

National PBM Drug Monograph Addendum Nesiritide (Natrecor®)

VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Also refer to the original nesiritide drug monograph at <http://www.pbm.va.gov/monograph/nesiritidemonograph.pdf>

Introduction^{1,2}

Nesiritide (Natrecor® Scios) was approved by the FDA in August 2001 for use in patients with acutely decompensated congestive heart failure (ADHF) who have dyspnea at rest or with minimal activity. The PBM-MAP and VISN Formulary Leaders reviewed nesiritide as a new molecular entity in April 2002 and recommended that the agent remain nonformulary. In a provider memo dated November 18, 2002, the MAP and Cardiology Advisory Group recommended that nesiritide be readily available at all VA medical centers (VAMC) where ADHF is treated (e.g., those with an ICU/CCU). Recommendations in the monograph and memo stated that nesiritide should be reserved for patients who had an inadequate response to or were unable to tolerate standard therapy (e.g., diuretics, vasodilators, ± inotropic agents). As the data were insufficient at the time to determine whether nitroglycerin or nesiritide should be used as second line therapy after high dose diuretics, it was recommended that this issue be discussed at the VISN and/or local levels to determine consensus on protocols and for reviewing utilization.

Recently (May 6, 2005), the manufacturer of nesiritide notified healthcare providers of recent changes to the Effect on Mortality section of the prescribing information for nesiritide, as well as results of two meta-analyses published on the safety of nesiritide compared to control therapy (generally diuretics and nitroglycerin). The results of the meta-analyses and the changes to the prescribing information are summarized in the following sections.

The manufacturer constituted an advisory panel to independently review the data on nesiritide. Due to the potential safety concerns with nesiritide and the inconclusive results based on the small number of events, the panel stated that a large clinical outcome trial should be initiated as soon as possible. The panel recommended that nesiritide should only be used in patients similar to those enrolled in the pivotal clinical trial, who presented to the hospital with ADHF and dyspnea at rest, which is slightly more restrictive than the currently FDA approved indication. The advisory panel also recommended that nesiritide not be used to replace diuretics and that it should not be used in the following situations: for intermittent infusion; for scheduled repetitive use; to improve renal function; to enhance diuresis.

Summary of Meta-Analyses^{3,4} (Refer to Tables 1 and 2)

Meta-analyses of data including FDA and drug sponsor documents in addition to clinical trials with nesiritide in patients with ADHF, reported a statistically significant increase in worsening renal function compared to noninotropic controls (RR 1.53; 95% CI 1.16-2.00; P=0.002) and compared to all controls (RR 1.54; 95% CI 1.20-1.99; P=0.001) in pooled data from five trials, and medical intervention due to worsening renal function (11% vs. 4%; RR 2.29; 95% CI 1.07-4.89; P=0.03) from pooled data of two trials compared to noninotropic controls. Another meta-analysis reported a trend toward an increase in 30-day mortality (7.2% vs. 4.0%; HR 1.74; 95% CI 0.97-3.12; P=0.059) from pooled data of three trials compared to noninotropic controls.

Nesiritide Prescribing Information Changes¹(Refer to Appendices 1 and 2)

The Effect on Mortality section of the Nesiritide Prescribing Information was expanded to include the 30-day mortality data from seven studies (311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], 348 [FUSION]), and 180-day mortality data from four studies (325, 326, PRECEDENT, VMAC) and 16-week data from FUSION. Pooled data from the seven studies (1717 patients) in the product labeling reported a 30-day mortality of 5.3% with nesiritide compared to 4.3% in the control group, a difference that was not statistically significant. Pooled data from the four studies (1167 patients) in the product labeling reported a 180-day mortality of 21.7% with nesiritide compared to 21.5% in the control group, a difference that was not statistically significant.

An additional change to the Nesiritide Prescribing Information is located in the section on Dosing Instructions, and recommends that the IV tubing be primed with 5ml of the solution for infusion (rather than 25ml) before connecting to the patient's vascular access port and before giving the bolus or infusion.

Results of In-Hospital Mortality from the ADHERE Registry⁵

An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE) of 65,180 patient episodes to compare in-hospital mortality of treatment with nesiritide, nitroglycerin, dobutamine, or milrinone has recently become available. The registry is a descriptive evaluation of consecutive patients admitted to participating hospitals that are discharged with a diagnosis of heart failure. The primary objectives of the registry are to document demographics, clinical characteristics, emergency and inpatient management, and medical treatment. The results of in-hospital mortality comparing nesiritide (NES) to nitroglycerin (NTG) as well as nesiritide or nitroglycerin to dobutamine (DOB) are summarized below (refer to the publication for results of additional pair-wise comparisons).

