APPLICATION NUMBER:
21-060

CHEMISTRY REVIEW(S)
PRIALT (ziconotide intrathecal infusion), 25, 100 mcg/mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA

Indication: PRIALT (ziconotide intrathecal infusion) is indicated for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine.

Presentations: 25 mcg/mL: 20 mL vial

Only the undiluted 25 mcg/mL formulation should be used for PRIALT naive pump priming.

100 mcg/mL: 1 mL vials

2 mL vials

5 mL vials

EER Status: Acceptable 23-DEC-2004

Consults:
DMETS – Tradename: PRIALT - acceptable 15-MAR-2004
Statistics -- NA
EA – no consult - waiver requested – granted
Micro – acceptable 13-DEC-2004
CDRH – Review of ____ for the infusion pump - acceptable

Post Approval Agreements: None

The original NDA was received 10-OCT-1999
The drug substance is manufactured by:

Manufacturing and controls information was reviewed and were found acceptable under DMF. The Elan acceptance specifications are acceptable (impurities are adequately controlled). The drug substance is synthetic peptide (25mer) with 3 disulfide linkages. The drug substance is adequately characterized. Note that an in vitro binding assay was required for confirmation of identity and activity. Drug re-test period of is supported by submitted stability data. The stability testing protocol and commitment are acceptable.

Conclusion
Drug substance is satisfactory.

The drug product is vials of 25 mcg/mL in 20 mL vials for pump priming, and 100 mcg/mL in 1, 2, 5 mL vials for pump filling.

Manufacturer:

The drug product formulation is an aqueous pH adjusted solution with methionine added as a stabilizer and NaCl added for toniccy. The manufacturing method is a standard aseptic vial filling operation. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The submitted stability data are adequate to support the requested 24 month expiry in all presentations when stored at 2-8°C (to also be shipped at this temperature). The stability testing protocol and commitment is considered adequate. The established name ziconotide is USAN.

The product is to be used only in the pumps which were qualified:
Medtronic Synchromed EL
Medtronic Synchromed II Infusion System
Simms Deltec Cadd Micro External Microdilusion Device and Catheter

Adequate studies were conducted relative to drug/device compatibility and drug delivery.

Labeling is acceptable.
NOTE: The established name, ziconotide intrathecal infusion is not in conformance with either USP or FDA nomenclature standards. Initial proposals were to call this ziconotide
(see Div Dir review dated 27-JUL-2001). After discussion of this with the Clinical review team it was concluded that use of the term _ _ _ in the established name could contribute to administration errors which would have serious safety implications.

The overall Compliance recommendation is acceptable as of 23-DEC-2004.

All associated DMFs are acceptable.

**Overall Conclusion**
From a CMC perspective the application is recommended for approval.

Eric P Duffy, PhD
Director, DNDC II/ONDC
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/s/

Eric Duffy
12/28/04 12:10:13 PM
CHEMIST
FOOD and DRUG ADMINISTRATION
CENTER of DRUG EVALUATION and RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE and ADDICTION
DRUG PRODUCTS (DACCADP)
HFD-170

NDA: 21-060

CHEMISTRY REVIEW #3
REVIEW DATE: 08-NOVEMBER-2004

SUBMISSION TYPE: AMENDMENT BC
DOCUMENT DATE: June 25, 2004
CDER DATE: June 28, 2004
ASSIGNED DATE:

NAME & ADDRESS OF APPLICANT:
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attn.: Linda B. Fradkin
Director, Regulatory Affairs
tel.: 650-614-1053 or 800-435-5108

DRUG PRODUCT NAME
Proprietary: Pristalt
Nonproprietary/USAN: ziconotide
Code Name/#: 
Chem. Type/Ther. Class: I P

PHARMACOL. CATEGORY/INDICATION:
Ziconotide is a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels.

DOSAGE FORM:

STRENGTHS:
25 µg/mL, 20 mL fill in 20 mL vial,
100 µg/mL, 1 mL fill in 2 mL vial,
2 mL fill in 2 mL vial
5 mL fill in 5 mL vial

ROUTE OF ADMINISTRATION: intrathecally

DISPENSED:

X Rx __ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Molecular formula: \( C_{102}H_{172}N_{36}O_{32}S_{7} \)

Molecular Weight: 2639.

Chemical Name:
1) \( \omega \)-conotoxin MVIIA
2) L-cysteinyll-L-lysylglycyl-L-lysylglycyl-L-alanyl-L-lysyl-L-cysteinyll-L-seryl-L-arginyll-L-leucyl-L-methionyl-L-tyrosyl-L-\( \alpha \)-aspartyl-L-cysteinyll-L-cysteinyll-L-threonyllglycyl-L-seryl-L-cysteinyll-L-arginyl-L-serylglycyl-L-lysylcysteinamide cyclic (1\( \rightarrow \)16), (8\( \rightarrow \)20), (15\( \rightarrow \)25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: \( \omega \)-conopeptide MVIIA; conotoxin MVIIA; \( \omega \)-CTX MVIIA; \( \omega \)-CmTx MVIIA; \( \omega \)-CmTx; \( \omega \)-CmTX; MVIIA

CAS Registry Number: 107452-89-1

Code Number: SNX-111
CONCLUSIONS & RECOMMENDATIONS:
This application is approvable from the chemistry standpoint pending the outcome of the inspection of facilities and the response to the comments related to passivation procedure of the pump. See addendum to Chemistry Review #3.

CC:
NDA 20-060
HFD-170/Division File
HFD-170/MTheodorakis
HFD-170/RHarapanhalli
HFD-170/SStradley
R/D Init. By
File name

Michael C. Theodorakis, Ph.D.
Senior Review Chemist

Ravi S. Harapanhalli, Ph.D.
Chemistry Team Leader
EXECUTIVE SUMMARY

Ziconotide is a preservative free formulation that is intended for intrathecal use via an external or implantable pump. The drug substance, ziconotide, a new molecular entity, is a synthetic 25- amino acid peptide with three intra-strand disulfide bridges involving the six cysteine residues. The molecule is equivalent in structure to omega conotoxin MVIIA that is present in the venom of marine snails of the genus Conus. This new peptide belongs to a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels.

