8.1 Medical Reviewer's Conclusions Regarding Nesiritide Safety

The three tables below summarize the information discussed in the sections above, and reflect this reviewer's judgement regarding the association of each adverse event with nesiritide administration. The strength of the association between nesiritide and a given adverse event is qualified as possible, probable, or definite in the individual reviews above, based on the conclusions of the Medical Reviewer.

Table 8.1.1 Adverse Events Possibly, Probably or Definitely Linked to Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular	Hypotension	Section 8.0.2a
	Bradycardia	Section 8.0.2b
	Decreased Pulmonary Pressure	Section 8.0.2e
Urogenital System	Renal Failure[a]	Section 8.0.8a
GI System	Nausea	Section 8.0.4b
Nervous System	Confusion	Section 8.0.5a
Metabolic System	Hyponatremia	Section 8.0.6b
	Hyperglycemia/ Hypoglycemia	Section 8.0.6c
	Decreased Serum Total Protein & Albumin	Section 8.0.6e
Hemic & Lymphatic	Increased hemoglobin, hematocrit, & RBC count	Section 8.0.11a
	Increased WBC Count	Section 8.0.11c
	Increased Platelet Count	Section 8.0.11.d

a. Includes increased BUN and creatinine.

Table 8.1.2 Adverse Events that are Unlikely to be Associated with Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular	Congestive Heart Failure[b]	Section 8.0.2d
	Other Ventricular & Atrial Arrthythmias	Section 8.0.2c
Body as a Whole	Headache	Section 8.0.3a
GI System	Increased AST/ALT	Section 8.0.4a
Metabolic System	Hyper- and Hypo-kalemia	Section 8.0.6a
Hemic & Lymphatic	Allergic Reactions to Nesiritide	Section 8.0.11f
Musculoskeletal System	Myalgias	Section 8.0.10a

a. This refers to CHF reported as an adverse event, not to the efficacy of nesiritide in the treatment of CHF.

Table 8.1.3 Adverse Events for Which Inadequate Data Exist to Determine Association with Nesiritide Administration.

Body System	Adverse Event	Further Information
Cardiovascular System	ECG Abnormalities	Section 11.1.4.5
Nervous System	Dizziness	Section 8.0.5a
	Nervousness	Section 8.0.5a
Urogenital System	Severe Renal Injury[a]	Section 8.0.8a
	Urinary Abnormalities	Section 11.1.4.5
Musculoskeletal System	Leg Cramps	Section 8.0.10a
Metabolic System	Hypermagnesemia	Section 8.0.6d
Hemic & Lymphatic	Sepsis	Section 8.0.11c
	Eosinophil Count	Section 8.0.11e
Special Senses System	Amblyopia	Section 8.0.12a

a. Renal adverse events resulting in permanent loss of renal function, including nephrotic syndrome, need for dialysis, papillary necrosis, and interstitial nephritis.

9.0 Combined Efficacy/ Safety Summary of Medical Reviewer

A recent Advisory Committee meeting discussed a 'Proposed Guidelines for the Clinical Evaluation of Drugs for the Treatment of Heart Failure'. In it, approval of an agent for short-term use in CHF is to be based on the demonstration in controlled clinical trials that 4 conditions are met. Each conditions, as it appears in the draft guidance, will be followed by the Medical Reviewer's opinion about nesiritide's success in meeting that condition.

1) The drug produces favorable hemodynamic effects that can reasonably be expected to be associated with symptomatic improvement over a relevant period of treatment (typically 24-48 hours). If it is expected that physicians might select a dose based on the drug's ability to produce a specific hemodynamic effect, a wide range of doses will need to be evaluated to define the relation of dose to effect.

A hemodynamically-significant effect of nesiritide compared with placebo was demonstrated for periods up to 24 hours in two trials. The hemodynamic effects of nesiritide are dose-dependent over a relatively narrow (2-fold) range of nesiritide doses (0.3 µg/kg bolus +0.015µg/kg/min infusion up to 0.6 µg/kg bolus + 0.030 g/kg/min infusion). In trial 704.325 there was an association between the dose of nesiritide, resultant serum concentration of nesiritide and a decrease in PCWP at the end of 6 hours. The mechanism of this improvement in hemodynamics is likely a combination of the known vasodilatory properties of nesiritide, in combination with an effect of nesiritide to increase the vascular permeability to small molecules, including proteins, allowing for fluid redistribution. The relative contributions of these two effects is unknown.

The available data suggest that the pharmacodynamic effects of a given dose of nesiritide are hard to predict in a given patient, and that several hours (4-6) must pass before the maximal pharmacodynamic effect can be assessed. They also suggest that once nesiritide is discontinued, 2-4 hours pass before the pharmacodynamic effect of nesiritide is lost.

The data available do not suggest the development of 'tolerance' to nesiritide of sufficient magnitude to reverse the overall significant effects of nesiritide in the whole population, although its development in sub-groups cannot be excluded. The data do suggest that the magnitude of the hemodynamic effect decreases between 3 and 24 hours. No hemodynamic data beyond 24 hours is available. Since the primary mechanism of action of nesiritide is the same as that of nitrates, a concern is whether additional data regarding the 24-48 hour period is needed, which is when the majority of the tolerance to IV nitrates develops.

Another aspect of dosing is the interaction between nesiritide and other vasoactive compounds (e.g., nitroprusside). With the exception of IV nitroprusside, data are available on the potential interactions between nesiritide and other parenteral vasoactive compounds in trials 704.325 and 704.325. There are two parts to the data. First, no patient who first received another parenteral agents was then administered nesiritide, either alone or in combination with the other drug. This limits our ability to recommend nesiritide dosing for patients who begin one vasoactive compound, and the physician considers starting nesiritide. Second, there were patients in both trials who were started on other vasoactive compounds after starting nesiritide. For patients stopping nesiritide and starting another agent, there were 59 such patients. For patients being co-administered another vasoactive compound with nesiritide, there were 50 such patients.

2) Use of the drug at doses within a defined therapeutic range produces (1) an improvement in symptoms and/or stabilization of clinical status; (2) a meaningful improvement in end-organ function that is deemed to be clinically relevant; (3) a decrease in the need for or duration of intensive care, specialized interventions or hospitalization; and/or (4) a reduction in the risk of death.

Use of the drug at doses within a defined therapeutic range

The therapeutic range defined by the trials in the NDA is narrow as discussed above. There is insufficient data to determine if there will be an interaction between nesiritide and other vasodilators that also act through the cGMP-dependent pathways (especially nitrates such as NTG and nitroprusside).. The higher dose of nesiritide (0.060) was not used in the two pivotal infusion studies (704.325, 704.326), related to the increased incidence of hypotension in that population in trial 704.311. Lower doses of nesiritide (<0.015µg/kg/min) were not adequately evaluated to determine their clinical efficacy, although the bolus studies suggest they have hemodynamic effects.

The use of nesiritide is also associated with another potential problem not shared by other available therapies that work by activating the cGMP-dependent protein kinase (NTG, nitroprusside): long pharmacodynamic half-life. Depending on the data used, the half-life of hemodynamic effects for nesiritide is approximately 2-3 hours, compared with minutes in the case of NTG and nitroprusside. This means that once the drug is started, no reasonable inference regarding its peak effect can be made before at least 6 hours has passed. It also means that the drug will have a persistent hemodynamic effect following withdrawal. These two properties will make this drug more difficult to titrate, as well as more difficult to manage any observed side-effect.

2) Use of the drug at doses within a defined therapeutic range produces (1) an improvement in symptoms and/or stabilization of clinical status; (2) a meaningful improvement in end-organ function that is deemed to be clinically relevant; (3) a decrease in the need for or duration of intensive care, specialized interventions or hospitalization; and/or (4) a reduction in the risk of death. (cont)

(1) Improvement in symptoms and/or stabilization of clinical status

Trial 704.325

With regard to improvement in symptoms, nesiritide was significantly better than placebo in one trial at improving the signs and symptoms of CHF through 6 hours. This trial (704.325) compared the effects of nesiritide in 85 patients with placebo in 42 patients. The weaknesses of the data collection in this trial have been discussed above, and these severely limit the independence of the symptom-relief and hemodynamic data for this trial. Since the same investigator who performed the investigator's assessment also filled out the patient's assessment, these data cannot be taken as independent (especially since the investigator also knew the PCWP data). In addition, the trial had some potentially confounding demographic imbalances at baseline, most significantly the higher percentage of females in the nesiritide high-dose group (40%) compared with placebo (21%). There was good agreement between the investigator's and patient's assessments of clinical status, and the symptomatic benefit was seen for both global assessments and for individual signs and symptoms at the end of 6 hours. These improvements, however, extended to 'symptoms' for which a change within 6 hours is highly suspicious (i.e., appetite, edema), again calling into question the validity of the data.

The sponsor also demonstrated an association between the degree of change in PCWP and an improvement in the global assessment score using data from trial 704.325. This, in combination with the earlier association between the dose of nesiritide and the degree of change in hemodynamics (especially PCWP), would support a link between the doses of nesiritide used in the trials, a pharmacodynamic effect (decreased PCWP) and a clinical outcome (improved Global Assessment score after 6 hours). These data suffer from the same problems discussed above.

Finally, the data from trial 704.325 suggest a small effect of nesiritide to decrease the median respiratory rate through 6 hours, relative to placebo. This difference was small (2 breathes per minute).

Thus, while the data, if replicated and convincing, could provide data for a beneficial effect of nesiritide on CHF symptoms, given the problems discusses above, they should be viewed as suggestive, and not definitive.

Trial 704.326

In study 704.326, the effect of nesiritide was compared with the current parenteral standards of care (nitroprusside, dobutamine, and dopamine). Through the end of 24 hours of study drug infusion, the effects of nesiritide on symptomatic benefit were similar to those of the standard agents. Overall, the effects of nesiritide and the active controls on CHF symptoms were similar, with no indication of superiority for nesiritide.

(2) a meaningful improvement in end-organ function that is deemed to be clinically relevant; (3) a decrease in the need for or duration of intensive care, specialized interventions or hospitalization; and/or (4) a reduction in the risk of death.

Nesiritide had no significant or clinically relevant beneficial effects on any end organ function, need for/or duration of intensive care, specialized interventions or hospitalization, or a reduction in the risk of death. As discussed above, there is persuasive evidence for an adverse effect of nesiritide on renal function, as marked by changes in serum creatinine. There is less definite evidence suggesting a beneficial effect of nesiritide to reduce ventricular arrhythmias.

3) Withdrawal of the drug or substitution of oral therapy (with any agent) for the drug is not associated with relapse or rebound phenomena, so that any short-term benefit can be sustained.

In the one long infusion trial, enrolling 'stable' decompensated CHF patients, when the effects of nesiritide withdrawal on PCWP were evaluated (704.311), no evidence of rebound or relapse was detected. In two other trials, which enrolled a more acutely decompensated CHF population (704.325 and 704.326), there was no clear evidence that patients withdrawn from nesiritide had a higher rate of re-hospitalization for CHF, compared with active controls.

4) Short- and long-term follow-up of patients treated with the drug for short periods does not reveal important safety concerns that would discourage its use.'

Follow-up through approximately 21 days revealed that nesiritide administration was possibly, probably, or definitely associated with several safety concerns, both short- and long-term. Of these adverse events, the increased incidence of hypotension, bradycardia, and the development of abnormal renal function are most worrisome.

Hypotension

There is a definite association between nesiritide use and clinically-significant hypotension, as assessed by:

1) the greater incidence of symptomatic hypotension in the nesiritide groups.

2) the increased incidence of discontinuations for decreased BP.

3) the greater severity of the hypotension in the nesiritide groups, as judged by degree of decrease in blood pressure, severity as judged by investigators, or duration.

4) the presence of individuals who developed hypotension during nesiritide infusion who had clearly adverse clinical outcomes and/or required additional medical interventions (see table 8.0.2b.20).

5) data from trial 704.326, comparing nesiritide with current therapy, which shows that hypotension leading to discontinuation of drug within 6 hours of initiation was significantly more common with nesiritide. These data are of particular interest, since they suggest that the use of nesiritide in practice will lead to significantly more hypotension than is caused by the drugs in current use. This statement is limited by the fact that 704.326 enrolled very few patients who received pure vasodilators (IV 18 got NTG, none NTP). There is, then, no way to know the frequency of these same adverse events for the other pure vasodilators (NTG, NTP). Given that the pharmacodynamic half-life of these agents is significantly shorter, it is possible that fewer episodes of severe hypotension or renal failure would be seen with these agents.

This effect is dose-dependent over the range of nesiritide doses tested in the three long infusion trials, with the highest incidence of severe hypotension seen in the 0.30 and 0.060 nesiritide dose groups.

Bradycardia

With regard to bradycardia, there is a definite association between nesiritide use and bradycardia, including bradycardia requiring medical intervention. More individuals in the nesiritide group were discontinued due to bradycardic events. In addition, some individuals who developed bradycardia with nesiritide required additional medications, including pressors, fluids, and atropine.

Renal Failure

There is a definite association between nesiritide use and the development of abnormal renal function, both assessed by elevated BUN/Creatinine and by the occurrence of adverse renal events. The incidence of a >50% increase in serum creatinine was nominally significantly higher in the nesiritide group in trial 704.326, as was the incidence of increases >0.5 mg/dl. Both of these measures identify populations who have developed significant renal compromise. There were also individuals who developed progressive increases in BUN/Crt consistent with a significant renal insult during and following nesiritide infusion. The clinical consequences of the renal failure are also not yet fully established, but the data suggest the majority of individuals who had renal injury in the infusion trials recovered to near baseline given sufficient follow-up. The database is too small to conclude that no patients will suffer clinically significant adverse renal events associated with the use of nesiritide.

Further, in the absence of urinalyses, some forms of renal injury could not be detected (especially nephrotic syndrome). Further, absent urinalyses, no firm conclusions can be drawn about the etiology of the observed increases in serum creatinine in the nesiritide groups (i.e., interstitial nephritis, acute tubular injury, and 'pre-renal' azotemia).

Another issue that complicates the effects of nesiritide on end-organ perfusion, and by extension on the incidence of renal damage, is the unknown contribution of nesiritide effects on vascular permeability. That effect is real is suggested by the data from ANP, as well as with the observed hemoconcentration that occurred during nesiritide infusion. The effect of this hemoconcentration will be to remove salt and water from the vascular space, where it is 'accessible' to the kidneys (and can then be excreted), and to translocate it to the interstitium. This observation may help explain the anti-natriuresis seen in the first 24 hours in study 704.311. It would also lead to a prediction of increased renal toxicity for patients who begin the trial with marginal perfusion of their kidneys. While such an insult is potentially reversible in most patients, there will likely be an increased incidence of severe renal injury in patients where their volume status is less carefully monitored than was the case in the NDA trials. If investigators follow weights as markers for fluid loss, they will be overly aggressive with their use of diuretics, as they will see no net weight loss. What they will miss is the fluid translocation, which will have the effect of fluid removal from the intravascular space, placing the kidneys at increased risk of injury from inadequate perfusion.

Other Adverse Events

Of the other adverse events, several of them can be linked via an effect of nesiritide to alter vascular permeability (increased RBCs, increased platelet count, increased WBCs, decreased total protein, decreased albumin). If this mechanism is operant, as has been reported for ANP and postulated by the sponsor (refs. 1, 6, 10, 13), then part of the hemodynamic effects of nesiritide may be related not to its vasodilatory properties but rather to its stimulating transudation of proteins (albumin, total protein) followed by water. Depending on the reversibility of this effect following nesiritide withdrawal, this might increase the risk of damage to critical organs (such as the kidney, as discussed above) by decreasing the effective intravascular volume in a way that is not amenable to withdrawal of the drug. In support of this speculation, the effects of nesiritide on total protein and albumin persisted beyond the period of nesiritide infusion (see section 8.0.6e above).Finally, there are some adverse events possibly linked to nesiritide administration, for which the data are inadequate to assess their clinical relevance. These include the small changes in electrolytes, hypo- and hyperglycemia, nausea and confusion.

Recommendations of Medical Officer

The data clearly demonstrate a significant hemodynamic effect of nesiritide that is dose-dependent and persists for at least 24 hours. Nesiritide was assessed over a narrow dose-range that is insufficient to detail the association between a given dose of nesiritide and the anticipated hemodynamic effect. Lower doses of nesiritide, with potential hemodynamic effects, were not explored adequately. The available data does show a dose-response curve for the administration of nesiritide and changes in hemodynamics, especially PCWP. Following discontinuation of nesiritide, hemodynamics return to baseline within 4 hours, without evidence for 'rebound.' While the effect of nesiritide on mean hemodynamics may diminish slightly with time, the significant effects of nesiritide on hemodynamics compared with placebo persist through 24 hours. Insufficient data are available to comment on the following critical aspects of use:

1) information about the use of nesiritide in patients who are already taking other parenteral CHF therapies (especially other vasodilators),

2) . information regarding the use of nesiritide in patients with CHF and myocardial infarction (these patients were excluded from the three pivotal trials),

3) information regarding the titration of nesiritide to achieve desired clinical effect,

4) information regarding the development of tolerance beyond 24 hours (where tolerance to nitrates develops), and

5) information about the effects of nesiritide at infusion doses below 0.015 μg/kg/min.

The link between nesiritide administration and clinical benefits is tenuous, with a single study (704.325) supporting a greater acute effect of nesiritide than placebo on the signs and symptoms of CHF through 6 hours. While this trial also suggest a link between the clear effects of nesiritide on PCWP and the observed improvement in signs and symptoms of CHF, problems in the collection of these data undermine their independence and strength. Another piece of data supporting a salutary effect of nesiritide on CHF is the small decrease in respiratory rate seen in the nesiritide groups, when compared with placebo. The data from trial 704.326 suggests that the effects of nesiritide on CHF signs and symptoms is comparable to the active controls with regard to symptomatic relief over the first 24 hours of therapy, although the data collection was, again, open-label. No other beneficial or adverse clinical effect of nesiritide (i.e., re-hospitalization rate, mortality rate) was suggested by the data in the NDA.

With regard to the safety profile of nesiritide, two features of nesiritide predict that its use will be associated with significant clinical adverse events. First, it operates via the same mechanism as currently available therapies (NTG, nitroprusside) with the added disadvantage of prolonged pharmacodynamic half-life. This prolonged half-life will make its use more difficult than for current therapies, and may increase the risk of adverse events and the need for hospital interventions (e.g., for prolonged hypotension).

Second, the administration of nesiritide under study conditions was associated with clinically significant adverse events at a higher rate than the comparators (either placebo or the active controls). Most concerning in this regard, severe hypotension was significantly more common following nesiritide use, compared with either the currently available parenteral therapies for CHF or with placebo. Unfortunately, no risk factors to identify patients at high risk for these hypotensive episodes were found. Bradycardia and adverse renal events were also more common following nesiritide use. While more data is needed to place the risk of these adverse events into clinical context, the NDA does suggest that some patients taking nesiritide will suffer significant clinical consequences related to these adverse events.

Recommendations of Medical Officer (cont)

Third, with regard to less common adverse events, inadequate data are available to fully assess the clinical consequences of some of the more potentially serious adverse events associated with nesiritide use, as well as for several other adverse events with potential clinical relevance (e.g., hypermagnesemia, hyperglycemia). In particular, the database is insufficient to exclude severe effects on the kidney, in part because of the absence of urinalysis data, and on the liver.

Nesiritide, then, has a demonstrated hemodynamic effect that is superior to placebo and persists through at least 24 hours. There is a suggested effect of nesiritide to relieve some of the acute symptoms of CHF, similar to currently available therapies. The available data are insufficient to demonstrate superiority of nesiritide to placebo with regard to symptom relief, which appears at best to be similar to the effects of other currently available parenteral therapies. Nesiritide use is associated with several clinically relevant adverse effects, especially hypotension. The prolonged pharmacodynamic half-life of nesiritide predicts that this hypotension will be more difficult to manage than for currently available therapies that work by the same intracellular mechanism (NTG, nitroprusside). Finally, the database is inadequate to address several important questions regarding its use: concomitant use of other parenteral vasodilators, potential titratability of nesiritide, the use in patients with acute myocardial ischemia, potential effect of nesiritide on vascular permeability, potential for the development of tolerance beyond 24 hours, and effective lower dose. With the availability of other therapies also working through the cGMP-dependent protein kinase to cause vasodilatation that have a shorter pharmacodynamic half-life, the presence of significant safety concerns, and the inadequate database, nesiritide is not approvable.

APPEARS THIS WAY
ON ORIGINAL

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HFD-110 Division File

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11.0 Appendix One: Methodologies Used for Safety Review

The safety review is broken into three logical sections, two of which appear in this appendix:

11.0 Methodologies used for Safety Review

11.1 Background Database for Safety Review

The third part of the safety review, the Integrated Review of Safety, is found in section 8.0 above.

11.0 Methodologies Used for Safety Review

11.0.1 Subsections of the Integrated Safety Review and Preliminary Comments

Section 11.0 will use the following outline:

1) Source materials for the safety review, including the numbers of subjects exposed in each of the treatment groups, along the extent of exposure;

2) General methodologies used to elicit adverse events within the database;

3) Specific search strategies used in the nesiritide database.

11.0.2 Source Materials and Methods for the Integrated Safety Review

The nesiritide NDA database includes 8 clinical trials in CHF, as summarized below. Details of the data submitted for each of these trials is to be found in sections 1.1 and 5.1 above, as well as in the reviews of each study. No follow-up safety data collected after submission of the NDA is available to this reviewer.

Table 11.0.2.1 (from table 5.1.1.1) Number of subjects in the trials submitted as part of the NDA database, grouped according the study drug administered[a].

Protocol	Control	Nesiritide	Trial Design
Phase II Dose-Ranging Studies			
704.305	6	24	Randomized, double-blind, placebo-controlled, single-dose bolus (0.3, 1,3, 10 or 15 µg/kg/min vs. placebo) study measuring hemodynamics.
704.306	4	12	Randomized, double-blind, placebo-controlled, four hour infusion (0.025 or 0.05 µg/kg/min vs. placebo) study measuring hemodynamics, neurohormone levels and renal function.
704.307	N/A (19)[b]	20	Randomized, double-blind, placebo-controlled, cross-over, escalating dose-infusion (0.003, 0.01, 0.03, and 0.1 µg/min) study measuring hemodynamics and renal function.
704.309	16	44	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (5 or 10 µg/kg q4 hours for 24 hours or 10 µg/kg q6 hours) were compared with placebo for hemodynamics & renal function.
704.310	17	43	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (3, 5, or 10 µg/kg q4 hours for 24 hours) were compared with placebo for effects on hemodynamics and renal function.
704.311	29	74	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Three doses (0.25 µg/kg bolus, then 0.015 µg/kg/min,0.5 µg/kg bolus, then 0.03 µg/kg/min, or 1.0 µg/kg bolus, then 0.06 µg/kg/min) as a 24-hour fixed dose infusion were compared with placebo for an effect on hemodynamics and renal function.
Phase III Clinical Efficacy & Safety Studies			
704.325	42	85	Randomized, double-blind, placebo-controlled, parallel-design, dose-ranging study. Two doses (0.3 µg/kg bolus, then 0.015 µg/kg/min, or 0.6 µg/kg bolus, then 0.03 µg/kg/min for 24 hours of continuous infusion) were compared with placebo (for 6 hours, followed by active control) for effects on hemodynamics and renal function, and symptomatic improvement in CHF.
704.326	102	203	Randomized, open-label, parallel-design, dose-ranging study. Two doses (0.3 µg/kg bolus, then 0.015 µg/kg/min, or 0.6 µg/kg bolus, then 0.03 µg/kg/min via continuous infusion) were compared with 'standard care' for effects on renal function, weight loss, duration of hospitalization, need for additional parenteral therapies, need for readmission, need for intubation, need for dialysis or ultrafiltration, and symptomatic improvement in CHF. Duration of infusion at discretion of individual investigators.
Total	**216**	**505**	

a. Data from NDA volume 78, table 1.

b. Cross-over designed trial.

Of the eight clinical trials in CHF, there were two clinical trials that primarily support the efficacy of the drug: 1) A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Dose-Ranging Study to Evaluate the Safety and Efficacy of a 24 Hour Intravenous Infusion of Natrecor hBNP in Subjects with Congestive Heart Failure (Trial #704.311, abbreviated Trial 311 in this review); and 2) A Randomized, Double-Blinded, Placebo-Controlled Study of Two Doses of Natrecor hBNP Administered as a Constant Infusion in Subjects with Decompensated CHF (Trial #704.325, abbreviated Trial 325 in this review). A third, open-label trial was also performed which included a substantial fraction of the total patient database, and focused on the safety of nesiritide in the decompensated CHF population (Trial #704.326, abbreviated Trial 326 in this review).

11.0.2 Source Materials and Methods for the Integrated Safety Review (cont)

Demographics

The demographics of the NDA population were summarized in section 5.1.2 above. Overall, the populations of the treatment groups were well-balanced, although in the placebo-controlled CHF trials the placebo group had a higher percentage of females and subjects >65 years of age (see table 5.1.2.2).

Natrecor Dose Exposure

The numbers of patients exposed to nesiritide at specified doses and durations are summarized in the tables below. Overall, 361 patients (71% of all subjects who got nesiritide) received ≥0.015 µg/kg/min of nesiritide (the lowest dose proposed for use by the sponsor). In addition, a total of 394/505 (78%) of the patients who received nesiritide got it in an infusion. The longest continuous infusion of nesiritide was 214.2 hours (approximately 9 days), and the longest interrupted exposure to nesiritide was 283.2 hours (approximately 12 days). The first table summarizes the data for the subjects who received nesiritide as an infusion.

Table 11.0.3.1 (from 5.1.3.1) Subjects enrolled in nesiritide infusion studies in NDA 20-920[a].

Duration of Infusion	Control		Infusion Nesiritide [b]			
	Placebo	Std. Care	<0.015	≥0.015-<0.020	0.020-<0.035	>0.035
0-12 hrs	26	5	3	25	36	20
12-26 hrs	26	33	17	71	62	16
26-50 hrs		28	8	27	33	
50-100 hrs		48	4	23	21	3
>100 hrs		30	1	11	10	3
Total	52	144	33	157	162	42
% of all Nesiritide subjects (n=505)	--	--	6%	31%	32%	8%

a. Data from NDA volume 78, page 192, and supplemental material requested from sponsor.

b. Mean infusion dose in µg/kg/min. Any subject who received nesiritide at 0.015 µg/kg/min, and had their dose reduced at any time were counted in the <0.015 group (there were 18 such patients).

The next table summarizes the data for the subjects who received nesiritide as a bolus during any of the studies in the NDA.

Table 11.0.3.2 (from 5.1.3.2) Subjects in bolus studies with nesiritide in NDA 20-920[a].

	Control		Bolus Nesiritide	
Bolus Studies	Placebo	Std. Care	≤21 µg/kg	>21 µg/kg
	39	0	45	66
% of all Nesiritide subjects (n=505)	--	--	9%	13%

a. Data from NDA volume 78, page 192, and supplemental material requested from sponsor.

Collection of safety data

The collection of safety data varied somewhat from trial to trial. The timing of safety data collection for the three largest trials (311,325 and 326) are summarized in the three tables below.

In trial 704.311 adverse events were collected during the infusion and through day 14 after the end of infusion. Collection of other relevant safety data, including labs and vital signs, is shown below.

Table 11.0.3.3 (from 6.1.10.1) Timetable for clinical observations and lab measurements in trial 704.311[a].

	Pre-infusion	Start infusion				Stop Infusion	Post-Infusion			
Time (hrs)		0	6	12	24	48	Day 1	Day 7	Day 15	Day 20-30
Drug Infusion										
History & Physical	X						X			
Vital Signs	X									
ECG	X									
Urine Collection (24 hr)										
CPK with isoenzymes										
Laboratories[c]	X	X					X			X
Hematology[c]	X	X					X			X
Plasma nesiritide		X	X	X	X	X	X			
Plasma nesiritide Ab		X								X
F/U Telephone call								X	X	
Adverse Events (AEs)										

a. Data from NDA volume 54, page 24.

b. Swan-Ganz catheter discontinued 4 hours after completion of infusion or when medically appropriate.

c. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol).

In study 704.325, adverse events were collected through day 14 post-treatment as reported by investigators. Additionally, on day 21, the subject's clinical course was reviewed with regard to the following: mortality status; duration of initial hospitalization; need for re-admission during the 21-day period; length of time on parenteral therapy for CHF; and the need for intubation, dialysis, and ultrafiltration.

Table 11.0.3.4 (from 6.2.10.1) Timetable for clinical observations and lab measurements in study 704.325[a].

Procedure	Screen	Baseline	Treatment Period											Post-Treatment		
Time			0	1.5	3	4.5	6	24	36	48	Day 3	Day 4	Day 5	<24 hrs after IV Tx	14	21
Med Hx, Physical Exam	X													X		
ECG	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X						
CBC, Chemistries[b]		X												X		
Plasma hBNP levels		X					X	X[e]								
Renin, aldo, norepi levels		X					X	X[f]								
hBNP Antibody level		X														X
I/Os, weights			X	X	X	X	X	X	X	X	X	X	X			
Na, K, CO_2, Cl, Crt, BUN								X		X	X	X	X			
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	
F/U Visit																X
Study Drug			X	X	X	X	X	X	X	X	X	X	X[g]			

a. Data from NDA volume 59, page 25.

b. Labs and hematology collected include: CBC (hemoglobin, hematocrit, WBC count and differential, platelet count); serum chemistries (BUN, creatinine, total bilirubin, AST/ALT, glucose, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol).

c. See Dosage/ Administration section above for description of protocol for withholding cardiac meds.

d. Swan-Ganz to be removed after 24 hours if medically appropriate. Cardiac measurements to be done as long as S-Ganz present.

e. Nesiritide subjects only.

f. Norepinephrine levels at selected sites only

g. Administration after 24 hours at discretion of investigator.

The table below details the type and timing of the clinical information collected during study 326. In general, AEs were collected through 14 days. Serious adverse events and deaths occurring within 21 days were also to be reported by the investigators.

Table 11.0.3.5 (from 6.3.10.1) Timetable for clinical observations and lab measurements in the study 326[a].

Procedure	Pre-infusion	Study Drug Infusion						Post-Infusion		
Time (hrs)		0	1	2	4	6	24[e]	Within 24 hrs	Day 14	Day 21
Informed Consent	X									
Medical History/ PE	X									
ECG	X									
Holter Monitors[f]	See Note									
CXR	X									
D/C Parenteral Cardiac Meds	X[b]									
Vital Signs	X	X	X	X	X	X	X[c]			
CBC, Chemistries[d]	X							X		
Anti-BNP antibody level	X									X
Assess Signs/ Sxs of CHF	X					X	X	X		
Assess Global Clinical Status						X	X	X		
Study Drug Administration		X	X	X	X	X	X	X		
Daily Weight							X			
Daily Na, K, CO_2, Cl, Crt, and BUN							X			
Adverse Event Collection										
F/U Visit										X

a. Data from NDA volume 66, page 14.

b. Parenteral meds to be discontinued only if taken for <4 hours. Patients who received parenteral therapy for CHF for >4 hours before entry were not eligible for the study.

c. Includes period during total period of parenteral therapy. Vital signs were obtained every 4 hours during the parenteral therapy.

e. Includes tests performed during extended parenteral therapy.

f. Holter monitors were performed at 15 sites for a maximum period during 72 hours of infusion.

11.0.4 General Methodologies Used for Safety Review

This section details the examination of AEs in the nesiritide safety database. In general, this was accomplished by examination of two data sets. The first comes from all patients with CHF who received nesiritide as part of the NDA. This will be used especially for overall adverse events incidence and for changes in measured values (labs, vital signs). The other primary data set used for analysis comes from the three 'long infusion' studies, which have been reviewed individually earlier in this review. This set will also be used for AEs, including measured AEs. The examination of dose-response effects of nesiritide will also use this data set. Wherever possible, all AEs potentially linked to the administration of nesiritide are further examined for dose-, time-, sex-, age-, race-dependency. The impact of other medications (ACE inhibitors, beta blockers, and digoxin) and the original etiology of the CHF will also be considered where possible. The small number of adverse events reported for many of the subgroups will complicate these examinations. The sponsor has prepared the majority of the data sets examined, and no independent confirmation of their accuracy has been performed. Any primary analysis performed by FDA reviewers will be identified as such. Unless stated otherwise, all p Values are per the sponsor, and the reader is referred to their documents for details of statistical analysis.

The data tables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation wherever possible. For all data presentation, nominal statistical significance (relative to placebo or baseline at a $p<0.05$) will be indicated by the use of shading for the relevant data. In many cases, the sponsor-derived p Value will also be stated. Details of the statistical methodology used by the sponsor to derive individual p Values are to be found in the NDA submission.

The comparative rates of adverse events for the three nesiritide dose groups also requires comment. With only 26 subjects in the highest nesiritide dose group (0.060 µg/kg/min), adverse event rate comparisons with the other nesiritide dose groups need to be interpreted with great caution.

A note also needs to be made about the conventions used for the labels in the data summary below. The long infusion trials had small differences in the doses of nesiritide used, especially with regard to the dose of the nesiritide bolus prior to the start of the infusion.

704.311

There were four treatment groups in study 704.311:

Group 1: Nesiritide: IV **bolus of 0.25 µg/kg** followed by a 0.015 µg/kg/min infusion.
Group 2: Nesiritide: IV **bolus of 0.50 µg/kg** followed by a 0.030 µg/kg/min infusion.
Group 3: Nesiritide: IV **bolus of 1.0 µg/kg** followed by a 0.060 µg/kg/min infusion.
Group 4: IV bolus of placebo followed by a placebo infusion.

704.325

There were three treatment groups in study 704.325:

Group 1: Nesiritide: **IV bolus of 0.3 µg/kg** followed by a 0.015 µg/kg/min infusion.
Group 2: Nesiritide: **IV bolus of 0.6 µg/kg** followed by a 0.030 µg/kg/min infusion.
Group 3: IV bolus of placebo followed by a placebo infusion.

704.326

There were three treatment groups in study 704.326:

Group 1: Nesiritide: **IV bolus of 0.3 µg/kg** followed by a 0.015 µg/kg/min infusion.
Group 2: Nesiritide: **IV bolus of 0.6 µg/kg** followed by a 0.03 µg/kg/min infusion.
Group 3: A standard care agent.

In presenting the safety data, the doses of nesiritide have been 'lumped' according to their infusion dose. These will be listed as nesiritide 0.0.015 or 0.015 µg/kg/min, nesiritide 0.030 or 0.30 µg/kg/min, or nesiritide 0.060/ 0.060 µg/kg/min. Given the small number of patients available for the safety summary, this 'lumping' was judged by the Medical Reviewer as in the interest of effective review. Where individual trial data is summarized, the bolus information will be included that is correct for the trial in question.

11.0.4.1 Approach to Eliciting Deaths and Serious Adverse Events

In the nesiritide NDA, an adverse experience (AE) was considered serious if the event resulted in one of the following: death; permanent or substantial disability; inpatient hospitalization; prolongation of existing inpatient hospitalization; cancer; or congenital anomaly. An adverse experience was also considered serious if it was considered to be immediately life-threatening, or was identified as such by the individual investigator. Overdoses (accidental or intentional) were also considered to be serious adverse experiences, whether or not they resulted in any clinical sequelae.

The clinical trials, including 704.311, 704.325, and 704.326, were performed under the auspices of an independent DSMB. As specified in the respective protocols, the DSMBs had access to interim, unblinded safety reports throughout the conduct of the trials. After discharge from the initial hospitalization through the 21-day follow-up period, all events meeting the definition of a serious adverse event were to be reported to the sponsor.

For AEs and SAEs, the two data sets that will be scrutinized include:

1) the set of all trials in CHF patients, including 235 control patients and 505 nesiritide, and

2) the set of trials using infusions of nesiritide in CHF patients, which enrolled 173 control and 362 nesiritide patients.

The summary tables below will focus on the 'CHF trials' population and the 'long infusion trials'. There were three trials that used infusions of nesiritide lasting ≥24 hours (704.311, 704.325, and 704.326), and all have been reviewed elsewhere in this review document. The data from a third set of safety analyses performed by the sponsor, from the 'placebo-controlled CHF trials' will be used infrequently.

11.0.4.2 Approach to Eliciting Adverse Events

Adverse experiences were defined as any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body or worsening of a preexisting condition temporally associated with the use of the study drug (active drug, control agents or placebo), whether or not they were considered to be related to the use of the product. Clinical adverse experiences determined by the investigator or volunteered by the patient were recorded throughout the study reporting period. Results from laboratory tests and any special examinations (i.e., physical examinations including vital signs, electrocardiograms, etc.) also were reviewed by the investigator to determine if any of the findings were adverse experiences.

When an adverse experience occurred, the investigator recorded pertinent information about the event on the case report form, including: date and time of onset; whether the event was a serious adverse experience; the relationship of the adverse experience to the study drug; the action taken regarding the test drug (i.e., none or drug discontinued); or whether the adverse experience caused the patient to be discontinued from the study. Additionally, for clinical adverse experiences, the investigator recorded the maximum intensity of the event, the date the adverse experience stopped, and its duration. Maximum intensity was recorded using a three-point scale of intensity: mild (easily tolerated); moderate (interfering with usual activity); or severe (incapacitating). The investigator using a five-point scale as follows graded the relationship between the adverse experience and the test drug: definitely not, probably not, possibly related, probably related, or definitely related.

After discharge from the initial hospitalization through a 14-day follow-up period, all clinical endpoints meeting the definition of adverse events were reported to the sponsor.

11.0.4.3 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

The sponsor mapped the terms used by the individual investigators to describe individual adverse events to COSTART terminology.

11.0.4.4 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

Key adverse event, in this usage, means an adverse event that will be discussed because it may be linked to the use of nesiritide. First, any adverse event identified in the nesiritide safety database occurring in >1% of the subjects in any group will be tabulated, and the percentage compared. Those AEs that occur with a differential frequency between the treatment and control groups will be examined, and if there is a consistent pattern, discussed further. Other adverse events, normally examined as part of usual NDA review, will also be included.

The occurrence of any adverse event linked to the administration of other natriuretic peptides will be explored. Hypotension is the primary AE identified in this way.

11.0.4.5 Laboratory Adverse Event Incidence

Laboratory safety measurements (hematology, serum chemistry, urinalysis, and miscellaneous) were performed at regular intervals during the clinical trials reported in this submission (see tables above). Since not all patients had all laboratory tests performed, the denominator for a laboratory adverse experience varies, and is the number of patients who had that laboratory test performed. The reporting of any laboratory adverse experience was always dependent on the individual investigator's assessment of its clinical importance. Thus, laboratory values within or outside the normal range could be interpreted as adverse by one investigator and not by another.

11.0.4.5.1 Extent of Laboratory Testing in the Development Program

The table below summarizes the collection of laboratory data in the Phase II-III database.

Table 11.0.4.5.1.1 Timing of laboratory data collection in the trials forming the NDA 20-920 safety database[a].

Study	Complete Lab Values[c]	Hematology[b]	Na^+, K^+, Cl^-, HCO_3, Crt, BUN
311	0 and within 24 hrs of infusion end, and at 20-30 days after infusion	0 and within 24 hrs of infusion end, and at 20-30 days after infusion	--
325	0, and within 24 hrs of infusion end	0, and within 24 hrs of infusion end	24 & 48 hours after start of infusion[d]
326	0, and within 24 hrs of infusion end	0, and within 24 hrs of infusion end	24 hours after start of infusion[d]

a. Data from respective study reviews.

b. Hematology includes hemoglobin & hematocrit.

c. A complete lab evaluation included: CBC with differential; serum chemistries (electrolytes, BUN, creatinine, ALT/AST, albumin, calcium, CPK, glucose, magnesium, phosphate, and bilirubin); urinalysis (for protein, glucose, blood, and bilirubin).

d. Then daily during study drug infusion.

Follow-up for abnormal laboratory findings

Investigators were instructed to provide outcome for all adverse experiences, and it was expected that abnormal laboratory values would be followed through resolution. No specific follow-up criteria were outlined, however, for abnormal laboratory values.

11.0.4.6 Specific Search Strategies Unique to the Nesiritide Review

The majority of the estimates of incidence of specific AEs will be based on the pooled data from the nine studies using nesiritide in patients with CHF. Where relevant, specific explorations for drug-disease interaction (i.e., hypertension, pre-existing hepatic disease), and drug-drug interactions will also be carried. These will utilize subsets of the larger population as appropriate.

11.1 Background Database for Safety Review

In the integrated safety summary, adverse events will be examined in the following order:

1) Deaths;
2) Serious Adverse Events (SAEs);
3) Adverse Events (AEs) related to clinical findings;
4) Adverse Events related to laboratory findings and special examinations;

and 5) Subject discontinuations.

Following this, selected adverse events will be examined, using the phase II-III database:

1) Special studies, including tolerance, overdose, withdrawal/ rebound, abuse potential, and human reproduction;

2) Selected adverse events linked to the administration of nesiritide or other natriuretic peptides from other INDs/ NDAs, or the literature.

and 3) Selected adverse events examined during normal examination of safety as part of all NDA reviews, including subgroup analyses of adverse events according to gender, race, age, and common clinical characteristics.

The data tables below have been submitted to the sponsor to allow for correction of typographical or other errors of presentation wherever possible. For all data presentation, nominal statistical significance (relative to placebo or baseline at a $p<0.05$) will be indicated by the use of shading for the relevant data. In some cases, the sponsor-derived p Value will also be stated. Details of the statistical methodology used by the sponsor to derive individual p Values are to be found in the NDA submission.

11.1.1 Deaths in the Nesiritide Safety Database

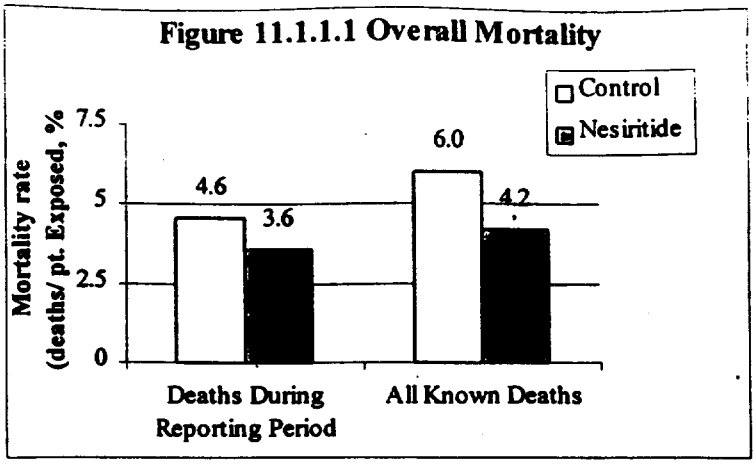
There were a total of 28 deaths occurred during the reporting periods of the CHF trials. An additional 6 deaths that occurred after the reporting period are also known to the sponsor. The first table summarizes the number of deaths and the number of patients for two relevant patient populations: all known deaths from all studies; and all known deaths from the nesiritide infusion studies (311, 325 and 326). The incidence of deaths during the studies is also tabulated. In this table the placebo patients from 704.325 are included in the placebo group. In that trial, patient in both placebo and nesiritide groups could receive active parenteral therapy after 6 hours.

Table 11.1.1.1 Known deaths in NDA 20-920[a].

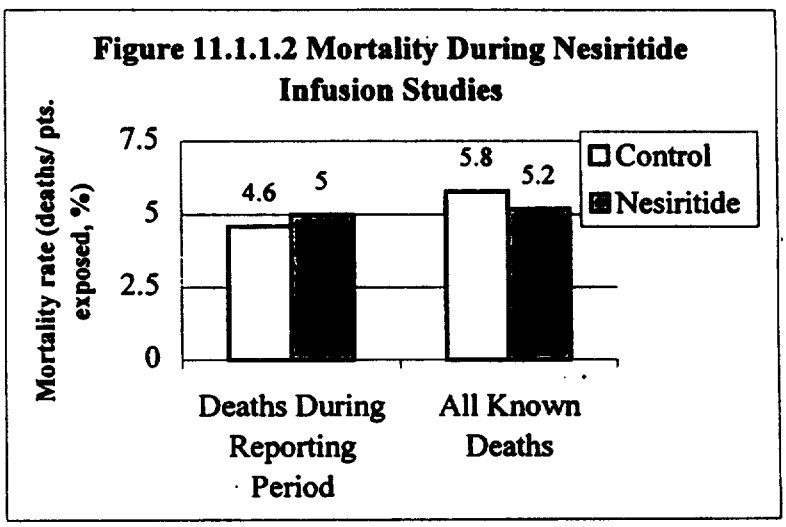
Group	Placebo	Active Control	Nesiritide Groups				Total Nesiritide
			Bolus	0.015 µg/kg/min	0.030 µg/kg/min	0.060 µg/kg/min	
	n=114[c]	n=102	n=143	n=169	n=167	n=26	n=505
All Known Deaths	8 (7.0%)	5 (4.9%)	2 (1.4%)	8 (4.7%)	10 (6.0%)	1 (3.8%)	21 (4.2%)
Deaths During Study	5 (4.4%)	5 (4.9%)	0 (0%)	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (3.6%)
	n=71	n=102	n=N/A	n=169	n=167	n=26	n=362
All Known Deaths From Infusion Studies[b]	5 (7.0%)	5 (4.9%)	N/A	8 (4.7%)	10 (6.0%)	1 (3.8%)	19 (5.2%)
Deaths During Infusion Studies[b]	3 (4.2%)	5 (4.9%)	N/A	8 (4.7%)	9 (5.4%)	1 (3.8%)	18 (5.0%)

a. Data from Listing 7, NDA vol. 81.
b. Studies 311, 325 and 326.
c. This does not include the 'placebo' group from 704.307, as they also received nesiritide during the trial.

For all known deaths during the nesiritide NDA, the following graphs summarize the relative incidence of death for nesiritide and control (including both placebo and active control groups).There were a total of 13 known deaths in the control groups (5.5%



Similarly, the graph below shows the mortality rate during the three infusion studies, where there were 10 known deaths in the control groups (5.8%) compared with 19 deaths in the nesiritide groups (5.2%).



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Narratives-for all deaths can be found in appendix two, based on sponsor-supplied narratives and review of individual case report forms by this reviewer. The table below summarizes the cause and timing of all known deaths.

Table 11.1.1.2 Known deaths in NDA 20-920[a].

Treatment Group/ Patient #	# of Days After Study Entry	Cause of Death
Placebo		
324010	15	Failed to wean after heart txp
381001	6	Ventricular arrhythmia
		Dilated cardiomyopathy
356103	19	Ventricular Fibrillation, EMD
370006	>21	Unknown
376016	6	Sudden Death, CHF
376022	21	Sudden Death, CHF
368001	16	Ventricular Fibrillation, CHF
503001	17	CHF, Bronchopneumonia
Active Control[b]		
493019	5	Cardiopulmonary arrest
		Ischemic cardiomyopathy
493021	18	End-stage cardiomyopathy
509001	21	Suspect large MI
538011	9	LV failure, MI
585002	21	CHF
Nesiritide Bolus		
315005	30	CHF
373301	30	Sudden Cardiac Death
		Dilated cardiomyopathy
Nesiritide 0.015 µg/kg/min infusion		
374001	4	CHF, ASVD
382013	5	Progressive Renal Insufficiency
		CHF
369003	8	CHF
493008	14	End-stage Cardiomyopathy
504003	11	Cardiopulmonary arrest, CHF
538010	9	Mitral regurgitation
		Chronic atrial flutter
550002	14	CHF
559005	7	CHF
		Tricuspid endocarditis
Nesiritide 0.030 µg/kg/min infusion		
017007	8	Acute Renal Failure, CHF
357002	15	MI
370002	20	Multisystem Organ Failure
382002	3	CHF, Respiratory failure
508004	2	'Poor cardiac function'
		'Cardiac standstill'
509002	6	CHF
524005	5	Ventricular fibrillation
528001	22	Cardiac arrest
		Ischemic cardiomyopathy
572001	20	CHF
585003	13	CHF
Nesiritide 0.060 µg/kg/min infusion		
382004	8	Ventricular Arrhythmia
		Congestive Cardiomyopathy

a. Data from NDA vol. 81, listing 7, and examination of individual case report forms.
b. In study 326 subjects were randomized to receive other IV cardiovascular meds.

11.1.2 Serious Adverse Events (SAEs) in the Nesiritide Safety Database

The first table shows the SAEs that were identified by investigators through day 14 of each study that occurred at ≥1% incidence in either of the treatment groups in the CHF trials.

Table 11.1.2.1 The occurrence of SAEs through 14 days in the nesiritide NDA database from all CHF trials[a].

Serious Adverse Event	Control n=235	Nesiritide n=505
# of Subjects with any SAE	19 (8%)	46 (9%)
Cardiovascular System		
Congestive Heart Failure	4 (2%)	11 (2%)
Heart Arrest	4 (2%)	7 (1%)
Ventricular Tachycardia	2 (1%)	4 (1%)
Sustained Ventricular Tachycardia	2 (1%)	4 (1%)
Hypotension, symptomatic	1 (<1%)	4 (1%)
Hypotension	1 (<1%)	4 (1%)
Bradycardic events	1 (<1%)	3 (1%)
Bradycardia	1 (<1%)	3 (1%)
Syncope	1 (<1%)	2 (<1%)
Body as a Whole		
Sepsis	0 (0%)	5 (1%)
Respiratory: None		
Urogenital System	3 (1%)	4 (1%)
Acute Kidney Failure	3 (1%)	2 (0%)
Metabolic and Nutritional System: None		
Nervous System: None		
Digestive System: None		

a. Data from NDA volume 79, appendix 8.4, table 27A.

Examination of the list of SAEs identified in the infusion studies found the following relevant differences between the control and nesiritide groups. None of these differences between nesiritide and the control group achieved nominal statistical significance.

Table 11.1.2.2 The occurrence of 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	Nominal p Value[a]
Cardiovascular	17 (10%)	12 (7%)	25 (15%)	2 (8%)	0.124
Congestive Heart Failure	3 (2%)	3 (2%)	7 (4%)	1 (4%)	0.356
Bradycardia[b]	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795
Hypotension[c]	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795
Body as a Whole	1 (1%)	3 (2%)	2(1%)	0 (0%)	0.659
Sepsis	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0.510
Urogenital	3 (2%)	0 (0%)	2 (1%)	1 (4%)	0.136
Acute Kidney Failure[d]	3 (2%)	0 (0%)	2 (1%)	0 (0%)	0.410

a. Data from appendix 8.4, table 27C and from company at request of reviewer. p Value per sponsor.
b. Included 'bradycardic events' and bradycardia.
c. Includes 'hypotension' and 'symptomatic hypotension.'
d. Includes 'acute kidney failure' and 'kidney function abnormal.'

11.1.3 Clinical Adverse Events (AEs) in the Nesiritide Safety Database

The table below summarizes the occurrence of Adverse Events (AEs) in the nesiritide NDA database from all CHF trials for all AEs that occurred with a >1% frequency in any group are of particular interest to the safety review. These AEs were identified by the individual investigators through day 14. Shaded rows are AEs where the difference between control and nesiritide was nominally statistically significant (<0.05) per sponsor.

Table 11.1.3.1 Adverse Events (AEs) in the 'all CHF' trials from NDA 20-920[a].

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Cardiovascular System	116 (49%)	300 (59%)	0.011
Hypotension	[illegible]	[illegible]	[illegible]
Symptomatic Hypotension	[illegible]	[illegible]	[illegible]
Ventricular Tachycardia	36 (15%)	75 (15%)	0.912
Sustained Ventricular Tachycardia	6 (3%)	9 (2%)	0.576
Congestive Heart Failure	20 (9%)	48 (10%)	0.785
Angina Pectoris	11 (5%)	36 (7%)	0.257
Ventricular Extrasystoles	13 (6%)	22 (4%)	0.464
Bradycardia	[illegible]	[illegible]	[illegible]
Sinus Bradycardia	0 (0%)	1 (<0.1%)	1.000
Nodal Arrhythmia	0 (0%)	3 (1%)	0.555
Tachycardia	10 (4%)	[illegible]	[illegible]
Atrial Fibrillation	5 (2%)	14 (3%)	0.804
Supraventricular Tachycardia	5 (2%)	12 (2%)	1.000
AV Node Conduction Abnormalities	4 (2%)	9 (2%)	1.000
AV Block, Complete	1 (<0.1%)	0 (0%)	0.318
AV Block, First Degree	3 (1%)	5 (1%)	0.714
AV Block, Second Degree	1 (<0.1%)	4 (1%)	1.000
Bigeminy	3 (1%)	8 (2%)	1.000
Syncope	2 (1%)	4 (1%)	1.000
Palpitations	1 (0%)	8 (2%)	0.285
Vasculitis	0 (0%)	1 (0%)	1.000
Body as a Whole	[illegible]	[illegible]	[illegible]
Headache	43 (18%)	80 (16%)	0.398
Pain	19 (8%)	50 (10%)	0.498
Catheter Pain	16 (7%)	42 (8%)	0.558
Abdominal Pain	16 (7%)	38 (8%)	0.879
Chest Pain	8 (3%)	28 (6%)	0.271
Fever	12 (5%)	21 (4%)	0.569
Sepsis	6 (3%)	14 (3%)	1.000
Allergic Reaction	1 (<0.1%)	0 (0%)	0.318
Gastrointestinal System	68 (29%)	168 (33%)	0.271
Nausea	[illegible]	[illegible]	[illegible]
Vomiting	15 (6%)	44 (9%)	0.310
Constipation	18 (8%)	25 (5%)	0.176
Diarrhea	13 (6%)	21 (4%)	0.451
GI hemorrhage	4 (2%)	7 (1%)	0.750
Abnormal LFTs	2 (1%)	1 (0%)	0.238
Jaundice	0 (0%)	1 (<0.1%)	1.000
Nervous System	[illegible]	[illegible]	[illegible]
Insomnia	19 (8%)	58 (11%)	0.196
Dizziness	16 (7%)	43 (9%)	0.469
Anxiety	11 (5%)	28 (6%)	0.725
Confusion	[illegible]	[illegible]	[illegible]
Nervousness	[illegible]	[illegible]	[illegible]

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

Table 11.1.3.1 Adverse Events (AEs) in the 'all CHF' trials from NDA 20-920 (cont)[a].

Adverse Event	Control n=235	Nesiritide n=505	Nominal p Value
Somnolence	4 (2%)	12 (2%)	0.787
Respiratory System	33 (14%)	95 (19%)	0.118
Dyspnea	15 (6%)	40 (8%)	0.548
Cough Increased	5 (2%)	20 (4%)	0.275
Epistaxis	2 (1%)	9 (2%)	0.517
Hypoxia	4 (2%)	7 (1%)	0.750
Metabolic & Nutritional System	42 (18%)	83 (16%)	0.673
Hypokalemia	10 (4%)	20 (4%)	0.843
BUN Increased	7 (3%)	15 (3%)	1.000
Hyperkalemia	6 (3%)	12 (2%)	1.000
Gout	4 (2%)	12 (2%)	0.787
Hypoglycemia	4 (2%)	8 (2%)	1.000
Hyponatremia	6 (3%)	6 (1%)	0.211
[illegible]	[illegible]	[illegible]	[illegible]
Edema	0 (0%)	1 (<0.1%)	1.000
[illegible]	[illegible]	[illegible]	[illegible]
Creatinine Increased	7 (3%)	29 (6%)	0.141
UTI	8 (3%)	15 (3%)	0.821
Oliguria	2 (1%)	13 (3%)	0.164
Hematuria	6 (3%)	5 (1%)	0.113
Kidney Function Abnormal	0 (0%)	7 (1%)	0.104
Acute Kidney Failure	3 (1%)	6 (1%)	1.000
Skin & Appendages	22 (9%)	58 (11%)	0.446
[illegible]	[illegible]	[illegible]	[illegible]
Rash	8 (3%)	12 (2%)	0.467
Pruritus	4 (2%)	15 (3%)	0.454
Musculoskeletal System	21 (9%)	30 (6%)	0.160
Leg Cramps	11 (5%)	13 (3%)	0.179
Arthralgias	8 (3%)	10 (2%)	0.304
Hemic & Lymphatic	12 (5%)	17 (3%)	0.308
Anemia	4 (2%)	8 (2%)	1.000
Thrombocytopenia	4 (2%)	5 (1%)	0.476
Ecchymosis	4 (2%)	4 (1%)	0.272
Special Senses and Endocrine	5 (2%)	13 (3%)	0.803

a. Data from NDA vol. 78, appendix 8.4, table 11A.

Examination of the list of AEs identified in the infusion studies (through day 14) found the following relevant differences. Shaded rows are AEs where the difference between control and nesiritide was nominally statistically significant.

Table 11.1.3.2 Adverse Events (AEs) in the first 14 days in the '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	Nominal p Value
Cardiovascular System					
Hypotension					
Symptomatic Hypotension					
Decreased Blood Pressure					
Ventricular Extrasystoles	13 (8%)	11 (7%)	8 (5%)	0 (0%)	0.477
Ventricular Tachycardia					
Nonsustained VT					
Congestive Heart Failure	11 (6%)	18 (11%)	20 (12%)	3 (12%)	0.274
Arrhythmia					
Bradycardia					
Bradycardia					
Sinus Bradycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
Nodal Bradycardia	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0.169
Atrial Fibrillation	5 (3%)	2 (1%)	8 (5%)	1 (4%)	0.188
Tachycardia	9 (5%)	5 (3%)	5 (3%)	1 (4%)	0.644
SVT	3 (2%)	4 (2%)	7 (4%)	0 (0%)	0.490
AV Node Conduction Abnormal	3 (2%)	5 (3%)	4 (2%)	0 (0%)	0.846
AV Block, First Degree	3 (2%)	3 (2%)	2 (1%)	0 (0%)	1.000
AV Block, Second Degree	1 (1%)	2 (1%)	2 (1%)	0 (0%)	0.804
Supraventricular Extrasystoles	2 (1%)	3 (2%)	1 (1%)	0 (0%)	0.781
Body as a Whole					
Headache					
Pain	15 (9%)	20 (12 %)	15 (9%)	0 (0%)	0.262
Back Pain	11 (6%)	9 (5%)	5 (3%)	1 (4%)	0.507
Sepsis	5 (3%)	3 (2%)	6 (4%)	1 (4%)	0.611
Asthenia	4 (2%)	8 (5%)	5 (3%)	1 (4%)	0.562
Digestive System	52 (30%)	67 (40%)	60 (36%)	7 (27%)	0.242
Nausea	25 (14%)	36 (21%)	32 (19%)	4 (15%)	0.398
Vomiting	13 (8%)	12 (7%)	17 (10%)	3 (12%)	0.614
Constipation	14 (8%)	13 (8%)	9 (5%)	0 (0%)	0.440
Diarrhea	10 (6%)	13 (8%)	4 (2%)	1 (4%)	0.140
GI Hemorrhage	4 (2%)	3 (2%)	4 (2%)	0 (0%)	0.961
Nervous System					
Insomnia	18 (10%)	25 (15%)	22 (13%)	1 (4%)	0.371
Coma					
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
Metabolic & Nutritional	34 (20%)	28 (17%)	34 (20%)	5 (19%)	0.813
BUN increased	7 (4%)	9 (5%)	5 (3%)	0 (0%)	0.615
Hypokalemia	9 (5%)	7 (4%)	5 (3%)	3 (12%)	0.216
Hyperkalemia	5 (3%)	6 (4%)	4 (2%)	0 (0%)	0.931
Hyperglycemia					
Hyponatremia	4 (2%)	0 (0%)	5 (3%)	0 (0%)	0.132
Acidosis	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0.795

Table 11.1.3.2 Adverse Events (AEs) in the first 14 days in the '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	Nominal p Value
Respiratory System	25 (14%)	33 (20%)	36 (22%)	2 (8%)	0.179
Dyspnea	11 (6%)	14 (8%)	14 (8%)	2 (8%)	0.858
Cough Increased	4 (2%)	5 (3%)	4 (2%)	0 (0%)	0.969
Epistaxis	2 (1%)	6 (4%)	3 (2%)	0 (0%)	0.457
Urogenital System	22 (13%)	28 (17%)	35 (21%)	3 (12%)	0.209
Creatinine Increased	7 (4%)	10 (6%)	15 (9%)	1 (4%)	0.300
Oliguria	2 (1%)	6 (4%)	6 (4%)	0 (0%)	0.410
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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
Skin & Appendages	15 (9%)	20 (12%)	23 (14%)	0 (0%)	0.114
Musculoskeletal	15 (9%)	10 (6%)	9 (5%)	1 (4%)	0.648
Leg Cramps	9 (5%)	5 (3%)	2 (1%)	0 (0%)	0.173
Hemic & Lymphatic	9 (5%)	3 (2%)	8 (5%)	1 (4%)	0.286
Special Senses	3 (2%)	4 (2%)	5 (3%)	1 (4%)	0.602
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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. The incidence of selected AEs from the table above is shown. Overall, similar trends in the incidence of AEs were seen in both sets.

Table 11.1.3.3 Adverse events during the first 24 hours in the 'long infusion' trials in NDA 20-920[a].

Adverse Event	Control n=173	Nesiritide 0.015 n=169	Nesiritide 0.030 n=167	Nesiritide 0.060 n=26	Nominal p Value
Cardiovascular System	48 (28%)	75 (44%)	73 (44%)	10 (38%)	0.004
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Urogenital					
Creatinine Increased	1 (1%)	3 (2%)	4 (2%)	0 (0%)	0.525
Kidney Function Abnormal	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.677
Acute Kidney Failure	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0.361
BUN Increased	2 (1%)	2 (1%)	2 (1%)	0 (0%)	1.000

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

11.1.3.1 Adverse Events in Patient Subgroups

The sponsor performed several analyses examining the effects of gender, age, race, and NYHA class at time of entry.

11.1.3.1a Drug-Demographic Interactions

AEs grouped by age (< or > 65 years old)

This comparison suffered from the small numbers of patients in the >65 years of age category, especially in the nesiritide 0.060 age group (n=9). In both the 24 hour and the 14 day periods, there were no identified AEs in the elderly population which were not seen in the overall population (see supplemental tables 13D and 14D for details). Specific details on the effect of age on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Summary

'Hypotension, bradycardia, and confusion were reported somewhat more frequently in elderly subjects' (age 65 years) than younger subjects, particularly at the 0.03 µg/kg/min dose (see table below). 'Generally, however, the safety profile for nesiritide does not appear to be markedly different for subjects < 65 years and those 65 years of age.'

AEs grouped by gender

This group comparison was also limited by the small # of females, especially in the nesiritide 0.060 group (n=3). The only difference of note was the absence of decreased pulmonary pressure as an AE in females, compared with 7 episodes in the nesiritide 0.030 and 0.060 groups in the men. Females in the nesiritide 0.030 dose group were also more likely to have symptomatic hypotension and nausea than men. Specific details on the effect of gender on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Summary

Women tended to have a higher incidence of symptomatic hypotension and nausea than did men at the 0.03 µg/kg/min but not at the 0.015 µg/kg/min nesiritide dose. Otherwise, the safety profile for nesiritide 'does not appear to be markedly different for men and women.'

11.1.3.1b Drug-Disease Interactions

AEs in the Patients with Renal Disease

Sponsor's Comments

Preclinical studies have suggested that the kidney may play a role in hBNP clearance(along with other factors such as clearance receptors and metabolism by neutral endopeptidases). This would raise the possibility that patients with renal insufficiency might have reduced clearance of nesiritide and, therefore, an exaggerated response to a given dose. The clinical pharmacokinetic analysis of data from study 704.325 in subjects with CHF (n = 65) showed a trend of a direct relationship between estimated creatinine clearance and hBNP clearance and a trend of an inverse relationship between serum creatinine and hBNP clearance. However, in a population analysis done on data from study 704.311 (n = 54), a statistically significant effect of creatinine clearance or serum creatinine on hBNP clearance was not detected. In that study, analyses suggested that hBNP clearance decreases no more than approximately 10.9% for each 10 ml/min decrease in creatinine clearance. In order to evaluate the clinical impact of renal insufficiency on the efficacy and safety profile of nesiritide , a number of evaluations were performed on data from individual studies. First, in study 704.325, there were no significant differences between the effects of nesiritide on the efficacy parameters in these subjects with or without renal insufficiency (baseline serum creatinine >2 mg/dL). Also, subjects with renal insufficiency did not have greater decreases in blood pressure or an increased incidence of symptomatic hypotension.

Secondly, in study 704.326, the general safety profile of nesiritide was not significantly different in those with and without renal insufficiency. For nesiritide subjects with (n = 41) and without (n = 160) chronic renal insufficiency, the incidence of symptomatic hypotension was12% and 14%, respectively; nausea 12% and 12%, confusion 12% and 3%, and bradycardia 2% and 6%, respectively.

Baseline renal insufficiency also did not carry an increased risk of worsened renal function during nesiritide infusion. Subjects with baseline serum creatinine >2 mg/dL were not more likely than subjects without renal insufficiency to have at least a 50% rise in serum creatinine following nesiritide administration. Thus, these analyses suggest that nesiritide does not have a significantly different safety profile in patients with and without renal insufficiency.

AEs grouped by NYHA Class III and IV

There were small numbers of patients in the nesiritide 0.060 groups, as in previous analyses. Four episodes of decreased pulmonary pressure occurred in the class III group, all in the nesiritide 0.030 and 0.060 dose-groups ($p<0.001$ vs. Control). Specific details on the effect of NYHA class (III or IV) on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Comments

The adverse event profiles for nesiritide in patients with NYHA Class III and IV CHF appear comparable. For example, in All CHF Studies, the incidence of symptomatic hypotension during the first 24 hours of nesiritide therapy was 11% in subjects with NYHA Class III CHF and 10% in subjects with NYHA Class IV CHF. Similarly, bradycardia events occurred in 3% of subjects with NYHA Class III CHF and in 3% of subjects with NYHA Class IV CHF receiving nesiritide (compared to 0% in both respective control groups).

AEs grouped by Original Etiology of CHF

Specific details on the effect of the original etiology of the CHF on selected AEs will be dealt with in the AE summary section 8.2. The sponsor had no specific comments on the interaction of CHF etiology and AEs.

11.1.3.1c Drug-Drug Interactions

The sponsor analyzed the data from the largest study (704.326) for drug-drug interactions. Specific details on the effect of interactions with ACE inhibitors, digoxin and beta-blockers on specific AEs will be dealt with in the AE summary section 8.2.

Sponsor's Comments

The sponsor examined the incidence of adverse events in patients receiving three other classes of drugs: ACE inhibitors, beta-blockers, and digoxin. None of these three medications appeared to alter the overall incidence of hypotension, although symptomatic hypotension was reported somewhat more frequently in subjects on ACE inhibitors or beta-blockers than in subjects not on these medications. Bradycardia events were also reported somewhat more frequently in nesiritide subjects receiving ACE inhibitors or beta-blockers than those that were not. The sponsor concluded that these data are difficult to interpret, given the low overall incidence of these events and the small sample size for this assessment. In general, however, use of any of these three agents before or during nesiritide administration does not appear to markedly alter the incidence or profile of adverse events.

11.1.3.2 Selected Analyses of AEs of Particular Interest

11.1.3.2a Hypotension

The tables above show a clear dose-related association between nesiritide administration and the incidence hypotension and an adverse event, including symptomatic hypotension and decreases in pulmonary pressures. The majority of these events occurred during the first 24 hours of study drug administration. The sponsor performed further analyses of hypotension.

First, the frequency and severity of hypotension was summarized. Both the severity of the hypotension and the effect on study drug administration were greatest in the nesiritide group. The effects also tended to be does-related, with the highest incidence of severe hypotension resulting in drug discontinuation occurring in the nesiritide 0.060 dose group.

Table 11.1.3.2a.1 Severity and effect of hypotension as an AE during the first 24 hours in the 'long infusion' trials in NDA 20-920[a].

Hypotension	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
Greatest Severity					
No hypotension reported	167 (97%)	155 (92%)	144 (86%)	22 (85%)	[redacted]
Mild	2 (1%)	4 (2%)	4 (2%)	1 (4%)	
[redacted]					
Greatest Effect on Study Drug Administration					
None	3 (2%)	3 (2%)	2 (1%)	2 (8%)	[redacted]
[redacted]					

a. Data from data table 23D.2 at request of reviewer (table 12D). Reflects trials 311, 325, and 326 data.

The sponsor also analyzed the severity of the hypotension that occurred during the first 24 hours in the 704.326 study. As shown below, there was a higher incidence of hypotension in the nesiritide groups for any systolic BP <100 mm Hg. Note that no patients received nesiritide 0.060 µg/kg/min in this study. In data not shown, the time to minimum SBP ranged widely, from 15 minutes to 1400 minutes in all three treatment groups.

Table 11.1.3.2a.2 Severity of hypotension during the first 24 hours in 704.326[a].

Changes in systolic BP (SBP)	Control n=102	Nesiritide 0.015 µg/kg/min n=103	Nesiritide 0.030 µg/kg/min n=100	Nominal p Value
[redacted]				
Median	100.0	94.0	90.0	
[redacted]				
Minimum SBP <60	1 (1%)	0 (0%)	2 (2%)	

a. Data from NDA vol. 79, appendix 8.4, table 25.

The mean and median decreases in systolic BP were also higher in the nesiritide groups in 704.326.

Table 11.1.3.2a.3 Severity of hypotension during the first 24 hours in 704.326[a].

Changes in systolic BP (SBP)	Control n=102	Nesiritide 0.015 µg/kg/min n=103	Nesiritide 0.030 µg/kg/min n=100	Nominal p Value
[redacted]				
Median Decrease in SBP (mm Hg)	19.0	26.0	29.0	

a. Data from NDA appendix 8.4, table 25.

11.1.4 Adverse Events Related to Laboratory Findings

11.1.4.1 Collection of Laboratory Data

The collection of laboratory measurements was detailed in section 11.0.4.5 above. Of note, no urinalyses during or after nesiritide administration were performed in any of the three long infusion trials.

11.1.4.2 Analyses Focused on Changes in Mean Laboratory Measurements

The first table summarizes the mean changes from baseline to the last available lab assessment on or before days two and five (separately) for all patients in the CHF trials. Shaded boxes represent differences between control and nesiritide that were nominally statistically significant.

Table 11.1.4.2.1 Mean changes in serum chemistries from baseline for all subjects in '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
Sodium	-0.8±3.3	-1.1±3.2		-1.2±3.8	-1.0±3.7
Potassium				0.0±0.69	0.1±0.68
Chloride	-0.3±3.6	-0.1±3.6			
Bicarbonate					
Glucose	-9.0±55	-2.7±59		-12.8±55	-8.0±62
BUN					
Creatinine					
Uric Acid				-0.3±2.3	-0.2±1.3
Total Protein	-0.3±0.80	-0.3±0.5		-0.2±0.7	-0.3±0.6
Albumin	-0.2±0.3	-0.3±0.3			
Total Bilirubin	+0.1±0.29	+0.1±0.6		+0.0±0.4	+0.0±0.8
Alkaline Phosphatase	-1.8±16	-4.6±15		-3.1±16	-7.2±26
LDH	+19.3±132	+3.0±175		-21.2±240	+2.8±149
AST	-5.4±24	-7.2±31		-11.9±61	-5.0±28
ALT	-5.1±19	-4.3±8		-7.8±41	-4.4±15
Calcium	-0.1±0.5	-0.2±0.5		-0.1±0.6	-0.1±0.5
PO_4	0.0±0.7	0.0±0.7		-0.1±0.9	0.0±0.8
Mg^{2+}	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.

Table 11.1.4.2.2 Mean changes in hematology from baseline for all subjects in '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
WBC #(10^3/mm^3)	0.6±1.4	0.9±1.6		0.3±1.8	0.6±1.9
RBC # (10^6/mm^3)	0.0±0.2	0.1±0.4		0.0±0.3	0.0±0.4
HGB (g/dL)				0.0±0.8	0.2±0.1
Hematocrit				0.0±2.7	0.4±3.1
Platelet #(10^3/mm^3)				-16.5±33	-10.9±37
Prothrombin Time (secs)	-0.6±5	-0.1±3		-0.6±4.8	-0.3±3.2
PTT (secs)	-0.9±8.6	-1.3±17		-1.4±9.2	-1.6±22

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

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The next two tables show similar data for mean changes in the long infusion studies, collected on or before the end of study day 2. Shading reflects nominally significant differences between control and nesiritide groups.

Table 11.1.4.2.31 Mean changes in serum chemistries from baseline for all subjects in '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
Sodium	-0.4±3.3	-0.8±3.0	-1.2±3.3	-1.8±5.3
Potassium	[illegible]	[illegible]	[illegible]	[illegible]
Chloride	-0.2±3.0	-0.1±3.4	0.0±3.6	-0.7±3.4
Bicarbonate	[illegible]	[illegible]	[illegible]	[illegible]
Glucose	-6.6±56	+4.9±42	+18.8±79	26.3±40
BUN	–3.3 ± 6.86	–1.8 ± 7.19	–0.7 ± 7.85	–2.5 ± 5.26
Creatinine	[illegible]	[illegible]	[illegible]	[illegible]
Uric Acid	-0.2±0.8	-0.2±0.7	+0.1±1.0	–0.2 ± 0.68
Total Protein	-0.3±1.1	-0.2±0.6	-0.3±0.5	–0.2 ± 0.50
Albumin	–0.1 ± 0.30	–0.2 ± 0.38	–0.2 ± 0.29 –	0.2 ± 0.34
Total Bilirubin	0.0±0.2	0.0±0.5	0.3±1.2	0.2 ± 0.4
Alkaline Phosphatase	2.5±16	-1.8±10	-1.0±13	–4.6 ± 10.0
LDH	-15.1±182	+16.5±66	+13.3±36	+30.6 ± 35.36
AST	-11.1±31	-11.3±17	-2.3±5.1	–2.2 ± 5.16
ALT	-8.5±28	-8.3±13	-3.6±5	–4.7 ± 3.67
Calcium	–0.1 ± 0.52	–0.1 ± 0.73	–0.1 ± 0.60	–0.2 ± 0.31
PO_4	0.0 ± 0.58	0.2 ± 0.96	–0.0 ± 0.60	–0.2 ± 0.63
Mg^{2+}	[illegible]	[illegible]	[illegible]	[illegible]

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

The next table summarizes the mean changes in hematology at or near the end of day 2 for the long infusion trials. Shading reflects nominally significant differences between control and nesiritide groups.

Table 11.1.4.2.4 Mean changes in hematology from baseline for all subjects in 'long infusion' trials[a].

Lab Test, change from baseline 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
WBC #(10^3/mm^3)	0.2 ± 1.43	0.9 ± 1.92	0.9 ± 1.66	1.8 ± 1.57
RBC # (10^6/mm^3)	–0.0 ± 0.24	0.3 ± 0.42	0.3 ± 0.42	0.1 ± 0.31
HGB (g/dL)	–0.0 ± 0.64	0.8 ± 1.20	0.8 ± 1.07	0.2 ± 0.93
Hematocrit	–0.2 ± 2.14	2.4 ± 3.88	2.4 ± 3.44	0.8 ± 2.58
Platelet #(10^3/mm^3)	–16.8 ± 26.17	8.0± 27.35	–1.4 ± 29.11	–10.3 ± 24.31
Prothrombin Time (secs)	0.2 ± 1.03	–0.5 ± 0.69	–0.2 ± 0.52	0.5 ± 1.72
PTT (secs)	–2.1 ± 13.99	7.9 ± 48.35	–3.3 ± 5.23	–6.6 ± 9.41

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

11.1.4.3 Analyses Focused on Extreme Laboratory Values

11.1.4.3.1 Shift Table Analysis

With the exceptions of the changes discussed below, there were no significant patterns in the shift table analysis. No trends were detected for the following labs: bilirubin, alkaline phosphatase, lactate dehydrogenase, ALT, calcium, or phosphorus.

11.1.4.3.1a Serum Chemistries

Bicarbonate

In the CHF studies, more patients in the nesiritide group had serum HCO_3 values below normal at days 2, 5 and at the last available assessment.

Table 11.1.4.3.1a.1 Observed rate of decreased bicarbonate values in the CHF trials[a].

Time of HCO_3 below normal	Control n=235	Nesiritide n=505	Nominal p Value[a]
Baseline	29 (12%)	60 (12%)	0.761
[redacted]			
Last Available	21 (9%)	64 (13%)	0.124

a. Data from NDA vol. 79, table 34A3. p Value per the sponsor for the entire frequency of high, normal and low lab values.

The trend was less apparent in the infusion studies, although there does appear to be a dose-related increase in the incidence of low bicarbonates at the 2 day point.

Table 11.1.4.3.1a.2 Observed rate of decreased bicarbonate values in the long infusion trials[a].

Time of HCO_3 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	20 (12%)	13 (8%)	22 (14%)	3 (12%)	0.991
Last Available on or before Day 2	10 (6%)	15 (10%)	25 (17%)	1 (7%)	0.286
Last Available on or before Day 5	12 (7%)	19 (11%)	19 (11%)	1 (4%)	0.422
Last Available	13 (8%)	17 (10%)	19 (11%)	4 (15%)	0.170

a. Data from NDA vol. 79, table 34A3. 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.

Serum Glucose

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 was a small # of patients who were hypoglycemic, with a higher incidence in the nesiritide groups.

Table 11.1.4.3.1a.3 Observed rate of decreased glucose concentrations in the 'all CHF' groups[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 11.1.4.3.1a.4 Observed rate of decreased glucose values in the 'long infusion' group[a].

Time of Bicarbonate 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	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 0.015 and 0.030 nesiritide dose groups and control.

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 BUNs during the trials in this group.

Table 11.1.4.3.1a.5 Observed rate of increased BUN concentrations in the 'all CHF' population[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 36A3. 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 11.1.4.3.1a.6 Incidence of patients with increased BUN after normal baseline BUN in the 'all CHF' population[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 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,b].

Time of BUN above normal	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%)	8 (5%)	9 (6%)	1 (4%)
Last Available on or before Day 5	10 (6%)	15 (9%)	12 (7%)	1 (4%)
Last Available	13 (8%)	16 (10%)	15 (9%)	3 (12%)

a. Data from supplemental data table from sponsor at reviewer's request.
b. Percentages are calculated using all subjects, regardless of baseline status.

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 11.1.4.3.1a.8 Observed rate of increased creatinine values in the long infusion trials[a,b].

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
[redacted]			

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 0.015 and 0.030 nesiritide dose groups and control.
b. Percentages are calculated using all subjects, regardless of baseline status.

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

Table 11.1.4.3.1a.9 Incidence of patients with increased creatinine after normal baseline creatinine in the '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. Nominal p Value per the sponsor for the entire frequency of high, normal and low lab values.

In the long infusion trials, there was a higher % of patients with elevated creatinines in the 0.030 dose group, compared with either the 0.015 group or the control group. Note the lower % of elevated creatinines in the nesiritide 0.015 dose group.

Table 11.1.4.3.1a.10 Observed rate of increased creatinine values 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	Nominal p Value[a]
Baseline	79 (46%)	62 (37%)	76 (46%)	13 (50%)	0.191
Last Available on or before Day 2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Last Available on or before Day 5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Last Available	73 (43%)	67 (40%)	90 (54%)	13 (50%)	0.048

a. Data from supplemental table 37D3 . 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 elevated creatinines after a normal baseline value was higher in the 0.030 µg/kg/min nesiritide group.

Table 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 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 table 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 11.1.4.3.1a.12 Observed incidence of increased creatinine values in trial 704.311[a].

Pre-specified increases in Creatinine	Placebo n=29	Nesiritide 0.015 n=23	Nesiritide 0.030 n=25	Nesiritide 0.060 n=26	Nominal p Value[a]
>1.0 mg/dl Increase	2 (7%)	1 (4%)	1 (4%)	1 (4%)	1.000
>0.5 mg/dl Increase	2 (7%)	3 (13%)	3 (12%)	4 (15%)	0.798
>100% Increase	1 (3%)	1 (4%)	1 (4%)	0 (0%)	0.795
>50% Increase	1 (3%)	2 (9%)	3 (12%)	3 (12%)	0.635
>25% Increase	6 (21%)	7 (30%)	5 (20%)	7 (27%)	0.804

a. Data from the sponsor. p Value per the sponsor comparing nesiritide dose groups and placebo.

Table 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 0.015 n=43	Nesiritide 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
[illegible]				
>25% Increase	7 (17%)	11 (26%)	8 (19%)	0.624

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

Table 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 0.015 n=103	Nesiritide 0.030 n=100	Nominal p Value[a]
>1.0 mg/dl Increase	3 (3%)	6 (6%)	6 (6%)	0.571
[illegible]				
>100% Increase	2 (2%)	3 (3%)	1 (1%)	0.874
[illegible]				

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.

In data not shown, this apparent dose-related increase in elevated creatinine was seen across almost all demographic subsets of studies 704.325 and 704.326: elderly, males/ females, white/black, by NYHA class, presence or absence of hypertension, presence or absence of diabetes, occurrence of hypotension, and use of ACE inhibitors (see tables 37D3 and 37D4for details).

Total Protein

In both the CHF trials as a whole there was a higher % of the nesiritide group developed low total protein levels. This abnormality tended to resolve by the last available assessment. There was also a slightly higher % of patients with low total proteins at the start of the trial in the nesiritide group.

Table 11.1.4.3.1a.14 Observed 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]
[illegible]			
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 infusion studies.

Table 11.1.4.3.1a.15 Observed 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
[illegible]					
Last Available on or before Day 5	23 (26%)	38 (39%)	42 (44%)	8 (36%)	0.051
Last Available	27 (25%)	36 (31%)	42 (36%)	1 (4%)	0.038

a. Data from NDA vol. 79, table 35C3 and 39C3. 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.

Serum Albumin

In both the CHF trials as a whole there was a higher % of the nesiritide group developed low serum albumin.

Table 11.1.4.3.1a.16 Observed rate of decreased albumin concentrations in the 'all CHF' trials[a].

Time of Albumin below normal	Control n=235	Nesiritide n=505	Nominal p Value[a]
Baseline	86 (38%)	219 (45%)	0.089
[redacted]			
Last Available	64 (36%)	164 (40%)	0.411

a. Data from NDA vol. 79, table 40A3. 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.

Table 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
[redacted]					

a. Data from supplemental 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 11.1.4.3.1a.18 Observed incidence of decreased albumin values after normal baseline value in the long infusion trials[a,b].

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, supplemental table 40D4.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

Aspartate Transaminase (AST)

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

Table 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
[redacted]					
Last Available	23 (20%)	22 (19%)	19 (15%)	2 (8%)	0.814

a. Data from NDA vol. 79, table 44C3. 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.

Serum Magnesium

In both the 'controlled CHF' the 'long infusion' populations there were a nominally significant association between nesiritide administration and increased magnesium levels.

The first table shows the controlled CHF studies.

Table 11.1.4.3.1a.20 Observed rate of elevated magnesium 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
[redacted]			

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

A similar trend was seen in the 'long infusion' studies.

Table 11.1.4.3.1a.21 Observed rate of increased serum magnesium levels in the '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
[redacted]					

a. Data from NDA vol. 79, table 48D3. 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 Mg^{2+} levels in patients who started with normal levels.

Table 11.1.4.3.1a.22 % of Patients with increased Mg^{2+} after normal baseline Mg^{2+} in the 'all CHF' trials[a].

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	10 (6%)	23 (6%)

a. Data from NDA vol. 79, table 48A4. p Value per the sponsor for the entire frequency of high, normal and low lab values.

Table 11.1.4.3.1a.23 Observed incidence of increased Mg^{2+} values after normal baseline value in the '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. 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.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

11.1.4.3.1ba Hematology

No trends were detected for the following hematology labs: erythrocyte count, hemoglobin, hematocrit, platelet count, PT, and PTT.

WBC Count

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 count.

Table 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 on or before Day 5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Last Available	14 (10%)	16 (11%)	29 (20%)	4 (15%)	0.186

a. Data from supplemental table 49D3. 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 count in the long infusion studies. This trend was diminished in the later timepoint, following study drug discontinuation.

Table 11.1.4.3.1b.2 Observed incidence of increased WBC values after normal baseline value in the long infusion trials[a,b].

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 49D4. 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.

b. Percentages are calculated from the total number of patients with available data, regardless of baseline status.

11.1.4.4 Adverse Events Related to Vital Signs

Blood Pressure

In all three long infusion trials there was an association between nesiritide dose and the frequency of hypotension. This reflected an acute effect of nesiritide to lower blood pressure, as shown in the tables below, which come from the individual study reviews.

Table 11.1.4.1.1 (from table 6.1.12.4.1) Effect of 3 hour infusion of nesiritide on blood pressure in trial 704.311[a].

	Placebo n=29	Nesiritide 0.25/ 0.015 n=22	Nesiritide 0.5/ 0.030 n=26	Nesiritide 1.0/ 0.060 n=26	Nominal p Value[b]
Systolic BP (mm Hg)	+1.2 (+1%)	-7.4 (-6%)	-4.3 (-3%)	-10.0 (-8%)	0.006

a. Data from NDA 20-998, vol. 54, Text Table 2. Data are expressed as absolute and (%) change from baseline for ITT population.

b. p Value comparing arithmetic means from baseline using ANOVA.