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July 13, 2005

Dear Healthcare Provider:

We are writing to provide you with information about the recommendations of an expert panel of cardiology and heart failure clinicians with regard to NATRECOR® (nesiritide). We recently asked Dr. Eugene Braunwald, Distinguished Hersey Professor of Medicine, Harvard Medical School, to convene such a panel to review and assess important data associated with this medicine. The panel also provided advice on the ongoing and planned clinical development program for NATRECOR® as well as recommendations for use.

With respect to recent questions raised about worsened renal function and mortality, the panel provided a consensus statement on each after review of the available data (see attached panel recommendations), including review of the original 2001 product labeling that has described these risks.[1] They endorsed our plan to add substantially to the current knowledge base about NATRECOR® by conducting several clinical trials, including a large trial of clinical outcomes to further assess the benefits and risks of NATRECOR®. The panel also strongly encouraged Scios and investigators to continue enrollment of patients in current NATRECOR® trials (e.g., FUSION II) and in the planned NATRECOR® trials.

The Panel also made recommendations about the appropriate use of NATRECOR® and encouraged us to engage in an educational campaign to ensure that clinicians understand when the use of NATRECOR® is appropriate and when it is not appropriate. The panel made the following specific, verbatim recommendations:

1) The use of Natrecor should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest, as were the patients in the largest trial that led to approval of the drug (VMAC). Physicians considering the use of nesiritide should consider its efficacy in reducing dyspnea, the possible risks of the drug summarized above, and the availability of alternate therapies to relieve the symptoms of congestive heart failure.

[1] The original package insert contained all available aggregate 6-month mortality data at the time of approval, and it was recently updated to include 30-day and 6-month mortality in individual studies and aggregate summaries of 30-day and 6-month mortality data, including data from studies completed since the product approval.

2) Nesiritide should *not* be used to replace diuretics. Furthermore, because sufficient evidence is not currently available to demonstrate benefit for the applications listed below, nesiritide should *not* be used:
   - For intermittent outpatient infusion
   - For scheduled repetitive use
   - To improve renal function
   - To enhance diuresis.
3) Scios should immediately undertake a pro-active educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used, as described above. Sponsor supported communications, including review articles of nesiritide, should reflect the above recommendations. Scios should ensure that current and future marketing and sales activities related to nesiritide are consistent with this educational program.

With patient care as our highest priority, we write today to help you understand the data supporting the use of NATRECOR® so that you can make the best medical decisions for your patients.

NATRECOR® for Acutely Decompensated Heart Failure

NATRECOR® 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. The recommended dose of NATRECOR® is an IV bolus of 2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min. Consistent with the clinical trials supporting its approval, the commercial use of NATRECOR® in clinical practice (non-investigational) should be strictly limited to patients with acutely decompensated heart failure with a clinical presentation severe enough to warrant hospitalization (whether presenting to an Emergency Department, Observation Unit, or direct admission to a Hospital Ward or Intensive Care Unit). NATRECOR® should be administered in a clinical setting where blood pressure can be closely monitored. NATRECOR® should not be initiated at a dose that is above the recommended dose.

The prescribing information for NATRECOR® reflects data from 10 clinical trials including 941 patients with CHF (chronic CHF NYHA class II-III 61%, class IV 36%; mean age 60 years, women 28%). There were five randomized, multi-center, placebo- or active-controlled studies in which 772 patients with decompensated CHF received continuous infusions of NATRECOR® at doses ranging from 0.01 to 0.03 mcg/kg/min. Of these patients, the majority (70%) received the NATRECOR® infusion for at least 24 hours; 48% received NATRECOR® for 24–48 hours, and 22% received NATRECOR® for greater than 48 hours.

All of the patients participating in each of these trials required hospitalization for acutely decompensated heart failure. The study trials permitted entry at any point during the treatment course of acutely decompensated congestive heart failure (ADHF), demonstrating that the use of NATRECOR® is safe and effective in a broad range of hospitalized patients. For example, the studies included patients in whom study drug (either NATRECOR® or control) was started as the first IV vasoactive therapy before or after IV diuretics, as replacement therapy for patients not sufficiently responsive to another IV vasoactive therapy, or as add-on therapy in patients refractory to dobutamine or dopamine.

