CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-920

Chemistry Review(s)
16-JUL-2001

FDA CDER ELS
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20970000
Applnc: SCIOS
2450 BAYSHORE PKY
MOUNTAIN VIEW, CA 94043-1173

Priority: 15
Org Code: 119
Action Goal: District Goal: 11-MAY-2001
Brand Name: NATRECOR (NESIRITIDE) 50 MG VIAL
IV INFUS
Established Name: NESIRITIDE
Generic Name: FJ (FOR INJECTION)
Dosage Form: 5 MG PER VIAL
Strength:

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 Recommendations:
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

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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

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Profile: CFN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-MAR-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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

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

Responsibilities: DRUG SUBSTANCE MANUFACTURER

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Profile: CTL
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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 STABILTY TESTER
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

MEMO TO NDA 20-920

NAME & ADDRESS OF APPLICANT:
Scios, Inc.
749 North Mary Avenue
Sunnyvale, CA 94086

DRUG PRODUCT NAME
Proprietary:
Natrex®
Established:
Nesiritide (USAN)
Code Name/#:
hBNP
Chem. Type/Ther. Class:
I 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_{146}H_{254}N_{90}O_{43}S_{4} 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)
**DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510**  
Review of Chemistry, Manufacturing and Controls

**NDA 20920**  
**CHEMISTRY REVIEW:** #2D  
**DATE REVIEWED:** 4th-June-2001

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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 5mL of 5% Dextrose injection (USP) or 0.9% Sodium Chloride injection (USP)

**STRENGTHS:**  
1.5 mg 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_{123}H_{266}N_{50}O_{37}S_{4}
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 20th 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 19th 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 years to a year retest date, and an expiration date of 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/MooreS/
    HFD-110/AdvaniJ/KSrinivasacharK/NguyenQ
R/D Init by: Team Leader

Komanduri Pardha, Review Chemist
filename: N#20920

AP (drug substance)
Redacted

page(s) of trade

secret and/or

confidential

commercial

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

NDA #: 20-920
REVIEW #: 3B
DATE VIEWED: 30-Apr-01
REVIEWER: JV Advani

SUBMISSION TYPE
DOCUMENT DATE
ORIGINAL
AMENDMENT
AMENDMENT
AMENDMENT
AMENDMENT
RESUBMISSION
AMENDMENT
AMENDMENT
AMENDMENT
ASSIGNED DATE
24-Apr-98
11-Mar-99
12-Apr-99
09-Jan-01
10-Jan-01
27-Apr-98
16-Mar-99
16-Apr-99
12-May-98 (Not approved)
17-Mar-99 (See review #2B)
14-Apr-99 (See review #2B)
22-Jan-01
30-Mar-01
02-Apr-01
26-Apr-01
06-June-01
12-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/Num:
Chem.Type/Ther.Class:

Natrecon®,
Nesiritide (USAN),
hBNP,
I 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
x
OTC
x
No

SPECIAL PRODUCTS:

[Chemical structure]

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

C_{143}H_{284}N_{10}O_{45}S_{4} 3464 g/mol (average mass of base form)
SUPPORTING DOCUMENTS:

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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.

JV Advani, Review Chemist
Redacted 22

pages of trade secret and/or confidential commercial information
NDA 20920 | CHEMISTRY REVIEW: #2D | DATE REVIEWED: 10\textsuperscript{th} April 2001

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

DRUG PRODUCT NAME  
Proprietary: Natrecor  
Nonproprietary/Established/USAusername (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 5mL of 5% Dextrose injection (USP) or 0.9% Sodium Chloride injection (USP)

STRENGTHS: 1.5mg/vial

ROUTE OF ADMINISTRATION: Injection

DISPENSED: \textbf{Rx} OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:  
Molecular weight: 3464 g/mol (average mass of base form)  
Empirical Formula: C\textsubscript{143}H\textsubscript{264}N\textsubscript{50}O\textsubscript{42}S\textsubscript{4}

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\textbf{1} & \textbf{5} & \textbf{10} & \textbf{15} & \textbf{20} & \textbf{25} & \textbf{30} & \textbf{32} \\

\end{tabular}
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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:

Natrexor is the proprietary name of human B-type Natriuretic Peptide, which is the drug substance of this NDA. The drug product (Natrexor 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 (Sec. Chem review dated 20th-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 Sec. Chem review dated 16th-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 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/JShow/KSrinivasachar/NguyenQ
R/D Init by: Team Leader

/S/

Komanduri Pardha, Review Chemist
filename: N920920
Redacted 2

page(s) of trade secret and/or confidential commercial information
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20920 CHEMISTRY REVIEW: #2C DATE REVIEWED: 20th-Mar-2000

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Resubmission 9th Jan 2001 10th Jan 2001 26th Feb 2001

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:
ANDA Suitability Petition / DESI / Patent Status:
PHARMACOLOGICAL CATEGORY/INDICATION:
DOSAGE FORM:
Lyophilized powder to be Reconstituted with 10mL of 5% Dextrose injection (USP) or 0.9% Sodium Chloride injection (USP)
STRENGTHS:
1.5 mg 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_{143}H_{244}N_{60}O_{42}S_{4}

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 19th 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/MooreS/
    HFD-110/AdvaniJ/KSrinivasacharK/NguyenQ
    R/D Init by: Team Leader

AE (drug substance)

Komanduri Pardha, Review Chemist
filename: N#20920
Redacted 5 pages of trade secret and/or confidential commercial information pp. 3-7
# Establishment Evaluation Request Summary Report

**Application:** NDA 20920/000  
**Stamp:** 27-APR-1999  
**Regulatory Due:** 10-JUL-2001  
**Applicant:** SCIOS  
2450 BAYSHORE PKY  
MOUNTAIN VIEW, CA 94043-1173

**Priority:** 15  
**Org Code:** 110  
**Action Goal:** District Goal: 11-MAY-2001  
**Brand Name:** NATRECOR(NESIRITIDE)  
**Dosage Form:** IV INFUSION  
**Strength:** 5 MG PER VIAL

**Generic Name:** NESIRITIDE

**Dosage Form:** FIJ (FOR INJECTION)

**Strength:** 5 MG PER VIAL

**F.D.A. Contacts:**  
Q. NGUYEN  
(HFD-110)  
301-594-5300  
Project Manager

J. ADVANI  
(HFD-110)  
301-594-5300  
Review Chemist

K. SRINIVASACHAR  
(HFD-110)  
301-594-5374  
Team Leader

---

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

### 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

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

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**Appears this way on original**

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**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

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- **Last Milestone:** OC RECOMMENDATION
- **Milestone Date:** 19-MAR-2001
- **Decision:** ACCEPTABLE
- **Reason:** BASED ON PROFILE
- **Responsibilities:** DRUG SUBSTANCE MANUFACTURER

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- **Milestone Date:** 16-JUL-2001
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- **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).
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20920                CHEMISTRY REVIEW: #1C                DATE REVIEWED: 16th Nov 1998

SUBMISSION TYPE          DOCUMENT DATE     CDER DATE     ASSIGNED DATE
Original                  24th Apr'98       28th Apr'98     4th May 1998

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

DRUG PRODUCT NAME
Proprietary: Natrecor
Nonproprietary/Established/USAUsername (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_{143}H_{244}N_{50}O_{42}S_{4}

SerProLysMetValGlnGlySerGlyCysPhoGlyArgLysMetAspArgIleSerSerSerSerGlyLeuGlyCysValLeuArgArgHis
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:

Natreco is the proprietary name of human B-type Natriuretic Peptide, which is the drug substance of this NDA. The drug product (Natreco 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. 5th Nov’98). 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.
Redacted 5
pages of trade secret and/or confidential commercial information pp. 3-7
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 20920 CHEMISTRY REVIEW: #1 DATE REVIEWED: 5th Nov 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:
X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Molecular weight: 3464 g/mol (average mass of base form)
Empirical Formula: C_{143}H_{264}N_{20}O_{45}S_{4}

SerProLysMetValGlnGlySerGlyCysPheClyArgLysMetAspArgIleSerSerSerSerGlyLeuGlyCysLyvAlLeuArgArgSis

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

c: HFD-510/Division File
HFD-510/Pardha/KSMoore/
HFD-110/JShort/KSrinivasasachar/DWillard
R/D Init by: Team Leader

Komanduri Pardha, Review Chemist
filename: N#20920
Redacted 33

pages of trade secret and/or confidential commercial information

pp.3-32 (4 pages attached)
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-920
REVIEW #: 2B
DATE REVIEWED: 15 Apr 99
REVIEWER: James H. Short, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ORIGINAL 24-Apr-98 27-Apr-98 12-May-98
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
Proprietary: Natrecor®
Established: Nesiritide
Chemical Name/Chem. Type/Ther.Class:
Naphthylbutyric Acid

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: x Rx ___ OTC

SPECIAL PRODUCTS:
x Yes ___ No

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


C_{146}H_{264}N_{50}O_{42}S_{4} 3464 g/mol (average mass of base form)

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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 A response was received, dated 18 Feb 98, indicating that the proposed proprietary name "Natrecor" was acceptable. After I started reviewing the NDA I requested that the L&N Committee reconfirm that the name "Natrecor" 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 "Natrico," 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 "Natrecor" is acceptable to the L&N committee.

The applicant has petitioned the USAN Council for approval of the name 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 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 (D3W) 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 4-16-99

James H. Short, Ph.D., Review Chemist
Redacted 10

pages of trade secret and/or confidential commercial information

p.-4-13
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20920/000
Applicant: SCIOS
2450 BAYSHORE PKY
MOUNTAIN VIEW, CA  94043-1173
Priority: 15
Action Goal:
Org Code: 110
District Goal: 26-FEB-1999
Brand Name: NATRECOR(NESIRITIDE)5.0MG VIAL
IV INFUSI
Established Name:
Generic Name: NESIRITIDE
Dosage Form: FIJ (FOR INJECTION)
Strength: 5 MG PER VIAL

FDA Contacts:
D. WILLARD (HFD-110) 301-594-5300, Project Manager
J. SHORT (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. EGAS (HFD-322) 301-594-0095

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

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

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-MAR-1999
Responsibilities: DRUG SUBSTANCE MANUFACTURER
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APPEARS THIS WAY ON ORIGINAL
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-920
DATE REVIEWED: 7-Dec-98

REVIEW #: 1B
REVIEWER: James H. Short, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
ORIGIINAL 24-Apr-98 27-Apr-98 12-May-98
AMENDMENT 17-Jul-98 20-Jul-98 22-Jul-98
 07-Aug-98 10-Aug-98 17-Aug-98

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

DRUG PRODUCT NAME
Proprietary: Natrecor®
Established: Nesiritide (USAN)
Code Name/#: hBNP
Chem.Type/Ther.Class: I S

PHARMACOL. CATEGORY/INDICATION:
Congestive heart failure

DOSAGE FORM: SVS
STRENGTHS: 5.25 mg/10 mL vial
ROUTE OF ADMINISTRATION: Intravenous injection
Rx/OTC: x Rx ___ OTC
SPECIAL PRODUCTS: __ Yes x No

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

SerProLysMetValGlnGlySerGlyCysPheGlyArgLysMetAspArgGluSerSerSerGlyLeuGlyCysLysValLeuArgArgHis

C₁₄H₂₆N₁₀O₄S₄ 3464 g/mol (average mass of base form)

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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 \( \text{[Generic Name]} \) 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 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 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

[Signature]

James H. Short, Ph.D., Review Chemist
Redacted 41 pages of trade secret and/or confidential commercial information pp. 3-44
### 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  
**Org Code:** 110  
**Action Goal:**  
**District Goal:** 26-FEB-1999  
**Brand Name:** NATRECOR(NESSIRITIDE) 5.0 MG VIAL IV INFUSION

**Established Name:**  
**Generic Name:** NESSIRITIDE  
**Dosage Form:** FIJ (FOR INJECTION)  
**Strength:** 5 MG PER VIAL

**FDA Contacts:**  
- **D. WILLARD (HFD-110):** 301-594-5300, Project Manager  
- **J. SHORT (HFD-110):** 301-594-5300, Review Chemist  
- **K. SRINIVASACHAR (HFD-110):** 301-594-5376, Team Leader

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

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**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

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**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

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

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER
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<td>MOUNTAIN VIEW, CA 94043</td>
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<td>20-JAN-1999</td>
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<td>Reason:</td>
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<th>Responsibilities:</th>
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<tr>
<td>DRUG SUBSTANCE RELEASE TESTER</td>
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<td>FINISHED DOSAGE RELEASE TESTER</td>
</tr>
<tr>
<td>FINISHED DOSAGE STABILITY TESTER</td>
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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.