

hemodynamic monitoring who were treated with Natrecor (62 of 124 patients) were allowed dose increases of Natrecor after the first 3 hours of treatment if the PCWP was ≥ 20 mm Hg and the SBP was ≥ 100 mm Hg. Dose increases of a 1 mcg/kg bolus followed by an increase of the infusion dose by 0.005 mcg/kg/min were allowed every 3 hours, up to a maximum dose of 0.03 mcg/kg/min. Overall, 23 patients in this subset had the dose of Natrecor increased in the VMAC trial.

In a second double-blind study, 127 patients requiring hospitalization for symptomatic CHF were randomized to placebo or to one of two doses of Natrecor (0.015 mcg/kg/min preceded by an IV bolus of 0.3 mcg/kg, and 0.03 mcg/kg/min preceded by an IV bolus of 0.6 mcg/kg). The primary endpoint of the trial was the change in PCWP from baseline to 6 hours, but the effect on symptoms also was examined.

Effects on Symptoms

In the VMAC study, patients receiving Natrecor reported greater improvement in their dyspnea at 3 hours than patients receiving placebo ($p = 0.034$).

In the dose-response study, patients receiving both doses of Natrecor reported greater improvement in dyspnea at 6 hours than patients receiving placebo.

Effects on Hemodynamics

The PCWP, right atrial pressure (RAP), CI, and other hemodynamic variables were monitored in 246 of the patients in the VMAC trial. There was a reduction in mean PCWP within 15 minutes of starting the Natrecor infusion, with most of the effect seen at 3 hours being achieved within the first 60 minutes of the infusion (see Pharmacodynamics).

In several studies, hemodynamic parameters were measured after Natrecor withdrawal. Following discontinuation of Natrecor, PCWP returns to within 10% of baseline within 2 hours, but no rebound increase to levels above baseline state was observed. There was also no evidence of tachyphylaxis to the hemodynamic effects of Natrecor in the clinical trials.

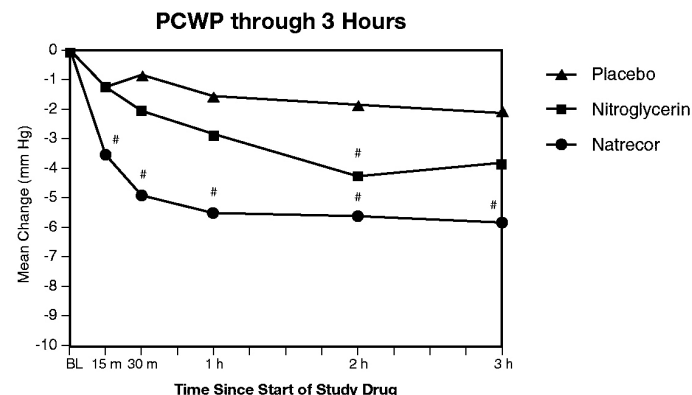
The following table and graph summarize the changes in the VMAC trial in PCWP and other measures during the first 3 hours.

Mean Hemodynamic Change from Baseline

Effects at 3 Hours	Placebo (n = 62)	Nitroglycerin (n = 60)	Natrecor (n = 124)
Pulmonary capillary wedge pressure (mm Hg)	-2.0	-3.8	-5.8 [†]
Right atrial pressure (mm Hg)	0.0	-2.6	-3.1 [†]
Cardiac index (L/min/M ²)	0.0	0.2	0.1
Mean pulmonary artery pressure (mm Hg)	-1.1	-2.5	-5.4 [†]
Systemic vascular resistance (dynes*sec*cm ⁻⁵)	-44	-105	-144
Systolic blood pressure [†] (mm Hg)	-2.5	-5.7 [†]	-5.6 [†]

[†] Based on all treated subjects: placebo n = 142, nitroglycerin n = 143, Natrecor n = 204

[‡] p < 0.05 compared to placebo



[†]p < 0.05 compared to placebo

The VMAC study does not constitute an adequate effectiveness comparison with nitroglycerin. In this trial, the nitroglycerin group provides a rough landmark using a familiar therapy and regimen.

Effect on Urine Output

In the VMAC trial, in which the use of diuretics was not restricted, the mean change in volume status (output minus input) during the first 24 hours in the nitroglycerin and Natrecor groups was similar: 1279 ± 1455 mL and 1257 ± 1657 mL, respectively.