Drug Substance:
The drug substance is synthesized, isolated, purified, tested, and packaged by

The applicant (Elan Pharmaceuticals) is responsible for the reference standard. The identity and purity of the primary drug substance reference standard was demonstrated by peptide mapping and amino acid sequencing, amino acid composition, disulfide bridge arrangement studies. A secondary standard has also been established, this is a working standard. The purity and stability of the working reference standard was demonstrated and it is acceptable.
The regulatory specifications for release of the drug substance includes a binding assay. The combination of the binding assay and a test to determine the presence and location of the disulfide bonds (2D-NMR, or peptide mapping with amino acid analysis, or enzymatic digestion of the peptide followed by sequencing or the bioassay) would be considered to be a measure of the activity of the drug substance for lot to lot release.

The applicant agreed for using a bio-assay to test the reference standard, and that lot-to-lot release of the product should include a 2D-NMR testing method. The applicant chose a bioassay that involved the inhibition of calcium channel efflux into cells for the purpose of testing the reference standard. The protocol for the bioassay has been approved and supportive data have been reviewed and found adequate.

**Drug Product:**
The drug product, Ziconotide ——— is a sterile, aqueous solution for intrathecal infusion. It is marketed in two strengths, 25 μg/mL and 100 μg/mL. The formulations contain ziconotide free base, formulated as the acetate salt in saline at pH 4.0-5.0. The formulations consist of ziconotide acetate (the active ingredient), sodium chloride \(\text{L-methionine \[ \text{water for injection (vehicle)}\]}

The 100 μg/mL formulation is supplied in single-dose, 2 mL vial (containing 1 and 2 mL fills), and 5 mL vial (5 mL fill). The 25 μg/mL formulation is supplied in single-dose 20 mL vial (20 mL fill). The ——— vials

The drug product is manufactured at ———.

Ziconotide ——— solution (100 μg/mL) has been shown to be stable for at least ——— at the recommended storage temperature (2-8°C) for the 1 mL, 2 mL and 5 mL fill lots. The product should be granted ——— expiration dating for the 1, 2, and 5 mL fills.

Ziconotide ——— solution (25 μg/mL) has been shown, to be stable for at least ——— at the recommended storage temperature (2-8°C) in 20 mL fill lots. Based on the statistical analysis of the stability data the product should be stable for ——— The Applicant requested 24 months of expiration dating period. It is recommended that the product be granted a maximum of 24 months expiration dating period.

The stability data indicate that the impurities, which increase
Both strengths of ziconotide were compatible with SynchroMed-II and SynchroMed-EL implantable pumps. However, the stability in the pump for both strengths was different. Also, the stability of the injection was different if the pump was naive (never exposed to ziconotide) as compared to an exposed pump. The information from these studies was used to construct a table for pump refill schedules for health care personnel that was included in the package insert.

SynchroMed-II and SynchroMed-EL implantable pumps are made of the same materials but are different in the size of the reservoir, and the residual volume. SynchroMed-II has a slightly larger reservoir (2 mL) than SynchroMed-EL. Adsorption of ziconotide is also slightly different. Both pumps are recommended in the package inset for intrathecal administration of ziconotide injection.

Ziconotide was also compatible with Simms Deltec Cadd-Micro external microinfusion device and catheter.

Nine other drug products, which are administered intrathecally, were tested for compatibility with the ziconotide. All admixtures tested were clear with no visible precipitation and were considered to be compatible with the ziconotide.

The Applicant claimed a categorical exclusion from submission of an Environmental Assessment for ziconotide. This claim is acceptable because ziconotide is a synthetic peptide consisting only of naturally occurring amino acids. The Applicant also provided calculations of expected introduction concentration of the active moiety into the aquatic environment. The drug concentration will not exceed the In this worst case scenario, the exposure to aquatic environment is estimated
to ______ per year for ______ years.

**Inspections:**
See Addendum to Chemistry review #3.

**Microbiology Consults:**
The microbiology review has been completed and recommended approval.

**Device Consult:**
The passivation process of the ______ reservoir of the pump was consulted to CDRH. The CDRH reviewer recommended approval but also asked for additional data to show that the passivation process was effective.

The lack of these data is not an approvability issue for the following reason. The passivation process has been run numerous times and the data show that around ______ of ziconotide are lost to adsorption on the ______ reservoir. If the process is 100% effective that is the best we should expect. If it is 100% ineffective, it could not get worse. Everything else should be in between.

The real concern, when I asked CDRH to review the process was if the passivation process was introducing toxic substances in the reservoir.

**Methods Validation:**
The FDA labs are currently verifying the methods and so the approval letter should contain the standard paragraph used in decision letters.

Part of the information in this executive summary has been extracted from the Team Leader's Memorandum by Albinus M. D'Sa dated June 5, 2000 that accompanied Chemistry Review #1.

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SPOTS:
Not applicable. This is a synthetic peptide.

SUPPORTING DOCUMENTS:

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RELATED DOCUMENTS

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CONSULTS:
A consult review by CDRH concerning issue of the passivation procedure used to treat the reservoir of the SynchroMed pumps was completed on November 10, 2004. The reviewer found the process to be generally acceptable. See attached CDRH review at the end of this review. The reviewer had the following comment:

"In Amendment 11 to Master File _____, you described the procedure used to passivate the reservoir for your pump. However, you have not provided the results of testing to verify that you have achieved an acceptable level of passivation. Please provide the protocol and results of your verification testing for your passivation procedure and provide the release criteria for the level of passivation the device will meet _____.

This comment should be sent to the DMF holder after action is taken on this NDA. During a meeting among Dr. Harapanhalli, Schultheis and this reviewer, it was decided that the information requests is unlikely to have any impact in the Agency’s decision for this product.

A consult request was issued recently to microbiology for the new 25 μg/mL formulation. The microbiology review was completed and the section was found to be adequate.
COMMENTS:

1. Ziconotide ———, preservative free, is an intrathecal formulation for the treatment of management of severe, chronic pain for patients for whom intraspinal analgesic therapy is clinically indicated. Ziconotide belongs to a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels. The maximum daily dose for ziconotide is 57.6 µg calculated on the basis of an infusion rate of 2.4 µg/h over a 24 hour period.