Mortality Odds Ratios	NES (n=4402) vs. NTG (n=5668)	NES (n=4270) vs. DOB (n=3301)	NTG (n=5713) vs. DOB (n=3478)
Unadjusted	1.64 (1.38-1.94) ^c	0.37 (0.32-0.44) ^c	0.24 (0.20-0.28) ^c
Adjusted for Covariates ^a	0.95 (0.78-1.16) ^d	0.47 (0.39-0.56) ^c	0.46 (0.38-0.57) ^c
Adjusted for Covariates and Propensity Score ^b	0.94 (0.77-1.16) ^d	0.47 (0.39-0.56) ^c	0.46 (0.37-0.57) ^c

^a Adjusted for covariates (age, gender, SBP, DBP, BUN, sCr, sodium, HR, dyspnea)

^b Adjusted for covariates and propensity score (NES vs. NTG: SBP, BUN, sCr, LVEF, symptom duration, edema, previous HF, QRS > 120 ms; NES vs. DOB: SBP, sodium, BUN, sCr, age, weight, LVEF, edema; NTG vs. DOB: SBP, sodium, BUN, HR, LVEF, symptom duration)

^c p < 0.005

^d p = 0.58

Conclusions and Recommendations⁶

Although long-term outcome trials with nesiritide in patients with ADHF are not available, nesiritide has been associated with an increase in worsening renal function also requiring medical intervention, as well as a trend toward an increase in mortality compared to control (the difference of results reported in the meta-analysis compared to mortality data included in the product labeling may be due to inclusion/exclusion criteria for pooled data). The increase in in-hospital mortality seen with nesiritide compared to nitroglycerin noted in a retrospective evaluation of observational data was no longer statistically significant when adjusted for differences in baseline demographics and clinical characteristics.

It is recommended that nesiritide be reserved for patients with ADHF who have had an inadequate response to or are unable to tolerate standard therapy including high dose diuretics and in most cases vasodilators (specifically, nitroglycerin given intravenously or by other routes, or nitroprusside), and for whom benefits appear to outweigh risk. It is emphasized that nesiritide should be used only in patients with ADHF presenting to the hospital with dyspnea at rest, and should not be used in the outpatient setting at this time.

References

1. Natrecor® (nesiritide) prescribing information. Fremont, CA: Scios Inc.; 2005 Apr.
2. Husten L. Braunwald committee recommends more clinical trials, conservative use of nesiritide. theheart.org newsletter 2005 Jun 14. http://www.theheart.org/viewArticle.do?primaryKey=506037&nI_id=tho17jun05. Accessed 2005 Jun 20.
3. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005;111:1487-91.
4. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005;293:1900-5.
5. Abraham WT, Adams KF, Fonarow GC, et al, the ADHERE Scientific Advisory Committee and Investigators, and the ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the acute decompensated heart failure national registry (ADHERE). *J Am Coll Cardiol* 2005;46:57-64.
6. The Task Force on Acute Heart Failure of the European Society of Cardiology. Guidelines on the diagnosis and treatment of acute heart failure – full text. *Eur Heart J* 2005. doi:10.1093/eurheartj/ehi117. <http://www.escardio.org/NR/rdonlyres/CBA6844E-56D7-43B4-B0FB-6A4FAF0C0E98/0/AHFFullTextFVFWehi117170205.pdf>. Accessed 2005 Jun 10.

Table 1. Meta-analysis	Inclusion and Endpoints	Comparisons and Trial Characteristics	Results	Summary																																																																																																																																		
<p>Sackner-Bernstein et al, Circulation 2005³</p> <p>Seven RCTs identified; five included (due to effects on sCr not available in 2 studies)</p>	<p>Data Sources FDA documents (Cardiovascular and Renal Drug Advisory Committee meeting documents, Scios NDA); PubMed (nesiritide, clinical trials, humans, English, through 7/2004); manual meeting search (AHA, ACC, HFSA). Data were extracted by two authors</p> <p>Inclusion Criteria Randomized, double-blind, parallel group studies of patients with ADHF where effect on sCr were reported</p> <p>Definition of Worsening Renal Function Increase in sCr > 0.5 mg/dL recorded at any time during inpatient stay of trial</p> <p>Worsening Renal Function Intervention Renal failure requiring dialysis or renal failure requiring medical intervention but not dialysis</p>	<p>Dose Comparisons A) FDA approved dose (≤ 0.03 mcg/kg/min) vs. noninotropic control therapies B) ≤ 0.03 mcg/kg/min vs. all control therapies (with or without mandated inotropic control therapies) C) Low dose (≤ 0.015 mcg/kg/min) vs. noninotropic control therapies D) Low dose (≤ 0.015 mcg/kg/min) vs. all control therapies E) All nesiritide doses (up to 0.06 mcg/kg/min) vs. noninotropic control therapies F) All nesiritide doses (up to 0.06 mcg/kg/min) vs. all control therapies</p> <p>Trial Characteristics</p> <table border="1"> <thead> <tr> <th>Study</th> <th>N</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>311</td> <td>103</td> <td>NI</td> </tr> <tr> <td>325</td> <td>127</td> <td>NI</td> </tr> <tr> <td>326</td> <td>305</td> <td>NI</td> </tr> <tr> <td>VMAC</td> <td>498</td> <td>NTG</td> </tr> <tr> <td>PRECEDENT</td> <td>255</td> <td>Inotrope</td> </tr> </tbody> </table> <p>NI=noninotropic agents</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Nesiritide Dose (bolus mcg) infusion mcg/kg/min</th> </tr> </thead> <tbody> <tr> <td rowspan="3">311</td> <td>(0.25) 0.015</td> </tr> <tr> <td>(0.5) 0.03</td> </tr> <tr> <td>(1.0) 0.06</td> </tr> <tr> <td></td> <td>Up to 24 hours</td> </tr> <tr> <td rowspan="2">325</td> <td>(0.3) 0.015</td> </tr> <tr> <td>(0.6) 0.03</td> </tr> <tr> <td></td> <td>Up to 5 days</td> </tr> <tr> <td rowspan="2">326</td> <td>(0.3) 0.015</td> </tr> <tr> <td>(0.6) 0.03</td> </tr> <tr> <td></td> <td>Up to 12 days</td> </tr> <tr> <td>VMAC</td> <td>(2.0) 0.01</td> </tr> <tr> <td></td> <td>(2.0) up to 0.03 > 24 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P=0.002) (calculated NNH=15 patients for up to 24 hours to up to 12 days treatment with nesiritide for ADHF) and vs. all controls (RR 1.54; 95% CI 1.20-1.99; P=0.001) (calculated NNH=15 patients for up to 24 hours to up to 14 days treatment with nesiritide for ADHF) Treatment with nesiritide statistically significantly increased the need for medical intervention (not including dialysis) for worsening renal function vs. controls (RR 2.29; 95% CI 1.07-4.89; P=0.03) (calculated NNH=14 patients for up to 5 days to up to 12 days treatment with nesiritide for ADHF) The increase in need for dialysis with nesiritide was not statistically significant vs. controls (RR 1.18; 95% CI 0.05-2.76; P=0.71) <p>Comments</p> <ul style="list-style-type: none"> Unable to adjust for factors other than treatment group Unable to assess long term outcomes <p>Quality Assessment</p> <ul style="list-style-type: none"> Good (based on internal and external validity)
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ACC=American College of Cardiology; AHA=American Heart Association; HFSA=Heart Failure Society of America; NDA=new drug application; NNH=number needed to harm; NTG=nitroglycerin; PRECEDENT=Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natreacor Therapy; RCT=randomized controlled trial; RR=relative risk; VMAC=Vasodilation in the Management of Acute Congestive heart failure

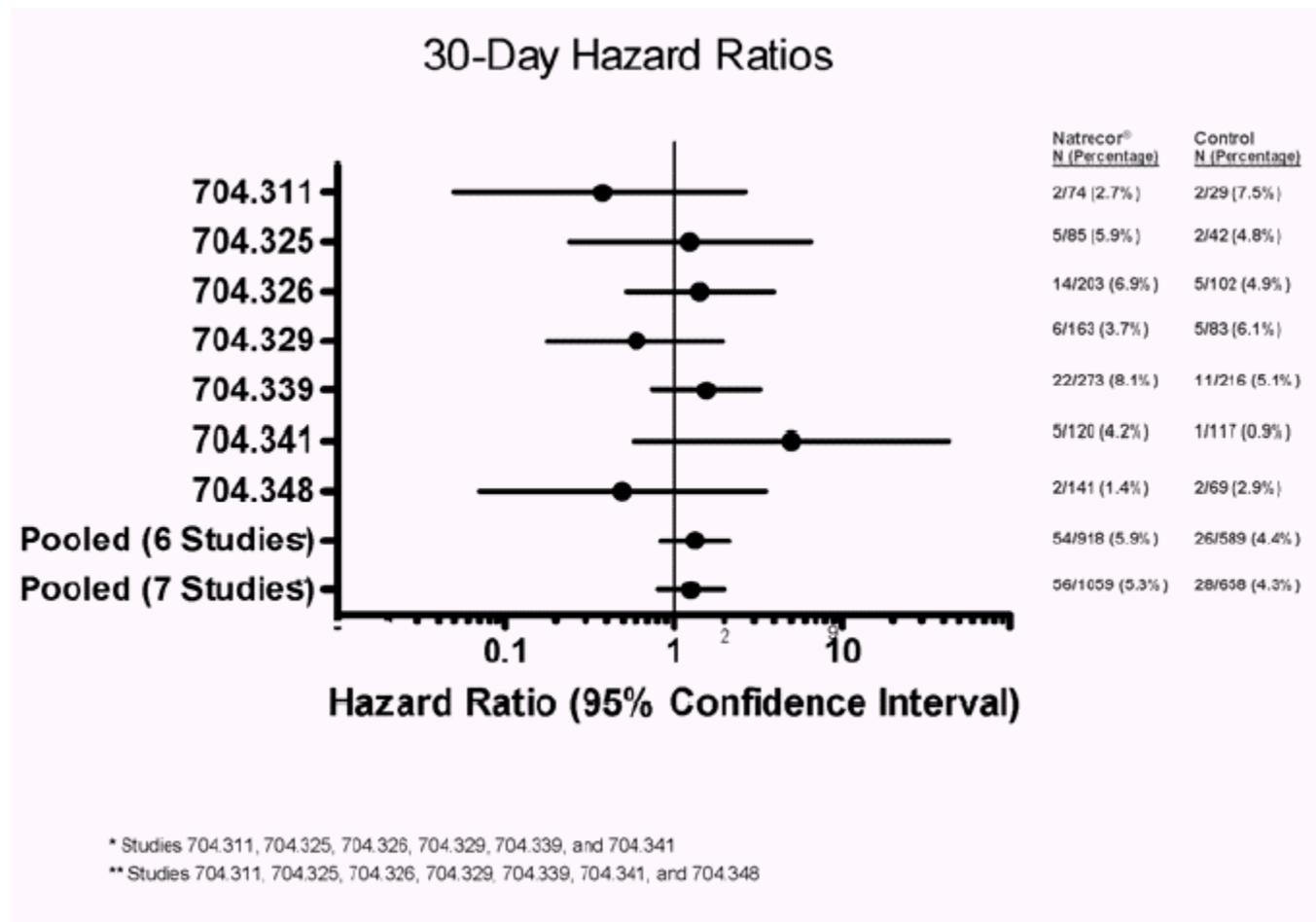
Table 2. Meta-analysis	Inclusion and Endpoints	Comparisons and Trial Characteristics	Results	Summary																																													
<p>Sackner-Bernstein et al, JAMA 2005⁴</p> <p>Twelve RCTs identified; three included that met criteria</p>	<p>Data Sources FDA documents (Cardiovascular and Renal Drug Advisory Committee meeting documents, Scios NDA); drug Sponsor (Scios Inc.); PubMed (nesiritide, clinical trials, humans, English); manual meeting search (AHA, ACC, HFSA) through 12/2004. Data abstracted by principal investigator</p> <p>Inclusion Criteria Randomized, double-blind, parallel group studies of patients with ADHF; nesiritide single infusion of \geq 6 hours; control therapy not mandating a positive inotropic agent; mortality during 30 days of follow-up reported</p> <p>Mortality Outcome Measure Death within 30 days</p>	<p>Trial Characteristics</p> <table border="1"> <thead> <tr> <th>Study</th> <th>N</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>NSGET</td> <td>127</td> <td>Placebo^a</td> </tr> <tr> <td>VMAC</td> <td>498</td> <td>NTG or placebo^b</td> </tr> <tr> <td>PROACTION</td> <td>237</td> <td>Placebo^c</td> </tr> </tbody> </table> <p>^a No IV vasodilators or inotropes allowed during 6 hour infusion ^b For 3 hours, then randomized again to NTG or nesiritide; catheterized patients randomized to adjustable dose nesiritide or other groups; dobutamine used at discretion of clinician (25.4% nesiritide group vs. 15.1% control; P=0.006) ^c NTG and diuretics (but not inotropes) allowed in each group</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Nesiritide Dose (bolus mcg) infusion mcg/kg/min</th> </tr> </thead> <tbody> <tr> <td>NSGET</td> <td>(0.3) 0.015 (0.6) 0.03 for 6 hours</td> </tr> <tr> <td>VMAC</td> <td>(2.0) 0.01 (2.0) up to 0.03 > 24 hours</td> </tr> <tr> <td>PROACTION</td> <td>bolus followed by 0.01 infusion minimum 12 hours</td> </tr> </tbody> </table>	Study	N	Control	NSGET	127	Placebo ^a	VMAC	498	NTG or placebo ^b	PROACTION	237	Placebo ^c	Study	Nesiritide Dose (bolus mcg) infusion mcg/kg/min	NSGET	(0.3) 0.015 (0.6) 0.03 for 6 hours	VMAC	(2.0) 0.01 (2.0) up to 0.03 > 24 hours	PROACTION	bolus followed by 0.01 infusion minimum 12 hours	<p>30-Day Mortality</p> <table border="1"> <thead> <tr> <th>Study</th> <th>Nesiritide n/N</th> <th>Control n/N</th> <th>RR (95% CI)</th> <th>P</th> </tr> </thead> <tbody> <tr> <td>NSGET</td> <td>6/85 (7.1%)</td> <td>2/42 (4.8%)</td> <td>1.48 (0.31-7.03)</td> <td>ND</td> </tr> <tr> <td>VMAC</td> <td>24/280 (8.6%)</td> <td>12/218 (5.5%)</td> <td>1.56 (0.80-3.04)</td> <td>ND</td> </tr> <tr> <td>PROACTION</td> <td>5/120 (4.2%)</td> <td>1/117 (0.9%)</td> <td>4.88 (0.58-41.1)</td> <td>ND</td> </tr> <tr> <td>Total</td> <td>35/485 (7.2%)</td> <td>15/377 (4.0%)</td> <td>1.74 (0.97-3.12)</td> <td>0.059*</td> </tr> </tbody> </table> <p>n=number of deaths N=total number of patients ND=not determined * Meta-analysis using fixed-effects model (crude 30 day mortality RR 1.91; 95% CI 1.01-3.27; P=0.04, unadjusted Kaplan-Meier 30 day survival HR 1.86; 95% CI 1.02-3.41; P=0.04, and survival adjusted for study HR 1.80; 95% CI 0.98-3.31; P=0.057)</p>	Study	Nesiritide n/N	Control n/N	RR (95% CI)	P	NSGET	6/85 (7.1%)	2/42 (4.8%)	1.48 (0.31-7.03)	ND	VMAC	24/280 (8.6%)	12/218 (5.5%)	1.56 (0.80-3.04)	ND	PROACTION	5/120 (4.2%)	1/117 (0.9%)	4.88 (0.58-41.1)	ND	Total	35/485 (7.2%)	15/377 (4.0%)	1.74 (0.97-3.12)	0.059*	<p>Summary of Results</p> <ul style="list-style-type: none"> ➤ Treatment with nesiritide showed a trend toward increased mortality vs. noninotropic controls (7.2% vs. 4.0%; HR 1.74; 95% CI 0.97-3.12; P=0.059) <p>Comments</p> <ul style="list-style-type: none"> ➤ Able to adjust for baseline differences in treatment groups of VMAC (use of dobutamine) ➤ Included mortality data based on ITT of patients excluded from trial publication (VMAC) ➤ Assumed mortality of patients lost to follow-up (NSGET) or listed as between 15 to 30 days (PROACTION) in favor of nesiritide ➤ Clinical trials not designed to determine difference in mortality ➤ Unable to assess impact of medications or procedures during 30 day follow-up <p>Quality Assessment</p> <ul style="list-style-type: none"> ➤ Good (based on internal and external validity)
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ACC=American College of Cardiology; AHA=American Heart Association; HFSA=Heart Failure Society of America; HR=hazard ratio; NDA=new drug application; NSGET=Nesiritide Study Group Efficacy Trial; NTG=nitroglycerin; PROACTION=Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; RCT=randomized controlled trial; RR=relative risk; VMAC=Vasodilation in the Management of Acute Congestive heart failure

Appendix 1.

ADVERSE REACTIONS Effect on Mortality. Natrecor® (nesiritide) prescribing information. Fremont, CA: Scios Inc.; 2005 Apr.
<http://www.fda.gov/cder/foi/label/2005/020920s008lbl.pdf>. Accessed 2005 Jun 2.

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