INDICATIONS AND USAGE

Natrecor (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of Natrecor reduced pulmonary capillary wedge pressure and improved dyspnea.

CONTRAINDICATIONS

Natrecor is contraindicated in patients who are hypersensitive to any of its components. Natrecor should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure < 90 mm Hg.

WARNINGS

Administration of Natrecor should be avoided in patients suspected of having, or known to have, low cardiac filling pressures.

PRECAUTIONS

General: Parenteral administration of protein pharmaceuticals or *E. coli*-derived products should be attended by appropriate precautions in case of an allergic or untoward reaction.

Natrecor is not recommended for patients for whom vasodilating agents are not appropriate, such as patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent upon venous return, or for patients suspected to have low cardiac filling pressures (see CONTRAINDICATIONS).

Renal: Natrecor may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with Natrecor may be associated with azotemia. When Natrecor was initiated at doses higher than 0.01 mcg/kg/min (0.015 and 0.03 mcg/kg/min), there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased. In the 30-day follow-up period in the VMAC trial, 5 patients in the nitroglycerin group (2%) and 9 patients in the Natrecor group (3%) required first-time dialysis.

Cardiovascular: Natrecor may cause hypotension. In the VMAC trial, in patients given the recommended dose (2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion) or the adjustable dose, the incidence of symptomatic hypotension in the first 24 hours was similar for Natrecor (4%) and IV nitroglycerin (5%). When hypotension occurred, however, the duration of symptomatic hypotension was longer with Natrecor (mean duration was 2.2 hours) than with nitroglycerin (mean duration was 0.7 hours). In earlier trials, when Natrecor was initiated at doses higher than the 2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion (i.e., 0.015 and 0.03 mcg/kg/min preceded by a small bolus), there were more hypotensive episodes and these episodes were of greater intensity and duration. They were also more often symptomatic and/or more likely to require medical intervention (see ADVERSE REACTIONS). Natrecor should be administered only in settings where blood pressure can be monitored closely, and the dose of Natrecor should be reduced or the drug discontinued in patients who develop hypotension (see Dosing Instructions). The rate of symptomatic hypotension may be increased in patients with a blood pressure < 100 mm Hg at baseline, and Natrecor should be used cautiously in these patients. The potential for hypotension may be increased by combining Natrecor with other drugs that may cause hypotension. For example, in the VMAC trial in patients treated with either Natrecor or nitroglycerin therapy, the frequency of symptomatic hypotension in patients who received an oral ACE inhibitor was 6%, compared to a frequency of symptomatic hypotension of 1% in patients who did not receive an oral ACE inhibitor.

Drug Interactions: No trials specifically examining potential drug interactions with Natrecor were conducted, although many concomitant drugs were used in clinical trials. No drug interactions were detected except for an increase in symptomatic hypotension in patients receiving oral ACE inhibitors (see PRECAUTIONS, Cardiovascular).

The co-administration of Natrecor with IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated (these drugs were not co-administered with Natrecor in clinical trials).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility of nesiritide. Nesiritide did not increase the frequency of mutations when used in an in vitro bacterial cell assay (Ames test). No other genotoxicity studies were performed.

Pregnancy: Category C: It is not known whether Natrecor can cause fetal harm when administered to pregnant women or if it can affect reproductive capacity. A developmental reproductive toxicology study was conducted in pregnant rabbits using doses up to 1440 mcg/kg/day given by constant infusion for 13 days. At this level of exposure (based on AUC, approximately 70 x human exposure at the recommended dose) no adverse effects on live births or fetal development were observed. Natrecor should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

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Nursing Mothers: It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when Natrecor is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Natrecor in pediatric patients has not been established.

Geriatric Use: Of the total number of subjects in clinical trials treated with Natrecor (n = 941), 38% were 65 years or older and 16% were 75 years or older. No overall differences in effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. Some older individuals may be more sensitive to the effect of Natrecor than younger individuals.

ADVERSE REACTIONS

Adverse events that occurred with at least a 3% frequency during the first 24 hours of Natrecor infusion are shown in the following table.

