

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-920**

Administrative Documents

Item 13

PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG SECTION

Two United States patents cover human b-type natriuretic peptide (Natreacor®) and its recombinant production. United States Patent No. 5,114,923 issued on 19 May 1992 and has an expiration date of 19 May 2009. This patent contains claims to peptides having at least the core amino acid sequence (17-member disulfide bonded ring) of Natreacor®, including specifically the 32-amino acid form of the peptide; pharmaceutical compositions for inducing natriuresis, diuresis, and/or vasodilation containing such peptides; and a method to induce natriuresis, diuresis, and/or vasodilation by the administration of such peptides. United States Patent No. 5,674,710 issued on 07 October 1997 and has an expiration date of 07 October 2014. This patent contains claims to isolated and purified recombinant DNA consisting essentially of DNA encoding peptides having at least the core amino acid sequence (17-member disulfide bonded ring) of Natreacor®, including specifically recombinant DNA encoding the 32-amino acid form of the peptide; a recombinant expression system capable, in a host cell, of expressing such peptides; a recombinant host cell or cell culture containing such an expression system; and a method of producing such peptides by culturing the recombinant host cell or cell culture under conditions which permit expression of the peptides. These two patents are located in Volume 1 pages 6-60, of the original NDA.

Item 14

**A PATENT CERTIFICATION WITH RESPECT TO
ANY PATENT WHICH CLAIMS THE DRUG SECTION**

21 U.S.C. 355(b)(2): An application for a drug for which the investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include a certification.

- (i) that such patent information has not been filed,
- (ii) that such patent has expired,
- (iii) of the date on which such patent will expire; or
- (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

All investigations in this amended New Drug Application were conducted by or for the applicant; hence, this section is not applicable.

EXCLUSIVITY SUMMARY FOR NDA # 20-920

SUPPL # _____

Trade Name Natreccor

Generic Name nesiritide

Applicant Name Scios Inc.

HFD # 110

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES // NO /___/

b) Is it an effectiveness supplement? YES /___/ NO //

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES // NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES // NO /___/ (letter dated 3/5/99)

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 yrs.

e) Has pediatric exclusivity been granted for this Active Moiety?

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

▲

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/ .

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

!
!

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES / ___ / Explain _____

NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / ___ /

NO / ___ /

If yes, explain: _____

Signature:
Title: Project Manager

Date:

Signature of Office/
Division Director: Robert Temple, M.D.

Date:

cc: Original NDA Division File HFD-93 Mary Ann Holovac

FDA Links ~~Searches~~ Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

[View as Word Document](#)

NDA Number: 020920 **Trade Name:** NATRECOR(NESIRITIDE)5.0MG VIAL IV INFUSI
Supplement Number: 000 **Generic Name:** NESIRITIDE
Supplement Type: N **Dosage Form:**
Regulatory Action: NA **COMIS Indication:** NATRECOR IS INDICATED FOR THE SHORT TERM INTRAVENOUS THERAPY OF CONGESTIVE HEART FAILURE/IN THESE PATIENTS/ NATRECOR RAPIDLY REDUCES PCWP AND SVR AND INCREASES
Action Date: 4/27/99

Indication # 1 short-term treatment of congestive heart failure

Label Adequacy: Adequate for ALL pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Ranges for This Indication

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	16 years	Waived	

Comments: Waiver granted, per discussions with Dr. Lipicky and Dr. Karkowsky, based of the infrequent nature of the disease process in pediatrics, the difference in etiology of pediatric and adult heart failure, and the availability of other, more adjustable pre- and afterload reducers.

This page was last edited on 6/13/01

Signature *JS*

Date 6-13-01

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-920 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

HF 110 Trade and generic names/dosage form: Natrecor (nesiritide) for Inf Action: AP AE NA

Applicant Scios Inc Therapeutic Class IS

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate _____ inadequate _____
Indication proposed in this application short term treatment of CHF

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
 Neonates (Birth-1 month) Infants (1 month-2 yrs) Children (2-12 yrs) Adolescents (12-16 yrs)

- 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from discussions with Drs. Kibicki and Karkowsky. (e.g., medical review, medical officer, team leader)

/S/ _____, RHPM April 13, 1999
Signature of Preparer and Title Date

cc: Orig NDA/BLA # _____
HF _____/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

Item 16

DEBARMENT CERTIFICATION SECTION

Certification Statement

In compliance with 21 U.S.C. § 335a (k) (1) (2), Scios Inc. hereby certifies that it has not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection this New Drug Application.

Signed by: Michael A. Crockett
Michael Crockett

Title: Associate Director, Regulatory Affairs

Date: January 7, 2001

Item 16
DEBARMENT CERTIFICATION SECTION

Certification Statement

In compliance with 21 U.S.C. § 335a (k) (1) (2), Scios Inc. hereby certifies that it has not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection this New Drug Application.

Signed by:



Karen J. Harder

Title: Director, Regulatory Affairs

Date:

21 April 1998

RHPM Approval/Labeling Review

Application: NDA 20-920
Natrecor (nesiritide) for Injection
1.5 mg/vial

Applicant: Scios Inc.

Background: An approvable letter, with marked-up draft labeling, was issued for NDA 20-920 on July 6, 2001. The marked-up labeling contained the agreed upon changes, which took into consideration the revisions suggested by Dr. Morse in his July 3, 2001 Memorandum regarding the pharmacology/toxicology language and by Dr. Simmons (in the NDA Action Letter Routing Record) regarding the structure and storage statements in the draft labeling, as well as Dr. Temple's comments. At the time the approvable letter was issued, the following still had to be resolved:

- 1) Following a pre-approval inspection, the Office of Compliance had issued a WITHHOLD overall recommendation on July 6, 2001 due to GMP issues related to the stability protocol. The approvable letter stated that a satisfactory inspection would be required before the NDA could be approved.

Resolution: The Office of Compliance issued an ACCEPTABLE overall recommendation on July 16, 2001. In his July 23, 2001 Memorandum, Dr. Advani stated that there are no other pending Chemistry, Manufacturing and Controls (CMC) issues and that the application may be approved from a CMC standpoint.

- 2) Final printed labeling should be submitted.

Resolution: Scios submitted revised draft labeling in submissions dated July 18 and 26, 2001. Teleconferences to discuss labeling issues were held with the sponsor on July 20, 26, and 31, 2001. As a result of these teleconferences, the agreed upon revised draft labeling was faxed to the sponsor on July 31, 2001. [Note: Inclusion of the refrigerated temperature storage instructions in the **DOSAGE AND ADMINISTRATION/Preparation and Storage** subsections was acceptable, per discussions between Drs. Simmons and Srinivasachar.] Scios submitted the final printed labeling in a submission dated July 31, 2001. When compared with the agreed upon revised draft labeling faxed to the sponsor on July 31, 2001, the following changes were noted in the package insert of the final printed labeling:

- In the last sentence under **DESCRIPTION/Special Populations**, the phrase "baseline CI" was changed to "baseline CI". Per Drs. Temple and Karkowsky, the correct phrase is "baseline CI" ("CI" for "Cardiac Index"). In an August 3, 2001 telephone conversation between Ms. Klara Dickinson of Scios Inc. and Dr. Quynh Nguyen, Ms. Dickinson stated that the "CI" was a typographical error and should be "CI". Because they had already printed 50,000 copies of the package insert, per Ms. Morgenstern, Scios could distribute the 50,000 copies, but they would have to correct the typographical error at the time of the next printing and report the change in the annual report. Ms. Dickinson agreed.

- Under **DOSAGE AND ADMINISTRATION/Preparation**, the last sentence of Step 4 has been changed from:

to:

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.

Per Drs. Temple, Srinivasachar and Advani, this change is acceptable.

- Minor editorial changes were made throughout the package insert of the final printed labeling under **DESCRIPTION/Mechanism of Action, Special Populations, Clinical Trials, PRECAUTIONS/Cardiovascular, Drug Interactions, Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy: Category C, Nursing Mothers, Pediatric Use, Geriatric Use, ADVERSE REACTIONS and ADVERSE REACTIONS/Clinical Laboratory, DOSAGE AND ADMINISTRATION/Preparation and Dosing Instructions**. These changes include punctuation, verb tense changes and spelling out of abbreviations after first-time use. These editorial changes are acceptable to Drs. Temple and Karkowsky.

Note: The following changes to the package insert were agreed upon by Drs. DeGeorge and DeFelice:

- Under the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the word "Natrecor" should be changed to "nesiritide."
- Under **PRECAUTIONS/Pregnancy: Category C**, the first two sentences should be changed to "Animal developmental and reproductive toxicity studies have not been conducted with nesiritide. It is not known whether Natrecor can cause fetal harm when administered to pregnant women or can affect reproductive capacity."

In an August 8, 2001 telephone conversation between Ms. Klara Dickinson of Scios Inc. and Dr. Quynh Nguyen, Ms. Dickinson agreed to make the above mentioned changes to the **PRECAUTIONS** section at the time of the next printing and to report these changes in the annual report.

Comments/Recommendation: There are no other unresolved issues for this NDA. An approval letter will be drafted for Dr. Temple's signature.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

qn/8-8-01

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

DATE: July 20, 2001
FROM: Andrew Haffer, Pharm.D., DDMAC
TO: Douglas Throckmorton, M.D., DCRDP

SUBJECT: Natrecor Labeling Comments

These comments are based on Scios' proposed changes dated 18 July 2001. These comments also incorporate remarks based on the 29 June 2001 version of the label attached to the AE letter.

General Comment:

- It is my understanding from the 7/17/01 labeling meeting that use of doses other than 2.0 +0.01 should not be recommended. The information provided in many sections of the label (Pharmacokinetics, Pharmacodynamics, Clinical Trials, Adverse Reactions, Dosage and Administration) regarding alternate doses in VMAC and 704.325 will allow for use and promotion of such doses. Further, the inclusion of ADE data for doses other than 2 + 0.01 appears to support their use. Additionally, a strong statement (like the one provided in the cardiovascular precaution) regarding the risk of hypotension with an increased doses should also be included in the dosage and administration section.
- Scios uses the terminology "standard dose" or "standard recommended dose" throughout the label to describe the 2 + 0.01 dose of Natrecor. "Standard" should be removed because it implies there are other doses that may be used.
- Scios proposes to replace "enrolled," and "randomized," with "treated." The phrase "treated with Natrecor" seems to create a very strong message about patients that receive this drug. Suggest replacing "treated" with "receiving."

Page 7, Description:

- In the first line the statement "new" should be removed from "new drug class" as this is promotional in tone. In promotional materials "new" may only be used for the first 6 months.

Page 7, MOA:

- The claim "Nesiritide has been shown to relax isolated human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the adrenergic agonist phenylephrine" appears to be based on *in vitro* data. If this statement is based on *in vitro* data, then the sentence should identify it as such.

Page 8, MOA:

- "In human studies, nesiritide consistently reduced PCWP, increased CI and decreased systemic arterial pressure in patients with heart failure." Is there adequate data to support that nesiritide consistently increased CI and decreased systemic arterial pressure?

- I agree with Scios that the statement “Naturally occurring ANP increases vascular permeability in animals and humans” should be removed.
- Scios proposes to delete the statement “The effect of nesiritide on vascular permeability has not been studied.” This important information should remain unless there is data to support its removal.

Page 10, Pharmacodynamics:

- The third paragraph includes the statement “...with dose-dependent effects on hemodynamics (e.g., reductions in PCWP, pulmonary artery pressure, mean right atrial pressure (RAP), blood pressure, and systemic vascular resistance; and increases in stroke volume and cardiac output)....” This claim should be removed because it suggests that higher doses of Natrecor will provide a greater benefit.

Page 11, Clinical Trials:

- The first paragraph “In controlled trials...before start of Natrecor” contains the same information provided in earlier sections of the label (**Special Populations and Effects of Concomitant Medications**).
- The last sentence of the second paragraph “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.” This statement should be strengthened. Suggest using “The occurrence of hypotension was closely monitored because of Natrecor’s long PK and PD half-life.”

Page 12, Clinical Trials:

- The last sentence of the second paragraph states “but improvement of symptoms also was examined” should be removed. These symptoms were not part of the primary endpoint (PCWP at 6 hours) for study 704.325.

Additionally, the description of these results under **Effects on Symptoms** (p 12) states “In the dose-response study, patients receiving both doses of Natrecor reported significantly greater improvement in dyspnea at 6 hours compared to patients receiving placebo.” This sentence should also be removed. [Page 69 of your review of 704.325 states “With regard to signs and symptoms of CHF, the data are open to investigator bias, and cannot be seen as independent of the hemodynamic results.”]

Page 12, Clinical Trials, Effects on Hemodynamics:

- The first sentence states “PCWP, RAP, CI, and other hemodynamic variables were monitored in 246 of the patients in the VMAC trial.” However, the primary endpoint of this trial were PCWP and dyspnea. Your review lists **RAP** and **CI** as “Other measurements of interest.” Do we want to include such measures in the label?
- Scios proposes to include information on PCWP and SBP in the remainder of the first paragraph. This information has already been provided in the proposed **Pharmacodynamics** section of the label.

Page 13, Clinical Trials, Effects on Hemodynamics:

- The first paragraph states “The following table and graph summarize the changes in the VMAC trial in pulmonary capillary wedge pressure and other measures during the first 3 hours.” Should the words “other measures” and the table listing these “Other measures of interest” be provided? Only PCWP and dyspnea were primary endpoints in VMAC?

Page 13, Clinical Trials, Effects on Urine Output and Sodium Excretion:

- This section contains a comparative analysis between Natrecor and nitroglycerin even though a statement that the VMAC does not support effectiveness comparisons immediately precedes it.

Page 14, Indication and Usage:

- The words “at rest” were removed from the end of the first sentence. This qualifying info is necessary to define the patient population that will receive a benefit from this drug.

Pages 17 & 18, Adverse Reactions:

- The last paragraph beginning on page 17 and ending on page 18 contains data from the PRECEDENT trial. If Scios has provided substantial evidence to support the claim that “Natrecor did not aggravate pre-existing non-sustained VT or the frequency of premature ventricular beats, compared to a baseline 24 hour Holter tape” shouldn’t this info be provided in a different section of the label?

Page 20, Dosage and Administration, Dosing Instructions:

- Scios has proposed to revise the Dose Adjustments section. However, their proposed changes minimize the risk of hypotension and allow for dosing above the recommended dose of 2 + 0.01. Information on increasing the dose is based on 23 patients in VMAC. Should such data be mentioned in the label?

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

DATE: July 17, 2001
FROM: Andrew Haffer, Pharm.D., DDMAC
TO: Douglas Throckmorton, M.D., DCRDP

SUBJECT: Natrecor Labeling Comments

These comments are based on the draft labeling attached to the AE letter dated 7/6/01. The labeling is dated 29 June 2001.

General Comment:

It is my understanding from the 7/17/01 labeling meeting that use of doses other than 2.0 +0.01 should not be used. It is my opinion that the information provided in the label regarding alternate doses in VMAC and 704.325 will allow for use and promotion of such doses. (e.g., the Aggrastat label described a dose in clinical trials section that was not allowed in the dosage and administration section and Merck promoted this dose, I believe it was the elective PCI dose). Further, the inclusion of ADE data for doses other than 2 + 0.01 appears to support their use. Additionally, a strong statement (like the one provided in the cardiovascular precaution) regarding the risk of hypotension with an increased doses should also be included in the dosage and administration section.

Page 3, Description:

In the first line the statement "new drug class" should be removed as this is promotional in tone.

Page 3, MOA:

The claim "Nesiritide has been shown to relax isolated human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the adrenergic agonist phenylephrine" appears to be based on *in vitro* data. If the statement is based on *in vitro* data, this contextual information should be added to the statement.

Page 4, MOA:

"In human studies, nesiritide consistently reduced PCWP, increased CI and decreased systemic arterial pressure in patients with heart failure." Is there adequate data to support increased CI and decreased systemic arterial pressure?

Is the statement "Naturally occurring ANP increases vascular permeability in animals and humans" necessary? It appears to impart a benefit on nesiritide that has not been studied. Further, the statement "The effect of nesiritide on vascular permeability has not been studied" should be moved up with the other info about the use of the drug in humans.

Page 7 & 8, Clinical Trials:

In paragraph 3, the claim "but symptoms were also examined" should be removed. These symptoms were not part of the primary endpoint. Also, the description the results under "Effects on Symptoms" located on page 8 for study 704.325 should be removed. [Page 69 of your review of 704.325 states "With regard to signs and symptoms of CHF, the data are open to investigator bias, and cannot be seen as independent of the hemodynamic results."]

Page 8, Clinical Trials, Effects on Hemodynamics:

"PCWP, RAP, CI, and other hemodynamic variables were monitored in 246 of the patients in the VMAC trial." However, the primary endpoint of the trial is PCWP and dyspnea. Your review lists RAP and CI as "Other measurements of interest." Do we want to include such measures in the label?

The third paragraph states "The following table and graph summarize the changes in the VMAC trial in pulmonary capillary wedge pressure and other measures...." Should the words "other measures" and the table listing these "Other measures of interest" be provided?

Page 9, Clinical Trials:

The bottom of page 9 includes the statement "The VMAC study does not constitute an adequate effectiveness comparison with nitroglycerin as only a single regimen was used. The nitroglycerin group provides a rough landmark of a familiar therapy and regimen." Is the nitroglycerin group a rough landmark or was it a comparison to standard therapy?

Further, although you state that "VMAC does not constitute an adequate effectiveness comparison with nitroglycerin," the very next section of the label entitled "Effect on Urine Output and Sodium Excretion" contains a comparison of Natrecor and NTG.

Page 11, Indication and Usage:

The words "at rest" were removed from the end of the first sentence. This qualifying info is necessary to define the patient population.

Page 14 and 15, Adverse Reactions:

The last paragraph beginning on page 14 and ending on page 15 contains data from the PRECEDENT trial. If there is substantial evidence to support the claim that "Natrecor did not aggravate pre-existing non-sustained VT or VPB's, compared to a baseline 24 hour Holter tape" shouldn't this info be provided in a different section of the label.

Page 17, Dosage and Administration, Dosing Instructions:

Should the word "standard" be removed from the dosage and administration section of the label? It is used several times, adds ambiguity, and implies there are other possible dosing regimens for Natrecor.

**APPEARS THIS WAY
ON ORIGINAL**

Minutes of a Pre-Approval Safety Conference between OPDRA and the Division of Cardio-Renal Drug Products

Date: July 17, 2001

Application: NDA 20-920
Natrecor (nesiritide) for Injection

Sponsor: Scios Inc.

Subject: Discussion of Safety Issues and Labeling

Participants

Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical, HFD-110
Patrick Marroum, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics, HFD-860
Angelica Dorantes, Ph.D., Clinical Pharmacologist and Biopharmaceutist, HFD-860
Natalia Morgenstern, Chief, Project Management Staff, HFD-110
Edward Fromm, Regulatory Health Project Manager, HFD-110
John Guzman, Regulatory Health Project Manager, HFD-110
Julie Beitz, M.D., Director, DDRE I, HFD-430
Claudia Karwoski, Pharm.D., Team Leader, DDRE I, HFD-430
Susan Lu, R.Ph., Team Leader, DDRE I, HFD-430
Michael Johnston, R.Ph., Safety Evaluator, DDRE I, HFD-430
Andrew Haffer, Pharm.D., Regulatory Review Officer, DDMAC, HFD-42
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Background

Natrecor (nesiritide) for Injection is a recombinantly manufactured preparation of human B-type natriuretic peptide (hBNP) proposed for the initial treatment of patients with decompensated congestive heart failure. On January 9, 2001, Scios submitted a major amendment to NDA 20-920 for Natrecor in response to the Agency's April 27, 1999 not-approvable letter. On July 6, 2001, Scios was issued an approvable letter with marked-up labeling enclosed. This meeting was scheduled to discuss labeling issues, as well as safety issues that the Division may have identified or would like the Office of Post-Marketing Drug Risk Assessment (OPDRA) to monitor once Natrecor is approved.

Meeting

Adverse Events Reporting

OPDRA stated that from 1996 to the present, 240 reports of adverse events were captured for intravenous nitroglycerin and from 1974 to the present, 545 reports were captured for dopamine using the Adverse Events Reporting System (AERS). These numbers reflect the use of the drugs in the acute care setting. OPDRA did not think that there would be much adverse event reporting for Natrecor, although hypotension and renal failure may be reported. It was noted that Scios is proposing to set up the ADHERE registry for heart failure patients, which they plan to have ready

at the time of drug launch. The firm will be contacted for information regarding this registry and their proposed protocol.

Labeling

OPDRA had the following comments regarding the draft labeling that was sent to the sponsor with the approvable letter dated July 6, 2001:

Pages 5 and 6: On page 6, under **Clinical Trials**, in the fourth paragraph, the drugs referenced should be consistent with those listed on page 5 under **Effects of Concomitant Medications**.

Page 10: Under **Effect on Urine Output and Sodium Excretion**, OPDRA noted that the net increase or decrease in volume status was not clear. The sponsor's language regarding natriuresis will need to be discussed further. The "and Sodium Excretion" part of the heading was also noted to be problematic.

Page 11: Under **INDICATIONS AND USAGE**, there is no language regarding the use of Natrecor after 48 hours. The labeling for milrinone and primacor state that there is no experience with infusions longer than 48 hours. Dr. Lipicky agreed that language should be included to discourage the long-term use of Natrecor.

Under **CONTRAINDICATIONS**, language regarding Natrecor not being an inotrope will need to be discussed further with Dr. Temple.

Under **PRECAUTIONS/General**, Dr. Karkowsky stated that no cases of an allergic reaction were seen in the clinical trials.

Page 17 and 18: The language under **Dose Adjustments** on page 18 was discussed. Dr. Throckmorton said that we do not have much data on dose adjustments. However, Dr. Karkowsky noted that in the VMAC trial, dose-adjustments were made and that one patient received the infusion for 151 days. On page 6, under **Clinical Trials**, the third paragraph makes reference to patients who received infusions for longer than 72 hours, which is not included in the **DOSAGE AND ADMINISTRATION** section. Addition of the statement: "There is limited experience with Natrecor longer than 72 hours (See Clinical Trials)" or language pertaining to use of Natrecor for "not longer than 48 hours" in the **DOSAGE AND ADMINISTRATION** section was considered.

In addition, use of the phrase "human B-type natriuretic peptide (hBNP)" with the trade name "Natrecor" was discussed. The Division of Drug Marketing and Communications (DDMAC) noted that use of the word "natriuretic" in this way would make a claim about the mechanism of action.

Conclusion

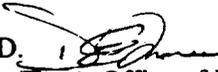
Labeling comments and safety issues regarding Natrecor were discussed. The firm will be contacted for information regarding their proposed heart failure registry.

Minutes Preparation: _____
 Quynh Nguyen, Pharm.D.

Concurrence, Chair: _____ 8/19/01
 Raymond Lipicky, M.D.

Memorandum

Date: 3 July 2001

From: David E. Morse, Ph.D. 
Asc. Director (Pharm./Tox.), Office of Drug Evaluation I

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Cc: Raymond Lipicky, M.D., Dir., DCRDP (HFD-110)
Albert DeFelice, Ph.D., TL Pharm./Tox., DCRDP (HFD-110)

Subject: NDA 20-920
NATRECOR® for Injection (nesiritide)
Review of Pharm./Tox. Information and Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 20-920, dated 8 Dec. 1998, written by T. Papoian, Ph.D.
2. NDA 20-920 Approval Package with Draft Product Labeling (29 Dec. 2000).

II. Background

The sponsor (Scios, Inc.) is seeking approval of NATRECOR® for Injection (nesiritide) for use in the short-term treatment of acute decompensated congestive heart failure. Nesiritide, produced via recombinant DNA technology, is a 32 amino acid peptide, which is identical to the endogenous hormone produced by the ventricular myocardium. Nesiritide has both venous and arterial vasodilatory effects, which alters cardiac preload and afterload, CI and PEWP. Since decompensated congestive heart failure is frequently associated with acute cardiovascular disease, patients would be expected to undergo only a limited duration of dosing with NATRECOR®.

III. Comments and Conclusions

1. A review of the action package for NDA 20-920, NATRECOR® for Injection, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including 2 week continuous IV infusion in rats and primates), for possible approval for short-term use in the treatment of acute decompensated congestive heart failure. Carcinogenicity and reproductive toxicity studies were not deemed necessary by the review division for the short-term treatment in an acutely morbid patient population.
2. Specific comments pertaining to the draft product labeling follow.
 - Reference to the brand name for nesiritide (i.e., NATRECOR®) should be eliminated from the discussion of all non-clinical studies in the product label, unless those studies were specifically conducted with the clinical drug formulation to be marketed. All

discussions of non-clinical studies conducted with other than the clinical drug formulation should make reference to the generic compound name of 'nesiritide.'

- Under the heading "Carcinogenesis, Mutagenesis, Impairment of Fertility" it is recommended that:
 - The sentence pertaining to the Ames assay results be revised to state, "Nesiritide did not increase the frequency of mutations when tested in an *in vitro* bacterial cell assay (Ames test)." ✓
 - The spelling of "genotoxicity" be corrected in the last sentence of this section.
- Under the heading "Pregnancy" it is recommended that:
 - The first sentence of the section be revised to state, "*In utero* embryo-fetal development and post-gestation maturation studies have not been conducted with nesiritide." ✓

IV. Summary

A review of the action package for NDA 20-920, NATRECOR® for Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for potential approval in a short-term acute use indication. The proposed product labeling, with possible revisions as outlined in the preceding section, adequately reflects the non-clinical safety data pertaining to nesiritide.

**APPEARS THIS WAY
ON ORIGINAL**

CSO NDA Overview

June 21, 2001

NDA 20-920 Natrecor (nesiritide) for Injection
1.5 mg/vial

Sponsor: Scios Inc.

Classification: 1S

Date of Application: April 24, 1998
Date of Receipt: April 27, 1998
Date of Major Amendment: January 9, 2001
Date of Receipt: January 10, 2001
User Fee Goal Date: July 10, 2001

Background

Scios Inc. has submitted this major amendment to NDA 20-920 for Natrecor (nesiritide) for Injection in response to the Agency's April 27, 1999 not-approvable letter. The proposed indication is for the initial treatment of patients with decompensated congestive heart failure. The original NDA was received on April 27, 1998. The related IND is

In the not-approvable letter, the Agency cited deficiencies concerning the overall results of controlled studies, symptom evaluation, onset and offset characteristics of symptomatic hypotension, need for an active-controlled study comparing Natrecor to an IV vasodilator such as nitroglycerin, durability of effect, dose response issues, and need for a broader CHF patient population. There were no chemistry, biopharmaceutics or pharmacology deficiencies listed in the not-approvable letter. A May 4, 1999 meeting was held with the sponsor to discuss issues raised in the not-approvable letter. As a result of this and other meetings held on July 20, 1999, January 19 and February 10, 2000, Scios designed the VMAC trial (Vasodilation in the Management of Acute Congestive Heart Failure), protocol 704.339, "A Multicenter, Randomized, Double-Blind, Placebo-controlled Study of the Hemodynamic and Clinical Effects of Natrecor (nesiritide) Compared with Nitroglycerin Therapy for Symptomatic Decompensated CHF."

This major amendment contains the data from the VMAC trial, original NDA, and the PRECEDENT trial (protocol 704.329) titled "Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy" in support of approval for this application. In an internal meeting on January 24, 2001, this submission was considered to be a complete response to the not-approvable letter.

Natrecor was re-presented to the Cardiovascular and Renal Drugs Advisory Committee on May 25, 2001. The Committee recommended 10-yes to 0-no that Natrecor be approved for treatment of decompensated heart failure. Natrecor was originally presented to the Advisory Committee on January 29, 1999. At that time, the Committee recommended 5-yes to 3-no that Natrecor be approved. Subsequent to the meeting, in a January 31, 1999 letter to Dr. Lipicky, Committee chairman Dr. Milton Packer stated that although he voted yes, he was later convinced that "approval is warranted but not at this time." A February 3, 1999 letter from Committee member Dr. JoAnn Lindenfield also agreed with Dr. Packer's letter.

Review

Medical Review

Reviewer: Abraham Karkowsky, M.D.
Labeling: See Dr. Throckmorton's 6-21-01 review for labeling recommendations, which incorporate comments from Dr. Karkowsky's review of the labeling.
Conclusion: The VMAC study supports the use of the low dose infusion rate of 0.01 µg/kg/min in subjects who are not catheterized and whose dyspnea can reliably be attributed to exacerbation of their congestive heart failure. The study by itself is insufficient to describe the effects of Natrecor as superior to that of nitroglycerin (see Dr. Karkowsky's 5-15-01 review and 5-15-01 addendum).
Secondary Reviewer: Douglas Throckmorton, M.D.
Labeling: See Dr. Throckmorton's 6-21-01 review for labeling recommendations.
Conclusion: Natrecor should be approved for use at a single dose of 0.010 µg/kg/min infusion following a bolus of 2 µg/kg (see Dr. Throckmorton's 6-21-01 review).

Statistical Review

Reviewer: James Hung, Ph.D.
Labeling: None
Conclusion: The VMAC trial clearly showed that Natrecor significantly decreased PCWP. Natrecor also showed a statistically significant symptomatic benefit with p=0.034 (see Dr. Hung's 4-19-01 review and 4-20-01, 4-24-01, 5-7-01 and 5-16-01 addenda).

Chemistry Review

Reviewer: J.V. Advani, Ph.D. (drug product)
Pardha Komanduri, Ph.D. (drug substance)
Labeling: See Dr. Advani's 6-15-01 review for labeling recommendations.
Conclusion: Dr. Advani: Approvable, pending a satisfactory overall recommendation from the Office of Compliance (see Dr. Advani's 6-15-01 review).
Dr. Komanduri: Approvable, pending acceptable inspection of new testing facility (see Dr. Komanduri's 4-9-01, 4-18-01, and 6-5-01 reviews).

Pharmacology Review

Reviewer: Belay Tesfamariam, Ph.D.
Labeling: See Dr. Tesfamariam's 4-10-01 review for labeling recommendations.
Conclusion: The lack of effect of Natrecor after 3 hours of infusion on blood pressure indicates that some degree of tolerance is evident after continuous exposure (see Dr. Tesfamariam's 4-10-01 review).

Biopharmaceutics Review

Reviewer: Angelica Dorantes, Ph.D.
Labeling: See Dr. Dorantes' 6-8-01 review for labeling recommendations.

Conclusion: No information was submitted for this section of the NDA since all of the clinical pharmacology and biopharmaceutics information was submitted under the original NDA. The original NDA was deemed acceptable when reviewed by Dr. Nakissa Sadrieh on March 25, 1999, except for the labeling, which Dr. Dorantes reviewed for this major amendment.

Microbiology Review

Reviewer: Bryan Riley, Ph.D.

Labeling: None

Conclusion: Recommended for approval based on product quality microbiology.

Safety Update: See Dr. Karkowsky's 5-15-01 review and 5-15-01 addendum and Dr. Throckmorton's 6-21-01 review.

Patent info: Included in package

Pediatric info: Waiver granted

DSI: No DSI audits were conducted for the major amendment submission.

Debarment Certification: Included in package

OPDRA Tradename Review: OPDRA had no objections to the use of the proprietary name, Natrecor, on initial review. Labeling revisions were recommended to minimize potential user error (see OPDRA's 3-29-01 initial review). On final review, OPDRA had no objections to the use of the proprietary name (see OPDRA's 5-4-01 final review).

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Date: June 18, 2001

To: Douglas Throckmorton, M.D., DCRDP

From: Andrew Haffer, Pharm.D., DDMAC

Re: Comments on proposed labeling for Natrecor

DDMAC has reviewed the proposed PI for Natrecor and offers the following comments. The comments below are provided under the header used in the proposed label. If you have any questions about these comments please do not hesitate to call.

General Comments

1. Can the names Natrecor and human B-type natriuretic peptide (hBNP) be used interchangeably?
2. Similarly, can the effects of hBNP be used to describe Natrecor. (e.g., Description, first paragraph states, "Human BNP has been shown to produce vasodilation, diuresis, natriuresis, and suppression of the RAA system (neurohormonal effects))." Has the drug been shown to have these effects or is this theoretical? The company will promote that the drug has all of these benefits.
3. I found the clinical trials section hard to follow because of the way it is setup. The description of each study should include the design and results of the study.
4. Several sections of the label (MOA, clinical studies, Indication) state that Natrecor does not have an affect on heart rate. Does it matter if the sponsor states "no affect on the heart rate" vs "no significant affect on heart rate?"

DESCRIPTION

- Second paragraph "Natrecor is identical to the 32 amino acid...." Is the drug actually "identical" to the endogenous hormone.

CLINICAL PHARMACOLOGY

- See general comments above regarding the use Natrecor vs hBNP, and the MOA for hBNP vs MOA for Natrecor.
- We suggest removing *in vitro* info on the MOA. Also, suggest removing animal info from MOA unless this info is necessary for safe use in humans. This MOA data can be promoted.

Comments on Natrecor proposed label

Pharmacokinetics and Metabolism

- See general comments on the interchangeability of Natrecor with hBNP.

Pharmacodynamics

- Animal Studies
 - Does the animal data support claims made in the label. For example, paragraph 2 states "Natrecor does not appear to have any direct effects on cardiac contractility or on measures of cardiac electrophysiology such as atrial and ventricular effective refractory times or atrioventricular node conduction." See comments above on removing info based on preclinical studies in animals.

Clinical Trials

- See general comment above on the confusing layout of this section.
- Paragraph 1. Describes the co-administration of Natrecor with diuretics, ACEi's, digoxin, and beta-blockers. However, as described later in the label we find out that Natrecor is physically and/or chemically incompatible with injectable formulations of bumetanide, enalaprilat, furosemide. Shouldn't this incompatibility info be given more prominence considering several sections of the label provide info on concomitant use.
- Paragraph 2. Does not define the "2 longest, pivotal efficacy trials."

Clinical Trial Design

- The description of the VMAC trial lists and defines "additional endpoints," such as, "overall global clinical evaluation." Does the study provide substantial evidence to support the inclusion of these "additional endpoints?"
- The description of trial 704.325 states, "Additional objectives were to evaluate...and urine output." Does this study provide substantial evidence to support the inclusion of these "Additional objectives?"

Effects on Symptoms

- Were these symptoms prespecified?
- "Global clinical status" and "global assessment" are not defined in the label.
- Do we know if the instruments used in these studies were valid? This instrument should also be defined in the label.
- VMAC: Global clinical status does not appear to be a prespecified endpoint from this study. This presentation should be removed.
- 704.325: The study protocol specified four symptoms (Dyspnea, Fatigue, lightheadedness, loss of appetite) for acute decompensated CHF. However, two of these symptoms (lightheadedness and loss of appetite) failed to reach significance at the 0.03ug/kg/min dose. Scios is only requesting that only the significant symptoms be placed in the label. We recommend that they present all four symptoms or remove all four symptoms. As for "Global Clinical Status," does the study support these results (improvement in 61% and 67% of Natrecor patients vs 14% for placebo). "Global clinical status" should be defined here as well.

Effects on Hemodynamics

- The 3 trials described utilized bolus/infusion or infusion only doses of Natrecor. This discussion regarding bolus only dosing should be removed (1st and 4th sentences).
- Should the graphs showing PCWP include std error bars?

Comments on Natreacor proposed label

- The 3rd paragraph, located after the second PCWP graph, states "The **complete** hemodynamic profile of Natreacor includes...increasing heart rate." Is the complete hemodynamic profile for Natreacor known? This sentence appears promotional in tone.
- The description of study 704.325 includes results and p values for many indicies. Was the study adequate to support these results?
- The last 3 paragraphs of this section provide dosing information. If this info is included, should it be moved to the dosing and administration section?

Effect on Arrhythmia

- This section includes many comparative results (with p values) from the PRECEDENT trial. Does PRECEDENT support these results? (This comparative data will surely be used in promotional materials.)
- Last Sentence: Is there adequate data to support the statement "Thus, there is not an increased frequency of ventricular ectopy or ventricular tachycardia with Natreacor therapy?"

Effects on Neurohormones and Urine Output

- Does study 704.325 support these findings? Was the "increase in urine output" significant?

INDICATIONS AND USAGE

- See prior comments on defining "overall clinical status."
- The last sentence of this section describes use in various demographic groups. This type of info is frequently promoted. Is there adequate evidence to support this info? If so, should it be located in the indication section of the label?

PRECAUTIONS

- General: The last sentence of this subsection states "However, acute renal failure or the need for dialysis did not occur more frequently in Natreacor patients than in control patients." This statement minimizes the risk of renal failure.
- Cardiovascular: Remove the statement "As with other intravenous vasodilators" as this minimizes the risk of hypotension.
- Cardiovascular: Is the ADE comparison between Natreacor and intravenous nitroglycerin relevant and informative?
- Cardiovascular: The 3rd sentence, "There were no adverse sequelae to any hypotension that has occurred with Natreacor," minimizes the risks associated with hypotension.

ADVERSE REACTIONS

- The first sentence, "Adverse reactions to Natreacor...blood pressure," is promotional in tone.

Effect on Mortality

- Mortality is a huge promotional item
- Was VMAC and these other phase III trials designed to demonstrate an effect on mortality? If not, should this data be included in the label?

Acute Coronary Syndromes and Preserved Systolic Function

Comments on Natrecor proposed label

- Is this section needed? There is no difference between these patients and other patients that received Natrecor.

Dosage and Administration

- The table lists "Project Weight." Should this be revised to read "Patient Weight?"

**APPEARS THIS WAY
ON ORIGINAL**

Memo

To: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

From: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Quynh Nguyen
Project Manager, HFD-110

Date: May 4, 2001

Re: OPDRA Consult 01-0095; Natrecor (Nesiritide for Injection); NDA 20-920

This memorandum is in response to an April 12, 2001, request from your Division for a re-review of the proprietary name, Natrecor. The goal date for this application is July 10, 2001.

OPDRA has not identified any additional proprietary or established names that have the potential for confusion with Natrecor since we conducted our initial review on February 23, 2001 (OPDRA consult 01-0018), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

**RHPM Review of Major Amendment for Natrecor (nesiritide) for Injection
In Response to April 27, 1999 Not-Approvable Letter
January 24, 2001**

NDA Number:	NDA 20-920
Drug Name:	Natrecor (nesiritide) for Injection, 1.5 mg/vial
Indication:	Short-term treatment of congestive heart failure
Sponsor:	Scios, Inc.
Therapeutic Classification:	1S
Date of Amendment:	January 9, 2001
Date of Receipt:	January 10, 2001
6-month Goal Date:	July 10, 2001
User Fee Status:	Waiver granted, March 25, 1998
Submission Complete As Required Under 21 CFR 314.50?	Yes (refer to original NDA)
Patent Information included?	Yes (refer to original NDA)
Exclusivity requested?	No
Debarment Statement included?	Yes
Financial Interests and Arrangements of Clinical Investigators Certification included?	Yes
Pediatric Rule addressed?	Yes, Waiver granted (refer to original NDA)

Background

Scios, Inc. has submitted this major amendment to NDA 20-920 for Natrecor (nesiritide) for Injection in response to the Agency's April 27, 1999 not-approvable letter. The proposed indication is for the initial treatment of patients with decompensated congestive heart failure. Scios filed the original NDA on April 24, 1998. The related IND is

Natrecor was presented to the Cardiovascular and Renal Drugs Advisory Committee on January 29, 1999. The Committee recommended 5-yes to 3-no that Natrecor be approved for use in closely monitored hospitalized patients with acutely decompensated heart failure with clinical confirmation of elevated filling pressure. However, a January 31, 1999 letter to Dr. Lipicky from

Dr. Milton Packer, chairman of the Advisory Committee, stated that although he voted yes, he was later convinced after further review of the deficiencies that "approval is warranted but not at this time". A February 3, 1999 letter from Advisory Committee member Dr. JoAnn Lindenfield also agreed with Dr. Packer's letter.

A February 5, 1999 meeting was held with the sponsor to discuss issues that arose during and following the Advisory Committee meeting, specifically dosing, labeling, and unknown effect of rate of infusion, as well as safety margin and patient population issues.

A not-approval letter was issued April 27, 1999, in which the Agency cited deficiencies concerning the overall results of controlled studies, symptom evaluation, onset and offset characteristics of symptomatic hypotension, need for an active-controlled study comparing Natrecor to an IV vasodilator such as nitroglycerin, durability of effect, dose response issues, and need for a broader CHF patient population. There were no chemistry, biopharmaceutics or pharmacology deficiencies listed in the not-approvable letter. A May 4, 1999 meeting was held with the sponsor to discuss issues raised in the not-approvable letter. As a result of this and other meetings held on July 20, 1999, January 19, 2000, and February 10, 2000, Scios designed the VMAC trial (Vasodilation in the Management of Acute Congestive Heart Failure), protocol 704.339, "A Multicenter, Randomized, Double-Blind, Placebo-controlled Study of the Hemodynamic and Clinical Effects of Natrecor (nesiritide) Compared with Nitroglycerin Therapy for Symptomatic Decompensated CHF."

An April 12, 2000 meeting was held with the sponsor to discuss the content and format of this NDA amendment.

Assigned Reviewers

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Completion Target Date</u>
Medical Sec. Medical	Abraham Karkowsky, M.D., Ph.D. Douglas Throckmorton, M.D.	
Biostatistics	Lu Cui, Ph.D.	
Chemistry	J.V. Advani, Ph.D.	
Pharmacology	Belay Tesfamariam, Ph.D.	
Biopharmaceutics	Angelica Dorantes, Ph.D.	
Microbiology	To be assigned	
Project Management	Quynh Nguyen, Pharm.D.	

Review

This amendment was submitted in 56 paper volumes, formatted and assembled in conjunction with the original NDA. In addition, Case Report Tabulations (CRTs) and electronic copies of the Case Report Forms (CRFs) have been provided for the Electronic Document Room. The sponsor

intends to submit to the Agency an electronic copy of the NDA, which will be an exact copy the paper files.

The sponsor submitted a Pediatric Waiver request (21 CFR 314.55(c)(2)). A letter from Dr. Barry Massie, M.D. of the University of California-San Francisco has been included as additional justification.

The sponsor included a Trade Name Review package to be re-reviewed. For the original NDA submission, the trade name Natrecor was reviewed and approved by the Agency's nomenclature committee on February 18, 1998.

Six copies of the draft package insert in Word on diskette were included as reviewer's aids.

This submission contains the data from the VMAC trial, original NDA, and the PRECEDENT trial (protocol 704.329) titled "Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy" to collectively support efficacy for this major amendment to NDA 20-920.

Recommendation

Provided that the reviewers have no objections, this major amendment should be considered a complete response to the Agency's not-approvable letter issued April 27, 1999.

Meeting

Dr. Lipicky stated that the major amendment was a complete response to the not-approvable letter issued April 27, 1999. There were no issues with the reviewers.

Natrecor should be presented before the Advisory Committee in May 2001.

/s/

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

Cc: NDA 20-290
HFD-110
HFD-110/QNguyen

RHPM Overview of NDA 20-920
Natrecor (nesiritide) for Injection, 5 mg/vial
April 16, 1999

Background

Scios Inc. submitted this NDA on April 24, 1998 for nesiritide injection to be used in the short term treatment of congestive heart failure. The related IND is

During an April 17, 1996 meeting between Scios Inc. and the Division, Scios discussed their proposal for a synthetic to recombinant switch for manufacture of the drug product. Scios stated that Phase III trials would be initiated with the synthetic drug product and then a switch would be made to the recombinant product. Dr. Lipicky stated at this meeting that the Division will look closely for differences between the synthetic and the recombinant groups in the clinical trials. Dr. Lipicky further stated that a formal analysis of the synthetic and recombinant data conducted separately is not required.

Natrecor was presented to the Cardiovascular and Renal Drugs Advisory Committee on January 29, 1999. The committee expressed concerns regarding the lack of data for patients with acute MI, drug interactions, and the absence of a comparison with the effects of nitroprusside or other agents on pulmonary capillary wedge pressure. Side effects, including renal dysfunction, bradycardia, and dose-related hypotension were discussed.

The Committee recommended 5-yes to 3-no, that infusion of 0.015 ug/kg/min Natrecor be approved for use in closely monitored hospitalized patients with acutely decompensated heart failure with clinical confirmation of elevated filling pressure.

A January 31, 1999 letter addressed to Dr. Lipicky from Dr. Milton Packer, chairman of the Cardiovascular and Renal Drugs Advisory Committee, regarding his vote at the January 29, 1999 meeting was received on February 1, 1999. This letter stated that three committee members

voted no (including the primary reviewer, Marvin Konstam), whereas five voted yes (including myself). Yet, in voting yes, I (and others) cited the substantial deficiencies of the NDA (primarily those described in this letter) but concluded that the drug might still be useful to many physicians. Now, having had an opportunity to think about these deficiencies during the past two days, I am now convinced that approval is warranted but not at this time.

Dr. Packer went on to describe an additional study he believes should be conducted prior to approval. In his letter (cc'ed to all Committee members), Dr. Packer encouraged other members of the Committee to write to Dr. Lipicky about their views. A February 3, 1999 letter to Dr. Lipicky from Dr. JoAnn Lindenfeld, another member of the Advisory Committee stated that, "I completely agree with the substance of Milton's letter..." Dr. Temple has stated that votes can not be changed subsequent to adjournment of the meeting.

A February 5, 1999 meeting was held with the sponsor to discuss issues that arose during and subsequent to the January 29, 1999 Cardiovascular and Renal Drugs Advisory Committee meeting for Natrecor. During this meeting the Division outlined three general issues that need resolution in the Natrecor application:

- The dose proposed by Scios is close to the dose where hypotension is observed.
- The labeling will be very restrictive if it is explicit in listing only those patients treated in the clinical trials.
- No data have been submitted to indicate when to change the infusing dose: the effect of the rate of infusion is basically unknown.

Dr. Lipicky stated at this meeting that Scios should submit logical arguments for why the available data are sufficient to address the issues of dose, safety margin, and patient population. The Division further noted that "it is unclear at this point in time whether analysis of existing data will be sufficient for approval: it may be the case that new data are needed."

The User Fee Goal Date for this application is April 27, 1999.

Group Leader Memorandum

Dr. Karkowsky's March 11, 1999 Global Review provides his rationale for recommending approval of Natrecor for the treatment of an acute exacerbation of congestive heart failure (CHF). Dr. Karkowsky further writes, however, that this approval recommendation "is not made with much enthusiasm." He notes that the database for Natrecor is marginal, instructions for optimizing dose are problematic, instructions for up-titration cannot be made based on the current state of knowledge of the relationship between the kinetics and the dynamics of Natrecor, and that the long dynamic half-life of Natrecor coupled with what appears to be substantial hypotensive effects at the recommended infusion regimen has implications with respect to adding Natrecor to concurrent therapies (particularly any therapies that also act through vasodilation). It is further noted in this review that "the adverse event profile of Natrecor is far from benign."

Dr. Karkowsky writes, "Despite what appears to be strong evidence that the two preparations result in the same bioactive material, there is some kinetic and dynamic information derived from animal studies which suggests that the synthetic and recombinant preparations act differently. Human kinetic and dynamic data, however, show that the two preparations act similarly, though the confidence intervals are wide."

Medical/Statistical Reviews

Drs. Throckmorton's and Cui's March 3, 1999 combined medical/statistical review states that nesiritide "has a demonstrated hemodynamic effect that is superior to placebo and

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

Dr. Karkowsky's March 11, 1999 review summarizes the results of the six small pharmacokinetic/pharmacodynamic non-pivotal studies conducted with Natrecor. Dr. Karkowsky writes that "None of the conclusions that are drawn from these studies can be stated with anything resembling strong conviction. The consequent conclusions, however, do not strongly differ from larger and better-controlled studies, which were reviewed by Dr. Throckmorton."

Pediatric Studies

The Division believes that pediatric studies are not required with Natrecor at this point in time. Dr. Karkowsky's April 9, 1999 memo to Dr. Temple (through Dr. Lipicky) outlines the rationale for this belief (in the package under Pediatric Page).

DSI Audits

DSI audits were conducted at two sites. The _____ site received a "VAI" classification on December 30, 1998. The _____ site received a "NAI" classification on April 14, 1999.

Pharmacology Review

Dr. Papoian's December 9, 1998 review states that based upon the animal studies reviewed, an approvable action is recommended.

Clinical Pharmacology/Biopharmaceutics Review

Dr. Sadrieh's March 25, 1999 review states that the "NDA for Natrecor (Nesiritide) Injection fulfills the requirements of the Office of Clinical Pharmacology and Biopharmaceutics."

Dr. Sadrieh further states that a "population PK analysis was carried out to determine the effects of demographics and clinical variables on PK parameters. No correlation was found between the CL of Natreacor and the following patient variables: age, gender, race/ethnicity, baseline pulmonary capillary wedge pressure and cardiac index, baseline (endogenous) hBNP concentration, NYHA classification of CHF, serum creatinine, and estimated creatinine clearance. However, in study 704.325, there was a suggestion of a slight trend towards a positive relationship between CL and creatinine CL, and an inverse relationship between CL serum and creatinine. A population PK study conducted with data from study 311 showed that Natreacor CL increased with increasing body weight. Therefore, body weight was a significant covariate for hBNP CL.

Data from studies 704.307 were analyzed using NONMEM. A saturation model (sigmoid Emax model) was determined to best describe the relationship between (predicted) steady state exogenous plasma hBNP concentration and each hemodynamic response tested. No apparent delay in response was noted after plasma hBNP concentrations had reached steady state. The analysis of hemodynamic responses at early (1 and 1.5 hours) and delayed (after 2.5 and 3.0 hours) times following escalation to the 0.03 ug/min/kg in 6 subjects suggested that in addition to the plasma levels of hBNP, pharmacodynamic responses had reached steady state. A direct relationship between steady state plasma concentrations of Natreacor and pulmonary capillary wedge pressure (PCWP), cardiac index (CI) and systemic vascular resistance (SVR) was found. The mean C50 for both PCWP and SVR was estimated to be 2400 infusion of 0.02 ug/min/kg. Based on the mean estimates of Emax for PCWP of -16 mm Hg in patients with Class II or III CHF and for SVR of 450 dynes.sec.cm⁻⁵, this infusion rate is predicted to decrease PCWP by about 225 dynes.sec.cm⁻⁵."

8 mmHg of SVR BY ADJUST

Dr. Sadrieh's April 15, 1999 review responds to an April 6, 1999 submission from the sponsor that sought to address two issues raised by Dr. Sardrieh's March 25, 1999 review. This review states that "It is the opinion of the Office of Clinical Pharmacology and Biopharmaceutics, that the concerns raised by the sponsor do not impact on the reviewer's conclusions which were based on the Pk/Pd analysis undertaken by Dr. Sambol for Scios."

Chemistry Reviews

Please note that there are different reviewers for drug substance and drug product. This is due to the switch from synthetic to recombinant methodology during the development of this drug. Dr. Komanduri from HFD-510 is reviewing the drug substance material.

Dr. Short from HFD-110 is reviewing the drug product portion of the application.

Drug Substance

Dr. Komanduri's draft review (received by FAX April 15, 1999) states that "the application may be approved with respect to the drug substance."

Drug Product

Dr. Short's April 16, 1999 review states that the "application may be approved from the CMC perspective." (NOTE: Pages 2 and 3 of Dr. Short's review contain comments that should be included in an approval or approvable letter. The Division has sent to the Office a not approvable letter.)

A "Request for Trademark Review," dated October 21, 1997 was sent to the Labeling and Nomenclature Committee under IND [redacted]. A response dated February 18, 1998 was received indicating that the proposed proprietary name Natrecor was acceptable. The Labeling and Nomenclature Committee reviewed the name Natrecor under the NDA on February 23, 1999. (We have not received a written review as of April 16, 1999.)

The applicant has petitioned the USAN Council for approval of the name [redacted] as the generic name for the drug substance. The applicant subsequently requested approval of the name "nesiritide." The sponsor had not received notification of approval of either name as of April 13, 1999.

The EER was acceptable on March 26, 1999.

Methods validation has not been requested as tests and specifications have not been finalized.

Environmental Assessment

Dr. Short's December 10, 1998 review states that a request for a categorical exclusion was submitted under 21 CFR 25.31(b). The request for categorical exclusion is acceptable (page 42 of December 10, 1998 review).

Microbiology Review

Dr. Urantani's microbiology review #3, dated April 8, 1999, states that the submission "is recommended for approval for issues concerning microbiology."

Summary

- 1) Reviewer recommendations for labeling are as follows:
 - a) Dr. Karkowsky's mark-up of the Natrecor labeling can be found under Appendix A (page 33) of his March 11, 1999 Global Review (under the Group Leader Review tab in the action package).

- b) On page 97 of Dr. Papoian's December 9, 1998 pharmacology review, he recommends that the following statement under **Carcinogenesis, Mutagenesis, and Impairment of Fertility** be changed from:

to:

Studies to determine mutagenicity in bacterial cells (Ames test) were negative.

- c) Dr. Short recommends the following labeling changes in his April 16, 1999 drug product review (page 3):
- i) The package insert should include solubilities in common organic solvents in the **DESCRIPTION** section of the package insert. These solubility data should not be in bold type.
 - ii) The phrase [redacted] should be deleted from the storage statement on the labels and in the package insert.
 - iii) For consistency, a blank line should be added following the statement about the heparinized catheters in the **DOSAGE AND ADMINISTRATION** section.
 - iv) Information concerning the 2.5 mg vials should be added to the **DESCRIPTION, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED** sections of the package insert.
 - v) In the **DOSAGE AND ADMINISTRATION** section of the package insert under Preparation of Solution, "1. [redacted]" should be changed to "1. Introduce 10 mL of 5% Dextrose Injection USP (D₅W) or 0.9% Sodium Chloride Injection USP..."

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Diana M. Willard
Regulatory Health Project Manager

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the approval package consisted of draft labeling

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: *April 9, 1999*

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader Division of Cardio-Renal Drug Products HFD-110

/S/

THROUGH: Dr. Raymond Lipicky, Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Need for Pediatric Studies for Nesiritide (Natrecor)

TO: Dr. Robert Temple, Office Director ODE-1.

Although I have recommended approval of Natrecor for the treatment of acute exacerbations of CHF, I do not feel that pediatric studies are warranted at this time. The rationale for not requiring pediatric studies is two-fold. First, I think that at present there are pre-load and after-load reducers (i.e. sodium nitroprusside, nitroglycerine) which, are more flexible in their usage than Natrecor. The need for an additional after-load reducer with a long offset time is questionable in a pediatric population suffering from acute exacerbations of CHF.

The second rationale is that the population of pediatric patients with exacerbations of their CHF is probably quite small. I do not think that the sponsor is likely to enroll a sufficient number of subjects that they will adequately define the appropriate dosage instruction in pediatric patients of different age groups.

Should a particular benefit of this drug be demonstrated in adults, than this issue can be revisited as a pediatric written request.

REQUEST FOR TRADEMARK REVIEW

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TO: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D. HFD-530
9201 Corporate Blvd. Rm N 461

FROM: Division of: Cardio-Renal Drug Products HFD-110
Attention: Robert Wolters Phone: 594-5376

DATE: October 21, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Proprietary Name: Natrecor NDA/ANDA IND ✓

Trademark status: Yes

Company Name: Scios, Inc

Other proprietary names by the same firm for companion products:

None

Established name including dosage form and strength:

An established name has not yet been adopted. Human brain-type natriuretic peptide.

Indications for use including dosing schedule (may be a summary if proposed statement is lengthy):

Lyophilized mg/mL

Congestive heart failure

Comments from the submitter: (concerns, observations, etc.)

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #882-(HFD-110)

NATRECOR

human natriuretic peptide for injection

The Committee noted sound-alike/look-alike conflicts with the following marketed products: NATRICO, NUTRECORT and NUTRICON. The committee felt there was a low potential for mix-up with these products since they are different dosage forms and in very different therapeutic classes. There were no misleading aspects found.

The Committee has no reason to find the proposed proprietary name unacceptable.

JSI 2/18/98, Chair
CDER Labeling and Nomenclature Committee

Minutes of Telephone Conference Calls between Scios and the FDA

Dates: July 20, 26, and 31, 2001

Application: NDA 20-920
Natreacor (nesiritide) for Injection

Sponsor: Scios Inc.

Subject: Discussion of Labeling Issues

July 20, 2001 Teleconference

FDA Participants

Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical, HFD-110
Patrick Marroum, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics, HFD-860
Angelica Dorantes, Ph.D., Clinical Pharmacologist and Biopharmaceutist, HFD-860
Belay Tesfamariam, Ph.D., Pharmacologist, HFD-110
Natalia Morgenstern, Chief, Project Management Staff, HFD-110
John Guzman, Regulatory Health Project Manager, HFD-110
Daryl Allis, N.P., Regulatory Health Project Manager, HFD-110
Julie Beitz, M.D., Director, DDRE I, HFD-430
Michael Johnston, R.Ph., Safety Evaluator, DDRE I, HFD-430
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Scios Inc.

George Schreiner, M.D., Chief Scientific Officer
Bim Strausser, M.D., Senior Director, Medical Affairs
Darlene Horton, M.D., Vice President, Medical Affairs
Ann Protter, Director, Clinical Information Systems
Mei Cheng, Ph.D., Associate Director, Biostatistics
Michael Crockett, Associate Director, Regulatory Affairs
Klara Dickinson, Sr. Manager, Regulatory Affairs
Larry Kleinmann, M.S., Scios Regulatory Consultant (Pacific BioDevelopment)
Joyce Chiarenza, Scios Labeling/Promotional Regulatory Consultant (Pacific BioDevelopment)

July 26, 2001 Teleconference

FDA Participants

Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical, HFD-110
Ed Fromm, Regulatory Health Project Manager, HFD-110
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Scios Inc.

Darlene Horton, M.D., Vice President, Medical Affairs
Mei Cheng, Ph.D., Associate Director, Biostatistics
Michael Crockett, Associate Director, Regulatory Affairs
Klara Dickinson, Sr. Manager, Regulatory Affairs
Marc Rohman, Associate Director, Marketing
Larry Kleinmann, M.S., Scios Regulatory Consultant (Pacific BioDevelopment)
Joyce Chiarenza, Scios Labeling/Promotional Regulatory Consultant (Pacific BioDevelopment)

July 31, 2001 Teleconference

FDA Participants

Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical, HFD-110
Ed Fromm, Regulatory Health Project Manager, HFD-110
Andrew Haffer, Pharm.D., Regulatory Review Officer, DDMAC, HFD-42
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Scios Inc.

Darlene Horton, M.D., Vice President, Medical Affairs
Mei Cheng, Ph.D., Associate Director, Biostatistics
Michael Crockett, Associate Director, Regulatory Affairs
Klara Dickinson, Sr. Manager, Regulatory Affairs
Larry Kleinmann, M.S., Scios Regulatory Consultant (Pacific BioDevelopment)
Joyce Chiarenza, Scios Labeling/Promotional Regulatory Consultant (Pacific BioDevelopment)

Background

Natrecor (nesiritide) for Injection is a recombinantly manufactured preparation of human B-type natriuretic peptide (hBNP) proposed for the initial treatment of patients with decompensated congestive heart failure. On January 9, 2001, Scios submitted a major amendment to NDA 20-920 for Natrecor in response to the Agency's April 27, 1999 not-approvable letter. On July 6, 2001, Scios was issued an approvable letter with marked-up labeling enclosed. These teleconferences were scheduled to discuss labeling issues.

Teleconferences

In a July 18, 2001 submission, the firm submitted revised draft labeling based on the changes recommended in the marked-up labeling sent with the July 6, 2001 approvable letter and their proposed changes. During the July 20, 2001 teleconference, changes to the draft package insert dated July 18, 2001 up to the **DESCRIPTION/Effect on Urine Output and Sodium Excretion** section (page 7) were discussed. On July 26, 2001, a second teleconference was held to discuss

16 pages redacted from this section of
the approval package consisted of draft labeling

Minutes of a Teleconference between Scios and the FDA

Date: March 28, 2001

Application: NDA 20-920
Natrecor (nesiritide) for Injection

Sponsor: Scios Inc.

Subject: Communication of clinical issues in the medical review

FDA Participants

Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D., Team Leader, Medical, HFD-110
James Hung, Ph.D., Team Leader, Statistical, Division of Biometrics I, HFD-710
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

Scios Inc.

Richard Brewer, President and Chief Executive Officer
Darlene Horton, M.D., Vice President, Medical Affairs
Mei Cheng, Ph.D., Associate Director, Biostatistics
Ann Protter, Associate Director, Clinical Information Systems
Michael Crockett, Associate Director, Regulatory Affairs
Betty Wilson, Sr. Administrative Assistant, Regulatory Affairs
Klara Dickinson, Sr. Manager, Regulatory Affairs

Background

Natrecor (nesiritide) for Injection is proposed for the initial treatment of patients with decompensated congestive heart failure. Scios submitted a major amendment to NDA 20-920 for Natrecor on January 10, 2001 in response to the Agency's not-approvable letter issued April 27, 1999. This teleconference was scheduled to communicate clinical issues in Dr. Karkowsky's preliminary review.

Teleconference

Mortality curves

Dr. Karkowsky noted that the trend to looking different with Natrecor did not look favorable relative to nitroglycerin. He encouraged the sponsor to include an explanation of the data in their briefing document to explain the possible "play-of-chance" that the two groups did not look different. This issue would be included in his review; however, it was undecided whether the issue would be directly raised by the Division since the questions to the Advisory Committee had not been formulated yet. The sponsor agreed to submit to the Division the data sets on mortality.

Symptom assessment

Since a large number of baseline symptom assessments were measured before patients received the infusion, Dr. Hung would need to perform another analysis normalizing symptom assessment to ensure that no biases were introduced. Dr. Karkowsky pointed out that 49 patients had symptom assessments measured more than an hour before the infusion was administered. The sponsor pointed out that according to the protocol, symptom assessment should have been made after one hour of infusion, but this was not always possible in the "real world" setting.

Hypotension

Dr. Karkowsky noted that the incidence of hypotension was lower in the VMAC study than in the PRECEDENT study, but this was based on point estimate values. There were no confirmatory studies of this relative to dobutamine.

Tolerance versus non-tolerance

There was a decrease in wedge pressure in patients on Natrecor over 24 hours compared to nitroglycerin. It would be helpful therefore if there are additional data on the issue of tolerance.

Renal dysfunction

Dr. Karkowsky pointed out that there were over 100 patients whose creatinine increased greater than 0.5 from baseline while on Natrecor or nitroglycerin.

Conclusion

The sponsor was told that the issues mentioned above would be subject for discussion at the Advisory Committee meeting in May 2001. The sponsor was invited to discuss these issues further at a later date.

Meeting Preparation:

IS/ 5-2-01
Quynh Nguyen, Pharm.D.

Concurrence, Chair:

IS/ T. 02 01
Douglas Throckmorton, M.D.

qn/4-23-01/5-2-01

rd: JHung/4-24-01
AKarkowsky/4-27-01
DThrockmorton/5-2-01
NMorgenstem/5-2-01

cc: NDA 20-920
HFD-110
IIFD-110/QNguyen
HFD-110/SMathews

**Minutes of a Teleconference
January 19, 2000**

FEB 3 2000

Application: NDA 20-920
Natrecor (nesiritide) for Injection, 5 mg/vial

Sponsor: Scios Inc.

Indication: Short Term Treatment of Congestive Heart Failure .

Purpose: Discuss Clinical Trial Design

Attending:

Scios:

Richard Brewer	President and Chief Executive Officer
Elliott Grosbard, M.D.	Senior Vice President of Development
Darlene Horton, M.D.	Associate Director, Medical Affairs
Mei Chang, Ph.D.	Senior Biostatistician
Michael Crockett	Associate Director, Regulatory Affairs
Klara Dickinson	Manager, Regulatory Affairs

FDA:

Raymond Lipicky, M.D.	Division Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader/Medical, HFD-110
Diana Willard	Regulatory Health Project Manager, HFD-110

Meeting Chair: Raymond Lipicky, M.D.

External Lead Participant: Elliott Grosbard, M.D.

Background: Scios Inc. submitted NDA 20-920 on April 24, 1998 for use of Natrecor for Injection in the short-term treatment of congestive heart failure (CHF). The application was presented to the Cardiovascular and Renal Drugs Advisory Committee on January 29, 1999. A not approvable (NA) letter, signed by Dr. Temple, issued on April 27, 1999.

A May 4, 1999 meeting was held between Scios and the Agency to discuss the NA letter as well as the design for a new trial to address the issues raised in the NA letter.

This teleconference was requested by the sponsor to discuss changes to the proposed clinical trial entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Hemodynamic and Clinical Effects of Natrecor (nesiritide) Compared with Nitroglycerin Therapy for Symptomatic Decompensated CHF."

Teleconference

Dr. Grosbard began by stating that

Dr. Lipicky stated that a possible deficiency in Scios' proposed study is the absence of mortality data: follow-up data should be collected for six months. Scios noted that collection of these data would significantly delay submission of the study results, a delay that would be very problematic for Scios. While stating that it is acceptable to submit the study results without the follow-up data, Dr. Lipicky added that the protocol should be amended and the data submitted when it is available.

Dr. Lipicky noted the possibility that when the data from the proposed study are submitted and reviewed, there may be then be similar products approved on the basis of placebo-controlled trials. As the Natrecor database contains no placebo-controlled data, this could place Natrecor at a disadvantage.

Summary

It is acceptable to submit data from the proposed study to the NDA prior to collection of six month follow-up data. The protocol should be amended and the follow-up data submitted when it is available.

Scios should be aware that the lack of placebo-controlled data in Natrecor clinical trials could potentially be an issue when a determination is made regarding an action on the application.

Signature, Minutes Prepare _____ /S/ _____ Diana Willard

Concurrence, Meeting Chair _____ /S/ _____ Raymond Lipicky, M.D.

- cc: original
- HFD-110
- HFD-110/DWillard
- HFD-110/ABlount
- HFD-110/SMatthews

Drafted: 2/2/00; Final: 2/2/00

RD: Karkowsky 2/2/00