Product Quality Microbiology Review
Review for HFD 170

10-December-2004

NDA: 21-060-AZ

Drug Product Name
Proprietary: Prialt®
Non-proprietary: Ziconotide

Drug Product Classification: New Molecular Entity/Priority Review

Review Number: 6

Subject of this Review
Submission Date: June 25, 2004
Receipt Date: June 28, 2004
Consult Date: November 10, 2004
Date Assigned for Review: November 10, 2004

Submission History (for amendments only)

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<td>January 21, 2000</td>
<td>P. Stinavage</td>
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<td>March 22, 2000</td>
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<td>September 20, 2000</td>
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<td>January 26, 2001</td>
<td>May 22, 2001</td>
<td>P. Stinavage</td>
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Applicant/Sponsor
Name: Elan Pharmaceuticals
Address: 800 Gateway Blvd.
         South San Francisco, CA 94080
Representative: Not provided
Telephone: Not provided
Name of Reviewer: Stephen E. Langille, Ph.D.
Conclusion: Recommended for approval
Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUPPLEMENT: Not applicable
2. SUPPLEMENT PROVIDES FOR: Not applicable
3. MANUFACTURING SITE: 
4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
   • Injection in 1, 2, 5, 10 and 20 mL vials
   • Intrathecal injection
   • 100 ug/mL or 25 ug/mL

5. METHOD(S) OF STERILIZATION: Aseptic fill
6. PHARMACOLOGICAL CATEGORY: Analgesic

B. SUPPORTING/RELATED DOCUMENTS: 5 product quality microbiology reviews by P. Stinavage (in DFS).

C. REMARKS: The applicant has provided the following information:
   • A response to the July 25, 2001 approvable letter
   • Information concerning a new 25 ug/mL product formulation
   • Changes and updates for the current 100 ug/mL formulation
   • Information regarding endotoxin limits and dosing information (NDA 21-060-N000-BI, Submitted on December 6, 2004)
   • The applicant provided a response to the product quality microbiology reviewer questions provided on November 30, 2004 (NDA 21-060-N000-BI, Submitted on December 2, 2004).

filename: C:/Reviews/N021060R6.DOC
Executive Summary

I. Recommendations

A. Recommendation on Approvability -
   NDA 21-060 is recommended for approval from the standpoint of
   product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or
   Agreements, if Approvable -
   Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to
   Product Quality Microbiology -
   The drug product will be aseptically filled in glass vials and closed

B. Brief Description of Microbiology Deficiencies -
   No deficiencies were identified based upon the information
   provided

C. Assessment of Risk Due to Microbiology Deficiencies -
   Not applicable

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
   Stephen E. Langille, Ph.D.
   Supervisor/Team Leader

C. CC Block
   In DFS
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___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stephen Langille
12/13/04 07:44:20 AM
MICROBIOLOGIST

David Hussong
12/13/04 10:09:10 AM
MICROBIOLOGIST
REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #4 OF NDA 21-060
22 May 2001

A. 1. NDA 21-060 AZ
    APPLICANT: Elan Pharmaceuticals
                800 Gateway Blvd.
                South San Francisco, CA  94080

2. PRODUCT NAME: SNX-11 (ziconotide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intrathecal administration. The product
strength is 100 μg/mL in 2, 5, mL vials.

4. METHODS OF STERILIZATION:
The drug product is aseptically filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
   INDICATION:
The drug product is used to manage severe, chronic pain in patients for
whom intraspinal analgesic therapy is clinically indicated.

B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999

2. DATE OF AMENDMENT: 26 January 2001 (Subject of this Review)

3. RELATED DOCUMENTS: DMF's

4. ASSIGNED FOR REVIEW: 16 May 2001

C. REMARKS: The product is to be manufactured at either of two sites:
This submission provides the final report of the second ziconotide drug product growth promotion study. The data contained in this submission do not differ substantively from the data submitted in the interim report (NDA 21-060 BC submitted 28 December 2000) (See Microbiologist’s Review dated 13 February 2001). For example, results indicate that maintained viability and appeared to flourish throughout the 61-day test period in both the saline control and the product solution. Also maintained viability throughout the 61-day period in both saline and the product. Counts of all other test organisms dropped below detection limits of the assay by Day 3 of the test. These results are essentially the same as those obtained at the 31-day time point. The conclusions remain the same as in the 13 February 2001 review.

D. CONCLUSIONS: The data presented indicate that at least two of the test organisms replicate over the 61-day test period. In addition, maintained viability over the test period. However, if the health professionals refilling the pump reservoir maintain strict aseptic technique during the procedure the risk of contaminating the reservoir should not exceed the rate of contamination observed with other hospital performed aseptic procedures. The clinical reviewer should assess if the therapeutic advantages of use of this product in the implanted infusion pump outweigh the
risk of infection caused by contamination of and subsequent bacterial multiplication in the pump reservoir.

The manufacturing process for the drug product remains approvable on the basis of sterility assurance. Specific comments regarding the manufacturing process provided in the Microbiologist's Review dated 18 April 2000 remain to be resolved.

________________________________________
Paul Stinavage, Ph.D.

cc: Original NDA 21-060
    HFD-805/Stinavage/Consult File
    HFD-170/Div File/L. Governale/McCormick/Hertz/Koble

Drafted by: P. Stinavage, 22 May 2001
R/D initialed by P. Cooney
2 Page(s) Withheld

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/s/ Paul Stinavage  2/13/01 02:10:04 PM  MICROBIOLOGIST  Interim results of second growth promotion study.

Peter Cooney  2/13/01 03:35:00 PM  MICROBIOLOGIST
A. 1. NDA 21-060 BC
   APPLICANT: Elan Pharmaceuticals
   800 Gateway Blvd.
   South San Francisco, CA  94080

2. PRODUCT NAME:  SNX-11 (ziconotide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intrathecal administration. The product
strength is 100 μg/mL in 2, 5, mL vials.

4. METHODS OF STERILIZATION:
The drug product is aseptically filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used to manage severe, chronic pain in patients for
whom intraspinal analgesic therapy is clinically indicated.

B. 1. DATE OF INITIAL SUBMISSION:  29 October 1999

2. DATE OF AMENDMENT:  28 December 2000 (Subject of this Review)

3. RELATED DOCUMENTS:  DMF's

4. ASSIGNED FOR REVIEW:  18 January 2001

C. REMARKS: The product is to be manufactured at either of two sites:
This submission provides the interim report of the second ziconotide drug product growth promotion study.

D. CONCLUSIONS: The clinical reviewer should assess if the therapeutic advantages of use of this product in the implanted infusion pump outweigh the risk of infection caused by contamination of and subsequent bacterial multiplication in the pump reservoir.

The manufacturing process for the drug product remains approvable on the basis of sterility assurance. Specific comments regarding the manufacturing process provided in the Microbiologist's Review dated 18 April 2000 remain to be resolved.

Paul Stinavage, Ph.D.

cc: Original NDA 21-060
    HFD-805/Stinavage/Consult File
    HFD-170/Div File/L. Governale/McCormick/Hertz/Koble

Drafted by: P. Stinavage, 13 February 2001
R/D initialed by P. Cooney
2 Page(s) Withheld

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Final report of initial drug product growth promotion study.

Peter Cooney
11/30/00 11:15:35 AM
MICROBIOLOGIST
REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW #2 OF NDA 21-060
14 November 2000

A.  1. NDA 21-060  BI
APPLICANT: Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

2. PRODUCT NAME: SNX-11 (ziconotide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intrathecal administration. The product strength is 100 µg/mL in 2, 5, 10 mL vials.

4. METHODS OF STERILIZATION:
The drug product is aseptically filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.

B.  1. DATE OF INITIAL SUBMISSION: 29 October 1999

2. DATE OF AMENDMENT: 20 September 2000 (Subject of this Review)

3. RELATED DOCUMENTS: DMF's

4. ASSIGNED FOR REVIEW: 25 September 2000

C. REMARKS: The product is to be manufactured at either of two sites:
This submission provides the final report of the first ziconotide drug product growth promotion study.