Adverse Event	VMAC Trial		Other Long Infusion Trials		
	Nitroglycerin (n = 216)	Natrecor Recommended Dose (n = 273)	Control* (n = 256)	Natrecor mcg/kg/min 0.015 (n = 253)	0.03 (n = 246)
Cardiovascular					
Hypotension	25 (12%)	31 (11%)	20 (8%)	56 (22%)	87 (35%)
Symptomatic Hypotension	10 (5%)	12 (4%)	8 (3%)	28 (11%)	42 (17%)
Asymptomatic Hypotension	17 (8%)	23 (8%)	13 (5%)	31 (12%)	49 (20%)
Ventricular Tachycardia (VT)	11 (5%)	9 (3%)	25 (10%)	25 (10%)	10 (4%)
Non-sustained VT	11 (5%)	9 (3%)	23 (9%)	24 (9%)	9 (4%)
Ventricular Extrasystoles	2 (1%)	7 (3%)	15 (6%)	10 (4%)	9 (4%)
Angina Pectoris	5 (2%)	5 (2%)	6 (2%)	14 (6%)	6 (2%)
Bradycardia	1 (< 1%)	3 (1%)	1 (< 1%)	8 (3%)	13 (5%)
Body as a Whole					
Headache	44 (20%)	21 (8%)	23 (9%)	23 (9%)	17 (7%)
Abdominal Pain	11 (5%)	4 (1%)	10 (4%)	6 (2%)	8 (3%)
Back Pain	7 (3%)	10 (4%)	4 (2%)	5 (2%)	3 (1%)
Nervous					
Insomnia	9 (4%)	6 (2%)	7 (3%)	15 (6%)	15 (6%)
Dizziness	4 (2%)	7 (3%)	7 (3%)	16 (6%)	12 (5%)
Anxiety	6 (3%)	8 (3%)	2 (1%)	8 (3%)	4 (2%)
Digestive					
Nausea	13 (6%)	10 (4%)	12 (5%)	24 (9%)	33 (13%)
Vomiting	4 (2%)	4 (1%)	2 (1%)	6 (2%)	10 (4%)

* Includes dobutamine, milrinone, nitroglycerin, placebo, dopamine, nitroprusside, or amrinone.

Adverse events that are not listed in the above table that occurred in at least 1% of patients who received any of the above Natrecor doses included: Tachycardia, atrial fibrillation, AV node conduction abnormalities, catheter pain, fever, injection site reaction, confusion, paresthesia, somnolence, tremor, increased cough, hemoptysis, apnea, increased creatinine, sweating, pruritus, rash, leg cramps, amblyopia, anemia. All reported events (at least 1%) are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

In placebo and active-controlled clinical trials, Natrecor has not been associated with an increase in atrial or ventricular tachyarrhythmias. In placebo-controlled trials, the incidence of VT in both Natrecor and placebo patients was 2%. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) trial, the effects of Natrecor (n = 163) and dobutamine (n = 83) on the provocation or aggravation of existing ventricular arrhythmias in patients with decompensated CHF was compared using Holter monitoring. Treatment with Natrecor (0.015 and 0.03 mcg/kg/min without an initial bolus) for 24 hours did not aggravate pre-existing VT or the frequency of premature ventricular beats, compared to a baseline 24-hour Holter tape.

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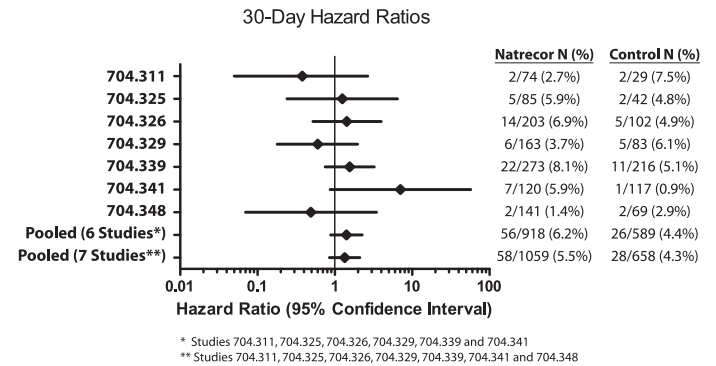
Clinical Laboratory

In the PRECEDENT trial, the incidence of elevations in serum creatinine to > 0.5 mg/dL above baseline through day 14 was higher in the Natrecor 0.015 mcg/kg/min group (17%) and the Natrecor 0.03 mcg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, through day 30, the incidence of elevations in creatinine to > 0.5 mg/dL above baseline was 28% and 21% in the Natrecor (2 mcg/kg bolus followed by 0.01 mcg/kg/min) and nitroglycerin groups, respectively.

