

8.0.2e Decreased Pulmonary Pressure

AEs

Examination of the list of AEs identified in the infusion studies (through day 14) found the following incidence of 'decreased pulmonary pressure' as an AE.

Table 8.0.2e.1 (from 11.1.3.2) Decreased pulmonary pressure as an AE in the first 14 days in the nesiritide infusion trials from NDA 20-920^a.

Decreased pulmonary pressure	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Overall, similar trends in the incidence of AEs were seen in both sets, showing that most of the decreased pulmonary pressure occurred during the first 24 hours of nesiritide administration.

Table 8.0.2e.2 Decreased pulmonary pressure as an AE during the first 24 hours in the 'long infusion' trials^a.

Decreased Pulmonary Pressure	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Decreased Pulmonary Pressures	0 (0%)	0 (0%)	3 (2%)	5 (19%)

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs were identified as 'decreased pulmonary pressure.'

Discontinuations

Table 8.0.2e.3 (from 11.1.5.3.1) Discontinuations prior to day 14 decreased pulmonary pressure in the 'all CHF' population^a.

	Control n=235	Nesiritide n=505	Nominal p Value ^a
Decreased Pulmonary Pressure	0 (0%)	5 (1%)	0.185

a. Data from NDA appendix 8.4, table 28A. p Value per sponsor.

Next, the discontinuations associated with AEs in the long infusion studies are summarized. The only discontinuations occurred in the nesiritide group.

Table 8.0.2e.4 (from 11.1.5.3.1) Discontinuations due to decreased pulmonary pressure in the 'long infusion' trials^a.

	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value ^b
Decreased Pulmonary Pressure	0 (0%)	0 (0%)	2 (1%)	3 (12%)	<0.001

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

There were no deaths associated with decreased pulmonary pressures.

Demographics

The small number of subjects who had decreased pulmonary pressure reported as an AE make subset analysis fruitless.

Reviewer's Conclusions Regarding Decreased Pulmonary Pressures

In the context of the other data showing an association between nesiritide and significant effects on systemic blood pressure, the association with decreased pulmonary pressures as AEs can be seen as an extension of the physiological effects of nesiritide. Nonetheless, this AE did result in a significant number of discontinuations, particularly in the highest dose nesiritide group.

In conclusion, there is a definite association between nesiritide administration and the development of clinically significant decreases in pulmonary pressure.

8.0.3 Adverse Events in the 'Body as a Whole' System

The following adverse events within the 'body as a whole' system will be examined: headache. Sepsis will be examined as part of the Hemic and lymphatic system review. Adverse events analyzed but not discussed further include injection site reactions and fever.

8.0.3a Headache

AEs

The occurrence of headaches reported as AEs in the 'all CHF' and 'long infusion' trials is shown below. The reported incidence of headache as an AE was similar in the treatment groups.

Table 8.0.3a.1 (from 11.1.3.1) Headache as an AE in the 'all CHF' trials from NDA 20-920^a.

Headache	Control n=235	Nesiritide n=505
Headache	43 (18%)	80 (16%)

a. Data from NDA appendix 8.4, table 11A.

Incidence of headache in the infusion studies (through day 14) is summarized below.

Table 8.0.3a.2 (from 11.1.3.2) Headache as an AE in the first 14 days in the 'long infusion' trials^a.

Headache	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Headache	34 (20%)	38 (22%)	22 (13%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs and Deaths

No SAEs or deaths relating to headache were identified in the 'all CHF' or the 'long infusion' trials populations.

Reviewer's Conclusions Regarding Headaches

The data do not support an association between nesiritide administration and an increased incidence of headaches.

8.0.4 Adverse Events in the Digestive System

The following adverse event within the digestive system will be examined: abnormal liver function tests (LFTs), and nausea.

8.0.4a Abnormal Liver Function

This section summarizes the occurrence of AEs related to abnormal LFTs in the NDA.

AEs and SAEs

Table 8.0.4a.1 (from 11.1.3.1) Liver function AEs in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Abnormal LFTs	2 (1%)	1 (0%)
Jaundice	0 (0%)	1 (1.0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.4a.2 Liver function AEs in the first 14 days in the nesiritide infusion trials from NDA 20-920^a.

Liver AEs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Abnormal LFTs	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Jaundice	0 (0%)	0 (0%)	0 (0%)	1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs were identified referable to abnormal liver function in 'all CHF' or 'long infusion' study populations.

Discontinuations and Deaths With Abnormal LFTs

There were no discontinuations and no deaths associated with abnormal LFTs identified.

Special Studies: Line Listing of Abnormal LFTs

A review of those patients who had abnormal post-baseline AST or ALT, with a normal baseline value, revealed the following patients with marked abnormalities.

Table 8.0.4a.3 Patients with marked F/U LFT abnormalities after a normal baseline, in NDA 20-920^a.

Study/ Treatment	Patient #	Abnormal AST or ALT	Day of abnormal measurement	Notes, F/U
Protocol 326/ Standard Care	555001	AST = 738 ALT = 1346	9	Last study value
Protocol 311/ Nesiritide 0.030	377005	AST = 223	3	Resolved, last AST 22
Protocol 326/ Nesiritide 0.030	572001	AST = 1116	8	Last study value

a. Data from ISS data tables, listing 8, 'Abnormal Post-baseline laboratory values.'

Special Studies: Measured Changes in Lab Values

There was not significant difference in the mean changes from baseline for ALT or AST (see tables 11.1.4.2.1 and 11.1.4.2.2 for details).

In the long infusion trials, there was an unexpected pattern of more patients with increased ASTs in the low-dose nesiritide dose relative to control, but a lower incidence in the high-dose group, relative to the control group. A similar pattern was not seen for ALT. In the 'all CHF trials' population, no differences between the control and nesiritide groups were detected.

Table 8.0.4a.4 (from 11.1.4.3.1a.19) Observed rate of increased ASTs in the 'long infusion' trials^a.

Time of AST above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	38 (23%)	34 (21%)	21 (13%)	7 (27%)	0.152
Last Available on or before Day 2	5 (16%)	7 (25%)	0 (0%)	0 (0%)	0.003
Last Available on or before Day 5	16 (17%)	23 (24%)	8 (8%)	0 (0%)	0.058
Last Available	23 (20%)	22 (19%)	19 (15%)	2 (8%)	0.814

a. Data from NDA vol. 79, table 44D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Reviewer's Conclusions Regarding LFT Abnormalities

The available data do not suggest an adverse effect of nesiritide on the liver, as reflected by changes in LFTs or the incidence of clinically significant liver disease. For clinically significant liver disease, the small number of subjects exposed to nesiritide limits this conclusion.

In conclusion, the data support the conclusion that nesiritide is unlikely to have an adverse effect on the liver, as detected by changes in AST and ALT. The data are inadequate to assess the incidence of severe hepatic injury.

8.0.4b Nausea

The incidences of nausea as an adverse event in the 'all CHF' and 'long infusion' trials are shown below.

Table 8.0.4b.1 (from 11.1.3.1) Nausea as an AE in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Gastrointestinal System	68 (29%)	168 (33%)	
Nausea	29 (12%)	79 (16%)	
Vomiting	15 (6%)	44 (9%)	0.310

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.4b.2 (from 11.1.3.2) Nausea as an AE in the first 14 days in the 'long infusion' trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	
Nausea	25 (14%)	36 (21%)	32 (19%)	4 (15%)	0.398
Vomiting	13 (8%)	12 (7%)	17 (10%)	3 (12%)	0.614

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs, Discontinuations, or Deaths

No SAEs, discontinuations, or deaths were associated with nausea as an AE.

Demographics

1. Gender

A lower percentage of the control females reported nausea, resulting in a nominally significant difference relative to the nesiritide group. At the 0.015 and 0.030 dose range, nausea was more common in females relative to males.

Table 8.0.4b.3 (from 8.0.2c.10) Nausea as an AEs in the 'long infusion' population^a according to gender.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male	n=127	n=120	n=113	n=23	
Nausea	22 (17%)	24 (20%)	15 (13%)	4 (17%)	0.576
Female	n=46	n=49	n=54	n=3	
Nausea	3 (7%)	12 (24%)	17 (31%)	0 (0%)	0.010

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data. p Values per the sponsor.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

2. Age

There was no difference in the incidence of nausea in the <65 and >65 year old age groups.

3. NYHA Class III or IV

There was no difference in the incidence of nausea in NYHA class III or IV groups.

4. Drug Interactions

Small numbers of available patients make it difficult to assess these interactions.

Reviewer's Conclusions Regarding Nausea

Nausea was a commonly reported adverse event in both the control and the nesiritide groups. There was a trend towards more reported nausea in the nesiritide group, for both the 'all CHF' and 'long infusion' populations (especially the 'all CHF' group). With regard to demographics, females had a slightly higher incidence of nausea in the nesiritide groups relative to males.

In conclusion, the data suggest a possible associate between nesiritide administration and a higher incidence of nausea.

8.0.5 Adverse Events in the Nervous System

AEs

The following adverse events within the nervous system will be examined: dizziness, nervousness, and confusion.

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**8.0.5a Dizziness, Nervousness and Confusion
AEs and SAEs**

Table 8.0.5a.1 (from 11.1.3.1) Nervous system AEs in the CHF trials from NDA 20-920^a.

Nervous system AEs	Control n=235	Nesiritide n=505	Nominal p Value
Nervous System	53 (23%)	161 (32%)	
Dizziness	16 (7%)	43 (9%)	0.469
Anxiety	11 (5%)	28 (6%)	0.725
Somnolence	4 (2%)	12 (2%)	0.787

a. Data from NDA appendix 8.4, table 11A. p Value per the sponsor.

The same AEs were examined in the long infusion studies.

Table 8.0.5a.2 (from 11.1.3.2) Nervous system AEs in the first 14 days in the 'long infusion' group^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Nervous System	40 (23%)	67 (40%)	54 (32%)	7 (27%)	0.011
Insomnia	18 (10%)	25 (15%)	22 (13%)	1 (4%)	0.371
Confusion	3 (3%)	6 (6%)	3 (3%)	0 (0%)	0.052
Dizziness	9 (5%)	17 (10%)	8 (5%)	3 (12%)	0.125
Nervousness	3 (2%)	10 (6%)	5 (3%)	0 (0%)	0.189
Somnolence	3 (2%)	3 (2%)	6 (4%)	0 (0%)	0.663

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs referable to confusion, insomnia, nervousness, or dizziness were reported.

Discontinuations

Discontinuations for dizziness were also considered in the hypotension AE section above.

Table 8.0.5a.3 (from 11.1.5.3.1) Discontinuations prior to day 14 for dizziness in the 'CHF trials' population^a.