The VMAC trial, the largest relied upon for the approval of the drug, was a randomized, double-blind study of 489 patients who required hospitalization for management of shortness of breath at rest or with minimal activity (such as talking, eating, or bathing) due to acutely decompensated CHF. Patients with acute coronary syndrome, preserved systolic function, arrhythmia, and renal insufficiency were not excluded. The study compared the effects of NATRECOR®, placebo, and IV nitroglycerin when added to background therapy (IV and oral diuretics, non-IV cardiac medications, dobutamine, and dopamine). VMAC was designed to show primary efficacy comparisons between NATRECOR® and placebo. The nitroglycerin arm was included to show the relative safety and tolerability of NATRECOR® in comparison to a commonly used IV vasodilator.

The primary endpoints of VMAC were the change from baseline in patients' dyspnea and the change from baseline in pulmonary capillary wedge pressure (PCWP), evaluated after three hours. Patients receiving NATRECOR® reported greater improvement in dyspnea at 3 hours than patients receiving placebo plus standard care ($p = 0.034$). NATRECOR® led to a significant reduction in PCWP compared to placebo at 3 hours, when added to standard care ($p < 0.001$). There was a significant reduction in mean PCWP, relative to placebo, within 15 minutes of starting the NATRECOR® infusion, with most of the effect observed at 3 hours being achieved within the first 60 minutes of the infusion.

Unsupported Uses of NATRECOR®

We understand that NATRECOR® is also being administered as intermittent and scheduled infusions to treat severely ill congestive heart failure patients, particularly in the outpatient setting. Although a clinical development program is currently underway in this setting (FUSION II trial), Scios does not recommend NATRECOR® for this use at this time.

To our knowledge, the only controlled clinical trial to assess the use of NATRECOR® for serial infusions in the outpatient setting is FUSION I (Follow-up Serial Infusion of Nesiritide). FUSION I was a pilot study (n=210) and was not powered to adequately assess the effectiveness or safety of serial infusions of NATRECOR®. The size of the study, its design, and its findings provide an inadequate basis to recommend the routine use of intermittent, serial, or scheduled repetitive infusions of NATRECOR®.

We also understand that in certain instances NATRECOR® is being used to replace diuretics, to improve renal function and/or to enhance diuresis. To date, adequate clinical data that demonstrate clinically relevant diuretic properties or positive renal effects of NATRECOR® does not exist. Scios does not recommend such use. Moreover, it is important to understand that clinical trial data show that the use of NATRECOR® was associated with a dose-dependent increase in serum

creatinine. In VMAC, the serum creatinine rose by more than 0.5 mg/dL above baseline in at least one blood draw in 7% of patients in the control groups and 8% in the nesiritide groups by 5 days, and by 21% and 28% respectively, by 30 days. Most of these increases occurred days after discontinuation of the drug.

Additional Safety Information

NATRECOR® may cause hypotension. If hypotension occurs during administration of NATRECOR®, the dose should be reduced or discontinued, and blood pressure should be monitored closely. At the recommended dose of NATRECOR®, the incidence of symptomatic hypotension (4%) was similar to that of IV nitroglycerin (5%). Asymptomatic hypotension occurred in 8% of patients treated with either drug. The mean duration of symptomatic hypotension was longer with NATRECOR® than IV nitroglycerin (2.2 versus 0.7 hours, respectively). Higher doses of NATRECOR® increased the risk of hypotension and elevated creatinine. 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.

Other adverse events reported at a rate of at least 5% during the first 24 hours of infusion with either NATRECOR® plus standard care or IV nitroglycerin plus standard care therapy, included, respectively: ventricular tachycardia (3%, 5%), nonsustained ventricular tachycardia (3%, 5%), headache (8%, 20%), abdominal pain (1%, 5%), and nausea (4%, 6%). NATRECOR® should not be used in patients with systolic blood pressure <90 mm Hg or as primary therapy in patients with cardiogenic shock. NATRECOR® is not recommended for patients for whom vasodilating agents are not appropriate and should be avoided in patients with low cardiac filling pressures.

In the seven NATRECOR® clinical trials that collected mortality data through 30 days, 5.3% in the NATRECOR® treatment group died as compared with 4.3% in the group treated with other standard medications. In the four clinical trials in which mortality was collected through 180 days, 21.7% in the NATRECOR® treatment group died as compared with 21.5% in the group treated with other standard medications. There are insufficient numbers of deaths to identify or exclude, with confidence, a moderate excess of risk to survival after treatment with NATRECOR®.