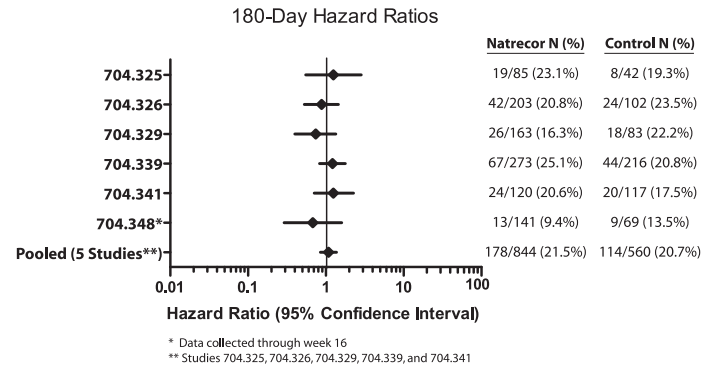
Effect on Mortality

Data from all seven studies in which 30-day data were collected are presented in the chart below. The data depict hazard ratios and confidence intervals of mortality data for randomized and treated patients with Natrecor relative to active controls through day 30 for each of the 7 individual studies (Studies 311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], and 348 [FUSION I]).

The figure (on logarithmic scale) also contains a plot for the six studies involving hospitalized or Emergency Department patients combined (n = 1507), and for all 7 studies combined (n = 1717). The percentage is the Kaplan-Meier estimate.



The figure below represents 180-day mortality hazard ratios for randomized and treated patients from all five individual studies where 180-day data were collected, 16 week hazard ratios for Study 348 (180-day data were not collected), and the five studies with 180-day data pooled (n = 1404).



There were few deaths in these studies, so the confidence limits around the hazard ratios for mortality are wide. The studies are also small, so some potentially important baseline imbalances exist among the treatment groups, the effects of which cannot be ascertained.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Natrecor. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: hypersensitivity reactions.

OVERDOSAGE

Overdose with Natrecor therapy has been reported and is primarily the result of either a miscalculated Natrecor dose or a mechanical error such as an infusion-pump malfunction or an infusion-pump programming error. The most frequently reported adverse event reported with Natrecor overdose is hypotension, which may be asymptomatic and most often resolves with drug stoppage, although in some cases hypotension may persist for several hours beyond discontinuation. Treatment of Natrecor overdose should include drug discontinuation and the administration of supportive measures (see PRECAUTIONS — Cardiovascular).

NATRECOR® (nesiritide) FOR INTRAVENOUS INFUSION ONLY**DOSAGE AND ADMINISTRATION****The Natrecor bolus must be drawn from the prepared infusion bag.**

Natrecor (nesiritide) is for intravenous use only. There is limited experience with administering Natrecor for longer than 48 hours. Blood pressure should be monitored closely during Natrecor administration.

If hypotension occurs during the administration of Natrecor, the dose should be reduced or discontinued and other measures to support blood pressure should be started (IV fluids, changes in body position). In the VMAC trial, when symptomatic hypotension occurred, Natrecor was discontinued and subsequently could be restarted at a dose that was reduced by 30% (with no bolus administration) once the patient was stabilized. Because hypotension caused by Natrecor may be prolonged (up to hours), a period of observation may be necessary before restarting the drug.

Preparation**The Natrecor bolus must be drawn from the prepared infusion bag.**

1. Reconstitute one 1.5 mg vial of Natrecor by adding 5 mL of diluent removed from a pre-filled 250 mL plastic IV bag containing the diluent of choice. After reconstitution of the vial, each mL contains 0.32 mg of nesiritide. The following preservative-free diluents are recommended for reconstitution: 5% Dextrose Injection (D5W), USP; 0.9% Sodium Chloride Injection, USP; 5% Dextrose and 0.45% Sodium Chloride Injection, USP, or 5% Dextrose and 0.2% Sodium Chloride Injection, USP.
2. Do not shake the vial. Rock the vial gently so that all surfaces, including the stopper, are in contact with the diluent to ensure complete reconstitution. Use only a clear, essentially colorless solution.
3. **Withdraw the entire contents of the reconstituted Natrecor vial** and add to the 250 mL plastic IV bag. This will yield a solution with a concentration of Natrecor of approximately 6 mcg/mL. The IV bag should be inverted several times to ensure complete mixing of the solution.
4. Use the reconstituted solution within 24 hours, as Natrecor contains no antimicrobial preservative. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted vials of Natrecor may be stored at 2–25°C (36–77°F) for up to 24 hours.