2. Chemistry Review #3 is concerned with the Applicant’s responses to the Agency’s Approvable and Discipline Review Letters both dated July 25, 2001.

3. See Chemistry Reviews #1 and #2.

4. The 1, 2, 5 mL and 20 mL fills are manufactured at ———.

5. ——— manufacturing and quality control facilities for this NDA were acceptable to Compliance as of December 3, 2004. One facility was pending.

6. A CDRH consult review was completed. It regards the passivation process for the reservoir of the pump.

7. No DMF reviews are pending.

8. The stability data (12 lots) support the Applicant’s request for an initial ——— expiration dating period for the 1 mL, 2 mL and 5 mL presentations of the 100 •g/mL strength injection when stored at 2°-8°C. It is recommended that the Applicant’s request be granted.

9. For the 25 •g/mL (20 mL) strength ——— stored at 2°-8°C, the Applicant provided ——— stability data (3 lots) and requested a 24 month expiration dating period. Based on the statistical analysis of the ——— data, the Applicant concluded that the 25 •g/mL was stable for at least ——— (see page 42, vol. 6). It is recommended that the Applicant’s request be granted.

10. The Applicant provided the usual three point stability commitment for post approval studies. A detailed post approval stability protocol was found in Chemistry Review #2.

11. The regulatory specifications for acceptance of the drug
product were revised to include total impurities and individual limits for the impurities being monitored. All specified impurities that appear in the drug product during storage and in the pump have been qualified. The qualification report is under evaluation by the review pharmacologist.

12. Methods validation is in progress.

13. Minor labeling corrections were made on the draft label on the common drive.

14. The Applicant qualified new primary and secondary standards. There were lots REFO17 and REFO18 respectively. REFO17 replaced the old primary standard NUY001. Secondary standard lot REFO18 replaced the old secondary lot REFO07. The correlation factor between the two standards was determined to be ___

15. The Applicant provided updates regarding the following. These updates were minor and do not change the conclusions of Chemistry Reviews #1 and #2.

   a. HPLC method ___ for testing of identity, concentration and purity of ziconotide drug substance and drug product was revised.

   b. HPLC test method ___ for identity, concentration and purity testing of ziconotide 25 μg/mL drug product was revised to include impurities identification.

   c. The HPLC test method qualification report for ___ was replaced with a method validation report.

   d. A revised copy of the test method for concentration of methionine in ziconotide drug product was included.

   e. Updated batch records from ___ were included for dispensing and compounding for both product strengths.

   f. Specifications for impurities have been revised based on limits qualified in a toxicology study.

   g. Updated stability data are provided using the "___" procedure. Statistical analysis of the results was provided.

   h. Updated floor plans are included for manufacturing facility.
i. A new ___________ training procedure is conducted for analysis of the HPLC traces was provided.

j. ____ was included as an alternate testing facility for release of drug product.
24 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling
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/s/

Michael Theodorakis
12/10/04 09:37:23 PM
CHEMIST

Ravi se also Addendum to Chemistry Review #3

Ravi Harapanhalli
12/12/04 09:01:22 PM
CHEMIST
3 Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling
2 Page(s) Withheld

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☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
DATE: July 27, 2001
TO: NDA 21-060
FROM: Eric P Duffy, PhD
       Director, Division of New Drug Chemistry II, HFD-820
SUBJECT: PRIALT (ziconotide) Injection AE Action
         NDA 21-060, PRIALT (ziconotide) -------

PRIALT (ziconotide) ------- is a peptide analgesic intended for intrathecal administration via
an implantable pump. The drug substance manufacture and controls for the synthetic 25mer
peptide is the subject of a DMF, which was found to be acceptable. The drug product is
formulated and aseptically processed. Sterility assurance measures remain approvable pending
response to deficiencies provided in our correspondence dated 18-APR-2000. The drug is
intended to be used in a Medtronic SynchroMed pump which is regulated by CDRH and has a
Device Master File, ------- A consult to CDRH responded to all the requests for
information the Division had conveyed. The previous CMC deficiencies principally related to
drug/pump interactions (eg. dilution upon first fill, adsorption) and the responses are deemed
satisfactory. Some additional issues related to use of this drug in the pump will be conveyed in
the present AE letter, in addition to questions regarding the regulatory specification.

Conclusion: I concur with the deficiency comments related in the AE letter to the sponsor.

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/s/

Eric Duffy
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CHEMIST
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☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
June 25, 2001

FROM: Nurse Consultant, Division of Postmarket Surveillance, PEB1
Office of Surveillance and Biometrics (HFZ-520)

SUBJ: Marketing experience with Medtronic Synchronized Pump

TO: Branch Chief, GHDB, Office of Device Evaluation

THROUGH: Branch Chief, Product Evaluation Branch 11, Division of Postmarket Surveillance, Office of Surveillance and Biometrics (HFZ-520)

The following is provided as per your request.

A Mende database search was performed identifying the criteria for Manufacture Name (Medtronic) and product code for the period mid-July 1996 to the present.

A total of 1,258 events were retrieved for the Syncromed and Syncromed EL infusion pump including accessories.

A frequency analysis was done on the above adverse events for the Device Problem and Patient Problem codes as follows: (enclosed is a copy of the entire list by rank).

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<td>27</td>
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NOTE: The total number of occurrences shown in the ‘count’ (column 2) differs from the total number of events. This happens when the reporter selects multiple occurrences of a data item ‘device problem codes’ or ‘patient problem codes in the same event.

A search was performed on these reports to identify those in which ‘morphine’ was noted in the text. Two hundred and thirty four events (234) were retrieved, however, this information did not indicate whether an anti-microbial was used with the drug.

Enclosed is the market share for the Cadd-Plus and Medtronic Synchromed pumps provided by the library.

Due to time constraints I’m sending what I have done so far and will be working on the information for the internal Cadd-Plus infusion system. Will send this upon completion.
Page(s) Withheld

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☑ § 552(b)(5) Deliberative Process
☐ § 552(b)(5) Draft Labeling
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/s/
____________________
Chien-Hua Niu
7/10/01 02:38:56 PM
CHEMIST

Dale Koble
7/10/01 02:46:27 PM
CHEMIST
FOOD and DRUG ADMINISTRATION  
CENTER of DRUG EVALUATION and RESEARCH  
DIVISION OF ANESTHETICS, CRITICAL CARE and ADDICTION  
DRUG PRODUCTS (DACCADP)  
HFD-170  

NDA:21-060  
CHEMISTRY REVIEW # 2  
REVIEW DATE: 14-MAY-2001  

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NAME & ADDRESS OF APPLICANT:  
Elan Pharmaceuticals  
Attn.: Linda B. Fradkin  
800 Gateway Blvd.  
Director, Regulatory Affairs  
South San Francisco, CA 94080  
tel.: 650-614-1053 or 800-435-5108

DRUG PRODUCT NAME  
Proprietary: Pivia  
Nonproprietary/USAN: ziconotide  
Code Name/#:  
Chem.Type/Ther.Class: 1 P

PHARMACOL.CATEGORY/INDICATION:  
Ziconotide is a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels.

DOSAGE FORM: Injection

STRENGTHS:  
100 µg/mL,  
1 mL fill in 2 mL vial,  
2 mL fill in 2 mL vial  
5 mL fill in 5 mL vial

ROUTE OF ADMINISTRATION: intrathecally

DISPENSED: X Rx ___ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

C K G K G A K C S R L M Y D C T G S C R S G K C amide

1 8 15 16 20 25

Molecular formula: \( C_{102}H_{172}N_{36}O_{32}S_7 \)

Molecular Weight: 2639.18

Chemical Name: 1) \( \omega \)-conotoxin MVIIA

2) L-cysteinyll-L-lysylglycyl-L-lysylglycyl-L-alanyl-
L-lysyl-L-cysteinyll-L-seryl-L-arginyl-L-leucyl-
L-methionyl-L-tyrosyl-L-\( \alpha \)-aspartyl-L-cysteinyll-
L-cysteinyll-L-threonyllglycyl-L-seryl-L-cysteinyll-
L-arginyl-L-serglycyl-L-lysylcysteinamide cyclic
(1\( \rightarrow \)16), (8\( \rightarrow \)20), (15\( \rightarrow \)25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: \( \omega \)-conopeptide MVIIA; conotoxin MVIIA; \( \omega \)-CTX
MVIIA; \( \omega \)-CmTx MVIIA; \( \omega \)-CmTx; \( \omega \)-CmTX; MVIIA

CAS Registry Number: 107452-89-1

Code Number: SNX-111
CONCLUSIONS & RECOMMENDATIONS:
This application is approvable from the chemistry standpoint. The comments and deficiencies listed in the Draft Letter must be conveyed to the Applicant.

CC:
NDA 20-060
HFD-170/Division File
HFD-170/MTheodorakis
HFD-170/DKoble
HFD-170/LGovernale
R/D Init. By
File name

/\$

Michael C. Theodorakis, Ph.D.
Senior Review Chemist

/\$

Dale L. Koble, Ph.D.
Chemistry Team Leader
**SPOTS:**
Not applicable. This is a synthetic peptide.

**SUPPORTING DOCUMENTS:**

<table>
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**RELATED DOCUMENTS**

IND 45,718 Ziconotide Elan Open,
**CONSULTS:**

a. A consult review request was issued to CDRH on 5/7/2001 concerning issues with the infusion pumps. See CDRH memorandum dated June 27, 2001 by Patricia Cricenti, Branch Chief, GHDB, DDIGD, CDRH, HFZ-480. The consult provided clarification on regulatory issues related to the infusion pumps and catheters.

b. A microbiology consult was completed on May 22, 2001. See Microbiology Review #4. It concluded that the manufacturing process was approvable.

c. A consult review of the 2D-NMR process for structure verification was completed by Dr. Niu on July 10, 2001. Dr. Niu determined that the two acceptance criteria proposed by the sponsor were acceptable when the method is used for lot to lot release test of bulk ziconotide.

**COMMENTS:**

1. Ziconotide preservative free, is an intrathecal formulation for the treatment of management of severe, chronic pain for patients for whom intraspinal analgesic therapy is clinically indicated. Ziconotide belongs to a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels. The maximum daily dose for ziconotide is 57.6 μg calculated on the basis of an infusion rate of 2.4 μg/h over a 24 hour period. See page 90, Volume 1.2.

2. Chemistry Review #2 is concerned with the Applicant’s responses to the Agency’s Approvable and Discipline Review

3. The 1, 2, and 5 mL fills are manufactured at

4. Three mechanisms lead to the decrease of ziconotide concentration in Medronic Synchromed Infusion systems (pumps) which were not previously exposed to ziconotide solutions (ziconotide naïve). These were adsorption, dilution due to pump's dead volume, and chemical degradation. The amount of ziconotide lost due to adsorption is approximately — The amount lost due to dilution in the — volume between the reservoir and the catheter ranged from — . The amount lost due to degradation — The refilling instructions in the labeling were revised.

5. The ziconotide was stable and retained its biological activity in the pump's — reservoir for —

6. All manufacturing and quality control facilities for this NDA were acceptable to Compliance as of April 2, 2001.

7. The 2D-NMR test procedure — was selected as method for assuring the activity of the drug substance on lot-to-lot release.

8. No consult review is pending.

9. No DMF reviews are pending.

10. The brand name Prialt was approved by Office of Post-Marketing Drug Risk Assessment.

11. The stability data support the Applicant’s request for an initial — expiration dating period for the 1 mL and 2 mL presentations, and a — expiration dating period for the 5 mL presentation.

12. The regulatory specifications for acceptance of the drug product should be revised to include total impurities and
individual limits for the impurities being monitored.

13.

14. Methods validation is in progress.

15. Labeling comments are included on page 44 of this review. They should be considered when labeling is reviewed in the next cycle.

