	5 (33.3)	3 (30.0)	30 (26.8)
	Oral candidiasis	0	0	3 (4.1)	0	0	3 (2.7)
	Pneumonia NOS	0	1 (7.1)	1 (1.4)	1 (6.7)	0	3 (2.7)
	Sepsis NOS	0	1 (7.1)	5 (6.8)	1 (6.7)	1 (10.0)	8 (7.1)
Injury, poisoning and procedural complications	Any AE	0	2 (14.3)	6 (8.2)	0	0	8 (7.1)
Investigations	Any AE	2 (14.3)	2 (14.3)	12 (16.4)	6 (40.0)	2 (20.0)	22 (19.6)

Table 7.1.5.1 Number and Percentage of Hypervolemic Hyponatremic Patients Who Had Treatment-emergent Adverse Events[1], Intravenous Studies 027, 071, 080

System Organ Class (SOC)	Preferred Term	Pbo N=14 n (%)	20 mg N=14 n (%)	40 mg N=73 n (%)	80 mg N=15 n (%)	120 mg N=15 n (%)	Any Coni Dose N=112 n (%)
	Blood creatinine increased	0	0	3 (4.1)	2 (13.3)	0	5 (4.5)
	Blood potassium decreased	0	0	3 (4.1)	0	0	3 (2.7)
	Blood urea increased	0	0	3 (4.1)	0	0	3 (2.7)
	Urine output decreased	0	0	2 (2.7)	0	1 (10.0)	3 (2.7)
	Weight decreased	0	0	1 (1.4)	2 (13.3)	0	3 (2.7)
Metabolism and nutrition disorders	Any AE	7 (50.0)	8 (57.1)	28 (38.4)	5 (33.3)	3 (30.0)	44 (39.3)
	Dehydration	0	0	3 (4.1)	0	1 (10.0)	4 (3.6)
	Hyperglycemia NOS	0	0	2 (2.7)	0	2 (20.0)	4 (3.6)
	Hypoglycemia NOS	0	1 (7.1)	2 (2.7)	0	1 (10.0)	4 (3.6)
	Hypokalemia	3 (21.4)	5 (35.7)	12 (16.4)	1 (6.7)	0	18 (16.1)
Musculoskeletal and connective tissue disorders	Any AE	1 (7.1)	0	7 (9.6)	2 (13.3)	3 (30.0)	12 (10.7)
	Muscle cramp	0	0	2 (2.7)	1 (6.7)	0	3 (2.7)
	Pain in extremity	0	0	3 (4.1)	0	1 (10.0)	4 (3.6)
Neoplasms	Any AE	0	2 (14.3)	2 (2.7)	0	0	4 (3.6)
Nervous system disorders	Any AE	1 (7.1)	3 (21.4)	14 (19.2)	3 (20.0)	1 (10.0)	21 (18.8)
	Cerebrovascular accident	0	1 (7.1)	1 (1.4)	0	1 (10.0)	3 (2.7)
	Dizziness	0	0	5 (6.8)	0	0	5 (4.5)
	Headache	0	2 (14.3)	2 (2.7)	1 (6.7)	0	5 (4.5)
Psychiatric disorders	Any AE	3 (21.4)	1 (7.1)	11 (15.1)	3 (20.0)	1 (10.0)	16 (14.3)
	Confusional state	1 (7.1)	0	7 (9.6)	1 (6.7)	0	8 (7.1)
	Insomnia	1 (7.1)	1 (7.1)	3 (4.1)	1 (6.7)	1 (10.0)	6 (5.4)
Renal and urinary disorders	Any AE	3 (21.4)	4 (28.6)	15 (20.5)	3 (20.0)	2 (20.0)	24 (21.4)
	Polyuria	0	1 (7.1)	4 (5.5)	0	0	5 (4.5)
	Renal failure acute	0	0	5 (6.8)	0	0	5 (4.5)
Respiratory, thoracic and mediastinal disorders	Any AE	6 (42.9)	5 (35.7)	20 (27.4)	4 (26.7)	2 (20.0)	31 (27.7)
	Pulmonary congestion	0	0	3 (4.1)	1 (6.7)	0	4 (3.6)
Skin and subcutaneous tissue disorders	Any AE	1 (7.1)	1 (7.1)	7 (9.6)	0	1 (10.0)	9 (8.0)
	Decubitus ulcer	0	0	3 (4.1)	0	0	3 (2.7)
	Pruritus	0	1 (7.1)	1 (1.4)	0	1 (10.0)	3 (2.7)
Vascular disorders	Any AE	2 (14.3)	4 (28.6)	21 (28.8)	7 (46.7)	2 (20.0)	34 (30.4)
	Hypertension NOS	0	0	2 (2.7)	1 (6.7)	0	3 (2.7)
	Hypotension NOS	2 (14.3)	2 (14.3)	6 (8.2)	5 (33.3)	1 (10.0)	14 (12.5)
	Orthostatic hypotension	0	1 (7.1)	7 (9.6)	1 (6.7)	0	9 (8.0)
	Phlebitis NOS	0	0	4 (5.5)	1 (6.7)	0	5 (4.5)

