

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-060

CHEMISTRY REVIEW(S)

NDA 21-21-060

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 tonicity. 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 Microdiffusion 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
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**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:

Prialt

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:

STRENGTHS:

25 µg/mL, 20 mL fill in 20 mL vial,

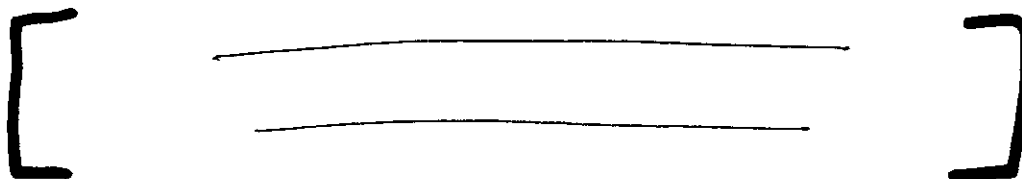
100 µg/mL, 1 mL fill in 2 mL vial,
2 mL fill in 2 mL vial
5 mL fill in 5 mL vial

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) ω -conotoxin MVIIA

2) L-cysteinyl-L-lysylglycyl-L-lysylglycyl-L-alanyl-L-lysyl-L-cysteinyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L- α -aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysylcysteinamide cyclic (1 \rightarrow 16), (8 \rightarrow 20), (15 \rightarrow 25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: ω -conoptide MVIIA; conotoxin MVIIA; ω -CTX MVIIA; ω -CmTx MVIIA; ω -CmTx; ω -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 (_____), L-methionine _____, 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:

Type/Number	Subject	Holder	Status	Review Date
DMF Type III			Reviewed by C.J.Sun LOA dated 4/24/98 Adequate	12/17/92
DMF Type III			Reviewed by C.J.Sun, LOA dated 4/27/98 Adequate	12/17/92
DMF Type III			Reviewed by R.H. Seevers; and Al Hakim; LOA dated 4/3/96 Adequate	3/11/98 9/12/96
DMF Type III			Reviewed by R.K. Kasliwal, LOA 6/22/98 Adequate	9/22/99
DMF Type II	Ziconotide drug substance		Reviewed by Drs. Niu and Guzewska, LOA dated 10/29/99 Adequate	2/28/00 5/10/96

RELATED DOCUMENTS

IND 45,718	Ziconotide Injection	Elan Pharmaceuticals	Open, reviewed by M.C. Theodorakis	
—	CADD-Micro Ambulatory Infusion Pump	[] []	LOA dated 9/7/99	
—	— —		LOA dated 9/7/99	
Device Drug Master File	SynchroMed Infusion System		LOA dated 2/4/99	

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.

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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 µg/mL strength injection when stored at 2°-8°C. It is recommended that the Applicant's request be granted.
9. For the 25 µg/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 µg/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 REF017 and REF018 respectively. REF017 replaced the old primary standard NUY001. Secondary standard lot REF018 replaced the old secondary lot REF007. 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.

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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
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Ravi se also Addendum to Chemistry Review #3

Ravi Harapanhalli
12/12/04 09:01:22 PM
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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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) [REDACTED]

PRIALT (ziconotide) [REDACTED] 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, [REDACTED]. 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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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1350 Piccard Drive
Rockville, MD 20850

June 25, 2001

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

SUBJ: Marketing experience with Medtronic Synchromed 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 Maude 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 Synchromed and Synchromed 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).

Device Problem Code

Rank	Count	%	Device Problem Code
9	51	2.03	1502 Pump, failure to
27	9	0.36	1120 Contamination
27	9	0.36	1384 Mechanical failure
29	7	0.28	1065 Blockage
31	5	0.20	1094 Clogged
34	2	0.04	1461 Plugged

Patient Problem Code			
Rank	Count	%	Patient Problem Code
4	173	5.16	1903 Infection
14	55	1.64	1735 Infection bacterial
17	43	1.28	2389 Meningitis
25	24	0.72	2058 Staph aureus
40	3	0.09	1968 muscular rigidity
42	1	0.03	2332 Blockage

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 Synchronmed 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.