Dosing Instructions**The Natrecor bolus must be drawn from the prepared infusion bag.**

The recommended dose of Natrecor is an IV bolus of 2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min. Natrecor should not be initiated at a dose that is above the recommended dose.

Prime the IV tubing with 5 mL of the solution for infusion prior to connecting to the patient's vascular access port and prior to administering the bolus or starting the infusion.

The administration of the recommended dose of Natrecor is a two step process:

Step 1. Administration of the IV Bolus

After preparation of the infusion bag, as described previously, withdraw the bolus volume (see Weight-Adjusted Bolus Volume table) from the Natrecor infusion bag, and administer it over approximately 60 seconds through an IV port in the tubing.

$$\text{Bolus Volume (mL)} = \text{Patient Weight (kg)} / 3$$

Natrecor Weight-Adjusted Bolus Volume Administered Over 60 Seconds (Final Concentration = 6 mcg/mL)

Patient Weight (kg)	Volume of Bolus (mL = kg/3)
60	20.0
70	23.3
80	26.7
90	30.0
100	33.3
110	36.7

NATRECOR® (nesiritide) FOR INTRAVENOUS INFUSION ONLY**Step 2. Administration of the Continuous Infusion**

Immediately following the administration of the bolus, infuse Natrecor at a flow rate of 0.1 mL/kg/hr. This will deliver a Natrecor infusion dose of 0.01 mcg/kg/min.

To calculate the infusion flow rate to deliver a 0.01 mcg/kg/min dose, use the following formula (see the following Weight-Adjusted Infusion Flow Rate for Dosing table):

$$\text{Infusion Flow Rate (mL/hr)} = \text{Patient Weight (kg)} \times 0.1$$

Natrecor Weight-Adjusted Infusion Flow Rate for a 0.01 mcg/kg/min Dose following Bolus (Final Concentration = 6 mcg/mL)

Patient Weight (kg)	Infusion Flow Rate (mL/hr)
60	6
70	7
80	8
90	9
100	10
110	11

Dose Adjustments: The dose-limiting side effect of Natrecor is hypotension. Do not initiate Natrecor at a dose that is higher than the recommended dose of a 2 mcg/kg bolus followed by an infusion of 0.01 mcg/kg/min. In the VMAC trial there was limited experience with increasing the dose of Natrecor above the recommended dose (23 patients, all of whom had central hemodynamic monitoring). In those patients, the infusion dose of Natrecor was increased by 0.005 mcg/kg/min (preceded by a bolus of 1 mcg/kg), no more frequently than every 3 hours up to a maximum dose of 0.03 mcg/kg/min. Natrecor should not be titrated at frequent intervals as is done with other IV agents that have a shorter half-life (see Clinical Trials).

Chemical/Physical Interactions

Natrecor is physically and/or chemically incompatible with injectable formulations of heparin, insulin, ethacrynate sodium, bumetanide, enalaprilat, hydralazine, and furosemide. These drugs should not be co-administered as infusions with Natrecor through the same IV catheter. The preservative sodium metabisulfite is incompatible with Natrecor. Injectable drugs that contain sodium metabisulfite should not be administered in the same infusion line as Natrecor. The catheter must be flushed between administration of Natrecor and incompatible drugs.

Natrecor binds to heparin and therefore could bind to the heparin lining of a heparin-coated catheter, decreasing the amount of Natrecor delivered to the patient for some period of time. Therefore, Natrecor must not be administered through a central heparin-coated catheter. Concomitant administration of a heparin infusion through a separate catheter is acceptable.

Storage

Store below 25°C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

HOW SUPPLIED

Natrecor (nesiritide) is provided as a sterile lyophilized powder in 1.5 mg, single-use vials. Each carton contains one vial and is available in the following package:

1 vial/carton (NDC 65847-205-25)

US patent No. 5,114,923 and 5,674,710.

Manufactured for Scios Inc.

Titusville, NJ 08560

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Rx only

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