Source: Applicant's Table 6.1, pg 33, 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 overall 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. For the System Organ Classes "General Disorders and Administration Site Conditions", "Musculoskeletal and Connective Tissue Disorders", "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. 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.

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.

7.1.5.2 Common Adverse Events Among All Patients With Hypervolemic Hyponatremia and Heart Failure Who Were Treated with Intravenous Conivaptan

The following table lists adverse events which occurred in at least 3 patients and which occurred with a frequency at least 1% higher in a conivaptan group than in the placebo group.

Table 7.1.5.2 Number and Percentage of Hypervolemic Hyponatremic Patients With CHF Who Had Treatment-emergent Adverse Events[1], Intravenous Studies 027, 071, 080

System Organ Class (SOC)	Preferred Term	Pbo N=10 n(%)	20 mg N=8 n(%)	40 mg N=50 n(%)	80 mg N=11 n(%)	120 mg N=10 n(%)	Any Coni Dose N=79 n(%)
All SOCs	Any AE	9 (90.0)	8 (100.0)	46 (92.0)	11 (100.0)	10 (100.0)	75 (94.9)
Blood and lymphatic system disorders	Any AE	2 (20.0)	3 (37.5)	4 (8.0)	2 (18.2)	3 (30.0)	12 (15.2)
	Anemia NOS	1 (10.0)	2 (25.0)	2 (4.0)	2 (18.2)	3 (30.0)	9 (11.4)
Cardiac disorders	Any AE	3 (30.0)	2 (25.0)	17 (34.0)	3 (27.3)	3 (30.0)	25 (31.6)
	Atrial fibrillation	0	1 (12.5)	2 (4.0)	0	1 (10.0)	4 (5.1)
	Cardiac failure NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Congestive cardiac failure aggravated	0	0	6 (12.0)	1 (9.1)	0	7 (8.9)
	Ventricular tachycardia	0	0	1 (2.0)	1 (9.1)	1 (10.0)	3 (3.8)
Gastrointestinal disorders	Any AE	4 (40.0)	2 (25.0)	22 (44.0)	5 (45.5)	2 (20.0)	31 (39.2)
	Constipation	1 (10.0)	1 (12.5)	4 (8.0)	4 (36.4)	1 (10.0)	10 (12.7)
	Diarrhea NOS	0	0	4 (8.0)	0	1 (10.0)	5 (6.3)
	Nausea	0	1 (12.5)	4 (8.0)	2 (18.2)	0	7 (8.9)
	Vomiting NOS	1 (10.0)	1 (12.5)	7 (14.0)	1 (9.1)	0	9 (11.4)
General disorders and administration site conditions	Any AE	6 (60.0)	4 (50.0)	35 (70.0)	8 (72.7)	7 (70.0)	54 (68.4)
	Aesthenia	0	0	4 (8.0)	0	1 (10.0)	5 (6.3)
	Chest pain	0	0	3 (6.0)	0	0	3 (3.8)
	Edema NOS	0	0	3 (6.0)	0	0	3 (3.8)
	Edema peripheral	0	0	5 (10.0)	0	0	5 (6.3)
	Fatigue	0	0	2 (4.0)	0	1 (10.0)	3 (3.8)
	Infusion site erythema	0	0	4 (8.0)	0	0	4 (5.1)
	Infusion site pain	0	0	2 (4.0)	1 (9.1)	0	3 (3.8)