D. CONCLUSIONS: Review of this submission does not alter the "Not Approvable" conclusion in the review dated 18 April 2000.

Paul Stinavage, Ph.D.

cc: Original NDA 21-060
    HFD-805/Stinavage/Consult File
    HFD-170/Div File/L. Governale/McCormick/Chamberlin

Drafted by: P. Stinavage, 14 September 2000
R/D initialed by P. Cooney
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REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW #2 OF NDA 21-060
18 April 2000

A. 1. NDA 21-060 BI
APPLICANT: Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

2. PRODUCT NAME: SNX-11 (ziconotide)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is intended for intrathecal administration. The product strength is 100 μg/mL in 2.5, mL vials.

4. METHODS OF STERILIZATION:
The drug product is aseptically filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used to manage severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.

B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999

2. DATE OF AMENDMENT: 22 March 2000 (Subject of this Review)

3. RELATED DOCUMENTS: DMF's

4. ASSIGNED FOR REVIEW: 28 March 2000

C. REMARKS: The product is to be manufactured at either of two sites:
The manufacturing process used at ___ differs from that used at __. Following vial filling at ___ the
At ___ the filled vials

D. CONCLUSIONS: The application is not recommended for approval on the basis of microbiological safety. Specific comments are provided in “E. Review Notes” and “List of Microbiology Deficiencies and Comments”. Moreover, the concerns communicated (see Teleconference with applicant minutes dated 30 March 2000, Letter to Applicant drafted 7 April 2000 by L. Governale) to the applicant regarding the use of an implantable pump for delivery of this drug product remain to be resolved.

Paul Stinavage, Ph.D. 19 Apr 2000

cc: Original NDA 21-060
HFD-805/Stinavage/Consult File
HFD-170/Div File/L. Governale/McCormick/D'Sa/Chamberlin/Thedorakis

4/18/00
Elan Pharmaceuticals, NDA 21-060, Ziconotide, Microbiologist's Rev. #2 of pre-NDA

Drafted by: P. Stinavage, 18 April 2000
R/D initialed by P. Cooney
4 Page(s) Withheld

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REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW #1 OF Pre-NDA 21-060
13 January 2000

A. 1. NDA 21-060
   APPLICANT: Elan Pharmaceuticals
               800 Gateway Blvd.
               South San Francisco, CA 94080

   2. PRODUCT NAME: SNX-11 (ziconotide)

   3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
      The product is intended for intrathecal administration. The
      product strength is 100 μg/mL in 2, 5, mL vials.

   4. METHODS OF STERILIZATION:
      The drug product is aseptically filled.

   5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
      INDICATION:
      The drug product is used to manage severe, chronic pain in
      patients for whom intraspinal analgesic therapy is clinically
      indicated.

B. 1. DATE OF INITIAL SUBMISSION: 29 October 1999

   2. DATE OF AMENDMENT: (none)

   3. RELATED DOCUMENTS: DMF's

   4. ASSIGNED FOR REVIEW: 10 November 1999

C. REMARKS: The application is a pre-NDA CMC submission that
   includes microbiology information. The product is to be
   manufactured at either of two sites:
The manufacturing process used at [redacted] differs from that used at [redacted]. Following vial filling at [redacted], the filled vials are loaded into a

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns. Specific comments are provided in “E. Review Notes” and “List of Microbiology Deficiencies and Comments”.

[Signature]
Paul Stinavage, Ph.D.
13 January 2000

cc: Original NDA 21-060
HFD-805/Stinavage/Consult File
HFD-170/Div File/McCormick/D'Sa/Chamberlin/
Theodorakis

Drafted by: P. Stinavage, 13 January 2000
R/D initialed by P. Cooney
Page(s) Withheld

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Section 552(b)(5) Deliberative Process

Section 552(b)(5) Draft Labeling
REQUEST FOR CONSULTATION

FROM: HFD-170/Dr. Cynthia McCormick

NAME OF DRUG: Ziconotide Soln. Injectable

NAME OF FIRM: Elan Pharmaceuticals

REASONS FOR REQUEST

I. GENERAL

NEW PROTOCOL
PRE-NDA MEETING
RESPONSE TO DEFICIENCY LETTER

PROGRESS REPORT
END OF PHASE II MEETING
FINAL PRINTED LABELING

NEW CORRESPONDENCE
RESUBMISSION
LABELING REVISION

ADVERSE REACTION REPORT
SAFETY/EFFICACY
x ORIGINAL NEW CORRESPONDENCE

MANUFACTURING CHANGE/ADDITION
PAPER NDA
FORMATIVE REVIEW

MEETING PLANNED BY
CONTROL SUPPLEMENT
OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

TYPE A OR B NDA REVIEW
CHEMISTRY REVIEW

END OF PHASE II MEETING
PHARMACOLOGY

CONTROLLED STUDIES
BIOPHARMACEUTICS

PROTOCOL REVIEW
OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

DISSOLUTION
DEFICIENCY LETTER RESPONSE

BIOAVAILABILITY STUDIES
PROTOCOL-BIOPHARMACEUTICS

PHASE IV STUDIES
IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/Epidemiology Protocol
REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY

DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSIS
SUMMARY OF ADVERSE EXPERIENCE

CASE REPORTS OF SPECIFIC REACTIONS (List below)
POISON RISK ANALYSIS

COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The firm has submitted a pre-NDA CMC submission which includes microbiology section. The chemistry reviewer is M. Theodorakis, phone 827-7425. This application is a priority for our Division, and we are asking that you provide us a response by January 25, 2000.

Please review the attached correspondence (2 volumes). Any questions please contact, Dr. Abi D’Sa Chemistry Team Leader or Nancy Chamberlin, CSO at 7-7410. Thank you for your assistance.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECIPIENT

SIGNATURE OF DELIVERER

DATE: 11-2-99

IND NO.
21-060

DATE OF DOCUMENT
10-29-99

NDA #
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 21060/000
Org Code: 170
Priority: 1P

Stamp Date: 28-DEC-1999
PDUFA Date: 28-DEC-2004
Action Goal:
District Goal: 29-OCT-2004

Brand Name: ZICONOTIDE SOLUTION 100MCG/ML
Generic Name: ZICONOTIDE SOLUTION 100MCG/ML
Dosage Form: INJECTION
Strength: 0.1 MG/ML

FDA Contacts:
S. STRADLEY Project Manager (HFD-170) 301-827-7430
M. THEODORAKIS Review Chemist (HFD-170) 301-827-7425
R. HARAPANHALLI Team Leader (HFD-170) 301-827-7410

Overall Recommendation:
ACCEPTABLE on 23-DEC-2004 by S. ADAMS (HFD-322) 301-827-9051
ACCEPTABLE on 02-APR-2001 by J. D AMBROGIO (HFD-322) 301-827-9049
ACCEPTABLE on 12-FEB-2001 by S. FERGUSON (HFD-322) 301-827-9009
WITHHOLD on 21-JUN-2000 by S. FERGUSON (HFD-322) 301-827-9009

Establishment: CFN: FEI:

CNP No: AADA:
Responsibilities:

Profile : CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 13-DEC-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No: AADA:

Responsibilities:

Profile : CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-NOV-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :
DMF No: AADA:

Responsibilities:

Profile: CTL
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 25-OCT-04
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:
ELAN BIOPHARMACEUTICALS
800 GATEWAY BLVD
SOUTH SAN FRANCISCO, CA 94080

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 21-DEC-04
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:
Responsibilities:

Profile : CTL
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

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| Responsibilities: | |

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Reason: BASED ON PROFILE

Establishment:

DMF No: AADA:

Responsibilities:

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Last Milestone: OC RECOMMENDATION
Milestone Date: 28-OCT-04
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:

DMF No: AADA:
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