	Control n=235	Nesiritide n=505	Nominal p Value
Dizziness	0 (0%)	6 (1%)	0.184

a. Data from NDA appendix 8.4, table 28A. p Value per sponsor.

Next, the discontinuations associated with AEs in the long infusion studies are summarized.

Table 8.0.5a.4 (from 11.1.5.3.1) Discontinuations due to nervous system AEs in the long infusion trials^a.

AE	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Nervous System	0 (0%)	1 (1%)	3 (2%)	2 (8%)	0.010
Nervousness	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Stupor	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Vertigo	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

There were no deaths attributable to any of these adverse events.

Demographics (for 'confusion' as an AE)

1. Age

Confusion was more common in the nesiritide group >65 years of age.

Table 8.0.5a.5 Confusion as an AE reported in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
<65 Years Old Confusion	n=103 2 (2%)	n=100 4 (4%)	n=90 3 (3%)	n=17 0 (0%)	0.821
>65 Years Old Confusion	n=70 3 (4%)	n=69 12 (17%)	n=77 10 (13%)	n=9 1 (11%)	0.076

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

2. Gender

Confusion was also more common in the nesiritide group of both men and women, although the small numbers in females make it difficult to draw conclusions about the trend.

Table 8.0.5a.6 Confusion as an AEs in the 'long infusion' population^a according to gender.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Male Confusion	n=127 3 (2%)	n=120 12 (10%)	n=113 9 (9%)	n=23 0 (0%)	0.039
Female Confusion	n=46 2 (4%)	n=49 4 (8%)	n=54 4 (7%)	n=3 1/(33%)	0.297

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

3. Other Medications

With small numbers, no drug-drug interaction enhancing the incidence of confusion in study 704.326 was detected.

Table 8.0.5a.7 Confusion as an AEs arranged by use of other medications in addition to nesiritide from study 704.326.

Confusion as an AEs	Nesiritide 0.015 and 0.030 µg/kg/min
ACE Inhibitor Use	
Yes	5/124 (4%)
No	4/49 (8%)
Digoxin Use	
Yes	5/117 (4%)
No	2/45 (4%)
Beta Blockers	
Yes	2/18 (11%)
No	7/183 (4%)

a. Data from ISS table 8-39, reflecting trial 326 data.

4. NYHA Class III or IV

Confusion as an AEs occurred with equal frequency in Class III and IV NYHA patients. There was a trend towards increased incidence of confusion in the nesiritide groups for both NYHA classes.

Table 8.0.5a.8 Confusion as an AEs in the 'long infusion' population^a according to NYHA Class^a.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III Confusion	n=107 1 (1%)	n=97 10 (10%)	n=81 7 (9%)	n=15 0 (0%)	0.011
NYHA IV Confusion	n=58 3 (5%)	n=64 6 (9%)	n=71 6 (8%)	n=9 1 (11%)	0.692

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

Reviewer's Conclusions Regarding Confusion

There was an association between nesiritide use and confusion that tended to be more commonly reported in patients >65 years old.

There was also a nominally significant increase in 'nervousness' in the nesiritide group in the 'all CHF' trial population. The database is too small to draw final conclusions about the clinical significance of the association.

No difference was detected with regard to the other nervous system AEs examined.

In conclusion, the data suggest a possible associate between nesiritide administration and a higher incidence of confusion. The data are inadequate to assess a relationship between nesiritide and nervousness.

8.0.6 Adverse Events in the Metabolic System

The following adverse event within the metabolic system will be examined: hypo- and hyperkalemia, hyperglycemia, hyponatremia, hyper-magnesemia, and changes in serum total protein and albumin. Elevated BUN and Creatinine (Cr) will be examined in the Urogenital System review.

8.0.6a Hyper- and Hypo-kalemia

AEs

The first two tables summarize the changes in potassium reported as AEs in the 'all CHF' and 'long infusion' populations. No significant differences are apparent.

Table 8.0.6a.1 (from 11.1.3.1) Changes in K⁺ as AEs in the 'all CHF' population^a.

K ⁺	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Hypokalemia	10 (4%)	20 (4%)
Hyperkalemia	6 (3%)	12 (2%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6a.2 (from 11.1.3.2) Changes in K⁺ as AEs in the first 14 days in 'long infusion' population^a.

K ⁺	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Hypokalemia	9 (5%)	7 (4%)	5 (3%)	3 (12%)	0.216
Hyperkalemia	5 (3%)	6 (4%)	4 (2%)	0 (0%)	0.931

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

Hyperkalemia as an SAE was rare in the database.

Table 8.0.6a.3 (from 11.1.2.1) Hyperkalemia as an SAE through 14 days in the 'all CHF' group^a.

Hyperkalemia as SAE	Control n=235	Nesiritide n=505
Hyperkalemia	1 (<1.0%)	0 (0%)

a. Data from NDA appendix 8.4, table 27A.

Table 8.0.6a.4 (from 11.1.2.2) Hyperkalemia as an SAEs through 14 days in the 'long infusion' trials^a.

Hyperkalemic SAEs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min
Hyperkalemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 27D and from company at request of reviewer.

Discontinuations and Deaths

There were no discontinuations or deaths directly attributable to Na⁺ or K⁺ disturbances reported.

Special Studies: Measured Changes in Lab Values

There was a tendency towards a higher mean K⁺ at day two in both the 'all CHF' and the 'long infusion' groups.

Table 8.0.6a.5 (from 11.1.4.2.1) Mean changes in K⁺ from baseline for all subjects in CHF trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Potassium	-0.1±0.65	-0.0±0.59	0.0±0.69	0.1±0.68

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.6a.6 (from 11.1.4.2.3.1) Mean changes in serum K⁺ from baseline for the 'long infusion' trials^a.

Lab Test, Change from Baseline to Day 2	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24
Potassium	-0.2±0.65	-0.0±0.61	0.0±0.63	+0.2±0.41

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Sponsors Comments on Changes in Potassium

In all populations, on day 2, there is a tendency for serum potassium to be decreased from baseline more in the control group than in the nesiritide group. By the last available time point, mean serum potassium tends to have increased slightly over baseline in the nesiritide group compared to the control group. For example, in the Long Infusion Studies, in the control, 0.015-, and 0.03-µg/kg/min nesiritide groups, the change in mean serum potassium from baseline at day 2 is -0.2, -0.0, and 0.0 mEq/L, respectively (p = 0.011) and at the last available timepoint is 0.0, 0.1, and 0.2 mEq/L, respectively (p = 0.020). This moderate potassium-sparing effect may be due to the reduction in aldosterone which accompanies nesiritide administration. There was not an increase in the incidence of the adverse event of hyperkalemia in the nesiritide groups compared to control, even for subjects on ACE inhibitors.

Reviewer's Conclusions Regarding Changes in Serum Potassium

There was no evidence to suggest a clinically adverse effect of nesiritide on serum potassium concentrations, or on the occurrence of adverse events related to serum potassium. At day two, patients who got nesiritide had a slightly higher (0.2 meq/dl) mean change in serum K⁺. Whether this reflects an interaction of nesiritide to decrease aldosterone levels or aldosterone-receptor interaction is not known.

In conclusion, an association between nesiritide administration and clinically relevant changes in serum potassium is unlikely.

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8.0.6b Hyponatremia.

AEs

The first two tables summarize the incidence of AEs related to serum Na⁺ in the 'all CHF' and 'long infusion' populations. No difference in the incidence of hyponatremia among the treatment groups was detected.

Table 8.0.6b.1 (from 11.1.3.1) Hyponatremia as an AEs in the 'all CHF' population^a.

Adverse Event	Control n=235	Nesiritide n=505
Hyponatremia	6 (3%)	6 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6b.2 (from 11.1.3.2) Hyponatremia as an AEs in the first 14 days in the 'long infusion' population^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Hyponatremia	4 (2%)	0 (0%)	5 (3%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs were identified relating to serum sodium concentrations.

Discontinuations and Deaths

There were no discontinuations or deaths directly attributable to changes in serum Na⁺ reported.

Special Studies: Measured Changes in Lab Values

No effect of nesiritide on changes in mean serum Na⁺ were detected in the 'all CHF' population shown below

Table 8.0.6b.3 (from 11.1.4.2.1) Mean changes in serum Na⁺ from baseline for 'all CHF' group^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Sodium (meq/l)	-0.8±3.3	-1.1±3.2	-1.2±3.8	-1.0±3.7

a. Data from NDA volumes 79-80, starting with table 31A1.

In the 'long infusion' population, there was a trend towards a dose-dependent decrease in mean serum Na⁺ in the nesiritide groups. In data not shown, equal numbers of subjects developed abnormally low serum Na⁺ in this group after starting with normal serum Na⁺.

Table 8.0.6b.4 (from 11.1.4.2.3.1) Mean changes in serum Na⁺ from baseline for all subjects in 'long infusion' groups^a.

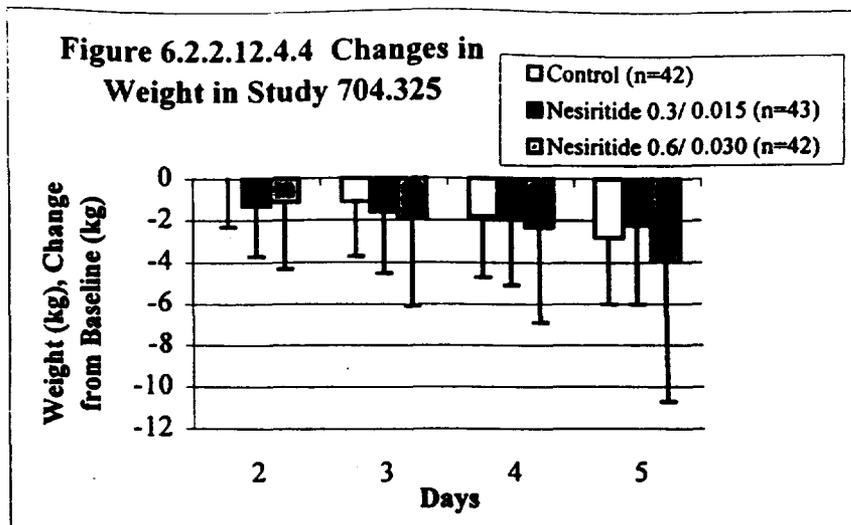
Lab Test, Change from Baseline to Day 2	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24
Sodium (meq/l)	-0.4±3.3	-0.8±3.0	-1.2±3.3	-1.8±5.3

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Special Studies: Effect on Body Weight and Urine Output

The sponsor measured the fluid balance over the first 24 hours of study drug infusion in study 704.325. If the subjects who received diuretics during the first 6 hours were removed, there was no significant difference in overall volume status at the end of 24 hours between control and nesiritide groups (see NDA volume 1.59, Appendix 1, Tables 57B for details).