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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
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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

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT BC	28-DEC-00	29-DEC-00	
AMENDMENT AC	26-JAN-01	29-JAN-01	31-JAN-01
AMENDMENT BZ	20-FEB-01	22-FEB-01	
AMENDMENT BZ	13-MAR-01		
Correspondence	20-MAR-01	21-MAR-01	
Correspondence	29-MAR-01	02-APR-01	

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

<u>Proprietary:</u>	Prialt
<u>Nonproprietary/USAN:</u>	ziconotide
<u>Code Name/#:</u>	
<u>Chem.Type/Ther.Class:</u>	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:

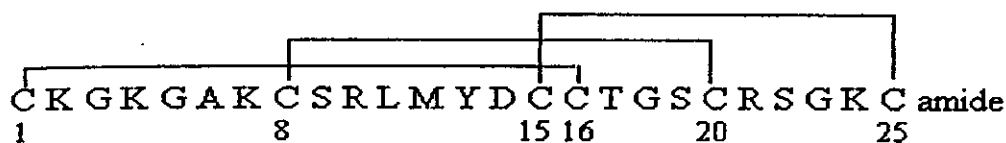
100 µg/mL,	1 mL fill in 2 mL vial,
	2 mL fill in 2 mL vial
	5 mL fill in 5 mL vial

ROUTE OF ADMINISTRATION:

intrathecally

DISPENSED:

X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Molecular formula: $C_{102}H_{172}N_{36}O_{32}S_7$

Molecular Weight: 2639.18

Chemical Name: 1) ω-conotoxin MVIIA

2) L-cysteinyl-L-lysylglycyl-L-lysylglycyl-L-alanyl-L-lysyl-L-cysteinyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L-α-aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysylcysteinamide cyclic (1→16), (8→20), (15→25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: ω-conopeptide MVIIA; conotoxin MVIIA; ω-CTX MVIIA; ω-CmTx MVIIA; ω-CmTx; ω-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

/S/

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

/S/

Dale L. Koble, Ph.D.
Chemistry Team Leader

SPOTS:









Not applicable. This is a synthetic peptide.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
DMF — Type III	[REDACTED]	[REDACTED]	Reviewed by C.J.Sun LOA dated 4/24/98 Adequate	12/17/92
DMF — Type III			Reviewed by C.J.Sun, LOA dated 4/27/98 Adequate	12/17/92
DMF — Type III			Reviewed by R.H. Seevers; and Al Hakim; LOA dated 4/3/96 Adequate	3/11/98 9/12/96
DMF — Type III			Reviewed by R.K. Kasliwal, LOA 6/22/98 Adequate	9/22/99
DMF — Type II	Ziconotide drug substance	[REDACTED]	Reviewed by Drs. Niu and Guzewska, LOA dated 10/29/99 Adequate	2/28/00 5/10/96

RELATED DOCUMENTS


IND 45,718	Ziconotide	Elan	Open,	
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		Pharmaceut icals	reviewed by M.C. Theodorakis	
510(k) 	CADD-Micro Ambulatory Infusion Pump		LOA dated 9/7/99	
			LOA dated 9/7/99	
	SynchroMed Infusion System		LOA dated 2/4/99	

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

Letters both dated June 27, 2000.

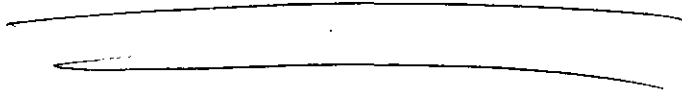
3. The 1, 2, and 5 mL fills are manufactured at
[_____]
4. Three mechanisms lead to the decrease of ziconotide concentration in Medronic SynchroMed Infusion systems (pumps) which were not previously exposed to ziconotide solutions (ziconotide naïve). These were adsorption, dilution due to pump's dead 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.

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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.

Appears This Way
On Original

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




DEPARTMENT OF HEALTH & HUMAN SERVICES


Public Health Service
Food and Drug Administration



Memorandum


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 100 µg/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

Tradename: Not Acceptable by OPDRA consult May 24, 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

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

1P
Priority: 170
Org Code:

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:

AADA:

Responsibilities:

Profile:

OAI Status: NONE

Estab. Comment:

(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
INSPECTION PERFORMED	25-JAN-2000		21-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:

AADA:

Responsibilities:

Profile:

OAI Status: NONE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-JAN-2000				THEODORAKI:
SUBMITTED TO DO	19-JAN-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	20-JAN-2000	GMP			BBARGO
DO RECOMMENDATION	20-JAN-2000			ACCEPTABLE	BBARGO
BASED ON FILE REVIEW					
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: _____

DMF No: _____

AADA: _____

Responsibilities: _____

Profile: _____

OAI Status: NONE

Estab. Comment: _____

(on 24-NOV-1999 by M. THEODORAKIS (HFD-

170) 301-827-7425)

PER S. KOEPKE AND C. SCHUMAKER, INV. REPORTED THAT FIRM NOT READY,
BUT FACILITY IS NOT _____ FOR SPONSOR. (on 21-JUN-
2000 by S. FERGUSON (HFD-324) 301-827-0062)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	24-NOV-1999				THEODORAKI:
SUBMITTED TO DO	26-NOV-1999	GMP			ADAMSS
ASSIGNED INSPECTION	03-JAN-2000	PS			EWEILAGE
OC RECOMMENDATION	21-JUN-2000			WITHHOLD	FERGUSONS
					FACILITY

Establishment: _____

DMF No: _____

AADA: _____

Responsibilities: _____

Profile: _____

OAI Status: NONE

Estab. Comment: _____

(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:
OC RECOMMENDATION	26-NOV-1999			ACCEPTABLE	ADAMSS
					BASED ON PROFILE

Establishment: _____

DMF No: _____

AADA: _____

Responsibilities: _____

Profile: _____

OAI Status: NONE

Estab. Comment: _____

827-7425)

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

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	24-NOV-1999				THEODORAKI:
SUBMITTED TO DO	26-NOV-1999	PS			ADAMSS
ASSIGNED INSPECTION	09-DEC-1999	PS			KRODEN
INSPECTION SCHEDULED	09-DEC-1999				KRODEN
INSPECTION PERFORMED	22-FEB-2000		16-FEB-2000		KRODEN

A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED WITH RESPECT TO THIS APPLICATION. WHILE THE INSPECTION WAS CLASSIFIED AS OAI, THE VIOLATIVE STATUS IS NOT RELATED ~~TO THE VIOLATIVE STATUS~~ T. 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 [REDACTED] 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	

Establishment:

I

DMF No: AADA:

Responsibilities

Profile: [REDACTED] UAL Status: NONE

Estab. Comment:

(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	PS			ADAMSS
DO RECOMMENDATION	20-APR-2000			ACCEPTABLE	WSHERER
				BASED ON FILE REVIEW	
				RECOMMEND APPROVAL BASED ON 9-20-1999 INSPECTION	
OC RECOMMENDATION	24-APR-2000			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Electronic Mail Message

Date: 6/6/00 9:56:36 AM
From: Cricenti, Patricia (PXC@CDRH.FDA.GOV)
To: McCormick, Cynthia G (MCCORMICKC@A1)
Cc: Governale, Laura A (GOVERNALEL@A1)
Subject: Ziconotide Device Issues

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 _____
ery specification _____
tions). 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 Elan 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. *Albinus D'Sa 6/6/00*
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. *SK 6/6/00*
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







[Handwritten signature area with large stylized letters L, T, and J]

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 trials, 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.

  
   f

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 _____ 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 _____ 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 at _____ that have never been exposed to the drug (naïve), 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 [REDACTED]. In this worst case scenario, the exposure to aquatic environment is estimated to [REDACTED] per year for [REDACTED] years.

Inspections:

All but one facility were inspected were found acceptable. The contract facility that performed the [REDACTED] testing for the bulk substance for [REDACTED] 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 these are 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 [REDACTED] testing for the bulk substance for [REDACTED] 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/MTheodorakis/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 (DACCADP)
HFD-170**

NDA:21-060

CHEMISTRY REVIEW #: 1

REVIEW DATE: 22-MAY-2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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: XXXXXXXXXX
Nonproprietary/USAN: ziconotide
Code Name/#:
Chem.Type/Ther.Class: 1 P

PHARMACOL.CATEGORY/INDICATION:

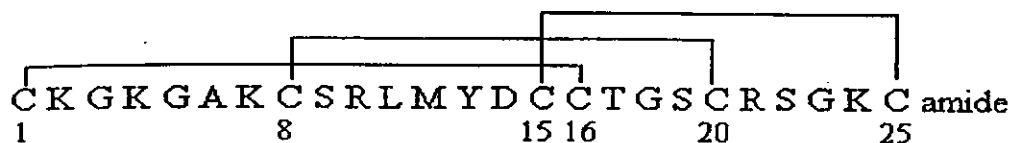
Ziconotide is a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive, calcium channels.

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
XXXXXXXXXX

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: 2639.18

Chemical Name: 1) ω-conotoxin MVIIA

2) L-cysteinyl-L-lysylglycyl-L-lysylglycyl-L-alanyl-L-lysyl-L-cysteinyl-L-seryl-L-arginyl-L-leucyl-L-methionyl-L-tyrosyl-L-α-aspartyl-L-cysteinyl-L-cysteinyl-L-threonylglycyl-L-seryl-L-cysteinyl-L-arginyl-L-serylglycyl-L-lysylcysteinamide cyclic (1→16), (8→20), (15→25)-tris(disulfide)

Generic name: USAN: ziconotide

Synonyms: ω-conopeptide MVIIA; conotoxin MVIIA; ω-CTX MVIIA; ω-CmTx MVIIA; ω-CmTx; ω-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 test 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

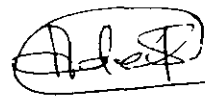
HFD-170/ADSa

HFD-170/LGovernale

R/D Init. By

File name


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





 006 5/29/00
Albinus M. D'Sa, Ph.D.
Chemistry Team Leader



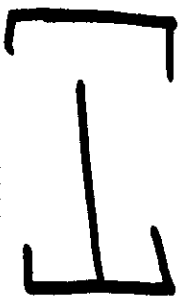
SK
6/6/00

SPOTS:

Not applicable. This is a synthetic peptide.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
IND 45,718	Ziconotide Injection	Elan Pharmaceuticals	Open, reviewed by M.C. Theodorakis	
DMF Type III			Reviewed by C.J. Sun LOA dated 4/24/98	12/17/92
DMF Type III			Reviewed by C.J. Sun, LOA dated 4/27/98	12/17/92
DMF Type III			Reviewed by R.H. Seevers; and Al Hakim; LOA dated 4/3/96	3/11/98 9/12/96
DMF Type III			Reviewed by R.K. Kasliwal, LOA 6/22/98	9/22/99
DMF Type II			Reviewed by Drs. Niu and Guzewska, LOA dated 10/29/99	2/28/00 5/10/96
	CADD-Micro Ambulatory Infusion Pump		LOA dated 9/7/99	


			LOA dated 9/7/99	
Device Drug Master File	SynchroMed Infusion System		LOA dated 2/4/99	

RELATED DOCUMENTS (if applicable):

NA

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 Guzewska, (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 [REDACTED]

It is a well-characterized peptide that is manufactured by [REDACTED] 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 [REDACTED]. See DMF [REDACTED]

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 [REDACTED]. It is supplied in single-dose, 2 mL (containing 1 and 2 mL fills), 5 mL, [REDACTED] vials [REDACTED]

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 [REDACTED]

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, [REDACTED]

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), [REDACTED]

8. The 1, 2, and 5 mL fills are manufactured at [REDACTED]

[_____]

9. In general, the manufacturing process at both manufacturing sites is similar to each other. The most significant differences are:

a. .

[

b.

c.

L

J

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

[

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

[

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12.

13.

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14.

15. The ziconotide injection was compatible with SIMS-Deltec
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-naïve 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.

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70 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

1 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling