

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
20-920**

**Chemistry Review(s)**

16-JUL-2001

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20920/000 Priority: 1S Org Code: 110  
Stamp: 27-APR-1998 Regulatory Due: 10-JUL-2001 Action Goal: District Goal: 11-MAY-2001  
Applicant: SCIOS Brand Name: NATRECOR(NESIRITIDE)5.0MG VIAL  
2450 BAYSHORE PKY IV INFUSI  
MOUNTAIN VIEW, CA 940431173 Established Name:  
Generic Name: NESIRITIDE  
Dosage Form: FIJ (FOR INJECTION)  
Strength: 5 MG PER VIAL

FDA Contacts: Q. NGUYEN (HFD-110) 301-594-5300 , Project Manager  
J. ADVANI (HFD-110) 301-594-5300 , Review Chemist  
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 16-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062  
WITHHOLD on 06-JUL-2001 by P. LEFLER (HFD-324) 301-827-0062  
ACCEPTABLE on 26-MAR-1999 by M. GARCIA (HFD-322) 301-594-0095

Establishment: DMF No:  
AADA No:

Profile: CTL OAI Status: NONE Responsibilities: FINISHED DOSAGE  
Last Milestone: OC RECOMMENDATION MANUFACTURER  
Milestone Date: 19-MAR-2001 FINISHED DOSAGE PACKAGER  
Decision: ACCEPTABLE FINISHED DOSAGE STERILITY  
Reason: BASED ON PROFILE TESTER

Profile: SVS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-APR-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: DMF No:  
AADA No:

Profile: CFN OAI Status: NONE Responsibilities: DRUG SUBSTANCE  
Last Milestone: OC RECOMMENDATION MANUFACTURER  
Milestone Date: 20-MAR-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: DMF No:  
AADA No:

Profile: CFN OAI Status: NONE Responsibilities: DRUG SUBSTANCE  
Last Milestone: OC RECOMMENDATION MANUFACTURER  
Milestone Date: 19-MAR-2001  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Establishment: DMF No:  
AADA No:  
SCIOS INC  
749 NORTH MARY AVENUE  
SUNNYVALE, CA 94086

Profile: CTL OAI Status: NONE Responsibilities: DRUG SUBSTANCE RELEASE  
Last Milestone: OC RECOMMENDATION TESTER  
Milestone Date: 16-JUL-2001 FINISHED DOSAGE RELEASE  
Decision: ACCEPTABLE TESTER  
Reason: DISTRICT RECOMMENDATION FINISHED DOSAGE STABILITY  
TESTER

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**MEMO TO NDA 20-920**

July 06, 2001

**NAME & ADDRESS OF APPLICANT:**

Scios, Inc.  
749 North Mary Avenue  
Sunnyvale, CA 94086

**DRUG PRODUCT NAME**

**Proprietary:**  
**Established:**  
**Code Name/#:**  
**Chem.Type/Ther.Class:**

Natrecor®  
Nesiritide (USAN)  
hBNP  
1 S

**PHARMACOL. CATEGORY/INDICATION:**

Congestive heart failure

**DOSAGE FORM:**

Lyophilized powder

**STRENGTHS:**

1.5 mg/5 mL vial

**ROUTE OF ADMINISTRATION:**

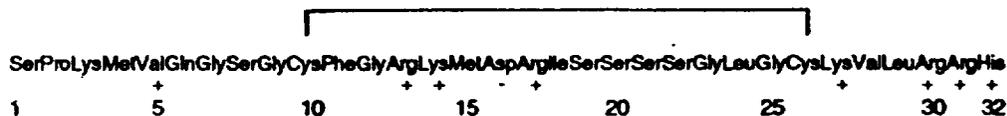
Intravenous injection

**Rx/OTC:**

Rx  OTC

**SPECIAL PRODUCTS:**

Yes  No



**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

C<sub>143</sub>H<sub>244</sub>N<sub>50</sub>O<sub>42</sub>S<sub>4</sub>      3464 g/mol (average mass of base form)

**CONSULTS:** EER

**REMARKS:**

An EER for a new site proposed after the action taken on the original application has been updated and a copy is attached with this memorandum.

**CONCLUSIONS & RECOMMENDATIONS:**

There are no other pending Chemistry Manufacturing and Controls issues and application may be approved from CMC standpoint. The Office of Compliance has issued a WITHHOLD overall recommendation due to several GMP issues related to stability protocol. Current Center Policy is to recommend Not Approval until all cGMP issues have been addressed.

  
\_\_\_\_\_  
Ramsharan D. Mittal, Review Chemist  
(Acting Team Leader)



SerProLysMetValGlnGlySerGlyCysPheGlyArgLysMetAspArgIleSerSerSerSerGlyLeuGlyCysLysValLeuArgArgHis  
1 5 10 15 20 25 30 32

**SUPPORTING DOCUMENTS:** None

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** In response to the comments that resulted out of the drug substance review of the resubmission (see chem review dated 20<sup>th</sup> Mar-2001), the sponsor has submitted this amendment. This amendment was assigned back to the division of Metabolism and Endocrine Drug Products as a consult.

The drug Product is being reviewed at the Cardio - Renal division.

**REMARKS/COMMENTS:**

The Agency has not approved the original NDA submission of Natrecor. The non-approval letter was based on submitting additional clinical data. The CMC section, that was submitted in the original NDA was found satisfactory with some phase IV commitments (see drug substance Chemistry review dated 19<sup>th</sup> July 1998). In the resubmission, the sponsor has provided an updated stability protocol for drug substance, minor changes in the stability programs for an update on some of the SOPs. The sponsor has also submitted a proposal in this resubmission to change the original expiration date of the drug substance lot, which was set at 3 years to a 2 year retest date, and an expiration date of 2 years.

In this amendment, the sponsor has submitted the responses to all the three comments on the stability data and one comment on bioassay test from the 4/09/01 and 4/18/01 Chemistry reviews.

**CONCLUSIONS & RECOMMENDATIONS:**

The responses submitted by the sponsor in this amendment are satisfactory.

Org. NDA # 20920

cc: HFD-510/Division File  
HFD-510/PardhaK/MoooreS/  
HFD-110/AdvaniJ/KSrinivasacharK/NguyenQ  
R/D Init by: Team Leader

TS/

Komanduri Pardha, Review Chemist  
filename: N#20920

AP (drug substance)

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information

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-920

**DATE VIEWED:** 30-Apr-01

**REVIEW #:** 3B

**REVIEWER:** JV Advani

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	24-Apr-98	27-Apr-98	12-May-98 (Not approved)
AMENDMENT	11-Mar-99	16-Mar-99	17-Mar-99 (See review #2B)
AMENDMENT	12-April-99	16-Apr-99	14-Apr-99 (See review #2B)
AMENDMENT (Resubmission)	09-Jan-01	10-Jan-01	22-Jan-01
AMENDMENT	30-Mar-01	02-Apr-01	26-Apr-01
AMENDMENT	06-June-01	08-June-01	12-June-01
AMENDMENT	08-June-01	13-June-01	13-June-01

**NAME & ADDRESS OF APPLICANT:**

Scios, Inc.  
 749 North Mary Avenue  
 Sunnyvale, CA 94086

**DRUG PRODUCT NAME**

**Proprietary:**  
**Established:**  
**Code Name/#:**  
**Chem.Type/Ther.Class:**

Natrecor®  
 Nesiritide (USAN)  
 hBNP  
 1 S

**PHARMACOL. CATEGORY/INDICATION:**

Congestive heart failure

**DOSAGE FORM:**

Lyophilized powder

**STRENGTHS:**

1.5 mg/5 mL vial

**ROUTE OF ADMINISTRATION:**

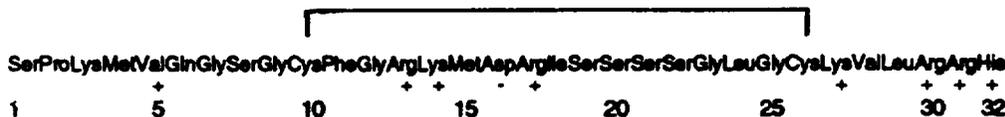
Intravenous injection

**Rx/OTC:**

Rx  OTC

**SPECIAL PRODUCTS:**

Yes  No



**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

C<sub>143</sub>H<sub>244</sub>N<sub>50</sub>O<sub>42</sub>S<sub>4</sub>            3464 g/mol (average mass of base form)

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Acceptable		
DMF			Acceptable	10/21/93	
DMF			Acceptable	9/12/96	
DMF			Acceptable	9/23/99	
DMR			Acceptable	4/20/95	