The sponsor also followed the weights of the subjects during the first 5 days of hospitalization in study 704.326. There was a non-significant trend towards greater weight losses, particularly in the high-dose nesiritide group during days 2 and 3. This difference tended to persist in the high-dose nesiritide group through day 5. At day 5, the control group and the high-dose nesiritide group had lost 2.8±3.2 and 3.9±6.8 kgs, respectively (p =0.479).



Sponsors Comments on Changes in Sodium

Since nesiritide been shown to have modest natriuretic properties in clinical studies and is also known to reduce aldosterone levels, it would be expected that nesiritide therapy might result in some alterations in serum electrolytes. In the three long infusion studies, there was a suggestion of a dose-related reduction in serum sodium during nesiritide infusion. In the control, 0.015-, and 0.03- $\mu\text{g}/\text{kg}/\text{min}$ nesiritide groups, the change in mean serum sodium from baseline to day 2 is -0.4 , -0.8 , and -1.2 mEq/L , respectively ($p = 0.097$). However, equal numbers of control and nesiritide -treated patients developed hyponatremia after starting with normal baseline serum sodium. Thus, nesiritide 'may have modest natriuretic properties, but this does not appear to result in clinically significant hyponatremia.'

Reviewer's Conclusions Regarding Changes in Serum Na^+

The dose-dependent decrease in mean serum Na^+ in the long infusion population suggests an effect of nesiritide on water handling by the kidney, not on sodium as suggested by the sponsor. Decreased serum Na^+ in this population means that, over a 2 day period, more water was retained in the intravascular space in the nesiritide groups. How this possible effect of nesiritide interacts with the effects of nesiritide on increasing intravascular permeability to proteins and other small molecules (see below) is unknown. This anti-diuretic property of nesiritide is worrisome in a patient population with decompensated CHF, although no clinically significant AEs were attributable to this change. One can also draw some reassurance from the lack of an increase in re-admissions for CHF in the nesiritide group (see above). If the clinician relies on changes in body weight to guide his/her diuretic use, however, this fluid in the interstitial space will not be available for excretion, and may make place the patients at increased risk of renal injury to intravascular volume contraction. In conclusion, then, there is a possible effect of nesiritide to decrease water excretion acutely, leading to decreases in serum Na^+ .

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8.0.6c Hyperglycemia/Hypoglycemia

AEs

The sponsor summarized the incidence of hyper- and hypoglycemia in the 'all CHF' and 'long infusion' groups. There was a trend towards a higher incidence of hyperglycemia in both of the nesiritide groups, and a trend towards a higher incidence of hypoglycemia in the 'long infusion' group.

Table 8.0.6c.1 (from 11.1.3.1) Hyperglycemic/ hypoglycemia AEs reported in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Metabolic & Nutritional System	42 (18%)	83 (16%)	0.673
Hyperglycemia	0 (0%)	10 (2%)	0.036
Hypoglycemia	4 (2%)	8 (2%)	1.000

a. Data from NDA appendix 8.4, table 11A. p Value per the sponsor.

Table 8.0.6c.2 (from 11.1.3.2) Hyperglycemic/ hypoglycemia AEs during the first 14 days in the 'long infusion' group^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
Hyperglycemia	0 (0%)	1 (1%)	5 (3%)	0 (0%)	0.069
Hypoglycemia	2 (1%)	1 (1%)	5 (3%)	2 (8%)	0.051

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data. p Value per sponsor.

SAEs

There were no recorded SAEs related to hypoglycemia. One SAE for hyperglycemia was reported, in the nesiritide 0.030 µg/kg/min group.

Table 8.0.6c.3 (from 11.1.2.1) Hyperglycemic SAEs through 14 days in the 'all CHF' group^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Hyperglycemia	0 (0%)	1 (<1.0%)

a. Data from NDA appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences.

Table 8.0.6c.4 (from 11.1.2.2) Hyperglycemic SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Hyperglycemia	0 (0%)	1 (1%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

Discontinuations and Deaths

There were no discontinuations or deaths due to glucose abnormalities reported.

Special Studies: Measured Changes in Lab Values

The first two tables summarize the mean changes in serum glucose.

Table 8.0.6c.5 (from 11.1.4.2.1) Mean changes in serum glucose from baseline for 'all CHF' group^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Glucose	-9.0±55	-2.7±59	-12.8±55	-8.0±62

a. Data from NDA volumes 79-80, starting with table 31A1.

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The next table summarizes the data for the 'long infusion' trial population at the end of 2 days. There is a trend towards a dose-dependent increase in mean serum glucose in the nesiritide group.

Table 8.0.6c.6 (from 11.1.4.2.3.1) Mean changes in serum glucose from baseline for subjects in 'long infusion' groups^a.

Lab Change Baseline to Day 2	Test, from Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24
Glucose	-6.6±56	+4.9±42	+18.8±79	+26.3±40

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Special Studies: Lab Shift Analyses

In both the CHF trial as a whole, and in the long infusion studies, a substantial % of patients were hyperglycemic at baseline (54% of both groups in the 'all CHF' population). At all timepoints measured, however, there were a small number of patients who were hypoglycemic, with a higher incidence in the nesiritide groups. No effect of nesiritide on the development of hyperglycemia was detected using this same analytic method.

Table 8.0.6c.7 (from 11.1.4.3.1a.3) Observed rate of decreased glucose concentrations in the 'all CHF' trials^a.

Time of Glucose Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	4 (2%)	14 (3%)	0.666
Last Available on or before Day 2	1 (1%)	4 (2%)	0.186
Last Available on or before Day 5	2 (1%)	14 (4%)	0.239
Last Available	4 (2%)	22 (5%)	0.299

a. Data from NDA vol. 79, table 35A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies, again with very few patients.

Table 8.0.6c.8 (from 11.1.4.3.1a.4) Observed rate of decreased glucose values in the long infusion trials^a.

Time of Glucose Below Normal	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value ^a
Baseline	4 (2%)	7 (4%)	6 (4%)	1 (4%)	0.805
Last Available on or before Day 2	0 (0%)	2 (6%)	1 (3%)	0 (0%)	0.492
Last Available on or before Day 5	2 (2%)	6 (5%)	7 (6%)	0 (0%)	0.712
Last Available	3 (2%)	6 (4%)	9 (6%)	2 (8%)	0.736

a. Data from NDA vol. 79, table 35D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Reviewer's Conclusions Regarding Changes in Serum Glucose

The data presented above are difficult to interpret. Depending on the analysis, there seems to be an effect of nesiritide on 'glucose handling' which can result in either an increase in hyper- or hypo-glycemia. The small numbers, and the absence of a putative mechanism for such an effect, make this conclusion less certain. In addition, aside from one SAE reported for hyperglycemia, there were no detected adverse clinical effects of these possible changes in serum glucose.

In conclusion, there is a possible effect of nesiritide on glucose handling in a subset of patients. No clinically significant effects of nesiritide on serum glucose were detected.

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8.0.6d Hypermagnesemia

AEs and SAEs

Adverse events related to serum magnesium levels were rare in the database, as summarized below.

Table 8.0.6d.1 (from 11.1.3.1) Changes in serum Mg²⁺ reported as AEs in the 'all CHF' group^a.

Adverse Event	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Hypomagnesemia	4 (2%)	4 (1%)
Hypermagnesemia	1 (1.0%)	0 (0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6d.2 (from 11.1.3.2) Changes in serum Mg²⁺ reported as AEs in the first 14 days in the 'long infusion' group^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)
Hypomagnesemia	4 (2%)	3 (2%)	1 (0.5%)	0 (0%)
Hypermagnesemia	1 (<1.0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to serum magnesium were reported.

Discontinuations and Deaths

There were no discontinuations directly attributable to changes in serum magnesium reported.

Special Studies: Measured Changes in Lab Values

The first table summarizes the measured changes in Mg²⁺ from baseline at days 2 and 5.

Table 8.0.6d.3 (from 11.1.4.2.1) Mean changes in serum Mg²⁺ from baseline for all subjects in 'all CHF' trials^a.

Change in Mg ²⁺	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Mg ²⁺ (meq/dl)	0.0±0.4	0.0±0.3	0.0±0.3	0.0±0.3

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Shift Analysis of Lab Abnormalities

In both the 'all CHF' the 'long infusion' populations there were a nominally significant association between nesiritide administration and increased magnesium levels. Note that this small difference persisted to the last available labs in the 'all CHF' studies.

Table 8.0.6d.4 (from 11.1.4.3.1a.20) Observed rate of increased serum Mg²⁺ concentrations in the 'all CHF' trials^a.

Time of Mg ²⁺ Above Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	19 (9%)	53 (11%)	0.367
Last Available on or before Day 2	5 (6%)	16 (10%)	0.473
Last Available			
Last Available			

a. Data from NDA vol. 79, table 48A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

Table 8.0.6d.5 (from 11.1.4.3.1a.21) Observed rate of increased serum Mg²⁺ levels in 'long infusion' trials^a.

Time of Mg ²⁺ above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	17 (11%)	20 (13%)	19 (13%)	2 (8%)	0.459
Last Available on or before Day 2	3 (9%)	4 (15%)	6 (21%)	2 (18%)	0.333
Last Available on or before Day 5	10 (10%)	13 (13%)	20 (21%)	2 (10%)	1.000
Last Available	11 (9%)	17 (10%)	26 (15%)	4 (15%)	1.000

a. Data from NDA vol. 79, table 48C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

There was, however, no clear trend towards the development of elevated Mg²⁺ levels in patients who started with normal levels.

Table 8.0.6d.6 (from 11.1.4.3.1a.22) Patients with increased Mg²⁺ after normal baseline in 'all CHF' trials^{a,b}.

Time of Increased Mg ²⁺	Control n=235	Nesiritide n=505
Last Available on or before Day 2	3 (4%)	8 (5%)
Last Available on or before Day 5	8 (5%)	16 (5%)
Last Available	16 (6%)	23 (6%)

a. Data from NDA vol. 79, table 48B4.

b. Percentages are calculated using all patients with available baseline, regardless of value.

Table 8.0.6d.7 (from 11.1.4.3.1a.23) Observed incidence of increased Mg²⁺ values after normal baseline value in 'long infusion' trials^{a,b}.

Time of Increased Mg ²⁺	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	3 (11%)	2 (8%)	1 (9%)
Last Available on or before Day 5	6 (6%)	5 (5%)	7 (7%)	1 (5%)
Last Available	7 (6%)	8 (7%)	8 (7%)	0 (0%)

a. Data from supplemental table 48D4.

b. Percentages are calculated using all patients with available baseline, regardless of value.