16. The deficiencies listed in the draft latter should be conveyed to the Applicant.
39 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

☐ § 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/
----------------------
Laura Governale
6/27/01 05:03:14 PM
CSO
consult scanned in and signed for Pat Cricenti
3 Page(s) Withheld

☑️ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
Date       June 23, 2000

From       Steven R. Koepke,
Deputy Director, Division of New Drug Chemistry II,
Office of New Drug Chemistry

Subject    NDA 20-060
Ziconotide Injection
Elan Pharmaceuticals

Ziconotide, a synthetic 25 amino acid peptide is formulated as a preservative free solution for intrathecal use. The peptide has three disulfide bridges that are required for biological activity. The Firm has not submitted a choice of a release test that would ensure this activity. The possible acceptable choices include 2D-nmr,

The drug product, Ziconotide Injection is a sterile aqueous solution that contains 100μg/mL of ziconotide free base formulated as the acetate salt and contains L-methionine. Ziconotide has been shown to be stable for at least 24 months at the recommended storage temperature of 2-8°C for the 5 sizes. There are limited stability data for the 1 and 2 mL sizes.

Ziconotide Injection has been shown to be compatible with suitable pumps and catheters. There is however a difference in the behavior in a naïve pump versus a pump that was previous exposed to drug product. At lower concentrations 25 μg/mL, the concentration of the drug product decreased below the labeled amount lower limit in 2 and 14 days respectively. This raises concerns about a possible effect on the efficacy of the drug product under these conditions.

Overall CMC recommendation: There are remaining CMC deficiencies as of CMC review #1 and the overall recommendation from Compliance is to withhold approval. We concur with the overall recommendation of Approvable.

Environmental assessment: Categorical exclusion was claimed (see CMC review #1) – adequate.
Microbiology: Recommended for Not Approval April 18, 2000
Facility Inspections: Withhold 21-June-2000
Labeling: The established name on the labeling is unacceptable. The established name should read in order to meet USP nomenclature for injection dosage form designation (USP 24 <1>). See also comments in CMC review #1.
Application: NDA 21060/000
Stamp: 28-DEC-1999
Regulatory Due: 28-JUN-2000
Applicant: ELAN PHARMS
Priority: 170
Org Code:

Action Goal:
District Goal: 29-APR-2000
Brand Name: ZICONOTIDE 100MCG/ML
1/2/5/10ML
Estab. Name:
Generic Name: ZICONOTIDE 100MCG/ML
1/2/5/10ML
Dosage Form: (INJECTION)
Strength: 0.1 MG/ML

Application Comment: ZICONOTIDE IS A SYNTHETIC 25 AMINO ACID POLYBASIC PEPTIDE (on 24-NOV-1999 by M. THEODORAKIS (HFD-170) 301-827-7425)

FDA Contacts: N. CHAMBERLIN (HFD-023) 301-827-6768 , Project Manager
M. THEODORAKIS (HFD-170) 301-827-7425 , Review Chemist
A. D SA (HFD-170) 301-827-7443 , Team Leader

Overall Recommendation: WITHHOLD on 21-JUN-2000 by S. FERGUSON (HFD-324) 301-827-0062

Establishment:

DMF No:
Responsibilities:
Profile:
Estab. Comment:

AADA:
OAI Status: NONE

(on 24-NOV-1999 by M. THEODORAKIS (HFD-170) 301-827-7425)

Milestone Name Date Req. Type Insp. Date Decision & Reason Creator
SUBMITTED TO OC 24-NOV-1999 THEODORAKI:
SUBMITTED TO DO 26-NOV-1999 10D ADAMSS
ASSIGNED INSPECTION '06-DEC-1999 PS KRODEN
INSPECTION SCHEDULED 06-DEC-1999 31-JAN-2000 KRODEN

A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED AT THE FIRM COVERING THIS APPLICATION. NO FDA-483 WAS ISSUED AND THE INSPECTION IS CLASSIFIED AS NAI. BASED ON THE INSPECTIONAL FINDINGS, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

DO RECOMMENDATION 25-JAN-2000 ACCEPTABLE KRODEN INSPECTION

A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED AT THIS FACILITY COVERING THIS APPLICATION. NO FDA-483 WAS ISSUED AND THE INSPECTION IS CLASSIFIED NAI. BASED ON THE INSPECTIONAL FINDINGS, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION 28-JAN-2000 ACCEPTABLE FERGUSONS DISTRICT RECOMMENDATION

Establishment

DMF No:
Responsibilities:
Profile:
OAI Status: NONE
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**A GMP/Pre-Approval Inspection was performed on 12/1/98 (NO 483 Issued) and on 5/24/99 a GLP Inspection was performed (NO 483 Issued).**

**OC Recommendation** 21-Jan-2000  
**Acceptable**  
**Fergusons**  
**Strict Recommendation**

### Establishment Details

**Establishment:**

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### DMF No.

#### Responsibilities:

#### Profile:

#### Estab. Comment:

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#### Profile:

#### Estab. Comment:

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**OC Recommendation** 26-Nov-1999  
**Acceptable**  
**Based on Profile**

### Establishment Details

**Establishment:**

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### DMF No.

#### Responsibilities

#### Profile:

#### Estab. Comment:

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**OC Recommendation** 26-Nov-1999  
**Acceptable**  
**Based on Profile**
A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED WITH RESPECT TO THIS APPLICATION. THE INSPECTION WAS CLASSIFIED AS OAI, THE VIOLATIVE STATUS IS NOT RELATED TO THE OAI. CGMP DEVIATIONS WERE NOTED ON THE FDA-483 REGARDING THIS PRODUCT. HOWEVER, THE FIRM CORRECTED THE DEVIATIONS AND IMPLEMENTED THE CORRECTIONS PRIOR TO THE CONCLUSION OF THE INSPECTION. BASED ON THIS FACT, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

DO RECOMMENDATION 22-FEB-2000 ACCEPTABLE KRODEN INSPECTION

A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED WITH RESPECT TO THIS APPLICATION. THE INSPECTION IS CLASSIFIED AS OAI, HOWEVER THE OAI VIOLATIONS DO NOT APPLY TO THIS PRODUCT. DEVIATIONS WERE NOTED ON THE FDA-483 FOR THE BUT DO NOT WARRANT WITHHOLDING OF THE APPLICATION. CORRECTIONS TO THE DEVIATIONS WERE VERIFIED AND IMPLEMENTED PRIOR TO THE CONCLUSION OF THE INSPECTION. BASED ON THIS FACT, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION 23-FEB-2000 ACCEPTABLE FERGUSONS DISTRICT RECOMMENDATION

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RECOMMEND APPROVAL BASED ON 9-20-1999 INSPECTION

OC RECOMMENDATION 24-APR-2000 ACCEPTABLE DAMBROGIOJ DISTRICT RECOMMENDATION
I have reviewed the information that Medtronics has submitted to CDER's deficiency letter dated February 14, 2000. This information was submitted to as Amendment 10. Also included was the 4 month safety update to NDA 21-060. This information will be submitted as an amendment to PMA (which is to add ziconotide to the pump indications).