We are committed to keeping you informed about those uses of NATRECOR® that have been proven to be effective and safe. If you have any questions about the use of NATRECOR® or need additional information, please call our Medical Information department at 877-4-NATRECOR (877-462-8732).

Conclusion

We remain confident that NATRECOR® is safe and effective when used as recommended to treat the patients described in the prescribing information. Although questions have been raised about the safety of NATRECOR®, it is important to note that more information from controlled clinical trials exists about NATRECOR® than for any other therapy available to treat these patients. Through a robust clinical development program, Scios remains committed to providing patients and the clinical community with additional efficacy and safety information about NATRECOR® in the hospital setting as well as for other potential indications. As with any medication, health care providers should decide to use NATRECOR® only after consideration of the demonstrated effectiveness and

safety profile of NATRECOR®, the demonstrated effectiveness and safety profile of alternative therapies, and the clinical presentation and co-morbidities of the patient.

Sincerely,

Darlene P. Horton, MD
Senior Vice President, Clinical Research and Medical Affairs

BELOW IS THE PANEL'S REPORT, ISSUED ON JUNE 13, 2005:

Nesiritide (Natrecor ®) is the first member of a new drug class, human B-type natriuretic peptide (hBNP) and is manufactured from E coli using recombinant DNA technology. The approval of the drug was based on the evaluation of 10 completed clinical trials involving 1456 patients with congestive heart failure. These trials showed that the drug reduced dyspnea and produced dose-dependent reductions in pulmonary capillary wedge pressure and systolic arterial pressure when added to standard care. Since approval, 2 additional trials involving 447 patients have been completed.

Nesiritide was approved in 2001 "for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity" and it has been widely used.

Two recent publications have raised questions about the safety of nesiritide with respect to worsening renal function and death. The data on which these analyses were based were available to and known by the FDA. Scios expanded these analyses to include data from all available trials, and convened this panel with the following objectives:

1) To review and discuss nesiritide efficacy and safety data;
2) To provide guidance on proposed clinical development strategies for nesiritide; and
3) To review the current package insert and to provide recommendations on the use of nesiritide.

The Nesiritide Advisory Panel met in Boston, MA on June 8, 2005. Prior to the meeting, the panel members reviewed substantial material provided by Scios, including the original (August 2001) and the current (April 2005) package inserts, communications sent to physicians by Scios, the recent papers by Sackner-Bernstein et al, as well as nesiritide publications, including a submitted paper.

At the meeting, in depth presentations of substantial additional analyses of existing data were made, plans for future trials were reviewed and extensive discussions were held with Scios scientific staff. The panel also held two closed-door executive sessions which were independent of the sponsor and during which the recommendations were prepared. Our conclusions and recommendations are based on the data supplied by Scios.

Eugene Braunwald, MD (Chairman)
Harvard Medical School

John C. Burnett, Jr., MD
Mayo Clinic College of Medicine

Wilson S. Colucci, MD
Boston University School of Medicine

Barry M. Massie, MD
University of California, San Francisco, School of Medicine

John J.V. McMurray, M.D.
University of Glasgow

Christopher M. O'Connor, MD
Duke University Medical Center

Milton Packer, MD
University of Texas Southwestern Medical School

Ileana Piña, MD, FACC
Case-Western Reserve University

Bertram Pitt, MD
University of Michigan Health System

James Young, MD
Cleveland Clinic Lerner College of Medicine

RENAL DYSFUNCTION

The panel noted that the use of nesiritide was associated with a dose-dependent increase in serum creatinine indicating renal dysfunction at doses described in the package insert (0.01 to 0.03 ug/kg/min), including the dose recommended for initiation of treatment (0.01 ug/kg/min). In the largest trial that led to the approval of the drug (VMAC), which used a dose of 0.01 ug/kg/min, the serum creatinine rose by more than 0.5 mg/dL above baseline in at least one blood draw in 7% of patients in the control groups and 8% in the nesiritide groups by 5 days, and by 21% and 28% respectively, by 30 days. Most of these increases occurred days after discontinuation of the drug.

The mechanism of these creatinine changes, their duration, implications for survival, longer term renal function and other clinical consequences is not clear. There is no evidence, however, that nesiritide results in improvement in renal function.