Reviewer's Conclusions

There was an association between nesiritide administration and the incidence of hyper-magnesemia in both populations reviewed, but this trend was not clearly dose-dependent in the 'long infusion' group. In addition, there was no trend towards elevated Mg²⁺ for those individuals who started with normal serum Mg²⁺ levels, and no change in overall mean serum Mg²⁺ levels.

One interpretation of this finding would be that nesiritide reduces blood flow to the kidney, which in turn reduces the amount of solute delivered to the thick ascending limb (where Mg²⁺ is reabsorbed in regulated fashion). This would lead to increased Mg²⁺ reclamation by the kidney, increasing serum Mg²⁺ levels. Interpretation of these data is also made more difficult by the heavy use of lasix in these trials, which promotes an increased Mg²⁺ excretion by inhibiting the thick ascending limb.

In conclusion, there is the data are inadequate to assess a possible association between nesiritide use and increased serum Mg²⁺.

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8.0.6e Changes in Serum Total Protein and Albumin

AEs

The AEs related to changes in serum protein reflect the effects of this loss of oncotic pressure: edema.

Table 8.0.6e.1 (from 11.1.3.1) Changes in serum protein, reported as AEs in the 'all CHF' group^a.

	Control n=235	Nesiritide n=505
Metabolic & Nutritional System	42 (18%)	83 (16%)
Edema	0 (0%)	1 (<1.0%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.6e.2 (from 11.1.3.2) Changes in serum proteins reported as AEs in the first 14 days in the 'long infusion' studies^a.

	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)
Peripheral Edema	1 (<1.0%)	2 (1%)	1 (<1.0%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

No SAEs referable to changes in serum albumin/ total protein, including edema, were reported.

Discontinuations and Deaths

There were no discontinuations or deaths due to changes in serum proteins reported, including edema.

Special Studies: Changes in Measured Lab Values

There was no significant effect of nesiritide on the mean changes in serum total protein or albumin.

Table 8.0.6e.3 (from 11.1.4.2.1) Mean changes in serum chemistries from baseline for the 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Total Protein	-0.3±0.8	-0.3±0.5	-0.2±0.7	-0.3±0.6
Albumin	-0.2±0.3	-0.3±0.3	-0.1±0.3	-0.2±0.4

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Shift Analysis of Lab Measurements

1. Total Protein

In both the 'all CHF' trials there were a higher % of the nesiritide group that developed a low total protein level. This abnormality was most prominent at days 2 and 5. There was also a higher % of patients with low total proteins at the start of the trial in the nesiritide group.

Table 8.0.6e.4 (from 11.1.4.3.1a.14) Rate of decreased total protein concentrations in the 'all CHF' trials^a.

Time of Total Protein Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	38 (17%)	102 (21%)	0.062
Last Available	32 (19%)	90 (22%)	0.316

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the 'long infusion' studies, where the trend towards decreased total proteins persisted throughout the measurements. This was most prominent at day two, when the majority of patients were still on study drug.

Table 8.0.6e.5 (from 11.1.4.3.1a.15) Rate of decreased total protein values in the 'long infusion' trials^a.

Time of Total Protein Below Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	32 (20%)	43 (27%)	40 (26%)	3 (12%)	0.135
Last Available on or before Day 2					
Last Available on or before Day 5					
Last Available					

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

2. Serum Albumin

In both the 'all CHF' trials there were a higher % of low serum albumin in the nesiritide group. Like the data for the changes in serum total protein, these changes were most prominent at days 2 and 5. Note that

Table 8.0.6e.6 (from 11.1.4.3.1a.16) Observed rate of decreased albumin concentrations in 'all CHF' trials^a.

Time of Albumin Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	86 (37%)	164 (32%)	0.411
Last Available on or before Day 2			
Last Available on or before Day 5	64 (27%)	164 (32%)	
Last Available	64 (36%)	164 (40%)	0.411

a. Data from NDA vol. 79, table 39A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was a similar trend in the infusion studies, where the differences persisted to the end of the measurement period.

Table 8.0.6e.7 (from 11.1.4.3.1a.17) Observed rate of decreased albumin values in the 'long infusion' trials^a.

Time of Albumin Below Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	65 (39%)	80 (48%)	76 (48%)	8 (31%)	0.170
Last Available on or before Day 2					
Last Available on or before Day 5					
Last Available					

a. Data from NDA vol. 79, table 40D3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

Similarly, the % of patients who developed decreased albumin after a normal baseline value was higher in the high-dose nesiritide group. This was particularly true at day two, when the nesiritide infusion was continuing in a significant % of the subjects.

Table 8.0.6e.8 (from 11.1.4.3.1a.18) Observed incidence of decreased albumin values after normal baseline value in the long infusion trials^a.

Time of Decreased Albumin	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	1 (3%)	6 (21%)	5 (18%)	4 (29%)
Last Available on or before Day 5	10 (11%)	17 (18%)	16 (17%)	4 (18%)
Last Available	10 (9%)	16 (14%)	17 (14%)	1 (4%)

a. Data from NDA vol. 79, table 37C4.

Reviewer's Conclusions Regarding Changes in Serum Proteins

In the discussion of the changes in hematology (see below), the sponsor posits an effect of nesiritide 'to enhance transcapillary permeability.' This effect has been reported for ANP in animals (refs. 6, 10 and 13). Such an effect, if real, might account for the pattern of changes in serum total protein and albumin seen, with protein transudation from the intravascular space. The association between nesiritide and decreased total protein and albumin, however, persists throughout the hospitalization in the long infusion trials, rather than ending when the nesiritide infusion stops. This suggests a long-term effect, and while no clinical consequences of these changes in serum proteins were detected, a permanent increase in transcapillary permeability might adversely affect intravascular volume regulation. Such a case might occur if clinicians monitor weights as the only measure of fluid loss, and are over-aggressive with diuretics. In such a case, coupled with the loss of proteins and water to the interstitium, would leave the intravascular space depleted risking impaired perfusion of vital organs, including the GI tract and kidneys.

An alternative hypothesis is that nesiritide decreases production of these proteins by the liver, or enhances their destruction. Given the known effects of ANP to alter vascular permeability, such an effect of nesiritide is the more attractive of the two hypotheses.

In conclusion, there is a probable association between the administration of nesiritide and a decrease in serum total protein and albumin, which tended to persist in the long infusion population. No clinical adverse effects were detected as the results of these changes, but the database is inadequate to exclude such effects or to determine the mechanism for the observed changes.

8.0.7 Adverse Events in the Respiratory System

No adverse events were identified that were potentially associated with study drug administration or were a normal part of NDA safety review in this system. Adverse events reviewed included dyspnea and increased cough.

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8.0.8 Adverse Events in the Urogenital System

The following adverse events within the Urogenital system will be examined: renal failure (including increases in serum BUN/Crt), and oliguria.

8.0.8a Renal Failure

AEs

The first tables summarize the incidence of urogenital AEs.

Table 8.0.8a.1 (from 11.1.3.1) Renal adverse events (AEs) in the CHF trials from NDA 20-920^a.

Renal AEs	Control n=235	Nesiritide n=505	Nominal p Value
Metabolic & Nutritional System BUN Increased	42 (18%) 7 (3%)	83 (16%) 15 (3%)	1.00
Urogenital System	25 (11%)	83 (16%)	0.05
Creatinine Increased	7 (3%)	29 (6%)	0.141
Oliguria	2 (1%)	13 (3%)	0.164
Hematuria	6 (3%)	5 (1%)	0.113
Kidney Function Abnormal	0 (0%)	7 (1%)	0.104
Acute Renal Failure	3 (1%)	6 (1%)	1.000

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.8a.2 (from 11.1.3.2) Renal AEs in the first 14 days in the 'long infusion' trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Metabolic & Nutritional System BUN Increased	7 (4%)	9 (5%)	5 (3%)	0 (0%)	0.615
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.813
Creatinine Increased	7 (4%)	10 (6%)	15 (9%)	1 (4%)	0.300
Oliguria	2 (1%)	6 (4%)	6 (4%)	0 (0%)	0.410
Hematuria	4 (2%)	3 (2%)	1 (1%)	0 (0%)	0.697
Acute Kidney Failure	3 (2%)	1 (1%)	3 (2%)	1 (4%)	0.389
Kidney Function Abnormal	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

The sponsor also summarized the data for the first 24 hours of the long infusion trials. Very few Urogenital AEs occurred in the first 24 hours.

Table 8.0.8a.3 (from 11.1.3.3) Renal AEs during the first 24 hours in the 'long infusion' trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Creatinine Increased	1 (1%)	3 (2%)	4 (2%)	0 (0%)
Kidney Function Abnormal	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Acute Kidney Function	0 (0%)	0 (0%)	1 (1%)	0 (0%)
BUN Increased	2 (1%)	2 (1%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 12C and from company at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

Urogenital SAEs

Examination of the list of SAEs in both the 'all CHF' and 'long infusion' studies found no difference in the incidence of Urogenital SAEs among the treatment groups. In study 704.325 and 704.326, there was also no difference in the number of patients who required hemodialysis/ hemofiltration (data not shown).

Table 8.0.8a.4 (from 11.1.2.1) Renal SAEs through 14 days in the 'all CHF' trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Urogenital System	3 (1%)	4 (1%)
Kidney Function Abnormal	0 (0%)	1 (<1.0%)
Nephritis	0 (0%)	1 (<1.0%)
Acute Kidney Failure	3 (1%)	2 (0%)

a. Data from NDA appendix 8.4, table 27A.

Urogenital SAEs (cont)

Table 8.0.8a.5 (from 11.1.2.2) Renal SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26	Nominal p Value
Urogenital ^c	3 (2%)	0 (0%)	1 (1%)	1 (4%)	0.136
Nephritis	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0.049
Kidney Function Abnormal	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Acute Kidney Failure	3 (2%)	0 (0%)	1 (1%)	0 (0%)	0.410

a. Data from appendix 8.4, table 27C and from company at request of reviewer. p Value per sponsor.
c. Includes nephritis, kidney function abnormal, and acute kidney failure.

Discontinuations

There was an increased incidence of withdrawals with Urogenital AEs in the nesiritide group for both the 'all CHF' and 'long infusion' trials. Note that all of the discontinuations for Urogenital AEs occurred in the nesiritide groups in the 'all CHF' and the 'long infusion' populations.

Table 8.0.8a.6 (from 11.1.5.3.1) Discontinuations prior to day 14 due to renal AEs in the 'all CHF' population^a.

AE associated with discontinuation	Control n=235	Nesiritide n=505	Nominal p Value
Urogenital System	0 (0%)	9 (2%)	0.064
Oliguria	0 (0%)	5 (1%)	0.185
Creatinine Increased	0 (0%)	4 (1%)	0.313
Acute Kidney Failure	0 (0%)	1 (<1.0%)	1.000
Metabolic & Nutritional System	0 (0%)	5 (1%)	0.185
BUN Increased	0 (0%)	4 (1%)	0.313
Hypovolemia	0 (0%)	1 (<1.0%)	1.000

a. Data from NDA appendix 8.4, table 28A.

Table 8.0.8a.7 (from 11.1.5.3.1) Discontinuations due to renal AEs in the 'long infusion' trials^a.

AE associated with discontinuation	Placebo	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Urogenital	0 (0%)	2 (1%)	7 (4%)	0 (0%)	0.020
Oliguria	0 (0%)	1 (1%)	4 (2%)	0 (0%)	0.125
Creatinine Increased	0 (0%)	1 (1%)	3 (2%)	0 (0%)	0.249
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Metabolic & Endocrine	0 (0%)	2 (1%)	3 (2%)	0 (0%)	0.325
BUN Increased	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Hypovolemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361

a. Data from supplemental table 28D, with p Value per sponsor.

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Deaths With Renal Failure

The deaths associated with renal failure are listed below. Most occurred distantly from study drug administration. Those deaths whose renal failure worsened during or shortly after study drug administration are summarized following the table.

Table 8.0.8a.8 (from 11.1.1.2) Known deaths associated with renal failure in NDA 20-920^a.

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
<u>Placebo</u> 368001	16	Ventricular Fibrillation, CHF
<u>Active Control^b</u> 509001 538011	21 9	Suspect large MI LV failure s/p MI
<u>Nesiritide Bolus</u> None		
<u>Nesiritide 0.015 µg/kg/min infusion</u> 382013 538010	5 9	Progressive Renal Insufficiency CHF Mitral regurgitation Chronic atrial flutter
<u>Nesiritide 0.030 µg/kg/min infusion</u> 017007 509002 528001 572001	8 6 22 20	Acute Renal Failure, CHF CHF Cardiac arrest Ischemic cardiomyopathy CHF
<u>Nesiritide 0.060 µg/kg/min infusion</u> None		

a. Data from NDA vol. 1.81, listing 7, and examination of individual case report forms.

b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

Placebo/ Active Control Group

1. *Subject 538-011 (Standard care: dobutamine)* Subject was a 78-year-old white man with a history of NYHA Class IV CHF, atrial fibrillation, ventricular ectopy, and chronic renal insufficiency. Dobutamine was administered for 8 days. On day 3, he developed acute renal failure. On day 4, he experienced bradycardia and a respiratory arrest requiring intubation and mechanical ventilation. He died on day 9 of severe left ventricular failure.

Nesiritide 0.015 Dose Group

1. *Subject 538-010 (Nesiritide, 0.015 µg/kg/min)* Subject was an 89-year-old white woman with NYHA Class III CHF, coronary artery disease, mitral regurgitation, and chronic atrial fibrillation. Nesiritide was administered for 65 hours, then discontinued because of clinical improvement. On day 4, dobutamine was initiated in response to worsening oliguria. The subject's general condition worsened over the ensuing days. Sepsis was suspected and broad spectrum antibiotics were initiated. Comfort measures only were initiated, and the subject died from a cardiopulmonary arrest on day 9.

Nesiritide 0.030 Dose Group

1. *Subject 509-002 (Nesiritide, 0.03 µg/kg/min)* Subject was a 61-year-old white man with NYHA Class IV CHF due to idiopathic, dilated cardiomyopathy, and a history of non-sustained VT. He received nesiritide for 5 days. For the first few days of the infusion, he responded very well with excellent diuresis and improvement in his congestive symptoms. On day 5, his condition deteriorated with worsening respiratory symptoms and decreased urine output. Nesiritide was discontinued and replaced with dobutamine and dopamine. Later on day 6, the subject died due to worsening CHF.

2. *Subject 528-001 (Nesiritide, 0.03 µg/kg/min)* Subject was a 71-year-old white man with a history of NYHA Class III CHF, ischemic cardiomyopathy, atrial fibrillation, bronchiolitis obliterans, and diabetes. He received nesiritide for 3 days to which he responded very well with diuresis and improvement in CHF symptoms. On day 5, he was noted to have hyperkalemia ($K^+ = 7.6$) and an elevated serum creatinine ($Crt = 3.9$ mg/dL). He was diagnosed as having nonoliguric acute renal failure which improved by day 8 ($K^+ = 4.3$, $Crt = 1.5$) after the administration of dobutamine, dopamine, and IV furosemide. He died on day 22 due to cardiac arrest.

Demographics of Renal Failure as an AE

1. Age

Adverse events related to renal function occurred at equal, low, rates in the < and >65 years of age groups.

Table 8.0.8a.9 Urogenital AEs in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
<65 Years Old	n=103	n=100	n=90	n=17	
Creatinine Increased	4 (3%)	3 (3%)	8 (9%)	1 (6%)	0.253
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
Acute Kidney Failure	2 (2%)	1 (1%)	2 (2%)	0 (0%)	0.899
BUN Increased	4 (4%)	3 (3%)	2 (2%)	0 (0%)	0.948
>65 Years Old	n=70	n=69	n=77	n=9	
Creatinine Increased	3 (4%)	7 (10%)	7 (9%)	0 (0%)	0.499
Kidney Function Abnormal	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0.692
Acute Kidney Failure	1 (1%)	0 (0%)	1 (1%)	1 (11%)	0.132
BUN Increased	3 (4%)	6 (9%)	3 (4%)	0 (0%)	0.553

a. Data from supplemental data table 13D at request of reviewer. Reflects trials 311, 325, and 326 data. p Value per sponsor.

2. Gender

Urogenital AEs occurred rarely, and there was no apparent influence of gender on their incidence.

Table 8.0.2b.10 Urogenital AEs in the 'long infusion' population^a according to age.

	Control	Nesiritide 0.015	Nesiritide 0.030	Nesiritide 0.060	Nominal p Value
Men	n=127	n=120	n=113	n=23	
Creatinine Increased	7 (6%)	6 (5%)	11 (10%)	1 (4%)	0.478
Nephritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	--
BUN Increased	7 (6%)	6 (5%)	3 (3%)	0 (0%)	0.618
Women	n=46	n=49	n=54	n=3	
Creatinine Increased	0 (0%)	4 (8%)	4 (7%)	0 (0%)	0.221
Nephritis	0 (0%)	0 (0%)	0 (0%)	1 (33%)	0.020
Kidney Function Abnormal	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0.357
Acute Kidney Failure	0 (0%)	0 (0%)	2 (4%)	1 (33%)	0.020
BUN Increased	0 (0%)	3 (6%)	2 (4%)	0 (0%)	0.389

a. Data from supplemental data table 15D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

3. Other Medications

There were no obvious interactions with nesiritide and other drugs which were associated with increased incidence of elevated creatinine as an AE, although the number of such patients was quite low in any of the trials, even in 704.326.

Table 8.0.2b.11 'Elevated Creatinine' as an AE, arranged by use of other medications in addition to nesiritide from study 704.326.

Elevated Creatinine in 704.326	Nesiritide 0.015 and 0.030 µg/kg/min
ACE Inhibitor Use	
Yes	3/124 (2%)
No	2/49 (4%)
Digoxin Use	
Yes	2/117 (2%)
No	2/45 (4%)
Beta Blockers	
Yes	0/18 (0%)
No	6/183 (3%)

a. Data from ISS table 8-39, reflecting trial 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

4. NYHA Class III or IV

Urogenital AEs occurred with equal frequency in Class III and IV NYHA patients.

Table 8.0.2b.12 Urogenital AEs in the 'long infusion' population^a according to NYHA Class^b.

	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
NYHA III	n=107	n=97	n=81	n=15	
Creatinine Increased	3 (3%)	6 (6%)	7 (9%)	0 (0%)	0.294
Kidney Function Abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Acute Kidney Failure	1 (1%)	1 (1%)	1 (1%)	1 (7%)	0.306
BUN Increased	5 (5%)	4 (4%)	2 (2%)	0 (0%)	0.888
NYHA IV	n=58	n=64	n=71	n=9	
Creatinine Increased	4 (7%)	3 (5%)	7 (10%)	1 (11%)	0.552
Kidney Function Abnormal	0 (0%)	1 (2%)	3 (4%)	0 (0%)	0.493
Acute Kidney Failure	2 (3%)	0 (0%)	2 (3%)	0 (0%)	0.554
BUN Increased	2 (3%)	4 (6%)	2 (3%)	0 (0%)	0.767

a. Data from supplemental data table 17D at request of reviewer. Reflects trials 311, 325, and 326 data.

b. Includes bradycardia, nodal arrhythmia, and sinus bradycardia.

5. Etiology of CHF

Increased creatinine as an AE occurred rarely, with equal frequency regardless of the original etiology of the CHF (with small numbers for analysis).

Table 8.0.8a.13 Increased creatinine as an AE in the 'long infusion' population^a according to cause of CHF^a.

Creatinine Increased as an AE	Control	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	Nesiritide 0.060 µg/kg/min	Nominal p Value
Hypertensive	0/13 (0%)	2/14 (14%)	2/12 (17%)	0/3 (0%)	0.527
Ischemic	6/89 (7%)	5/88 (6%)	7/87 (8%)	1/16 (6%)	0.918
Idiopathic/Dilated	0/38 (0%)	0/40 (0%)	5/35 (14%)	0/5 (0%)	0.014

a. Data from supplemental tables provided at request of reviewer. Reflects trials 311, 325, and 326 data.

Special Studies: Measured Changes in Lab Values

At day 2 and 5, the nesiritide group had a smaller decline in mean BUN than the controls in the 'all CHF' and in the 'long infusion' populations.

Table 8.0.8a.14 (from 11.1.4.2.1) Mean changes in renal chemistries from baseline for 'all CHF' trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
BUN	-3.6±6.9	-1.4±7.1	-4.3±10.4	-1.4±10.2
Creatinine	-0.1±0.5	0.0±0.3	-0.1±0.5	0.0±0.4

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.8a.15 (from 11.1.4.2.31) Mean changes in renal chemistries from baseline for 'long infusion' trials^a.

Lab Test, Change from Baseline to Day 2	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24	Nominal p Value
BUN	-3.3 ± 6.86	-1.8 ± 7.19	-0.7 ± 7.85	-2.5 ± 5.26	0.022
Creatinine	-0.1 ± 0.53	-0.0 ± 0.32	+0.1 ± 0.37	0.0 ± 0.13	<0.001

a. Data from NDA volumes 79-80, starting with table 31A1 and from supplemental data sets submitted at reviewer's request.

Special Studies: Incidence of Development of Elevated BUN and Creatinine

1. Elevated Blood Urea Nitrogen (BUN)

In the CHF trials, the incidence of elevated BUN at baseline was >50% in both the control and the nesiritide group. There was no significant difference in the % of patients with elevated BUN during the trials in this group.

Table 8.0.8a.16 (from 11.1.4.3.1a.5) Observed rate of increased BUN concentrations in 'all CHF' trials^a.

Time of Increased BUN	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	124 (53%)	276 (55%)	0.619
Last Available on or before Day 2	98 (47%)	218 (51%)	0.339
Last Available on or before Day 5	113 (49%)	258 (52%)	0.473
Last Available	119 (51%)	288 (57%)	0.124

a. Data from NDA vol. 79, table 36A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

There was, however, an increased % of patients in the nesiritide group who had normal BUNs at baseline and had elevated BUNs at 2 and 5 days and last available measured.

Table 8.0.8a.17 (from 11.1.4.3.1a.6) Incidence of patients with increased BUN after normal baseline BUN in 'all CHF' trials^a.

Time of Increased BUN	Control n=235	Nesiritide n=505
Last Available on or before Day 2	5 (2%)	23 (5%)
Last Available on or before Day 5	10 (4%)	38 (8%)
Last Available	20 (9%)	62 (12%)

a. Data from NDA vol. 79, table 36A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

In the long infusion trials, there was again no difference in the incidence of increased BUN (data not shown, see table 36C3 for details). The number of patients with normal BUN at baseline and elevated BUN at time of follow-up was also similar in the treatment groups.

Table 8.0.8a.18 (from 11.1.4.3.1a.7) Observed rate of increased BUN concentrations in the long infusion trials for patients with normal BUN at baseline^a.

Time of BUN Above Normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Last Available on or before Day 2	4 (3%)	8 (5%)	9 (6%)	1 (4%)	NS
Last Available on or before Day 5	10 (6%)	15 (9%)	12 (7%)	1 (4%)	NS
Last Available	13 (8%)	16 (10%)	15 (9%)	3 (12%)	NS

a. Data from supplemental data table 36D4 from sponsor at reviewer's request.

2. Elevated Creatinine

Among all patients enrolled in the CHF trials, there were more with abnormally elevated creatinines at days 2, 5 and at final available assessment in the nesiritide group.

Table 8.0.8a.19 (from 11.1.4.3.1a.8) Observed rate of increased creatinine values in the 'all CHF' trials^a.

Time of Creatinine Below Normal	Control n=235	Nesiritide n=505	Nominal p Value ^a
Baseline	87 (37%)	186 (37%)	0.837
Last Available on or before Day 2	71 (34%)	165 (39%)	0.134
Last Available	71 (34%)	165 (39%)	0.134

a. Data from NDA vol. 79, table 37A3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

2. Elevated Creatinine (cont)

A higher % of patients with normal creatinines at baseline also had elevated creatinines at follow-up in the nesiritide group.

Table 8.0.8a.20 (from 11.1.4.3.1a.9) Incidence of patients with increased creatinine after normal baseline creatinine in 'all CHF' trials^a.

Time of Increased creatinine	Control n=235	Nesiritide n=505
Last Available on or before Day 2	7 (3%)	33 (8%)
Last Available on or before Day 5	13 (6%)	42 (8%)
Last Available	20 (9%)	64 (13%)

a. Data from NDA vol. 79, table 37A4.

In the long infusion trials, there were a higher percentage of patients with elevated creatinines in the 0.030 dose group, compared with either the 0.015 group or the control group.

Table 8.0.8a.21 (from 11.1.4.3.1a.10) Observed rate of increased creatinine values in 'long infusion' trials^a.

Time of Increased creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	79 (46%)	62 (37%)	76 (46%)	13 (50%)	0.140
Last Available on or before Day 2					
Last Available on or before Day 5					
Last Available					

a. Data from supplemental table 37C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Similarly, the percentage of patients who developed elevated creatinines after a normal baseline value was higher in the 0.030 $\mu\text{g}/\text{kg}/\text{min}$ nesiritide group.

Table 8.0.8a.22 (from 11.1.4.3.1a.11) Observed incidence of increased creatinine values after normal baseline value in the long infusion trials^a.

Time of Increased creatinine	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	4 (3%)	7 (5%)	18 (12%)	0 (0%)
Last Available on or before Day 5	10 (6%)	12 (7%)	17 (10%)	1 (4%)
Last Available	11 (7%)	16 (10%)	22 (13%)	2 (8%)

a. Data from NDA vol. 79, table 37C4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

The number of patients with pre-specified increases in serum creatinine also tended to be higher in the nesiritide groups, relative to control. The tables below shows the data for trials 704.311, 704.325, and 704.326. Note that there were relatively few patients with two or more serum creatinines in the 704.311 study.

Table 8.0.8a.23 (from 11.1.4.3.1a.12) Observed incidence of increased creatinine values in trial 704.311^a.

Pre-specified increases in creatinine	Control	Nesiritide 0.25/0.015	Nesiritide 0.50/0.030	Nesiritide 1.0/0.060	Nominal p Value ^a
>1.0 mg/dl Increase	2 (7%)	1 (4%)	1 (4%)	1 (4%)	1.000
>0.5 mg/dl Increase	4 (14%)	4 (17%)	5 (20%)	6 (23%)	0.861
>100% Increase	1 (3%)	1 (4%)	1 (4%)	0 (0%)	0.795
>50% Increase	2 (7%)	4 (17%)	4 (16%)	3 (12%)	0.631
>25% Increase	8 (28%)	10 (43%)	9 (36%)	10 (38%)	0.678

a. Data from the sponsor, table 37D7. p Value per the sponsor.

Table 8.0.8a.24 (from 11.1.4.3.1a.13) Observed incidence of increased creatinine values in trial 704.325^a.

Pre-specified increases in creatinine	Control n=42	Nesiritide 0.3/0.015 n=43	Nesiritide 0.6/0.030 n=42	Nominal p Value ^a
>1.0 mg/dl Increase	0 (0%)	2 (5%)	4 (10%)	0.122
>0.5 mg/dl Increase	2 (5%)	7 (16%)	8 (19%)	0.124
>100% Increase	1 (2%)	1 (2%)	4 (10%)	0.322
>50% Increase	2 (5%)	7 (16%)	8 (19%)	0.124
>25% Increase	7 (17%)	11 (26%)	8 (19%)	0.624

a. Data from NDA vol. 79, table 37D1. p Value for the comparison between the 0.015 and 0.030 nesiritide dose groups and control

Table 8.0.8a.25 (from 11.1.4.3.1a.13) Observed incidence of increased creatinine values in trial 704.326^a.

Pre-specified increases in creatinine	Control n=102	Nesiritide 0.3/0.015 n=103	Nesiritide 0.6/0.030 n=100	Nominal p Value ^a
>1.0 mg/dl Increase	3 (3%)	6 (6%)	6 (6%)	0.571
>100% Increase	2 (2%)	3 (3%)	1 (1%)	0.874
>50% Increase	3 (3%)	10 (10%)	10 (10%)	0.124
>25% Increase	11 (11%)	22 (22%)	17 (17%)	0.624

a. Data from NDA vol. 79, table 37D2. p Value per the sponsor for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

3. Urinary Abnormalities

The sponsor did not perform urinalyses during either the 704.325 or 704.326 trials. In the 704.311 trial only baseline urinalyses were obtained. In the absence of this data, an effect of nesiritide on urinary abnormalities cannot be evaluated or excluded.

Special Studies: Need for Medical Intervention Due to Renal Failure

In trial 704.325, the need for medical intervention, including the need for dialytic intervention was collected, and is summarized in the table below. Note that interventions for worsening renal failure (short of dialysis) were more nominally significantly more common in the nesiritide groups. This trend was less dramatic in trial 704.326.

Table 6.2.13.5 Requirement for intervention due to worsening renal failure in study 704.325^a.

Intervention for worsening renal function	Placebo n=42	Nesiritide 0.3/ 0.015 n=43	Nesiritide 0.6/ 0.030 n=42	Nominal p Value
No Intervention	41 (98%)	37 (86%)	33 (79%)	0.033
Medical Intervention without Dialysis	1 (2%)	6 (14%)	9 (21%)	0.033
Dialysis	1 (2%)	0 (0%)	2 (5%)	—

a. Data from NDA vol. 59, Appendix 1, Table 61.

Table 6.3.12.3.9 Need for selected medical interventions through 21 days in study 704.326^a.

Intervention for Worsening Renal Function	Standard Care n=102	Nesiritide 0.3/ 0.015 n=103	Nesiritide 0.6/ 0.030 n=100	Nominal Value
Intervention without Dialysis	6 (6%)	12 (12%)	7 (7%)	0.610
Dialysis	2 (2%)	1 (1%)	2 (2%)	—

a. Data from NDA volume 66, Appendix 1, Table 35. Includes all subjects discharged before day 21. p Value per sponsor.

Special Studies: Individual Patient Lab Review with Renal Failure

The following selected patients in trial 704.326 had courses consistent with a severe renal injury during their hospital stays.

Table 8.0.8a.26 Selected patients with marked renal lab abnormalities^a.

Protocol 704.326 Treatment Grp/ Pt. #	Day	BUN/ Crt	Notes
Standard Care 493019	0		
	3		
	4		
	5		Last lab known, Ultimately died of endstage CHF
Nesiritide 0.015 µg/kg/min 536002	0		
	2		
	10		
	15		
	30		
	48		F/U creatinine 1.0
547003	0		
	2		
	3		
	4		F/U creatinine 1.0
Nesiritide 0.060 µg/kg/min 525002	0		
	2		
	3		
	4		
	5		
	6		
	7		
	8		F/U creatinine 1.1
572001 (Control)			

a. Data from individual data listings of patients and electronic data sets.

Following the NDA submission, the sponsor also obtained follow-up serum creatinines for those patients who had abnormal creatinines at last value (≥ 2 mg/dl and 50% increase over baseline). These data are shown below. The single patient who did not resolve his creatinine to within 0.5 mg/dl of baseline is patient 572-001, described in the patient narrative below.

8.0.8a.27 Resolution of elevated serum creatinines from subjects with increased creatinine in studies 704.325 and 704.326^a.

Creatinine ≥ 2 mg/dl and 50% increase over baseline	Control	Nesiritide 0.015	Nesiritide 0.030
Transient	1	7	12
Not Transient ^b	0	0	1
Insufficient Follow-up	1	2	1

a. Data from sponsor' briefing book for Advisory Committee.

b. Follow-up creatinine >0.5 mg/dl above baseline.

1. *Subject 572-001 (Nesiritide, 0.060 µg/kg/min)* This was a 73 year old WM with a history of ischemic cardiomyopathy, 'chronic renal insufficiency' (admitting creatinine 1.2) and previous MI. After receiving nesiritide for one day, he was switched to dobutamine for lack of clinical improvement. He was also later treated with nitroprusside and milrinone, and levophed. His subsequent hospital course was complicated by multifocal atrial tachycardia and hypotension, oliguric acute renal failure, intermittent chest pain, and elevated cardiac enzymes indicative of a myocardial infarction, worsening hyponatremia, gastrointestinal bleed and progressively worsening cardiac and renal function. The subject died on day 20 because of endstage heart failure.

2. *Subject 525-002 (Nesiritide, 0.060 µg/kg/min)* This was a 74 year-old WM with dilated idiopathic cardiomyopathy and CHF. He had a history of hypertension, a fib, acromegaly, and chronic renal insufficiency (baseline creatinine 1.3). He was not on ACE inhibitors, or NSAIDs, but did receive Norvasc, lasix, and Rhythmol. He received nesiritide for 6 days, with no other parenteral vasoactive medications. On the first day of infusion, his creatinine rose to 1.9, followed by a return to near baseline (1.4). On day 7, after completing his nesiritide, his serum creatinine began to rise again, and peaked at time of last value, taken just before discharge (BUN 51, Cr 2.1). At time of last follow-up his creatinine had returned to 1.0 mg/dl.

Another patient in the bolus infusion study 704.309 (reviewed by Dr. Karkowsky) had an adverse renal event resulting in hemodialysis and ultrafiltration, which is summarized below.

1. *Subject 359-002 (Nesiritide, 10 µg/kg bolus q6 hours)* This 54 year old WF had NYHA III CHF due to ischemic cardiomyopathy diabetes mellitus (baseline creatinine 2.0 and 2.1). She tolerated the nesiritide administration. On day 2 her urine output declined and her creatinine rose to 2.6, then 3.8, then 4.3. She was treated with Zaroxilyn and Demadex and renal dose dopamine, but required hemodialysis and ultrafiltration. She later developed central line sepsis, drug-induced ototoxicity, a fib, and anemia.

Sponsor's Comments

In all of the populations analyzed, on day 2, there is a tendency for mean serum BUN and creatinine to be decreased from baseline more in the control group than in the nesiritide group. By the last available time point, mean serum BUN and creatinine tend to have increased slightly over baseline in the nesiritide group compared to control. This phenomenon occurs in a dose-related manner.

Clinically significant renal dysfunction requiring dialysis was not more frequent in nesiritide subjects than in control subjects. Thus, nesiritide administration may be associated with a modest dose-related increase in serum creatinine in a minority of subjects (~10% of nesiritide subjects receiving the 0.015 µg/kg/min dose) but does not appear to be associated with marked increases in serum creatinine or increases in clinically significant acute renal failure. This phenomenon might be related to nesiritide inhibition of the renin-angiotensin system in a small group of patients dependent on that system's effects on renal perfusion.

Reviewer's Conclusions Regarding Urogenital AEs

By several measures, nesiritide use was associated with adverse effects on the kidney. In particular, in the nesiritide group there was an increased percentage of subjects with specified increases in creatinine, and the increased number of subjects withdrawn from the trials for urogenital AEs (all referable to abnormal renal function). The rate of oliguria was also significantly increased in the nesiritide group, suggesting that administration of nesiritide induces a sodium- and water-avid state in susceptible patients, perhaps related to inadequate renal perfusion. While there was no difference in the need for dialysis, such a rare event would be unlikely to be detected in this small database. There were individuals who developed clearly abnormal renal function in association with nesiritide infusion. No demographic was identified in the small database that correlated with increased risk for renal injury, although the sponsor claimed in their briefing documents that a serum creatinine of ≥ 2 mg/dl at trial entry was an independent risk for increased creatinine during nesiritide infusion. In the absence of data regarding urinalyses, renal injuries such as Nephrotic syndrome and Acute Interstitial Nephritis, which would be manifest by the development of urinary abnormalities, cannot be evaluated or excluded. Without the urinalysis data, we are also forced to speculate about the nature of the renal injury that leads to the observed increases in serum creatinine.

In conclusion, the data support a probable association between nesiritide administration and clinically significant renal adverse effects, leading to significant increases in serum creatinine as well as marked, persistent increases in serum creatinine, suggesting permanent renal injury. The database is inadequate to exclude an effect on severe renal injury, such as nephrotic syndrome, papillary necrosis, and interstitial nephritis. It is also inadequate to assess the effect of nesiritide on other renal toxicities that might be detected by urinary abnormalities.

8.0.9 Adverse Events in the Skin & Appendage System

No adverse events were identified that were potentially associated with study drug administration or were a normal part of NDA safety review in this system. Adverse events reviewed included rash and urticaria.

8.0.10 Adverse Events in the Musculoskeletal System

The following adverse event within the Musculoskeletal system will be examined: leg cramps/ myalgia.

8.0.10a Myalgias and Leg Cramps

AEs and SAEs

The two major AEs and SAEs related to the Musculoskeletal system are summarized below for the 'all CHF' and 'long infusion' populations. In the long infusion trials, both overall Musculoskeletal and leg cramps were reported at a lower rate in the nesiritide groups.

Table 8.0.10a.1 (from 11.1.3.1) Adverse Events (AEs) in 'all CHF' trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Musculoskeletal System	21 (9%)	30 (6%)
Myalgia	1 (<1.0%)	2 (<1.0%)
Leg Cramps	11 (5%)	13 (3%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.10a.2 (from 11.1.3.2) Musculoskeletal AEs in the first 14 days in 'long infusion' trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)
Myalgia	1 (<1.0%)	1 (<1.0%)	0 (0%)	1 (4%)
Leg Cramps	9 (5%)	5 (3%)	2 (1%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs due to leg cramps or myalgias were reported.

Discontinuations and Deaths

No discontinuations or deaths due to myalgias or muscle cramps were reported.

Reviewer's Conclusions Regarding Musculoskeletal AEs

No evidence of an adverse effect of nesiritide on the musculoskeletal system was found. The data are inadequate to interpret the smaller incidence of leg cramps reported in the nesiritide groups.

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8.0.11 Adverse Events in the Hemic & Lymphatic System

The following adverse events within the hemic & lymphatic system will be examined: changes in hemoglobin/ hematocrit, WBC count (including sepsis and infections), platelet count, and eosinophil count. Adverse events reviewed but not discussed further include PT and PTT.

8.0.11a Changes in hemoglobin, hematocrit, and RBC count

AEs and SAEs

The occurrence of hemic and lymphatic AEs in the 'all CHF' and 'long infusion' trials is summarized below. No adverse effect of nesiritide is evident.

Table 8.0.11a.1 (from 11.1.3.1) Hemic AEs in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505
Hemic & Lymphatic	12 (5%)	17 (3%)
Anemia	4 (2%)	8 (2%)
Ecchymosis	4 (2%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.11a.2 (from 11.1.3.2) Hemic AEs in the first 14 days in 'long infusion' trials from NDA 20-920^a.

Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)
Anemia	3 (2%)	1 (1%)	5 (3%)	1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to changes in hemoglobin/ hematocrit were reported.

Discontinuations and Deaths

No discontinuations or deaths for bleeding or changes in hemoglobin/ hematocrit were reported.

Special Studies: Measured Changes in Lab Values

At the end of 2 and 5 days in the 'all CHF' population there was an increased hematocrit in the nesiritide group.

Table 8.0.11a.3 (from 11.1.4.2.2) Mean changes in RBC labs from baseline for all subjects in CHF trials^a.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
RBC # (10 ⁶ /mm ³)	+0.0±0.2	+0.1±0.4	+0.0±0.3	+0.0±0.4
HGB (g/dL)	-0.1±0.7	+0.3±0.96	+0.0±0.8	+0.2±0.1
Hematocrit			+0.0±2.7	+0.4±3.1

a. Data from NDA volumes 79-80, starting with table 31A1.

Sponsor's Comments

In the placebo-controlled studies, there is a very subtle trend of a transient increase in RBC count, hemoglobin and hematocrit in the nesiritide group compared to control. 'This phenomenon has been noted occasionally in other studies with natriuretic peptides in the literature and may reflect transient hemoconcentration due to the ability of natriuretic peptides to enhance transcapillary permeability.'

Reviewer's Conclusions Regarding RBC Counts

There was a small effect of nesiritide to increase the mean change in hemoglobin/ hematocrit and RBC count, measured after 2 and 5 days in the 'all CHF' population. This was not associated with any detected AEs. The data are inadequate to test the hypothesis proposed as a mechanism by the sponsor.

In conclusion, the data support a possible effect on RBC concentration, perhaps related to hemoconcentration.

8.0.11c WBC Count/Infections Including Sepsis

AEs

The first two tables summarize the incidence of AEs related to WBC count, including sepsis, in the 'all CHF' and 'long infusion' trials. No differences are evident among the treatment groups.

Table 8.0.11c.1 (from 11.1.3.1) Hemic & lymphatic AEs in 'all CHF' trials^a.

Adverse Event Related to WBCs	Control n=235	Nesiritide n=505
Hemic & Lymphatic Leukopenia	12 (5%) 1 (0.1%)	17 (3%) 0 (0%)
Body as a Whole Sepsis Line infection	6 (3%) 1 (0.1%)	14 (3%) 1 (0.1%)

a. Data from NDA appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following.

Table 8.0.11c.2 (from 11.1.3.2) Hemic & lymphatic AEs in the first 14 days in the 'long infusion' trials.

Adverse Event Related to WBCs	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=26
Hemic & Lymphatic Leukopenia Sepsis	9 (5%) 1 (1%) 5 (3%)	3 (2%) 0 (0%) 3 (2%)	8 (5%) 0 (0%) 6 (4%)	1 (4%) 0 (0%) 1 (4%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

SAEs

In both the 'all CHF' and the 'long infusion' studies there were more SAEs related to sepsis in the nesiritide groups than in control.

Table 8.0.11c.3 (from 11.1.2.1) Hemic & lymphatic SAEs through 14 days in 'all CHF' trials^a.

Serious Adverse Event	Control n=235	Nesiritide n=505
Sepsis Infection	0 (0%) 1 (<1.0%)	5 (1%) 0 (0%)

a. Data from NDA appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences.

Table 8.0.11c.4 (from 11.1.2.2) Hemic & lymphatic SAEs through 14 days in the 'long infusion' trials^a.

Serious Adverse Event	Control n=173	Nesiritide 0.015 µg/kg/min n=169	Nesiritide 0.030 µg/kg/min n=167	Nesiritide 0.060 µg/kg/min n=24	Nominal p Value
Sepsis	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510

a. Data from appendix 8.4, table 27C and from company at request of reviewer.

Discontinuations

No discontinuations due to sepsis were reported.

Deaths

One death associated with severe infection occurred in the standard care group, and is summarized below.

1. *Subject 509-001 (Standard care: dobutamine)* Subject was a 61-year-old white man with a history of NYHA Class III CHF, a previous myocardial infarction, chronic renal insufficiency, non-sustained VT, and bradycardia. During the study, he was treated with dobutamine for 1 day with no improvement and was discharged to home at his request. On day 10, he was readmitted with bullous cellulitis. On study day 13, he developed worsening renal function and received hemodialysis beginning on day 19. On day 21, he died following a cardiac arrest, presumably associated with a myocardial infarction.

Special Studies: Changes in Mean Hematology Values

The changes in mean WBC count for the 'all CHF' and 'long infusion' trials are summarized below. In the 'long infusion' studies, there was a trend towards greater WBC # after 2 days in the nesiritide groups.

Table 8.0.11c.5 (from 11.1.4.2.2) Mean changes in WBC # from baseline for 'all CHF' trials^a.

WBC #	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
WBC # (10 ³ /mm ³)	+0.6±1.4	+0.9±1.6	+0.3±1.8	+0.6±1.9

a. Data from NDA volumes 79-80, starting with table 31A1.

Table 8.0.11c.6 (from 11.1.4.2.4) Mean changes in WBC# from baseline for all subjects in 'long infusion' trials^a.

WBC # Change from Baseline Day 2	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=24
WBC # (10 ³ /mm ³)	0.2 ± 1.43	0.9 ± 1.92	0.9 ± 1.66	1.8 ± 1.57

a. Data from supplemental data sets submitted at reviewer's request.

Special Studies: Incidence of Elevated WBC Counts

In the long infusion population, but not in the CHF trials population, there was an association between dose of nesiritide and incidence of elevated WBC #.

Table 8.0.11c.7 (from 11.1.4.3.1b.1) Observed rate of increased WBC # in the 'long infusion' trials^a.

Time of WBC #above normal	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^a
Baseline	14 (8%)	16 (10%)	22 (13%)	3 (12%)	0.408
Last Available on or before Day 2	2 (6%)	5 (14%)	6 (19%)	4 (25%)	0.468
Last Available	14 (10%)	16 (11%)	29 (20%)	4 (15%)	0.186

a. Data from NDA vol. 79, table 48C3. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the nesiritide dose groups and control.

There was also an increased incidence of elevated WBC # after 2 days in patients who started with a normal baseline WBC count in the long infusion studies. This trend was diminished in the later timepoints.

Table 8.0.11c.8 (from 11.1.4.3.1b.2) Observed incidence of increased WBC values after normal baseline value in the 'long infusion' trials^a.

Time of Increased WBC	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Last Available on or before Day 2	2 (6%)	4 (11%)	3 (10%)	3 (19%)
Last Available on or before Day 5	8 (7%)	8 (7%)	10 (8%)	3 (13%)
Last Available	9 (7%)	11 (8%)	15 (10%)	2 (8%)

a. Data from supplemental table 48D4. p Value per the sponsor for the entire frequency of high, normal and low lab values for the comparison between the 0.015 and 0.030 nesiritide dose groups and control.

Reviewer's Conclusions Regarding Changes in WBC Count

Two parts of this review require comment. First, the observed increases in WBC count. While no mechanism for an effect of nesiritide on WBC count is evident, the data are consistent and roughly dose-dependent in the 'long infusion' studies. There is also an increase in the % of patients in the nesiritide group who develop elevated WBC counts relative to control (with a small number of patients overall). The data are consistent with the nesiritide causing hemoconcentration, related to the extravasation of fluid and proteins such as was seen for total protein and albumin, but no data exist to test this theory. This is also consistent with the effects reported for ANP.

The second aspect to this body system review that requires comment is the increased # of SAEs due to sepsis in the nesiritide group. While the numbers are provocative (0 cases in control, 5 cases in the nesiritide group), the data are inadequate to either conclude or exclude an effect of nesiritide on this adverse event.

In conclusion, there is a possible effect of nesiritide to increase WBC count. The data are inadequate to determine whether there is an effect of nesiritide on the incidence of sepsis.

8.0.11.d Platelet Count

AEs and SAEs

The incidence of AEs related to platelet function in the 'all CHF' and 'long infusion' trials are summarized below. In the long infusion group, the only patients who developed thrombocytopenia were in the control group.

Table 8.0.11d.1 (from 11.1.3.1) AEs related to platelets in 'all CHF' trials from NDA 20-920*.

Adverse Event	Control n=235	Nesiritide n=505
Hemic & Lymphatic Thrombocytopenia	12 (5%) 2 (2%)	17 (3%) 5 (1%)
Ecchymosis	4 (2%)	4 (1%)

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.11d.2 (from 11.1.3.2) AEs related to platelets in the first 14 days in 'long infusion' trials*.

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26
Hemic & Lymphatic Thrombocytopenia	9 (5%) 3 (2%)	3 (2%) 0 (0%)	8 (5%) 2 (1%)	1 (4%) 0 (0%)
Ecchymosis	4 (2%)	1 (1%)	3 (2%)	0 (0%)

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

No SAEs related to platelet count or function were reported.

Discontinuations and Deaths

No discontinuations or deaths directly attributable to changes in platelet count were reported.

Special Studies: Measured Changes in Lab Values

The table below summarizes the changes from baseline to 2 and 5 days for platelet count. At both time points the nesiritide group tended to have a higher mean platelet count.

Table 8.0.11d.3 (from 11.1.4.2.2) Mean changes in platelet count from baseline for all subjects in CHF trials*.

Lab Test	Control n=235	Nesiritide n=505	Control n=235	Nesiritide n=505
	Change from Baseline Day 2	Change from Baseline Day 2	Change from Baseline Day 5	Change from Baseline Day 5
Platelet # (10 ³ /mm ³)			-16.5±33	-10.9±37

a. Data from NDA volumes 79-80, starting with table 31A1.

Special Studies: Incidence of Abnormal Platelet Counts

There was no trend towards a higher % of either study group developing either abnormally low or high platelet counts.

Reviewer's Conclusions Regarding Platelet Counts

Similar to the data for the WBCs, there is an indication of increased platelet counts in the patients who received nesiritide. This effect, however, did not translate into an increase in abnormal platelet counts. The mechanism of this increase is unknown, but may be related to the hemoconcentration suggested by the sponsor as an explanation for the increase in hemoglobin and hematocrit (and discussed above in the WBC section).

In conclusion, the data support a possible association between nesiritide and a transient increase in platelet count.

8.0.11e Eosinophil Count

AEs and SAEs

There were no AEs or SAEs referable to eosinophilia in the database.

Discontinuations and Deaths

No discontinuations or deaths due to changes in eosinophil count were reported.

Special Studies: Changes in Eosinophil Lab Values

Eosinophil counts were not collected in the database.

Reviewer's Conclusions Regarding Eosinophilia

The database is inadequate to assess possible effects of nesiritide on eosinophil counts.

8.0.11f Allergic Reactions

AEs and SAEs

There were no AEs or SAEs referable to allergic reactions to nesiritide in the database. As an indirect marker for allergic reactions, the occurrence of pruritus and urticaria are summarized below.

Table 11.1.6.5.1 Pruritus, rash and urticaria in the long-infusion studies through day 14^a.

	Control n=173	Nesiritide n=0.015 n=169	Nesiritide n=0.030 n=167	Nesiritide n=0.060 n=26	Nominal p Value
Pruritus	4 (2%)	6 (4%)	6 (4%)	0 (0%)	0.844
Urticaria	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0.593
Rash	5 (3%)	2 (1%)	9 (5%)	0 (0%)	0.150

a. Data from supplemental table 11D per the sponsor.

Discontinuations and Deaths

No discontinuations or deaths due to allergic reactions to nesiritide were reported.

Special Studies: Development of antibodies to Nesiritide

The sponsor collected baseline and day 21 titers of anti-nesiritide antibodies in trial 704.325. A total of 61 subjects who received nesiritide had baseline and follow-up antibody titers measured, and none of the subjects had an increase in anti-BNP antibody titers at day 21, relative to baseline.

Reviewer's Conclusions Regarding Allergic Reactions

An association between nesiritide and allergic reactions, based on the available data, is unlikely.

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8.0.12 Adverse Events in the Special Senses System

The following adverse event within the special senses system will be examined: amblyopia.

8.0.12a Amblyopia

AEs and SAEs

The incidence of amblyopia in the 'long infusion' and 'all CHF' trials is shown below. For both groups, the incidence of amblyopia was higher in the nesiritide group.

Table 8.0.12a.1 (from 11.1.3.1) Amblyopia as an AE in the CHF trials from NDA 20-920^a.

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Special Senses	5 (2%)	13 (3%)	0.803
Amblyopia	1 (0.4%)	7 (1.4%)	0.447

a. Data from NDA appendix 8.4, table 11A.

Table 8.0.12a.2 (from 11.1.3.2) Amblyopia as an AE in the first 14 days in the nesiritide infusion trials^a.

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602
Amblyopia	0 (0%)	1 (0.6%)	1 (0.6%)	0 (0%)	

a. Data from appendix 8.4, table 11C and from company at request of reviewer (table 11D). Reflects trials 311, 325, and 326 data.

Discontinuations

The only discontinuation for amblyopia occurred in the nesiritide group.

Table 8.0.12a.3 (from 11.1.5.3.1) Discontinuations due to amblyopia in the long infusion trials^a.

AE	Placebo n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value ^b
Amblyopia	0 (0%)	1 (<1.0%)	0 (0%)	0 (0%)	0.677

a. Data from supplemental table 28D, with p Value per sponsor.

Deaths

No deaths due to amblyopia were reported.

Reviewer's Conclusions Regarding Amblyopia

Here again we are faced with an adverse event occurring at a higher frequency in the nesiritide group, but with very few overall cases in the database of a very uncommon adverse event. In addition, no animal data or putative mechanism for an effect of nesiritide on the eye is apparent.

In conclusion, the data are inadequate to assess the potential effect of nesiritide on amblyopia.

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