FDA CDER Questions

1. In regard to the SynchroMed Infusion Pump delivery system for ziconotide, please provide additional documentation which would demonstrate the specifications for drug delivery accuracy over the recommended period of use.

The SynchroMed and SynchroMed EL Infusion pumping mechanism has a fluid specification. In the original approval for the pump on March 14, 1988, subsequent amendments Medtronics has provided flow rate accuracy data.

2. "...you will need to include documentation to show that your SynchroMed Pumps will continue to meet the flow accuracy specifications when delivering ziconotide." To further satisfy the question of flow accuracy which Medtronics conducts using normal saline, a test report from Eran showing the viscosity of ziconotide at various concentrations is virtually identical to water, Sodium Chloride Injection, USP, and drug product vehicle (placebo). Viscosity Testing was conducted at

Conclusion:

From a device perspective Medtronic's response's regarding flow rate accuracy is satisfactory in that they provided the data to demonstrate how the pump meets the performance specification and provided data to show that the viscosity of ziconotide is similar to normal saline which is the liquid Medtronics uses to evaluate flow accuracy in the pumps.
DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

DATE:       June 5, 2000
FROM:       Albinus M. D'Sa, Ph.D.
            Team Leader, Division of New Drug Chemistry II, HFD-820
TO:         NDA 21-060
SUBJECT:    Chemistry Team Leader's Memo-Overview
THRU:       Steven Koepke, Ph.D.
            Deputy Director, Division of New Drug Chemistry II, HFD-820

This overview is provided at the request of Cynthia McCormick, M. D., Division
Director, Division of Anesthetics, Critical Care and Addiction Drug Products, HFD-170.
The purpose of this memo is to summarize the issues that are involved in the CMC
review of the new molecular entity ziconotide and to provide a status report on the issues
that are still pending for the CMC part of this application.

Michael Theodorakis, Ph.D., reviewed the CMC section. The consults included: Chien
Hua Niu, Ph.D. (for the peptide drug substance), and Paul Stinavage, Ph.D.
(microbiology). Hung Trinh, CDRH, reviewed the infusion pump.

Ziconotide injection, is a preservative free formulation that is intended for intrathecal use.
The drug substance, ziconotide, a new molecular entity, is a synthetic 25- amino acid
peptide with three intra-strand disulfide bridges involving the six cysteine residues. The
molecule is equivalent in structure to omega conotoxin MVIIA that is present in the
venom of marine snails of the genus Conus. This new peptide belongs to a new class of
calcium channel blockers that selectively block neuronal N-type, voltage-sensitive,
calcium channels.

**Drug Substance:**
The drug substance is synthesized, isolated, purified, tested, and packaged by
The review issues addressed pertained to the position of the disulfide bridges, the
determination of the structure of the bulk drug substance used in the clinical trails, and
comparing it to what was already reported in the literature. The position of the disulfide
bridges was addressed by enzymatic digestion followed by sequencing of the peptide and
by two-dimensional NMR studies. The NMR data provided the inter-atomic
distances. The applicant then used computer molecular modeling to define three-
dimensional conformational structure that agreed with the NOE data. Thus the structure
of the peptide was adequately compared to the literature data.

The applicant (Elan Pharmaceuticals) is responsible for the reference standard. The
identity and purity of the primary drug substance reference standard was demonstrated by
peptide mapping and amino acid sequencing, amino acid composition, disulfide bridge

The purity and stability of the working reference standard was demonstrated and it is
acceptable.

The regulatory specifications for release of the drug substance includes a binding assay.
The combination of the binding assay and a test to determine the presence and location of
the disulfide bonds (2D-NMR, or peptide mapping with amino acid analysis, or
enzymatic digestion of the peptide followed by sequencing or the bioassay) would be
considered to be a measure of the activity of the drug substance for lot to lot release.

Thus with regard to the drug substance the following are pending:

a. Review of the bioassay data,
b. A minor clarification from the DMF holder regarding a discrepancy found
   in the certificate of analysis for the drug substance,
c. Selection of one of the four aforementioned methods to be used for lot-to-
   lot release of the drug substance.

**Drug Product:**
The drug product, Ziconotide Injection, is a sterile, aqueous solution for intrathecal
infusion. It contains 0.1 mg/mL of ziconotide free base, formulated as the acetate salt in
saline at pH 4.0-5.0. The formulation consists of ziconotide acetate HCl (the active
ingredient), sodium chloride (tonicity adjusting agent), L-methionine water
for injection.
It is supplied in single-dose, 2 mL (containing 1 and 2 mL fills), 5 mL (5 mL fill), vials.

The 1, 2, and 5 mL fills are manufactured at

In general, the manufacturing process at both manufacturing sites is similar to each other. The quality of the drug product manufactured by both facilities is satisfactory as corroborated by the release and stability testing data of the drug product.

Ziconotide injection solution has been shown, to be stable for at least 24 months at the recommended storage temperature (2-8°C) for the 5 mL sizes. Limited stability data is available for the 1 mL and the 2 mL fill lots. The product should be granted 24-months expiration dating for the 5 mL fills and a maximum of expiry for the 1 and 2 mL fills.