Studies to clarify the mechanism and reversibility of the observed changes in creatinine should be undertaken. These should examine renal function in a more systematic and comprehensive way and relate changes in renal function to clinical outcomes. Additional analyses of existing data to identify the characteristics of patients who experience creatinine elevation should be conducted.

MORTALITY

The panel noted that completed trials show that the use of nesiritide was associated with a trend toward an increase in mortality rate at 30 days, with a hazard ratio of approximately 1.3, a 30% increase. However, the confidence intervals around this ratio are wide and the number of deaths in a pooled analysis of all six of the controlled clinical trials (84) is insufficient to identify or exclude, with confidence, a moderate excess of risk to survival. Also, there are potentially important imbalances in baseline characteristics and in other treatments received concomitantly, and the trials differ with respect to the treatments with which nesiritide was compared. No increased hazard is observed at 180 days. Because of the small numbers of events in the current database and the inconclusive nature of these findings, the panel recommends that additional studies be conducted to assess the effect of nesiritide on survival.

CLINICAL TRIALS

1) The panel strongly recommends continued enrollment in ongoing trials of nesiritide, as well as enrollment in trials that are soon to commence. The panel notes that these trials have been or will be reviewed by regulatory agencies and that the safety of patients in all of these trials is carefully monitored by appropriately constituted and independent Data Safety and Monitoring Committees.
2) The panel endorses Scios' plan to conduct, in a timely manner, a large (several thousand subjects) trial of clinical outcomes to assess further the benefits and risks of nesiritide compared to standard therapy. This trial should be initiated without delay.

   The panel recommends that this trial should include patients presenting to a hospital with acute decompensated heart failure and severe dyspnea. It should be adequately powered to detect an approximately 15% reduction in the combined risk of mortality and cardiorenal morbidities at an early time point, e.g. 30–90 days, and mortality at a later time point, e.g., 180 days. The study design should consider stratification by important co-variates including the use of inotropic agents and other previously identified markers of high risk for adverse outcomes. It should evaluate effects of nesiritide on renal function e.g., Cystatin C. A pharmaco-economic analysis should be included. The trial should also evaluate symptomatic changes and ventricular remodeling in nested substudies. Strong efforts should be made to harmonize this trial with other global trials so that the results can be pooled.
3) Additional mechanistic studies, including an examination of the effect of doses lower than those approved should be considered. Further exploration of the data from the completed trials should be carried out to examine the effects of nesiritide in subgroups of patients.

FINAL RECOMMENDATIONS

1) The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest, as were the patients in the largest trial that led to approval of the drug (VMAC). Physicians considering the use of nesiritide should consider its efficacy in reducing dyspnea, the possible risks of the drug summarized above, and the availability of alternate therapies to relieve the symptoms of congestive heart failure.
2) Nesiritide should *not* be used to replace diuretics. Furthermore, because sufficient evidence is not currently available to demonstrate benefit for the applications listed below, nesiritide should *not* be used:
   - for intermittent outpatient infusion
   - for scheduled repetitive use
   - to improve renal function
   - to enhance diuresis.
3) Scios should immediately undertake a pro-active educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used, as described above. Sponsor supported communications, including review articles of nesiritide, should reflect the above recommendations. Scios should ensure that current and future marketing and sales activities related to nesiritide are consistent with this educational program.

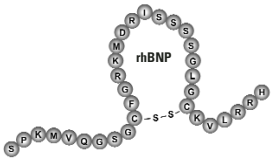
FOR INTRAVENOUS INFUSION ONLY

℞ Only

DESCRIPTION

Natrecor® (nesiritide) is a sterile, purified preparation of a new drug class, human B-type natriuretic peptide (hBNP), and is manufactured from *E.* coli using recombinant DNA technology.

Nesiritide has a molecular weight of 3464 g/mol and an empirical formula of $C_{143}H_{244}N_{50}O_{42}S_4$. Nesiritide has the same 32 amino acid sequence as the endogenous peptide, which is produced by the ventricular myocardium.



Natrecor is formulated as the citrate salt of rhBNP, and is provided in a sterile, single-use vial. Each 1.5 mg vial contains a white- to off-white lyophilized powder for intravenous (IV) administration after reconstitution. The quantitative composition of the lyophilized drug per vial is: nesiritide 1.58 mg, mannitol 20.0 mg, citric acid monohydrate 2.1 mg, and sodium citrate dihydrate 2.94 mg.

Mechanism of Action

Human BNP binds to the particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3'5'-cyclic monophosphate (cGMP) and smooth muscle cell relaxation. Cyclic GMP serves as a second messenger to dilate veins and arteries. Nesiritide has been shown to relax isolated human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine.

In human studies, nesiritide produced dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure in patients with heart failure.

In animals, nesiritide had no effects on cardiac contractility or on measures of cardiac electrophysiology such as atrial and ventricular effective refractory times or atrioventricular node conduction.

Naturally occurring atrial natriuretic peptide (ANP), a related peptide, increases vascular permeability in animals and humans and may reduce intravascular volume. The effect of nesiritide on vascular permeability has not been studied.

Pharmacokinetics

In patients with congestive heart failure (CHF), Natrecor administered intravenously by infusion or bolus exhibits biphasic disposition from the plasma. The mean terminal elimination half-life ($t_{1/2}$) of Natrecor is approximately 18 minutes and was associated with approximately 2/3 of the area-under-the-curve (AUC). The mean initial elimination phase was estimated to be approximately 2 minutes. In these patients, the mean volume of distribution of the central compartment (Vc) of Natrecor was estimated to be 0.073 L/kg, the mean steady-state volume of distribution (Vss) was 0.19 L/kg, and the mean clearance (CL) was approximately 9.2 mL/min/kg. At steady state, plasma BNP levels increase from baseline endogenous levels by approximately 3-fold to 6-fold with Natrecor infusion doses ranging from 0.01 to 0.03 mcg/kg/min.

Elimination

Human BNP is cleared from the circulation via the following three independent mechanisms, in order of decreasing importance: 1) binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis; 2) proteolytic cleavage of the peptide by endopeptidases, such as neutral endopeptidase, which are present on the vascular lumenal surface; and 3) renal filtration.

Special Populations

Although Natrecor is eliminated, in part, through renal clearance, clinical data suggest that dose adjustment is not required in patients with renal insufficiency. The effects of Natrecor on PCWP, cardiac index (CI), and systolic blood pressure (SBP) were not significantly different in patients with chronic renal insufficiency (baseline serum creatinine ranging from 2 mg/dL to 4.3 mg/dL), and patients with normal renal function. The population pharmacokinetic (PK) analyses carried out to determine the effects of demographics and clinical variables on PK parameters showed that clearance of Natrecor is proportional to body weight, supporting the administration of weight-adjusted dosing of Natrecor (i.e., administration on a mcg/kg/min basis). Clearance was not influenced significantly by age, gender, race/ethnicity, baseline endogenous hBNP concentration, severity of CHF (as indicated by baseline PCWP, baseline CI, or New York Heart Association [NYHA] classification), or concomitant administration of an ACE inhibitor.

Natrecor® (nesiritide) for Injection

Effects of Concomitant Medications

The co-administration of Natrecor with enalapril did not have significant effects on the PK of Natrecor. The PK effect of co-administration of Natrecor with other IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated. During clinical studies, Natrecor was administered concomitantly with other medications, including: diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, statins, class III antiarrhythmic agents, beta-blockers, dobutamine, calcium channel blockers, angiotensin II receptor antagonists, and dopamine. Although no PK interactions were specifically assessed, there did not appear to be evidence suggesting any clinically significant PK interaction.

Pharmacodynamics

The recommended dosing regimen of Natrecor is a 2 mcg/kg IV bolus followed by an intravenous infusion dose of 0.01 mcg/kg/min. With this dosing regimen, 60% of the 3-hour effect on PCWP reduction is achieved within 15 minutes after the bolus, reaching 95% of the 3-hour effect within 1 hour. Approximately seventy percent of the 3-hour effect on SBP reduction is reached within 15 minutes. The pharmacodynamic (PD) half-life of the onset and offset of the hemodynamic effect of Natrecor is longer than what the PK half-life of 18 minutes would predict. For example, in patients who developed symptomatic hypotension in the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial, half of the recovery of SBP toward the baseline value after discontinuation or reduction of the dose of Natrecor was observed in about 60 minutes. When higher doses of Natrecor were infused, the duration of hypotension was sometimes several hours.

Clinical Trials

Natrecor has been studied in 10 clinical trials including 941 patients with CHF (NYHA class II-III 61%, NYHA class IV 36%; mean age 60 years, women 28%). There were five randomized, multi-center, placebo- or active-controlled studies (comparative agents included nitroglycerin, dobutamine, milrinone, nitroprusside, or dopamine) in which 772 patients with decompensated CHF received continuous infusions of Natrecor at doses ranging from 0.01 to 0.03 mcg/kg/min. (See the ADVERSE REACTIONS section for relative frequency of adverse events at doses ranging from the recommended dose up to 0.03 mcg/kg/min). Of these patients, the majority (n = 541, 70%) received the Natrecor infusion for at least 24 hours; 371 (48%) received Natrecor for 24–48 hours, and 170 (22%) received Natrecor for greater than 48 hours.

In controlled trials, Natrecor has been used alone or in conjunction with other standard therapies, including diuretics (79%), digoxin (62%), oral ACE inhibitors (55%), anticoagulants (38%), oral nitrates (32%), statins (18%), class III antiarrhythmic agents (16%), beta-blockers (15%), dobutamine (15%), calcium channel blockers (11%), angiotensin II receptor antagonists (6%), and dopamine (4%). Natrecor has been studied in a broad range of patients, including the elderly (42% >65 years of age), women (30%), minorities (26% black), and patients with a history of significant morbidities such as hypertension (67%), previous myocardial infarction (50%), diabetes (44%), atrial fibrillation/flutter (34%), nonsustained ventricular tachycardia (25%), ventricular tachycardia/fibrillation (12%), preserved systolic function (9%), and acute coronary syndromes less than 7 days before the start of Natrecor (4%).

The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial was a randomized, double-blind study of 489 patients (246 patients requiring a right heart catheter, 243 patients without a right heart catheter) who required hospitalization for management of shortness of breath at rest due to acutely decompensated CHF. The study compared the effects of Natrecor, placebo, and IV nitroglycerin when added to background therapy (IV and oral diuretics, non-IV cardiac medications, dobutamine, and dopamine). Patients with acute coronary syndrome, preserved systolic function, arrhythmia, and renal insufficiency were not excluded. The primary endpoints of the study were the change from baseline in PCWP and the change from baseline in patients' dyspnea, evaluated after three hours. Close attention was also paid to the occurrence and persistence of hypotension, given nesiritide's relatively long (compared to nitroglycerin) PK and PD half-life.

Natrecor was administered as a 2 mcg/kg bolus over approximately 60 seconds, followed by a continuous fixed dose infusion of 0.01 mcg/kg/min. After the 3-hour placebo-controlled period, patients receiving placebo crossed over to double-blinded active therapy with either Natrecor or

nitroglycerin. The nitroglycerin dose was titrated at the physician's discretion. A subset of patients in the VMAC trial with central 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.

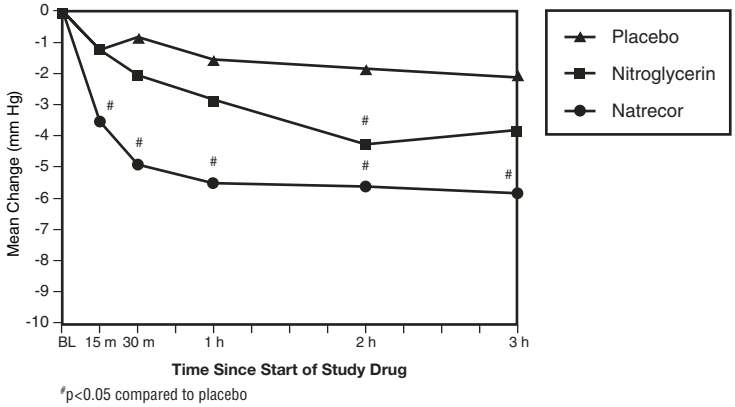
The following table and graph summarize the changes in the VMAC trial in PCWP and other measures during the first 3 hours.

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

PCWP through 3 Hours



#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.

Natrecor® (nesiritide) for Injection

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. No serious allergic or anaphylactic reactions have been reported with Natrecor.

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: Animal developmental and reproductive toxicity studies have not been conducted with nesiritide. It is also not known whether Natrecor can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Natrecor should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

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.

	VMAC Trial		Other Long Infusion Trials		
				Natrecor mcg/kg/min	
Adverse Events	Nitroglycerin (n = 216)	Natrecor Recommended Dose (n = 273)	Control* (n = 256)	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.

Clinical Laboratory

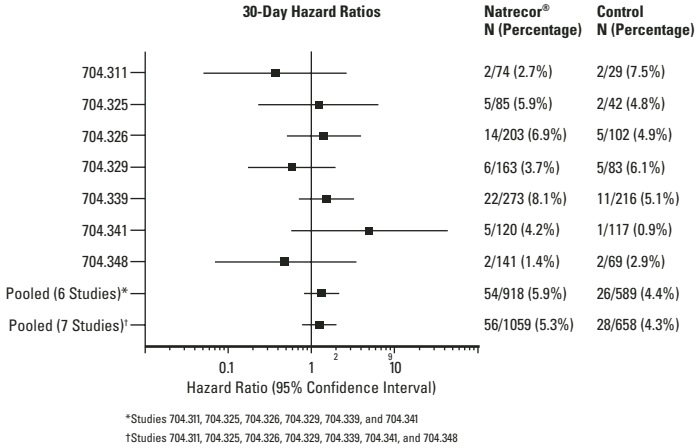
In the PRECEDENT trial, the incidence of elevations in serum creatinine to >0.5 mg/dL above baseline through day 14 was higher in the Natrecor 0.015 mcg/kg/min group (17%) and the Natrecor 0.03 mcg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, through day 30, the incidence of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

Natrecor® (nesiritide) for Injection

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]).

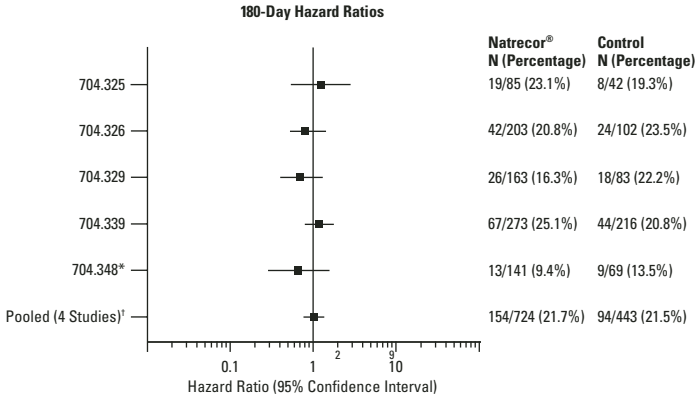
The figure (on logarithmic scale) also contains a plot for the six studies involving hospitalized or Emergency Department patients combined (n = 1507), and for all 7 studies combined (n = 1717). The percentage is the Kaplan-Meier estimate.



*Studies 704.311, 704.325, 704.326, 704.329, 704.339, and 704.341

†Studies 704.311, 704.325, 704.326, 704.329, 704.339, 704.341, and 704.348

The figure below represents 180-day mortality hazard ratios for randomized and treated patients from all four individual studies where 180-day data were collected, 16 week hazard ratios for Study 348 (180-day data were not collected), and the four studies with 180-day data pooled (n = 1167).



*Data collected through week 16

†Studies 704.325, 704.326, 704.329, and 704.339

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.

OVERDOSAGE

No data are available with respect to overdosage in humans. The expected reaction would be excessive hypotension, which should be treated with drug discontinuation or reduction (see PRECAUTIONS) and appropriate measures.

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 left at Controlled Room Temperature (20 – 25˚C; 68 – 77˚F) as per United States Pharmacopeia (USP) or may be refrigerated (2 – 8˚C; 36 – 46˚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.

Bolus Volume (mL) = 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

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):

Infusion Flow Rate (mL/hr) = Patient Weight (kg) x 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

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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 Natrecor at controlled room temperature (20 – 25˚C; 68 – 77˚F); excursions permitted to 15 – 30˚C (59 – 86˚F; see USP Controlled Room Temperature), or refrigerated (2 – 8˚C; 36 – 46˚F). Keep in carton until time of use.

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.
Distributed by Scios Inc.
6500 Paseo Padre Parkway
Fremont, CA 94555

20030302
Revised April 2005