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**Panel of Cardiology Experts Provides Recommendations to Scios  
Regarding NATRECOR®**

**Fremont, Calif.**, June 13, 2005 — An expert panel of cardiology and heart failure clinicians chaired by Eugene Braunwald, M.D. met on Wednesday, June 8<sup>th</sup> to review and assess important data associated with the acute heart failure treatment NATRECOR® (nesiritide). The panel, which was convened by Dr. Braunwald at the request of Scios, also provided guidance and counsel on the ongoing and planned clinical development program for the product as well as recommendations for use.

The panel's report (see following) consists of three main sections summarizing the panel discussion: effects on renal function, mortality and proposed clinical trials. In the area of clinical trials, the panel strongly encouraged Scios and their clinical investigators to continue enrollment in ongoing trials of NATRECOR®. With respect to recent questions raised about renal function and mortality, the panel endorsed the company's plan to conduct several trials, including a large trial of clinical outcomes to further assess the benefits and risks of NATRECOR®.

In addition, the panel's report includes recommendations to the company regarding the appropriate clinical use of NATRECOR® and the need for related education for health care providers. The panel described patients for whom it considers the drug to be appropriate and uses for which the drug should not be prescribed. The panel also made specific recommendations regarding company education of physicians about appropriate use.

"We accept the panel's recommendations and are pleased the panel endorsed our current and planned development programs," said Darlene Horton, M.D., Senior Vice President of Clinical Research and Medical Affairs at Scios.

Scios noted that the panel recommended a use for NATRECOR® that is slightly narrower than what is outlined in its approved label. The company is contacting regulatory agencies to discuss how to best address this recommendation.

"The panel also described uses for which it believes NATRECOR® is inappropriate," said Dr. Horton. "Scios fully agrees that these are areas for which there are not sufficient data to support the use of NATRECOR®. The company will continue and build upon its efforts to educate physicians regarding appropriate use."

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“Scios appreciates the robust scientific discussion and the thoughtful guidance provided by the panel. Acutely decompensated heart failure patients suffer from a debilitating life-threatening condition, for which there are few good treatment options. The company is committed to the continued study of these patients to improve their health and well being,” added Dr. Horton.

The panel’s full report, including its specific recommendations as outlined above, is attached. Scios has also posted the full report to [www.SCIOSINC.com](http://www.SCIOSINC.com) and to [www.NATRECOR.com](http://www.NATRECOR.com).

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### **IMPORTANT SAFETY INFORMATION**

NATRECOR® (nesiritide) 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).

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. 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%).

Higher doses of NATRECOR® increased the risk of hypotension and elevated creatinine. 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 seven NATRECOR® clinical trials, at 30 days, 5.3% in the NATRECOR® treatment group died as compared with 4.3% in the group treated with other standard medications. In four clinical trials, at 180 days, 21.7% in the NATRECOR® treatment group died as compared with 21.5% in the group treated with other medications. There is not enough information to know if there is an increased risk of death after treatment with NATRECOR®.

### **BELOW IS THE PANEL’S REPORT**

Nesiritide (Natreacor ®) 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.

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### **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-variables 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.