**RELATED DOCUMENTS (if applicable):** IND [ ]

**CONSULTS:** Microbiology satisfactory (see microbiology review of 2/14/01)

**REMARKS:**

In response to our non-approval letter for the Natrecor NDA 20-920 dated April 27, 1999, Applicant conducted another clinical trial to study clinical effects of Natrecor compared with Nitroglycerin and also evaluated a new dosing 0.01 µg/kg/min infusion more appropriate for a 24-hour period infusion. Based on the existing 2.5-mg vial, a substantial percentage of the contents of the product remain unused at the conclusion of a 24-hour infusion period for an average patient. The applicant has thus developed a 1.5- mg vial configuration. Scios has provided the CMC information for this new 1.5-mg vial in this amendment. Applicant intends to launch the product with the 1.5-mg vial configuration only. Applicant has provided the comparability protocol of 1.5-mg vial and the 5-mg and 2.5 mg configurations provided in NDA 20-920.

A "Request For Trademark Review," dated 17 Jan 01, was sent to the Office of Post-Marketing Drug Risk Assessment (OPDRA). A response was received, dated 11 Mar 01, indicating that the proposed proprietary name was acceptable. Additionally, the USAN council adopted the generic name nesiritide in 1999.

An EER for a new site proposed after the action taken on the original application has been sent out to the office of compliance and the pre approval inspection of this site is pending.

**CONCLUSIONS & RECOMMENDATIONS:**

Deficiencies and comments regarding the drug product were conveyed to the applicant on May 25, 2001 and firm responded to these in an amendment of 6/6/01. Further discussions on final specifications of related substances and expiration dating with the applicant were by a telephone communication on 6/6/01. CMC have now been satisfactorily resolved and labeling recommendations as indicated on page 23, will be sent to the applicant in the action letter.

The application may be approved for Chemistry Manufacturing and Controls, pending a satisfactory overall recommendation from Office of Compliance.

  
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 JV Advani, Review Chemist

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commercial

information



**SUPPORTING DOCUMENTS:** None

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** The application has been resubmitted to the Cardio-Renal division. The review of the hBNP drug Substance portion of the resubmission, assigned to the division of Metabolism and Endocrine Drug Products as a consult has been completed and submitted. The drug Product section is being reviewed at the Cardio - Renal division. The bioassay test that was proposed in the resubmission is assigned as a consult to this division.

**REMARKS/COMMENTS:**

Natrecor is the proprietary name of human B-type Natriuretic Peptide, which is the drug substance of this NDA. The drug product (Natrecor in this NDA) is a lyophilized powder (1.5mg/vial) to be reconstituted with 5 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. The proposed indication for the product is the short-term treatment of congestive heart failure.

The hBNP drug substance information provided in the resubmission has been reviewed and found satisfactory (See Chem review dated 20<sup>th</sup>-Mar-2001). The present review is to review the bioassay proposal submitted in the resubmission. The sponsor has submitted a cell-based bioassay test for the drug product in the original NDA submission, and it was approved with a phase IV commitment to narrow the acceptance range limits of the bioassay (see chem review dated 16<sup>th</sup>-Nov-1998). In the resubmission, the sponsor proposes to replace the approved cell-based bioassay with a receptor-based assay to test the biological activity of the drug product. The current review is specifically aimed at evaluating the bioassay proposal developed for the drug Product rhBNP. For a detailed drug product review of the resubmission, see Chem. Review from Cardio-Renal division.

This is only a proposal and the sponsor did not provide complete description of the receptor based assay in this proposal. Therefore, this review is mainly aimed at evaluating the acceptability or non-acceptability of the receptor based assay, rather than the review of the method itself.

**CONCLUSIONS & RECOMMENDATIONS:**

The receptor based assay method is more a chemical assay and does not provide any cellular response to the hBNP drug product, unlike the cell-based-bioassay. The sponsor intends to test several batches of hBNP drug product to compare and demonstrate that both the methods provide similar results. As a release test for the recombinant drug product rhBNP, it is essential to monitor the proper folding of the three dimensional structure and that can be precisely done alone by a cellular response vs the receptor binding affinity. Therefore, at this time it is not acceptable to the Agency to replace the current cell based bioassay with the receptor based assay for release testing the drug product.

Org. NDA # 20920  
cc: HFD-510/Division File  
HFD-510/PardhaK/SMoore/  
HFD-110/JShor/KSrinivasachar/NguyenQ  
R/D Init by: Team Leader

/S/

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Komanduri Pardha, Review Chemist  
filename: N#20920

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information



**SUPPORTING DOCUMENTS:** None

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** The application has been resubmitted to the Cardio-Renal division. The hBNP drug Substance portion of the CMC section was re-assigned to the division of Metabolism and Endocrine Drug Products as a consult. The drug Product is being reviewed at the Cardio - Renal division.

**REMARKS/COMMENTS:**

The Agency has not approved the original NDA submission of Natrecor. The non-approval letter was based on submitting additional clinical data. The CMC section, that was submitted in the original NDA was found satisfactory with some phase IV commitments (see drug substance Chemistry review dated 19<sup>th</sup> July 1998). No changes in the CMC section of the hBNP drug substance were reported in this resubmission, and a cross-reference was made to the drug substance portion of the original NDA.

In this resubmission, the sponsor has provided an updated stability protocol for drug substance, minor changes in the stability programs for , an update on some of the SOPs. The sponsor has also submitted a proposal in this resubmission to change the original expiration date of the drug substance lot, which was set at years to a - year retest date, and an expiration date of years.

**CONCLUSIONS & RECOMMENDATIONS:**

The chemistry, manufacturing and controls (CMC) submitted in this resubmission are satisfactory and the application is approvable with respect to the drug substance pending acceptable inspection of the new testing facility. See list of Comments and deficiencies. Also, refer to the separate chemistry review of the drug product.

Org. NDA # 20920

cc: HFD-510/Division File  
HFD-510/PardhaK/MoooreS/  
HFD-110/AdvaniJ/KSrinivasacharK/NguyenQ  
R/D Init by: Team Leader

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Komanduri Pardha, Review Chemist  
filename: N#20920

**AE (drug substance)**

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20920/000 Priority: 1S Org Code: 110  
 Stamp: 27-APR-1998 Regulatory Due: 10-JUL-2001 Action Goal: District Goal: 11-MAY-2001  
 Applicant: SCIOS Brand Name: NATRECOR(NESIRITIDE)5.0MG VIAL  
 2450 BAYSHORE PKY IV INFUSI  
 MOUNTAIN VIEW, CA 940431173 Established Name:  
 Generic Name: NESIRITIDE  
 Dosage Form: FLJ (FOR INJECTION)  
 Strength: 5 MG PER VIAL

FDA Contacts: Q. NGUYEN (HFD-110) 301-594-5300 , Project Manager  
 J. ADVANI (HFD-110) 301-594-5300 , Review Chemist  
 K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 26-MAR-1999 by M. GARCIA (HFD-322) 301-594-0095

Establishment:

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 19-MAR-2001  
 Decision: ACCEPTABLE  
 Reason: BASED ON PROFILE  
 Profile: SVS OAI Status: NONE  
 Last Milestone: SUBMITTED TO DO  
 Milestone Date: 27-MAR-2001

Responsibilities: FINISHED DOSAGE  
MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE STERILITY  
TESTER

Establishment:

DMF No:  
AADA No:

Profile: CFN OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 20-MAR-2001  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER

Establishment:

DMF No:  
AADA No:

APPEARS THIS WAY  
ON ORIGINAL



FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20920/000  
Stamp: 27-APR-1998 Regulatory Due: 10-JUL-2001  
Applicant: SCIOS  
2450 BAYSHORE PKY  
MOUNTAIN VIEW, CA 940431173

Priority: 1S  
Action Goal:  
Brand Name: NATRECOR(NESIRITIDE)5.0MG VIAL  
IV INFUSI  
Established Name:  
Generic Name: NESIRITIDE  
Dosage Form: FIJ (FOR INJECTION)  
Strength: 5 MG PER VIAL

Org Code: 110  
District Goal: 11-MAY-2001

FDA Contacts: Q. NGUYEN (HFD-110) 301-594-5300 , Project Manager  
J. ADVANI (HFD-110) 301-594-5300 , Review Chemist  
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 16-JUL-2001 by J. D AMBROGIO (HFD-324) 301-827-0062  
WITHHOLD on 06-JUL-2001 by P. LEFLER (HFD-324) 301-827-0062  
ACCEPTABLE on 26-MAR-1999 by M. GARCIA (HFD-322) 301-594-0095

Establishment:

DMF No:  
AADA No:

Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 19-MAR-2001  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE  
MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE STERILITY  
TESTER

Profile: SVS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-APR-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment:

DMF No:  
AADA No:

Profile: CFN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 20-MAR-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER

Establishment:

DMF No:

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

1

2

AADA No:

Profile: **CFN** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **19-MAR-2001**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**

Establishment: **2938495**  
**SCIOS INC**  
**749 NORTH MARY AVENUE**  
**SUNNYVALE, CA 94086**

DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **16-JUL-2001**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE  
TESTER**  
**FINISHED DOSAGE RELEASE  
TESTER**  
**FINISHED DOSAGE STABILITY  
TESTER**

**APPEARS THIS WAY  
ON ORIGINAL**

**Environmental Assessment**

**The request for categorical exclusion is acceptable (see Dr. Advani's 6-15-01 review).**

ORIGINAL

DEC 15 1998

DF

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510  
Review of Chemistry, Manufacturing and Controls

NDA 20920                      CHEMISTRY REVIEW: #1C                      DATE REVIEWED: 16<sup>th</sup> Nov 1998

SUBMISSION TYPE    DOCUMENT DATE    CDER DATE                      ASSIGNED DATE

Original                      24<sup>th</sup> Apr 1998                      28<sup>th</sup> Apr 1998                      4<sup>th</sup> May 1998

NAME & ADDRESS OF APPLICANT:                      Scios Inc.  
2450, Bayshore parkway  
Mountain View, CA 94043

**DRUG PRODUCT NAME**

Proprietary:                      Natrecor

Nonproprietary/Established/USAuse name (or equivalent):                      Nesiritide

Code Name/#:

Chem. Type/Ther. Class:                      Human B-type Natriuretic Peptide (recombinant)

ANDA Suitability Petition / DESI / Patent Status:                      N/A

**PHARMACOLOGICAL CATEGORY/INDICATION:**                      Short term treatment of Congestive heart failure

**DOSAGE FORM:**                      Lyophilized powder to be Reconstituted with 10mL of 5% Dextrose injection (USP) or 0.9% Sodium Chloride injection (USP)

**STRENGTHS:**                      5mg/vial

**ROUTE OF ADMINISTRATION:**                      Injection

**DISPENSED:**                        X   Rx       OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Molecular weight: 3464 g/mol (average mass of base form)

Empirical Formula: C<sub>143</sub>H<sub>244</sub>N<sub>50</sub>O<sub>42</sub>S<sub>4</sub>

SerProLysMetValGlnGlySerGlyCysPheGlyArgLysMetAspArgIleSerSerSerSerGlyLeuGlyCysLysValLeuArgArgHis  
1                      5                      10                      15                      20                      25                      30                      32

**SUPPORTING DOCUMENTS:**

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** The application has been submitted to the Cardio-Renal division. The review of the hBNP drug Substance, assigned to the division of Metabolism and Endocrine Drug Products as a consult has been completed and submitted. The drug Product section is being reviewed at the Cardio - Renal division. The bioassay study on drug product is assigned as a consult to this division.

**REMARKS/COMMENTS:**

Natrecor is the proprietary name of human B-type Natriuretic Peptide, which is the drug substance of this NDA. The drug product (Natrecor in this NDA) is a lyophilized powder(5mg/vial) to be reconstituted with 10 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. The proposed indication for the product is the short-term treatment of congestive heart failure.

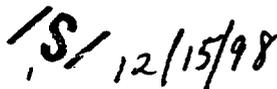
The details of manufacturing, isolation, purification and stability studies of the rhBNP are reviewed earlier (See Chem Review dt. 5<sup>th</sup> Nov'1998). The present review is to review the bioassay and acceptance criteria performed by the sponsor on the drug product as a quality control. For a detailed drug product review see Chem. Review from Cardio-Renal division.

**CONCLUSIONS & RECOMMENDATIONS:**

The bioassay performed on the drug product and acceptance criteria are found satisfactory. With respect to this particular aspect of CMC, the application is approvable. See draft letter.

Org. NDA # 20920  
cc: HFD-510/Division File  
HFD-510/PardhaK/SMooore/  
HFD-110/JShort/KSrinivasachar/DWillard  
R/D Init by: Team Leader

  
Komanduri Pardha, Review Chemist  
filename: N#20920



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D. Wilford

NOV 10 1998

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510  
Review of Chemistry, Manufacturing and Controls

NDA 20920                      CHEMISTRY REVIEW: #1                      DATE REVIEWED: 5<sup>th</sup> Nov 1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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Original	24 <sup>th</sup> Apr 1998	28 <sup>th</sup> Apr 1998	4 <sup>th</sup> May 1998
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**NAME & ADDRESS OF APPLICANT:** Scios Inc.  
2450, Bayshore parkway  
Mountain View, CA 94043

**DRUG PRODUCT NAME**

Proprietary: Natrecor

Nonproprietary/Established/USA username (or equivalent): Nesiritide

Code Name/#:

Chem. Type/Ther. Class: Human B-type Natriuretic Peptide (recombinant)

**ANDA Suitability Petition / DESI / Patent Status:** N/A

**PHARMACOLOGICAL CATEGORY/INDICATION:** Short term treatment of Congestive heart failure

**DOSAGE FORM:** Lyophilized powder to be Reconstituted with 10mL of 5% Dextrose injection (USP) or 0.9% Sodium Chloride injection (USP)

**STRENGTHS:** 5mg/vial

**ROUTE OF ADMINISTRATION:** Injection

**DISPENSED:**  Rx  OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Molecular weight: 3464 g/mol (average mass of base form)

Empirical Formula: C<sub>143</sub>H<sub>244</sub>N<sub>50</sub>O<sub>42</sub>S<sub>4</sub>

SerProLysMetValGlnGlySerGlyCysPheGlyArgLysMetAspArgIleSerSerSerSerGlyLeuGlyCysLysValLeuArgArgHis  
 1                      5                      10                      15                      20                      25                      30                      32

**SUPPORTING DOCUMENTS:** DMF

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** The application has been submitted to the Cardio-Renal division. The review of the hBNP drug Substance is assigned to the division of Metabolism and Endocrine Drug Products as a consult. The drug Product is being reviewed at the Cardio - Renal division.

**REMARKS/COMMENTS:**

Natrecor is the proprietary name of human B-type Natriuretic Peptide, which is the drug substance of this NDA. The drug product (Natrecor in this NDA) is a lyophilized powder(5mg/vial) to be reconstituted with 10 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. The proposed indication for the product is the short-term treatment of congestive heart failure.

Short- term infusion of graded doses of hBNP is associated with favorable hemodynamic effects (decreased cardiac filling pressures, increased cardiac index) and favorable renal excretory effects (diuresis and natriuresis) in patients with severe congestive heart failure. Administration of hBNP enhanced renal excretory function by significantly increasing urine volume and urinary sodium excretion. The pharmacological effects of BNP are mediated by the activation of membrane-bound guanylate cyclase.

The amino acid sequence of hBNP drug substance corresponds to residues 77-108 of human Pro-BNP and is identical to the amino acid sequence of the synthetic peptide. Human BNP is a 32-amino acid peptide which contains a disulfide bond connecting the cysteines at position 10 & 26. The drug substance portion of this NDA comprises the manufacturing of hBNP drug substance using recombinant DNA technology. The sponsor has shown that the synthetic and recombinant peptides are identical by both physical and chemical methods. The recombinant hBNP (rhBNP) drug substance is produced as a fusion protein to stabilize hBNP protein by forming insoluble inclusion bodies within the *E.Coli* cytoplasm.

**CONCLUSIONS & RECOMMENDATIONS:**

The chemistry, manufacturing and controls (CMC) are satisfactory and the application is approvable with respect to the drug substance. See list of Comments and deficiencies. Also, refer to the separate chemistry review of the drug product.

Org. NDA # 20920

cc: HFD-510/Division File  
HFD-510/PardhaK/SMoore/  
HFD-110/JShort/KSrinivasachar/DWillard  
R/D Init by: Team Leader

  
Komanduri Pardha, Review Chemist  
filename: N#20920

AE (drug substance)



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PP. 3-32  
(4-Page attachment)

D. Willard

APR 16 1999

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 20-920

**DATE REVIEWED:** 15 Apr 99

**REVIEW #:** 2B

**REVIEWER:** James H. Short, Ph.D.

<b>SUBMISSION TYPE</b>	<b>DOCUMENT DATE</b>	<b>CDER DATE</b>	<b>ASSIGNED DATE</b>
ORIGINAL	24-Apr-98	27-Apr-98	12-May-98
AMENDMENT	11-Mar-99	16-Mar-99	17-Mar-99
AMENDMENT	12-April-99	13-Apr-99	14-Apr-99

**NAME & ADDRESS OF APPLICANT:**

Scios, Inc.  
2450 Bayshore Parkway  
Mountain View, CA 94043

**DRUG PRODUCT NAME**

<b>Proprietary:</b>	Natreacor®
<b>Established:</b>	Nesiritide
<b>Code Name#:</b>	hBNP
<b>Chem. Type/Ther. Class:</b>	I S

**PHARMACOL. CATEGORY/INDICATION:**

Congestive heart failure

**DOSAGE FORM:**

SVS

**STRENGTHS:**

2.5 and 5 mg/10 mL vial

**ROUTE OF ADMINISTRATION:**

Intravenous injection

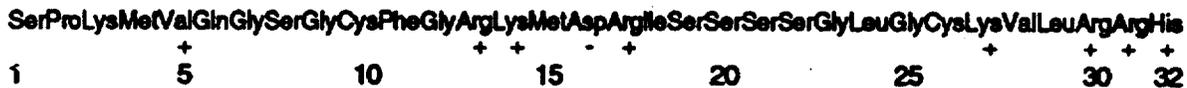
**Rx/OTC:**

Rx  OTC

**SPECIAL PRODUCTS:**

Yes  No

**CHEMICAL NAME. STRUCTURAL FORMULA. MOLECULAR FORMULA. MOLECULAR WEIGHT:**



3464 g/mol (average mass of base form)

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Natreacor	Scios	Acceptable		
DMF			Acceptable	10/21/93	
DMF			Acceptable	9/12/96	
DMF			Acceptable	4/20/95	
IND					

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** Dr. Brenda Uratani, HFD-160, has reviewed the microbiology section of this applicant, and has found the methods used to assure the sterility of the product to be satisfactory. In her review #3 she confirms that there are no issues that would affect approval of the 2.5 mg strength.

The drug substance portion of this review was consulted to HFD-510, and it was reviewed by Dr. Pardha Komanduri, under the direction of Dr. Stephen Moore, Chemistry Team Leader. Deficiencies conveyed to the company were coordinated with Dr. Komanduri and Dr. Moore. The replies in the two amendments were also reviewed by Dr. Komanduri as well as by myself.

**REMARKS:**

A "Request For Trademark Review," dated 21 Oct 97, was sent to the Labeling and Nomenclature Committee during the review of IND [redacted]. A response was received, dated 18 Feb 98, indicating that the proposed proprietary name "Natreacor" was acceptable. After I started reviewing the NDA I requested that the L&N Committee reconfirm that the name "Natreacor" is still acceptable. Dr. Boring has brought to our attention that there is a drug product listed in the American Drug Index (1997) by the name of "Natrigo," which is marketed by Drug Products. This company is apparently defunct. On 15 Apr Dr. Boring sent an email to Diana Willard stating that the name "Natreacor" is acceptable to the L&N committee.

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 firm has not yet received notification of approval of either name.

An EER was sent to the Office of Compliance on 5 Jun 98. All facilities were found acceptable as of 26 Mar 99. A copy of the report is attached.

Validation of the analytical methods will be requested now that specifications for the drug substance and for the drug product have been set.

This drug substance has been added to the SPOTS data base.

The specifications for the drug substance are the same as were submitted in the original application. The specifications for the drug product have been modified as noted below, and a revised copy of the currently agreed upon specifications for the 5 mg vial are attached (p. 13). For the 2.5 mg vial the assay range and specification for total impurities are half of the figures specified for the 5 mg vial.

**CONCLUSIONS & RECOMMENDATIONS:**

The application may be approved from the CMC perspective.

The following requests should be conveyed to the applicant in the action letter:

1. You will be expected to report your reevaluation of specifications for related substances in the drug substance and in the drug product in your first annual report or submit a supplement, as appropriate.
2. Bioassay results determined at the [redacted] month time point for the 5 mg strength of the drug product should be submitted as soon as they become available. Along with these results a revised stability protocol should be provided.

3. We will permit a          month expiration date for both the 2.5 and 5.0 mg vials for the present.
4. You should include solubilities in common organic solvents in the DESCRIPTION section of the Package Insert, and the solubility data should not be in bold type.
5. The phrase          should be deleted from the storage statement on the labels and in the Package Insert.
6. For the sake of consistency you should place a blank line following the statement about the heparinized catheters in DOSAGE AND ADMINISTRATION section of the Package Insert.
7. You will need to include appropriate information concerning the 2.5 mg vials in the DESCRIPTION, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections of the Package Insert.
8. In the DOSAGE AND ADMINISTRATION section of the Package Insert under Preparation of Solution, "1.          should be changed to "1. Introduce 10 mL of 5% Dextrose Injection USP (D<sub>5</sub>W) or 0.9% Sodium Chloride Injection USP ... "

cc:

Org. NDA 20-920  
HFD-110/Division File  
HFD-810/JShort/3/17/99  
HFD-110/PM  
HFD-810/CHoiberg

R/D Init by: KSrinivasach

          
S  
4-16-99

          
S  
          
James H. Short, Ph.D., Review Chemist

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P.-4-13

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20920/000  
Stamp: 27-APR-1998 Regulatory Due: 27-APR-1999  
Applicant: SCIOS  
2450 BAYSHORE PKY  
MOUNTAIN VIEW, CA 940431173

Priority: 1S  
Action Goal:  
Brand Name: NATRECOR(NESIRITIDE)5.0MG VIAL  
IV INFUSI  
Established Name:  
Generic Name: NESIRITIDE  
Dosage Form: FIJ (FOR INJECTION)  
Strength: 5 MG PER VIAL

Org Code: 110

District Goal: 26-FEB-1999

FDA Contacts: D. WILLARD (HFD-110)  
J. SHORT (HFD-110)  
K. SRINIVASACHAR (HFD-110)

301-594-5300 , Project Manager  
301-594-5300 , Review Chemist  
301-594-5376 , Team Leader

Overall Recommendation:

**ACCEPTABLE on 26-MAR-1999 by M. EGAS(HFD-322)301-594-0095**

Establishment:

DMF No:  
AADA No:

Profile: SVS OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 10-JUN-1998  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE  
MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE STERILITY  
TESTER

Establishment:

DMF No:  
AADA No:

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-JUN-1998  
Decision: ACCEPTABLE  
Reason: BASED ON FILE REVIEW

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER

Establishment:

DMF No:  
AADA No:

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 26-MAR-1999

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

---

Establishment: **SCIOS INC**  
**2450 BAYSHORE PARKWAY**  
**MOUNTAIN VIEW, CA 94043**

DMF No:  
AADA No:

Profile: **CTL**            OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **20-JAN-1999**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE**  
**TESTER**  
**FINISHED DOSAGE RELEASE**  
**TESTER**  
**FINISHED DOSAGE STABILITY**  
**TESTER**

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**APPEARS THIS WAY  
ON ORIGINAL**



**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** Microbiology

**REMARKS:**

A "Request For Trademark Review," dated 21 Oct 97, was sent to the Labeling and Nomenclature Committee. A response was received, dated 18 Feb 98, indicating that the proposed proprietary name was acceptable.

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 firm has not yet received notification of approval of either name.

The applicant certifies that copies of the technical sections of the application have been sent to SFO-DO and to KAN-DO.

The amendment of 17 Jul 98 deals with equipment problems which occurred during manufacture of the drug substance by [redacted]. On 31 Jul 98 I sent a copy of this amendment to Mark Lynch. I have not received a response at the time of completion of this review.

The amendment of 7 Aug 98 provides for [redacted] as distributor of the drug product.

**CONCLUSIONS & RECOMMENDATIONS:**

The deficiencies noted during the review of this application are compiled below and will be conveyed to the applicant.

NOT APPROVABLE

cc:  
Org. NDA 20-920  
HFD-110/Division File  
HFD-810/JShort/6/3/98  
HFD-110/PM  
HFD-810/KSrinivasachar  
HFD-810/CHoiberg  
R/D Init by: KSrinivasachar

 James H. Short, Ph.D., Review Chemist

12-15/98

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PP-3-44



FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Establishment:  
**SCIOS INC**  
**2450 BAYSHORE PARKWAY**  
**MOUNTAIN VIEW, CA 94043**

DMF No:  
AADA No:

Profile: **CTL**                      OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **20-JAN-1999**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE**  
**TESTER**  
**FINISHED DOSAGE RELEASE**  
**TESTER**  
**FINISHED DOSAGE STABILITY**  
**TESTER**

**APPEARS THIS WAY  
ON ORIGINAL**

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

**Page 42 of Dr. Short's December 10, 1998 drug product review states that:**

**A categorical exclusion has been submitted under 21 CFR 25.31(b). There is no information (e.g., use of wild plants or animals as a biomass source) that indicates that additional environmental information is warranted. The applicant states that the drug substance, at the point of entry into the aquatic environment (EIC, environmental induction concentration ) will be less than 1 ppb based on the figures provided. The request for categorical exclusion is acceptable.**