Ziconotide injection, diluted in 0.9% sodium chloride injection, USP, is compatible with suitable implantable or extra corporeal pumps and catheters. There is a difference in the stability of the drug based on the concentration of the solution and whether or not the pump has been previously been exposed to ziconotide (page 65 of the Chemistry Review). At concentrations 25 μg/mL in pumps that have never been exposed to the drug (naive), the concentration of the drug decreased below the labeled amount lower limit in 2 and 14 days respectively. For concentrations of 100 μg/mL, the drug concentration remained stable for over under simulated use conditions. These data support the applicant’s table in the package insert regarding the initial use and refill of the SynchroMed infusion system.

Nine other drug products, which are administered intrathecally, were tested for compatibility with the ziconotide injection. All admixtures tested were clear with no visible precipitation and were considered to be compatible with the ziconotide injection.
The Applicant claimed a categorical exclusion from submission of an Environmental Assessment for ziconotide. This claim is acceptable because ziconotide is a synthetic peptide consisting only of naturally occurring amino acids. The Applicant also provided calculations of expected introduction concentration of the active moiety into the aquatic environment. The drug concentration will not exceed the In this worst case scenario, the exposure to aquatic environment is estimated to per year for years.

**Inspections:**
All but one facility were inspected were found acceptable. The contract facility that performed the testing for the bulk substance for was not ready for inspection. The Applicant has been informed about this issue. This is an approvability issue.

**Microbiology Consults:**
Dr. Paul Stinavage has recommended non-approval of this application because there is still a remaining issue as to whether or not the non-preserved injection solution in the pump will support microbial growth when it is implanted in patients for 30 days.

**Device Consult:**
The Device was consulted to CDRH. The reviewer, Hung Trinh, requested information to demonstrate that the pump was accurately able to deliver the drug for the duration of use, 30 days. The Applicant's response is being currently reviewed. All other issues have been adequately addressed.

**Methods Validation:**
The FDA labs are currently verifying the methods and so the approval letter should contain the standard paragraph used in decision letters.

**Summary:**
A test must be included in the regulatory specifications and testing procedures for lot-to-lot release of the drug substance that is an indicator of the biological activity of the molecule.

The ziconotide injection samples placed on stability must be tested to determine whether they meet the binding assay specification. The post approval stability protocol must be revised to include monitoring of the binding assay.

Data must be submitted to demonstrate whether or not the non-preserved injection solution in the pump will support microbial growth when it is implanted in patients for 30 days.

The inspection for the facility that performs the testing for the bulk substance for is pending due to the fact that the firm is not ready to be inspected.
CC List:
NDA 20-060
HFD-170/Division file:
HFD-170/CMcCormick/BRappaport/LGovernale
HFD-170/MTedorakis/AD'Sa
HFD-510/CNiu
HFD-820/SKoepke/JGibbs
HFD-800/YChiu
FOOD and DRUG ADMINISTRATION
CENTER of DRUG EVALUATION and RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE and ADDICTION
DRUG PRODUCTS (DACCDP)
HFD-170

NDA: 21-060

CHEMISTRY REVIEW #: 1
REVIEW DATE: 22-MAY-2000

SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE
--- | --- | --- | ---
ORIGINAL | 10-OCT-99 | 02-NOV-99 | 02-NOV-99
AMENDMENT [BC] | 12-JAN-00 | 13-JAN-00 |
CORRESPONDENCE | 04-FEB-00 |
AMENDMENT [BC] | 10-MAR-00 | 13-MAR-00 |
AMENDMENT [BC] | 22-MAR-00 | 23-MAR-00 |
AMENDMENT [BC] | 07-APR-00 | 10-APR-00 |
AMENDMENT [SU] | 24-APR-00 | 25-APR-00 |
AMENDMENT [BC] | 01-MAY-00 | 02-MAY-00 |
AMENDMENT [BC] | 11-MAY-00 | 12-MAY-00 |

NAME & ADDRESS OF APPLICANT:
Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attn.: Linda B. Fradkin
Director, Regulatory Affairs
tel.: 650-614-1053 or 800-435-5108

DRUG PRODUCT NAME
Proprietary: 
Nonproprietary/USAN: Ziconotide

Code Name/#: 
Chem. Type/Ther. Class: 1 P

PHARMACOL. CATEGORY/INDICATION:
Ziconotide is a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels.

DOSAGE FORM: Injection

STRENGTHS: 100 μg/mL,
1 mL fill in 2 mL vial,
2 mL fill in 2 mL vial
5 mL fill in 5 mL vial

ROUTE OF ADMINISTRATION: intrathecally

DISPENSED: X Rx ___ OTC
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

C K G K G A K C S R L M Y D C C T G S C R S G K C amide

1 8 15 16 20 25

Molecular formula: \( \text{C}_{102}\text{H}_{172}\text{N}_{36}\text{O}_{32}\text{S}_{7} \)

Molecular Weight: 2639.18

Chemical Name: 1) \( \omega \)-conotoxin MVIIA

2) L-cysteinyl-L-lysylglycyl-L-lysylglycyl-L-alanyl-
   L-lysyl-L-cysteinyl-L-seryl-L-arginyll-Leucyl-
   L-methionyl-L-tyrosyl-L-\( \alpha \)-aspartyl-L-cysteinyl-
   L-cysteinyl-L-threonylglucyl-L-seryl-L-cysteinyl-
   L-arginyl-L-serylglucyl-L-lysylcysteaminamide cyclic
   (1\( \rightarrow \)16), (8\( \rightarrow \)20), (15\( \rightarrow \)25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: \( \omega \)-conopeptide MVIIA; conotoxin MVIIA; \( \omega \)-CTX
           MVIIA; \( \omega \)-CmTx MVIIA; \( \omega \)-CmTx; \( \omega \)-CmTX; MVIIA

CAS Registry Number: 107452-89-1

Code Number: SNX-111
CONCLUSIONS & RECOMMENDATIONS:

a. Dr. Niu is currently reviewing the response to his review of DMF.

b. The validation of the analytical methods is in progress.

c. Inspection of all but one facility has been completed. One contract facility that was conducting the _____ test for _____ refused to be inspected. The Applicant will probably withdraw this contract facility and the responsibility for performing the _____ will be transferred to _____ which is the manufacturer of the drug substance, ziconotide. The Applicant has been informed about this issue.

d. All chemistry related consult reviews, namely the microbiology and tradename reviews, have been completed. Response to deficiencies identified in Microbiology Review #2 is still awaited.

e. This application is approvable from the chemistry standpoint. The comments and deficiencies listed in the Draft Letter must be conveyed to the Applicant.

CC:
NDA 20-060
HFD-170/Division File
HFD-170/MTheodorakis
HFD-170/ADSa
HFD-170/L.Governale
R/D Init. By
File name

Michael C. Theodorakis, Ph.D.
Senior Review Chemist

Albinus M. D'Sa, Ph.D.
Chemistry Team Leader
**SPOTS:**
Not applicable. This is a synthetic peptide.

**SUPPORTING DOCUMENTS:**

<table>
<thead>
<tr>
<th>Type/Number</th>
<th>Subject</th>
<th>Holder</th>
<th>Status</th>
<th>Review Date</th>
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<tr>
<td>IND 45,718</td>
<td>Ziconotide Injection</td>
<td>Elan Pharmaceuticals</td>
<td>Open, reviewed by M.C. Theodorakis</td>
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<td>DMF Type III</td>
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<td>Reviewed by C.J.Sun, LOA dated 4/24/98</td>
<td>12/17/92</td>
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<td>DMF Type II</td>
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<td>Reviewed by Drs. Niu and Guzewska, LOA dated 10/29/99</td>
<td>2/28/00</td>
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<td>CADD-Micro Ambulatory</td>
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<td>LOA dated 9/7/99</td>
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CONSULTS:
All chemistry initiated consult reviews have been completed.

a. Consult review for DMF Type II, for ziconotide drug substance has been completed. See Chemistry Review by Dr. Chen-Hua Niu, (HFD-510), dated 2/28/00. The deficiencies were conveyed to the Applicant (see Agency letter dated 3/21/00). Also see Chemistry Review by Marila Guzewaska, (HFD-120), dated 5/10/96.

b. Two consult microbiology reviews were completed by Dr. Paul Stinavage. See Microbiology Reviews dated 1/13/00 and 4/18/00. In his first review, he found it acceptable and recommended approval pending resolution of microbiology concerns. Subsequently, Dr. Stinavage in his Microbiology Review #2, dated 4/18/2000, reversed his recommendation to not approvable.

COMMENTS:
1. Ziconotide injection, preservative free, is an intrathecal formulation for the treatment of management of severe, chronic pain for patients for whom intraspinal analgesic therapy is clinically indicated. Ziconotide belongs to a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels. The maximum daily dose for ziconotide is 57.6 µg calculated on the basis of an infusion rate of 2.4 µg/h over a 24 hour period. See page 90, Volume 1.2.

2. NDA 21-060 contains reports bearing the name of Elan Pharmaceuticals and Neurex Corporation. After completion of a large part of the ziconotide development program, Neurex Corporation was acquired by Elan Corporation plc., (August
1998). Reports completed before that date bear the Neurex name. All subsequent reports bear the Elan name.

3. The drug substance, ziconotide, is synthesized, isolated, purified, tested, and packaged by [ ]
   It is a well-characterized peptide that is manufactured by peptide synthesis to a purity and potency suitable for pharmaceutical use. The drug substance is stable for at least 24 months when stored desiccated at the recommended storage condition of [See DMF]
   This DMF was recently reviewed by Dr. Niu (HFD-510) and by Dr. Guzewska (HFD-120).

4. Ziconotide injection contains 0.1 mg/mL of ziconotide free base formulated as the acetate salt in saline at pH 4.0-5.0. It also contains L-methionine [ ]. It is supplied in single-dose, 2 mL (containing 1 and 2 mL fills), 5 mL, [ ] vials

5. The identity and purity of the primary reference standard, Lot NUY001, was demonstrated by peptide mapping and amino acid sequencing, amino acid composition, disulfide bridge [ ]
   The results showed that lot No. NUY001 has a purity level which makes it suitable for its use as the primary reference standard. Also, the purity and stability of the working reference standard was demonstrated and it is acceptable.

6. Ziconotide injection has been shown, to be stable for at least 24 months at the recommended storage temperature (2-8°C) for the 5 mL size, [Ziconotide injection, diluted in 0.9% sodium chloride injection, USP, is compatible with suitable implantable or extra corporeal pumps and catheters.

7. The drug product, Ziconotide Injection, is a sterile, aqueous solution for intrathecal infusion. The formulation consists only of ziconotide acetate HCl (the active ingredient), sodium chloride (tonicity adjusting agent), L-methionine (antioxidant), water for injection (vehicle),

8. The 1, 2, and 5 mL fills are manufactured at
9. In general, the manufacturing process at both manufacturing sites is similar to each other. The most significant differences are:
   a. 
   b. 
   c. 

The quality of the drug product manufactured by either process is satisfactory as corroborated by the release and stability testing data of the drug product.

10. The typical batch size for drug product manufactured by the

11. The primary containers for the drug product are 2, 5,
14.

15. The ziconotide injection was compatible with SIMS-Delttec CADD-Micro external pumps and Medtronic SynchroMed and SynchroMed EL implantable pumps.
16. In the implantable SynchroMed pumps, there was a much more appreciable drop in the concentration of ziconotide peptide. The peptide loss was exacerbated by dilution to low concentrations of ziconotide as well as the use of ziconotide-naive pumps or saline diluent. Ziconotide

17.

18.

19. The placebo drug product was an isotonic solution of sodium
chloride and methionine. It is an injection. See page 82, Volume 1.2. It is adequate.

20. In accordance with 21 CFR 25.15(d), the Applicant claimed a categorical exclusion from submission of an Environmental Assessment for ziconotide. Because ziconotide is a synthetic peptide consisting only of naturally occurring amino acids, it qualifies for the Environmental Assessment exclusion under 21 CFR 25.31(c). The Applicant provided calculations proving that the expected introduction concentration of the active moiety into the aquatic environment will not exceed the In this worst case scenario, the exposure to aquatic environment is estimated to per year for years.
70 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling
____ Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling