CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ELAN PHARMACEUTICALS
NEW DRUG APPLICATION

ZICONOTIDE
ITEM13

13. PATENT INFORMATION

The undersigned declares that Patent Nos. 5,364,842, 5,795,864 and 5,859,186 cover the formulation, composition and/or method of use of ziconotide. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,364,842, which will expire on 30 December 2011, is a method of use patent that is assigned to Elan Pharmaceuticals, Inc. U.S. Patent No. 5,795,864, which will expire on 27 June 2015, is a drug formulation patent that is assigned to Elan Pharmaceuticals, Inc. U.S. U.S. Patent No. 5,859,186, which will expire on 30 December 2011, is a method of use patent that is assigned to Elan Pharmaceuticals, Inc. The original assignee for all of the aforementioned patents was Neurex Corporation. These patents were transferred to Elan Pharmaceuticals, Inc., on 14 August 1998. Refer to Table 13-1 for additional patent information.

Carl Battle

Feb. 10, 2004

Carl Battle

Date

Senior Vice President, Chief Patent Counsel

Elan Pharmaceuticals, Inc.

Table 13-1: Ziconotide Patent Information

Patent Number	Date Filed	Status	Date Issued	Assignee	Date Transferred	Assignee	Expiration Date	Patent Type
5,364,842	06/23/1993	Granted	11/15/1994	Neurex Corporation	8/14/1998	Elan Pharmaceuticals, Inc.	12/30/2011	Method of use of ziconotide (analgesia) in the absence of an opiate
5,795,864	06/27/1995	Granted	08/19/1998	Neurex Corporation	8/14/1998	Elan Pharmaceuticals, Inc	06/27/2015	Stable formulation
5,859,186	07/03/1996	Granted	01/12/1999	Neurex Corporation	8/14/1998	Elan Pharmaceuticals, Inc	12/30/2011	Method of use of ziconotide (analgesia, neuropathic pain) (method of producing analgesia; method of treating neuropathic pain)

ELAN PHARMACEUTICALS **ZICONOTIDE**

NEW DRUG APPLICATION **ITEM 13**

13. PATENT INFORMATION

The undersigned declares that Patent Nos. 5,364,842, 5,795,864, and 5,859,186 cover the formulation, composition and/or method of use of ziconotide. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,364,842, which will expire on 30 December 2011, is a method of use patent that is assigned to Elan Pharmaceuticals, Inc.
U.S. Patent No. 5,795,846, which will expire on 27 June 2015, is a drug formulation patent that is assigned to Elan Pharmaceuticals, Inc.
U.S. Patent No. 5,859,186, which will expire on 30 December 2011, is a method of use patent that is assigned to Elan Pharmaceuticals, Inc. The original assignee for all of the aforementioned patents was Neurex Corporation. The patents were transferred to Elan Pharmaceuticals, Inc., on 14 August 1998. Refer to Table 13-1 for additional patent information.

Jean Duvall — December 10, 1999

Jean Duvall — Date

Vice President, Intellectual Property
Elan Pharmaceuticals

Table 13-1: Ziconotide Patent Information

Patent Number	Date Filed	Status	Date Issued	Assignee	Date Transferred	Assignee	Expiration Date[a]	Patent Type
5,364,842	06/23/93	granted	11/15/94	Neurex Corp.	08/14/98	Elan Pharmaceuticals, Inc.	12/30/11	method of use of ziconotide (analgesia) in the absence of an opiate
5,795,864	06/27/95	granted	08/19/98	Neurex Corp.	08/14/98	Elan Pharmaceuticals, Inc.	06/27/15	stable formulation
5,859,186	07/03/96	granted	01/12/99	Neurex Corp.	08/14/98	Elan Pharmaceuticals, Inc.	12/30/11	method of use of ziconotide (analgesia, neuropathic pain) (method of producing analgesia; method of treating neuropathic pain)

[a] These dates are in the years 2011, 2015, and 2011, respectively.

ELAN PHARMACEUTICALS ZICONOTIDE

NEW DRUG APPLICATION ITEM 14

14. PATENT CERTIFICATION

In accordance with 21 CFR Part 314.50h (i) (ii), in the opinion and to the best knowledge of Elan Pharmaceuticals, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in the application were conducted or that claim a use of such drug or drugs. All investigations of this application were conducted by or for the applicant.

Jean Duvall

December 10, 1999

Jean Duvall

Date

Vice President, Intellectual Property
Elan Pharmaceuticals

Exclusivity Checklist:

Not applicable at this time.

EXCLUSIVITY SUMMARY FOR NDA # 21-060 SUPPL #_____

Trade Name Prialt Generic Name (ziconotide intrathecal infusion) (100mcg/mL in 1, 2 and 5 mL vials and 25 mcg/mL in 20 mL vials)

Applicant Name Elan Pharmaceuticals HFD #170

Approval Date If Known PDUFA Date December 28, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

[redacted]

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Sara Stradley Date: December 2, 2004
Title: Regulatory Project Manager

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
12/23/04 02:01:27 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-060 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: June 28, 2004 **Action Date:** PDUFA =December 28, 2004
Division goal = Dec. 23, 2004

HFD-170 **Trade and generic names/dosage form:** Prialt (ziconotide intrathecal infusion) (100mcg/mL in 1, 2 and 5 mL vials and 25 mcg/mL in 20 mL vials)

Applicant: Elan Pharmaceuticals **Therapeutic Class:** 1P

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: This new drug application provides for the use of Prialt (ziconotide intrathecal infusion) 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.

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

√ **No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: pending further development of safety data in adults
Date studies are due (mm/dd/yy): 12/28/2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-060**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: **NDA 21-060**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sara Stradley
12/23/04 07:44:00 AM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21060	**Trade Name:**	ZICONOTIDE SOLUTION 100MCG/ML 1/2/5 ML
Supplement Number:		**Generic Name:**	ZICONOTIDE SOLUTION 100MCG/ML 1/2/5 ML
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	NA	**Proposed Indication:**	For management of severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric ~~content not necessary because of pediatric waiver~~ Studies deferred

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Sponsor submitted request for Pediatric Use Information waiver on November 23, 1999.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, LAURA GOVERNALE

Laura Governale
Signature

June 5, 2000
Date

ADM-1

23 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

16. DEBARMENT CERTIFICATION

Elan Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Mark Brunswick, Ph.D.

Interim Head of U.S. Regulatory Affairs

Elan Pharmaceuticals, Inc.

11/1/94

Date

ELAN PHARMACEUTICALS ZICONOTIDE

NEW DRUG APPLICATION ITEM 16

16. DEBARMENT CERTIFICATION

On behalf of Elan Pharmaceuticals, I hereby certify that we did not and will not use in any capacity the services of an individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 21-060 for Ziconotide.

Jan Wallace, M.D.

Sr. Vice President, Clinical and Regulatory Affairs
Elan Pharmaceuticals

14 Dec 99
Date

18. USER FEE COVER SHEET

The User Fee was submitted on December 28, 1999 with the original NDA, Item 18, Volume 1, p. 113 (NDA Vol. 2.001). For ease of review, included in this submission is a copy of the letter, check and original FDA Form 3397.

December 13, 1999

Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

Mellon Bank
3 Mellon Bank Center
27th Floor
FDA 360909
Pittsburgh, PA 15259-0001
(201) 261-4360

Re: NDA 21-060
Ziconotide Solution, Preservative Free
User Fee Number: 3873

Dear Sir/Madam:

In accordance with The Prescription Drug User Fee Act of 1992, Elan Pharmaceutical is submitting the required User Fee for NDA 21-060. As instructed by the Food and Drug Administration, we are submitting the designated User Fee dollar value for the year 1999 as the year 2000 figure has not been established at this time. Enclosed is a check for $272,282.00 and a copy of Form FDA 3397.

Do not hesitate to contact me at (650) 614-1053 or 1-800-435-5108 if there are any questions or comments regarding this submission. A copy of this letter and the User Fee check as well as Form FDA 3397 (original) will be included in the NDA submission.

Sincerely,

Linda B. Fradkin

Linda B. Fradkin
Director, Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

2. TELEPHONE NUMBER *(Include Area Code)*

(650) 614-1053 or (800) 435-5108

3. PRODUCT NAME

Ziconotide

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

3873

6. LICENSE NUMBER / NDA NUMBER

21-060

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
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Lynda P. Franklin	Director, Regulatory Affairs	December 13, 1999

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December 27, 2004

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetics, Critical Care, and
Addiction Drug Products, HFD-170
Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Attn: Sara Stradley, Regulatory Project Manager

RE: Ziconotide (Prialt intrathecal infusion) Intrathecal Pain Program
NDA 21-060
Withdrawal of Amendment: CMC (Stability Update)
Final Labels and Package Insert

Dear Dr. Rappaport:

Reference is made to NDA 21-060 for intrathecal (IT) pain and the July 2001 FDA Approvable Letter to our June 2004 complete response and our December 20, 2004 Stability Update.

We would like to formally withdraw our CMC (Stability Update) submitted on December 20, 2004.

In this submission are the final carton and vial labels for all dosage forms and the final Package Insert.

If there is further information required, please do not hesitate to contact me by phone at 858-202-7964, or by facsimile at 858-558-2549.

Sincerely,

Mark Brunswick, Ph.D.
Interim Head U.S. Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Elan Pharmaceuticals, Inc.	12/20/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(858) 202-7964	(858) 558-4120
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
7475 Lusk Blvd. San Diego, CA 92121	N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Ziconotide	PRIALT	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Omega Conotoxin		SNX-11
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injectable (liquid)	25 mcg/mL in 20mL fill vials and 100 mcg/mL in 1mL, 2mL, and 5mL fill vials	Intrathecal

(PROPOSED) INDICATION(S) FOR USE:
For the management of severe, chronic pain in patients for whom intrathecal therapy is warranted.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Stability update

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 *THIS APPLICATION IS* ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to NDA 21-060 submitted December 28, 1999

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Please refer to NDA 21-060 submitted December 28, 1999

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Mark Brunswick, Ph.D. Director, Regulatory Affairs	12/27/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
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ADM-3

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_____ § 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: December 23, 2004

TO: DIVISION FILE

FROM: Sara E. Stradley, MS, Regulatory Project Manager

SUBJECT: **Pre-Approval Safety Conference with ODS on Dec. 20, 2004**
NDA 21-060, PRIALT

The Division stated that this is the first new analgesic drug product in many years for this limited population.

The route of administration limits the use PRIALT. It was decided that this drug product would only be used by a specialty group since it requires the use of an intrathecal pump. The appropriate adverse events are listed in the package insert.

The following slides were presented to ODS with regards to the PRIALT new drug application.

ADM-4

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_____ § 552(b)(5) Draft Labeling

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/s/

Sara Stradley
12/23/04 05:02:18 PM

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 23, 2004 12:46 PM
To: 'Brunswick, Mark'; Stradley, Sara
Subject: comments on carton/container

Mark-

Increase the prominence of the established name (ie. ziconotide intratheal infusion) on all vial and carton labels.

For carton labels, increase the prominence of the BOXED texts preferably by using different color contrast and increased font size.

Increase the prominence of the mcg/mL (i.e., 25 mcg/mL) on carton label.

Add the strength to the vial label (i.e., 25 mcg/mL)

Also include the names of the micro infusion pumps on the carton labels. This should be on the PI and cartons, but due to space limitations, this may be dropped on the immediate container (vial) label.

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Phone 301-827-7430
Fax 301-443-7068

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/s/

Sara Stradley
12/23/04 12:58:31 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Friday, December 17, 2004 3:22 PM
To: 'Morrissey, Steven'; Stradley, Sara
Cc: 'Brunswick, Mark'
Subject: RE: an information request

Some further clarification-

So does this mean that you looked for the cleaning agent component (either directly or via chemical structure comparison)? Or does this mean this is the only impurity you think is related to left over components from the [redacted] reservoir?

Sara

-----Original Message-----
From: Morrissey, Steven [mailto:Steven.Morrissey@elan.com]
Sent: Friday, December 17, 2004 3:11 PM
To: 'Stradley, Sara'
Cc: Brunswick, Mark
Subject: RE: an information request

Ms. Stradley,

We have followed up on your question with our CMC group and have confirmed the following: Impurity [redacted] is formed by reaction of ziconotide with [redacted] from the pump. There are no impurities associated with the cleaning reagent.

This information will be submitted formally in a hard copy letter to the file. If there are any other questions, please let Mark and me know.

Steve

-----Original Message-----
From: Stradley, Sara [mailto:STRADLEYS@cder.fda.gov]
Sent: Friday, December 17, 2004 10:45 AM
To: 'Brunswick, Mark'; Stradley, Sara
Cc: 'Morrissey, Steven'
Subject: an information request

Mark/Steve-

Have you have tried to determine if any of the long list of impurities that were identified in the pump can be connected to any of the components of the [redacted] cleaning product?

Sara Stradley

your co-operation.
****

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/s/

Sara Stradley
12/22/04 05:44:46 PM
CSO

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, November 30, 2004 9:24 AM
To: 'Brunswick, Mark'
Cc: Stradley, Sara
Subject: Information needed ASAP

Mark
We need the following information as soon as possible. If possible send me your response via email to expedite the review of this information and then send the paper copy to the NDA. Thanks. If you have any questions, please let me know.

Please provide the following Product Quality Microbiology information for NDA 21-060

1. Although the media fill acceptance criteria for both the . [redacted] facilities were found to be acceptable in 2001, advanced aseptic processing technology can achieve contamination rates far lower than [redacted] with a 95% confidence level. The media fill alert and action limits for both manufacturing facilities should be adjusted to better reflect modern manufacturing standards.

2. Please provide the endotoxin limit for the water for injection used at the [redacted] facility.

3. Provide the following information with regard to glass vial sterilization validation:

   a. [redacted]

   b. [redacted]

   c. [redacted]

4. With regard to the stability protocol, provide the method and schedule for endotoxin and sterility testing

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
phone 301-827-7430
fax 301-443-7068

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/s/

Sara Stradley
11/30/04 09:28:48 AM
CSO

Office Director's Sign-Off Memorandum

Date:	Thursday, December 23, 2004
NDA:	21- [redacted]
Sponsor:	Elan Pharmaceuticals
Proprietary Name:	Prialt (ziconotide intrathecal infusion)
From:	Robert J. Meyer, MD Director, ODE II

INTRODUCTION: Prialt is a sterile, preservative-free formulation containing ziconotide as its active ingredient. Ziconotide is a synthesized polypeptide of 25 amino acids in length. It is intended to replicate the toxin of the marine snail *Conus magnus*. The drug is currently proposed for administration via a micropump into the intrathecal space. The indication as proposed by the sponsor in the relevant submission reads: *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.*

This NDA was first submitted in late 1999 and has been given 2 previous approvable actions, largely due to inadequate showings of safety, efficacy and a consistent, acceptable method of use. In the original NDA, while the sponsor submitted two studies that showed apparent efficacy, it turned out that the dose-titration was being changed during the study to address issues of intolerability and safety and therefore little data was presented to convincingly establish the efficacy and safety of any one set titration scheme. Further, one study site was determined to be unblended to therapy and removing that site from the analysis rendered some of the efficacy findings less credible.. Therefore, the sponsor was asked to perform another adequate and well-controlled study to define a dosing strategy for intrathecal (IT) administration that was both safe and effective.

This resubmission was received on June 25, 2004, with a regulatory due date of December 28th, 2004. The resubmission includes the result of an additional controlled trial, as well as more safety data utilizing a lower start dose and slower titration scheme than contained in the original NDA. There are also further data on CMC, particularly having to do with the previously noted poor stability in the pump and apparent loss of drug substance to pump surfaces, and further preclinical data.

CMC: As noted above, Prialt is formulated as a sterile, preservative-free solution – both important for in intrathecal drug, where preservatives may present safety issues not germane to systemic administration. The drug is only to be used in specific microinfusion pumps due to issues of compatability and stability. These include two implantable pumps that are already approved by CDRH and one external pump. These are the Medtronic SynchroMed® EL, the MedTronice SynchroMed® II Infusion System and Simms Deltec Cadd Micro® External Microinfusion Device and Catheter. By

adopting a recommendation for priming the pump with the 25 mcg/mL solution, the sponsor has defined a method of use that allows for reasonable stability for the drug.

The drug substance is synthesized by [redacted] the drug product by [redacted] The drugs is formulated in two strengths, the 25 mcg/mL mentioned above as well as a 100 mcg/mL. The latter dilution is available in 1, 2 and 5 mL vials, the 25 mcg is available in 20 mL vials. The sponsor has shown adequate compatability and stability for both strengths in the relevant pumps. The lower dilution when first used is stable for 14 days, then later for 60 days on refill. The 100 mcg dilution is also stable for 60 days when used undiluted (it is not to be used initially) or 40 days if diluted.

The microbiology review found the methods of manufacture and packaging to be adequate and acceptable.

Final recommendations from Compliance on the EERs is that the various sites involved in the production and testing of this product are acceptable as of 12-23-04. There is one site that was not expected prior to approval for [redacted] testing. It was identified late and is a foreign inspection. On the other hand, the CMC reviewers feel that [redacted] testing is routine test (there being a high likelihood that their contract testing facility is providing adequate information) and if the site does not meet the regulations upon post-approval inspection, Elan should be able to quickly institute an alternative that is acceptable.

Pharm/Tox:

The sponsor provided adequate data to support the IT use of ziconotide, including IV and IT data in acute and subchronic studies. The subacute toxicities seen were mainly neurologic, but with relatively few histologic correlates. The sponsor did perform studies of hERG channels and safety pharmacology that did not suggest any effect on QTc. The drug does block AV conduction at very high exposures, but this should not be relevant for IT administration of low doses. The reproductive toxicology testing was done IV and ziconotide was initially shown to be teratogenic based on skeletal abnormalities. Newly submitted data show that these pelvic bone lesions were due to delays in ossification and not absence of structural bone. The drug is embryolethal when given IV to rats in high doses.

Genotoxicity assays, in vitro and in vivo, were negative. Carcinogenicity testing was not conducted due to the IT route and the impracticality of conducting such a study. As a middle ground, a SHE cell assay was conducted that was also negative, so the CAC committee felt given the limited systemic availability of the drug from the IT route and the practical considerations and the clean genotoxicity testing, not carcinogenicity study was needed.

The sponsor did studies of various impurities of ziconotide compared to "clean" ziconotide in beagle dogs and found to added, associated toxicities. The impurities (designated by letters of the alphabet - [redacted] are considered qualified.

Biopharmaceutics: Ziconotide is felt to act on the N-type calcium channels located on the primary nociceptive (A-δ and C) afferent nerves in the superficial layers of the dorsal horn in the spinal cord, which in turn is thought to block excitatory neurotransmitters affecting pain. When given by the IT route, the half-life is about 4.5 hours with a volume distribution approximating that of the total CSF. It is felt to be cleared by slow passage into the systemic circulation where it is broken down by peptidases into constituent amino acids and polypeptide fragments. IT administration results in measurable systemic levels by a sensitive assay in less than ½ of subjects. There is no evidence that exposure increases with longer durations of IT therapy. Given its low systemic levels and route of elimination, ziconotide IT is not expected to have important interactions with other drugs, nor with diseases and demographics.

Clinical / Stastical:.

Efficacy:. The sponsor submitted one additional adequate and well-controlled study for ziconotide, which was designated as study 301. The details of the study can be found in the primary medical officer review. Essentially, it was a study where patients were removed from prior therapy (mostly IT, since patients were required to have a pump already in place), stabilized on systemic opiates and then randomized to a three-week treatment period with ziconotide vs. placebo. The drug was started at a low dose of 0.1 mcg/hr and could only be increased every 2 – 3 days by no more than 0.1 mcg/hr to a total daily dose of 0.9 mcg/hr (though the highest achieved was 0.8 mcg/hr). A total of 220 patients were randomized (1:1 randomization) with 112 being randomized to Prialt. The efficacy assessment was judged by rating of pain on a visual analogue scale (0 – 100). During the three week treatment/titration period, 9 subjects discontinued from active and 8 from placebo. The reasons for discontinuation (AEs and lack of effect) were balanced across the two groups. On the VAS, there was a statistically significant difference with ziconotide, which had a 14.7% reduction in VAS compared to placebo with a 7.2% reduction. The main way for imputing for missing data due to early termination was to assign these patients a zero reduction in score, but sensitivity analysis by the sponsor showed that the treatment difference persists even with other forms of imputation. Using a responder analysis, there again was a small, but significant separation of drug from placebo, with 16.1% responders with ziconotide vs. 12% with placebo (using a 30% reduction in the VAS as a response). This small increment was found no matter what level of response one assessed, including 50% reduction (8% vs. 2%). Notably, systemic opiates could be titrated during the three week treatment period. The dose of opiates during study treatment was only slightly lower with ziconotide compared with placebo. While this near equality in opiate use means the results are less confounded by changes in the additional pain medications, it also again signals only a modest effect of the drug in analgesia (since ziconotide patients did not importantly less in the way of additional opiates).

ADM-5

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_____ § 552(b)(5) Draft Labeling

Safety: There were numerous neurologic adverse effects clearly related to the drug, some of them of significant concern. There is a high rate of ziconotide related dizziness, somnolence, confusion, ataxia, memory impairment and other similar effects compared to placebo. While the extent and seriousness of these occurrences was lessened with the start low, go slow titration studied in 301, they were not eliminated. Notably, however, 90 of 112 ziconotide patients who were offered the chance to continue active treatment following their enrollment in study 301 elected to continue, so these patients apparently felt that the benefits outweighed the tolerability issues they experienced. One issue of concern after the initial review was suicidal tendencies and suicides. It should be noted that in study 301, the HAM-D depression assessment actually favored ziconotide over placebo, suggesting that depression is not worse on drug, rather it appears to be somewhat improved compared to placebo (as might be expected for an effective pain medicine). Also, the original trials included AIDS and terminal cancer patients, a group where suicide may have different considerations than other patients. To further explore this issue, we requested that the sponsor perform two new analyses. The first was the rate of suicide related terms in placebo vs. ziconotide for all patients in all clinical trials. There were 3 such occurrences total for ziconotide (including one complete suicide) and 1 in placebo. For this broad group of patients, this gives a rate of 0.08 per patient year with drug and 0.20 per patient year with placebo. However, when just the controlled dataset is considered, the rate for drug is 0.27 per patient year and for placebo is 0.10. These data do not clearly answer the issue as to whether any suicide risk may be presented by the drug, so this potential risk bears discussion in the Warnings and Precautions sections of the labeling.

One additional, notable issue is that of apparent muscle toxicity with ziconotide. This is not something that was demonstrated in the preclinical studies even with systemic administration. Given this and the low systemic bioavailability, a direct effect of ziconotide would be hard to understand, but could be possible. On the other hand, this drug causes sedation and decreased level of alertness, meaning that secondary muscle damage due to positional considerations (failing to turn or otherwise relieve compression of dependant muscles) is possible. In fact, the only case of clear rhabdomyolysis reported in the original database was of a patient who was found down and clearly had inactivity/dependant related muscle damage. Because the database does not rule out a primary effect, the occurrence of muscle findings will be labeled as will recommendations for monitoring CPKs.

One last issue was that an earlier medical review had raised is if the drug might prolong QT. Given the totality of the data available, I don't believe this is a concern. Firstly, there are few preclinical data to suggest a risk, including the safety pharmacology studies and the in vitro channel studies. More importantly, ECGs in 301 were analyzed for cardiac conduction and did not show evidence of a notable effect on the QT and the QTc intervals.

Labeling and nomenclature:

DMETs has found the name for ziconotide – Prialt - to be acceptable. DMETs has also made valuable suggestions on the package and container labeling for this product that is

available in multiple vial sizes and dilutions. While large doses of Prialt have been given IT without dire consequences, it is of considerable importance to try to lessen the possibility of misadministration.

Regulatory Conclusions:

1. Prialt should be approved for use in the treatment of 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. The drug will not only be labeled for use with microinfusion pumps, but the specific pumps for which it has been shown to be compatible and in which it has been shown to be stable will be listed in the PI.

   This is a highly restricted population and one with few other options for management of severe pain. In this population, the risks shown to date would be outweighed by the proven, if modest, efficacy. Clearly, this drug should not be used without due consideration of experts. Given the fact that it needs to be administered intrathecally, there is near certainty that only experts in pain management will prescribe the drug. This route of treatment is almost exclusively practiced by anesthesiologists and some neurologists or neurosurgeons with specific expertise and experience. The labeling will carefully highlight the known risks, especially the neuropsychiatric and apparent muscle toxicities.

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
12/23/04 03:17:32 PM
MEDICAL OFFICER

ADM-7

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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
Rockville, MD 20857

IND 45,718

10/21/04

Elan Biopharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Mark Brunswick, PhD
Director, Regulatory Affairs

Dear Dr. Brunswick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ziconotide (Prialt).

We also refer to your amendment dated October 13, 2004, containing details on the new [redacted] mL intrathecal pump that has been implanted in several patients.

We have completed the clinical and chemistry reviews of your submission and have the following comments and recommendations.

1. We agree with your plans to initiate stability studies on the Medtronic Synch II [redacted] mL pump. In addition, we recommend that you evaluate the effect of the procedure to prepare a naïve [redacted] mL pump on the delivered dose.

2. We agree with your plan to exclude additional patients from receiving the new [redacted] mL pump.

3. You may continue to treat patients who currently have indwelling [redacted] mL pumps and monitor them for adverse events. We recommend discarding remaining ziconotide in the pump after 60 days.

4. Data from the [redacted] mL and 20 mL pump may be combined in the study report if drug stability is similar, however, it may be useful to also separately analyze and present the data for patients using each pump.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience

associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Rigoberto Roca
10/21/04 11:10:33 AM
for Bob Rappaport, M.D.

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 28, 2004	**DESIRED COMPLETION DATE:** September 28, 2004 **PDUFA DATE:** December 28, 2004	**ODS CONSULT #:** 01-0042-1

TO: Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care and Addiction Drug Products
HFD-170

THROUGH: Sara Stradley
Project Manager
HFD-170

PRODUCT NAME: **Prialt®** (Ziconotide Injection) 25 mcg/mL (20 mL) 100 mcg/mL (1 mL, 2 mL and 5 mL) **NDA#:** 21-060	**NDA SPONSOR:** Elan Pharmaceuticals

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name, Prialt®. However, DMETS does have safety concerns with the proposed label and labeling in regard to the safe administration of the drug product. See section III of this review for a listing of these concerns with proposed revisions to minimize potential errors with the use of this drug product. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DDMAC finds the proprietary name of Prialt acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242, Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 19, 2004

NDA# 21-060

NAME OF DRUG: Prialt® (Ziconotide Injection)
25 mcg/mL (20mL) and 100 mcg/mL (1 mL, 2 mL and 5 mL)

NDA HOLDER: Elan Pharmaceuticals

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), for a re-review of the proprietary name of Prialt. Revised container, carton and insert labeling were provided for review and comment. This is the second submission for this application. Prialt was previously reviewed by DMETS and found acceptable on April 13, 2001 (see consult number 01-0042, dated April 10, 2001).

PRODUCT INFORMATION

Prialt contains ziconotide that is indicated for the pain management of severe chronic pain in patients whom intrathecal therapy is warranted. Ziconotide does not bind to opioid receptors, therefore the pharmacological effects can not be blocked by opioid antagonists. The most frequently observed adverse events were asthenia, headache, confusion, dizziness, nystagmus and somnolence. Ziconotide should be started at no more than 2.4 mcg per day and further titrated to patient response. The patient's dose may be increased by 2.4 mcg per day at intervals of 2 to 3 times per week, up to the recommended maximum dose of 21.6 mcg per day. There is a lower incident of serious adverse events when the drug dose in increased by slow titration. Ziconotide is to be administered intrathecally by a programmable implanted variable-rate microinfusion device or an external microinfusion device and catheter. This administration should occur by or under the direction of a physician experienced in this technique. The product is available in the following two concentrations: 25 mcg/mL (20 mL) and 100 mcg/mL (1 mL, 2mL and 5 mL).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Prialt, to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Prialt. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical expertise, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Prialt acceptable from a promotional perspective.

2. Since the initial consult, the Expert Panel identified four additional proprietary names that were thought to have potential for confusion with Prialt. These products with their dosage forms available and usual dosage are listed in table 1 (see page 4).

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=tess&state=2fmprd.1.1

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

[redacted]			
Triacet	Triamcinolone Cream 0.025%, 0.05% and 0.1%	Apply sparingly to affected areas 2 to 4 times daily	LA
Portia®	Ethinyl Estradiol/Levonorgestrel Tablets 0.03 mg/0.15mg, 21 and 28 day packages.	One tablet daily	LA
Procrit®	Epoetin Alfa Injection: 2000 units/mL, 3000 units/mL, 4000 units/mL, 10000 units/mL, 20000 units/mL, 40000 units/mL	Adults: 50-100 Units/kg three times per week intravenously or subcutaneously Children: 50 units/kg three times per week intravenously or subcutaneously	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Prialt were captured by the Expert Panel Discussions (EPD) or the previous DMETS review (April 2001, 01-0042).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Prialt with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Prialt (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Outpatient RX: Prialt give to home health nurse 20 mL vial	Prialt 20 mL vial Patient to give to home health nurse No refills
Inpatient RX: [illegible]	

2. Results:

One verbal prescription respondent interpreted the name as pre-op, which is a currently marketed hexachlorophene topical sponge and an abbreviation for pre-operative. An inpatient order respondent interpreted the name as the word "primal." Primal is defined as "being first in time; original; primeval" or "of first importance; primary"[5]. Additionally, one voice participant interpreted the name as Dualt, which is similar to the currently marketed drug product of Duac. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Prialt, the primary concerns related to look-alike confusion with [redacted], Portia, Procrit, Triacet, Dualt and Pre-Op. Upon further review of the names gathered from EPD, the names [redacted] and Portia were not reviewed further due to a lack of convincing look-alike similarities with Prialt; in addition to numerous differentiating product characteristics such as the product strength, indication of use, frequency of administration, route of administration and dosage form.

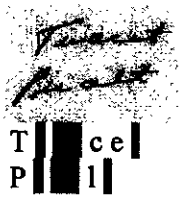
DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. A negative finding is not predicative as to what may occur once the drug is widely prescribed; as these studies have limitations primarily due to a small sample size. Although there were no positive hits, one voice participant interpreted the name as Dualt, which is similar to the currently marketed drug product, Duac. Additionally, two respondents from the verbal prescription study interpreted the name as pre-op. Pre-op is also a standard abbreviation for "before surgery" and name for a marketed hexachlorophene topical sponge. The abbreviation of Pre-op may sound similar to Prialt. However, orders for Prialt will have to indicate the dose, dosing schedule, or strength of the drug product that should help distinguish the product from the pre-op as a term. The term is an indicator of actions that occur before surgery and will primarily be written with orders for surgical

[5]Lexico Publishing Group, LLC, available from World Wide Web @ http://dictionary.reference.com/search?q=primal.

*** Proprietary and confidential information that should not be released to the public.

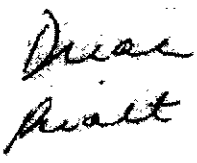
preparation and/or other pharmaceutical products. DMETS believes the possibility for confusion to be minimal. Furthermore, an inpatient order respondent interpreted the proposed name as the word "primal." Primal is defined as "being first in time; original; primeval" or "of first importance; primary"[6]. However, this term has no relevance in medicine or medical documentation and DMETS could not find a scenario where a misinterpretation for "primal" could result in confusion or error. Henceforth will not be dicussed further. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Prialt.

1. Triacet may look similar to Prialt when scripted. Triacet contains triamcinolone cream for topical use; strengths include 0.025%, 0.05% and 0.1%. A standard dosing regimen is the application of a small amount to the affected area two to four times daily. Triamcinolone cream is used to relieve inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, as an alternative of adjunctive treatment in psoriasis, seborrheic dermatitis, severe diaper rash, disidrosis, nodular prurigo, chronic discoid lupus erythematosus, alopecia areata, lymphocytic infiltration of the skin, and other such conditions. The visual similarities result from the shared and identically placed "ria" and "t" in the names with a potential resemblance of "acet" to "ialt" when scripted (see below).



However, the differing leading "T" compared to "P" and "ce" of Triacet that lengthens the name; both serve as a distinguishing marks. The products do not share overlapping characteristics such as strength (0.025%, 0.05% and 0.1% compared with 25 mcg/mL or 100 mcg/mL), dosing interval (two to four times daily compared with a continuous infusion rate), indication of use (dermatoses compared to pain management), dosage form (cream compared to injectable), route of administration (topical compared to intrathecal), and storage conditions (room temperature compared to refrigeration). The likelihood for confusion is minimal given these differences.

2. Duac may look similar to Prialt when scripted. Duac contains benzoyl peroxide (5%) and clindamycin phosphate (1%) in a gel formulation. Duac is used topically for the treatment of inflamed acne vulgaris. A standard dosing regimen for inflammatory acne vulgaris acne is application of the product daily. The visual resemblance results from the similarity of "Pri" to "Du" when scripted, which can be compounded by the tendency of the endings to taper off (see below). However, this requires the reader to disregard the finalizing "t" on Prialt; regardless of prominence.



These drug products can share the one overlapping criteria of storage. Duac should be stored cold (preferred refrigeration), but once dispensed may be maintained at room temperature. However, the products differ in many other characteristics as seen by the following: strength (5% and 1% compared to 25 mcg/mL or 100 mcg/mL), dosing interval (once compared

[6]Lexico Publishing Group, LLC, available from World Wide Web @ http://dictionary.reference.com/search?q=primal.

with a continuous infusion rate), indication of use (acne compared to pain management), dosage form (gel compared to injectable), and route of administration (topical compared to intrathecal). The likelihood for confusion is minimal given these differences.

3. Procrit may look similar to Prialt when scripted. Procrit contains epoetin alfa (erythropoetin) indicated for anemia associated with chronic renal failure, zidovudine therapy and cancer chemotherapy. Procrit is dosed at 50 to 100 units per kilogram for adults and 50 units per kilogram for children, three times per week. This drug product may be administered via the intravenous or subcutaneous route. The similarities result from the shared leading "Pr" and "t" ending. Additionally, the "crit" may resemble "alt" when scripted with the "i" written with a high upswing (see below).

[redacted]ocri[redacted]
ial

The products have significant differences in characteristics, which include the following: route of administration (intravenous/subcutaneous compared with intrathecal pump), strength (2,000-40,000 units/mL compared 25 mcg/mL and 100 mcg/mL), standard dose and frequency (Procrit is dosed as units per kilogram, two to three times per week compared with 2.4 mcg per day as a constant infusion, up to 21.6 mcg per day), and indication of use (anemia compared to pain management). As the products have differentiating characteristics, DMETS believes the possibility for confusion to be minimal.

4. Pre-op is a currently marketed hexachlorophene topical sponge (480 mg). Hexachlorophene is a topical bacteriostatic agent used as a surgical scrub and bacteriostatic skin cleanser. Hexachlorophene also can be used to control outbreaks of gram-positive infections. This is a product usually supplied by a hospital central supply, therefore prescriptions will rarely be written. However, a hospital outpatient order could be written for a patient to undergo surgery. The verbal similarities result from the shared leading "pre" sound and the analogous sounding "op" and "alt" that is due to the leading vowels and articulation correlations (stops) of the endings of "p" and "t." The drug products of Pre-op and Prialt share no overlapping characteristics which are detailed as follows: strength (480 mg compared with 25 mcg/mL or 100 mcg/mL), dosing interval (one time use compared with an infusion rate), indication for use (topical cleansing compared to pain management), dosage form (sponge compared to injectable), and route of administration (topical compared to intrathecal). The likelihood for confusion is minimal due to these characteristics and the fact that the drug product of Prialt will have specialized dosing.

ADM-8

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proposed proprietary name, Prialt®. However, DMETS does have safety concerns with the proposed label and labeling in regard to the safe administration of the drug product. See section III of this review for a listing of these concerns with proposed revisions to minimize potential errors with the use of this drug product. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DDMAC finds the proprietary name Prialt acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results (Prialt)

Inpatient	Outpatient	Voice
Prialt	Prialt	Pre-Elt
Prialt	Prialt	Premelt
Prialt	Dualt	Pre-op
Prialt	Prialt	PreAlt
Prialt	Priaet	Pre-alt
Prealt	Prialt	Prealt
Prialt	Pualt	Prevelt
Prialt	Prialt	Prealt
Prialt	Priacet (or Prialt)	Prealt
Primal	Prialt	Prealt
Prialt	Prialt	Prialt
Prialat	Pualt	Pre elt
Prialt	Pmalt	Prealt
Prialt	Prialt	Preout
Prialt	Prialt	PreAlt
Prialt	Prealt	Prehelt
Prialt	Prialt	Preout
Prialt	Prialt	Prialt
Prialt	Priaet	
Prialt	Prialt	

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/s/

Kimberly Culley
11/15/04 08:43:27 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/15/04 01:10:13 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

8/5/04

Elan Pharmaceuticals, Inc.
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Mark Brunswick, PhD
Director, Regulatory Affairs

Dear Dr. Brunswick:

We acknowledge receipt on June 28, 2004 of your June 25, 2004 resubmission to your new drug application for Prialt (ziconotide).

We consider this a complete, class 2 response to our July 25, 2001 action letter. Therefore, the user fee goal date is December 28, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until June 30, 2009. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

If you have any question, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
8/5/04 08:15:32 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

9/12/03 mtg

Elan Biopharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Mark Brunswick, Ph.D.
Director, Regulatory Affairs

Dear Dr. Brunswick:

Please refer to the teleconference between representatives of your firm and FDA on September 12, 2003. The purpose of the meeting was to discuss the proposed teratology study submitted April 28, 2003, and the proposed impurities action plan submitted on May 2, 2003.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: September 12, 2003

Location: teleconference

NDA: 21-060 (ziconotide)

Sponsor: Elan Pharmaceuticals

Type of Meeting: Guidance

Meeting Chair: Sharon Hertz, M.D., Team Leader, Analgesics
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

Elan Pharmaceuticals	Title
Mark Brunswick, Ph.D.	Director, Regulatory Affairs
Dave Ellis, M.D., Ph.D.	Director, Clinical Development
George Shopp, Ph.D.	Sr. Scientist, Pharmacology
Mel Lederman, M.D., Ph.D.	Sr. Director, Clinical Development
Ron Kartzinel, M.D., Ph.D.	Sr. Director, Clinical Development
Jill Rogers	Associate Director, Project Management
Sheri Barrack, Ph.D.	Sr. Director, Pharmaceutical Development
Nancy Santilli, R.N.	Sr. Director, New Product Planning
James Callaway, Ph.D.	VP, Biopharmaceutical Development Services
David Shield	----------
FDA	**Title**
Bob Rappaport, M.D.	Division Director
Sharon Hertz, M.D.	Team Leader, Analgesics
D. Elizabeth McNeil, M.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Mike Theodorakis, Ph.D.	Chemistry Reviewer
Dan Mellon, Ph.D.	Pharmacology/Toxicology Supervisor
Adam Wasserman, Ph.D.	Pharmacology/Toxicology Reviewer
Sara Stradley, M.S.	Regulatory Project Manager

Meeting Objective: To discuss the proposed teratology study submitted April 28, 2003, and the proposed impurities action plan submitted on May 2, 2003.

General Discussion: After brief introductions, the teleconference focused on the questions from the August 12, 2003, meeting package and the questions listed in the May 2, and April 28, 2003 submission.

Clinical

The Division stated that the information on the mapping of terms provided in the May 2, 2003 submission was very helpful. However there is still concern about the lack of consistency between the preferred terms and the verbatim terms. The following are several examples. The page numbers refer to the thesaurus for adverse events from Study 98-022 provided in the Sponsor's submission dated May 2, 2002.

Page	Preferred term	Verbatim terms, examples
76	Dizziness	Lightheaded, feels faint, dizzy with position change
39	Postural hypotension	Lightheaded
69	Abnormal gait	Unsteady gait
71	Ataxia	Ataxia, ataxic gait, lack of balance
89	Incoordination	Disequilibrium, decreased motor coordination
71	Aphasia	
76	Dysarthria	Slurred speech, garbled speech
100	Speech d/o	Slurred speech, stuttering aphasia
87	Impaired verbal expresion	Difficulty with speech
75	Difficulty concentrating	
90	Mental slowing	Decreased mental clarity
73	Confusion	Mental fogginess
90	Memory impairment	Memory confused
101	Thinking abnormal	Goofy comments, rambles
70	Agitation	Frustration/irritability
92	Nervousness	Increased irritability
105	Hypoventilation	Difficulty taking deep breath
104	Dyspnea	
P 117	Deafness	Difficulty hearing
117	Ear d/o	Muffled hearing
115	Abnormal vision	Can't focus, fuzzy vision
116	Blurred vision	

This overlap of terms can cause a dilution in the AE profile. The verbatim and preferred terms need to be consistent. The Sponsor stated they have tried but find it difficult to separate certain terms (i.e., dizziness, postural hypotension). The Sponsor plans to review the dictionary.

Pre-Clinical

Question 1 (Aug 12, 2003): Does the Agency concur with the 10X safety margin as the criteria for qualifying impurity specifications?

The Division concurs with the use of a 10-fold safety margin to establish the qualification of an impurity. However, the 10-fold safety margin should be based upon the NOAEL value for the delivered dose of the impurity in the toxicology study, not the highest dose of the impurity tested. Analysis of the results of the study with the specifics of the toxicological changes would be required to establish a risk:benefit determination. The Division stated that the highest dose tested in the 28-day dog study gave an exposure ratio greater than 10 for most impurities, however, this value does not address safety. The Division stated the need to evaluate the data based on a safety margin. The Division remains concerned, as two dogs in the high dose and two dogs in the mid-high dose had to be euthanized on days 6 and 12 of the study. In addition it was noted that the amount of drug that was actually delivered at the 100 ng/kg/hr dose was far lower than targeted (26-34% of the interested dose). Therefore, this study does not provide adequate qualification of the impurities. The Division reiterated that an adequate safety margin was needed.

The Sponsor stated they have different impurities being generated at different rates and under different conditions. The Sponsor also explained that the approach of testing the impurities by using a toxicity study with a highly stressed product is difficult as the toxicity of ziconotide is so great that the pharmacological effects of ziconotide may mask the toxicologic effects of the impurity. The Division inquired if the Sponsor could remove the parent compound from the highly stressed product and thus test the degradation products alone.

The Sponsor stated that the stressed product was made in the lab and they are assuming that the ziconotide levels can be lowered. The Sponsor will explore using prep chromatography to remove the ziconotide from the impurities. It was questioned if the toxic effects are pharmacological effects due to the presence of ziconotide or toxicological effects due to the presence of the degradation products. The Sponsor will compare the effects of the stressed material (with out ziconotide) versus ziconotide.

The Division stated they would, if time permits, review the protocol. The Sponsor asked for clarification on the appropriate species. The Division stated that a dog or rodent study

would be acceptable but the dog may have fewer side-effects due to the larger size of the spinal column and therefore less spinal compression.

Question 2 (Aug 12, 2003): Does the Agency concur with the specifications for impurities in the drug product?

The Division stated that the current specifications for the impurities are not acceptable. Adequate qualification for the safety of an impurity should be based upon the NOAEL dose (delivered) in the animal study not the maximum dose tested. An additional animal toxicology study will be required to adequately qualify Impurities [redacted] under recommended storage conditions.

Question 3 (Aug 12, 2003): Does the Agency agree with the specifications for impurities in the pump?

The Division stated that the current specifications for the impurities are not acceptable. Adequate qualification for the safety of an impurity should be based upon the NOAEL dose (delivered) in the animal study not the maximum dose tested. An additional animal toxicology study will be required to adequately qualify Impurities [redacted]

The Sponsor stated that they have identified some impurities that are not real. These impurities are only formed under harsh conditions. The Sponsor stated that forced degradation produces certain products not seen at normal storage conditions and in the pump. The Division is concerned about the impurities that occur under normal conditions. It was agreed that the monitoring of some impurities could be discontinued if they are only the result of stressed conditions. These include impurities [redacted]

The Division asked for clarification on the manual integration mentioned in the meeting package. The Sponsor stated that they are analyzing information using manual computer integration (HPLC). It is a data driven process, not a "manual" process. Their method also involves a decision data tree. The Sponsor will provide us a detailed report on this method.

Question 4 (Aug 12, 2003 Letter): Does the Agency agree with the proposal to qualify Impurity [redacted] utilizing safety data from the clinical trials? If not, does the Agency agree with qualifying Impurity [redacted] using the proposed rat 28-day intrathecal toxicology study?

The Division stated that the data from clinical trials does not provide histological analysis of tissues to adequately address all potential toxicological changes. Human data can be

used to supplement animal data to establish qualification of the impurities, provided the impurity profile of the clinical batches are analyzed.

The Division stated that the 28-day rat intrathecal toxicity study appears to be adequate in design. Ideally, a safety margin of 10 should be established from the study. Based upon the proposed specification for the drug product in the pump (, the Sponsor should include a treatment group to the treatment group. The Division also reminded the Sponsor that ziconotide should be removed from the impurities prior to testing.

It was discussed that the impurities should be qualified. However, following this initial qualification, The Division is willing to accept the value for the specification for each individual unspecified degradation product.

The Sponsor stated that for the 25 ug product the impurities are measured on a mass versus percentage basis. This product was requested by the Division to eliminate an extra dilution step for patient safety. The Sponsor expressed concern that they could not obtain the same threshold for both formulations. The Division stated that the 25 ug and 100 ug formulation should have the same qualification threshold in terms of % of drug substance.

Question from April 28, 2003 submission: Does the Agency agree that utilizing the dual-staining technique to identify cartilage and bone as originally proposed would be sufficient to show incomplete versus absent ossification in the event a higher dose is selected for evaluation in the proposed teratology study?

The Division stated this was acceptable.

NOTE:
The questions from the May 2, 2003 submission were addressed above.

Question 1 (May 2, 2003): Does the Agency agree with the proposed plan for establishing new specifications for drug product, after storage at 2-8°C and after exposure to the pump at 37°C?

Question 2 (May 2, 2003): Does the Agency agree that an impurity would be considered qualified if it has been tested in the original 28-day dog IT toxicology study at a level ¡Â 3-fold that seen in stability and pump studies?

Question 3 (May 2, 2003): Does the Agency agree with the proposed 28-day IT protocol, if it is required to be conducted, to further qualify impurities?

Question 4 (May 2, 2003): Does the Agency agree that we can move forward into clinical trials with the existing impurity limits for the new 25 mg/ml formulation? (A CMC information amendment will be submitted separately to IND).

Action Items

1. Repeat the 28-day dog study using higher levels of the impurities.

2. Revise calculations for safety margin based on NOAEL and the actual delivered dose.

3. Following initial qualification of degradation products above [redacted], the future drug product specification for impurity may be [redacted].

4. It is acceptable to use the dual-staining technique to identify cartilage and bone to show incomplete versus absent ossification.

5. Revise the AE dictionary so that the verbatim and preferred terms are consistent.

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/s/

Sara Stradley
10/7/03 02:43:48 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

Elan Pharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

3/25/03 mtg

Attention: Mark Brunswick, Ph.D.
Director, Regulatory Affairs

Dear Dr. Brunswick:

Please refer to the meeting between representatives of your firm and FDA on March 25, 2003. The purpose of the meeting was to discuss the clinical program for the resubmission of the NDA for ziconotide (Prialt).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: March 25, 2003

Location: Parklawn Building, Conference Room L (3:00-4:30)

NDA: 21-060 (Prialt/ziconotide)

Sponsor: Elan Pharmaceuticals

Type of Meeting: Guidance

Meeting Chair: Bob Rappaport, Acting Division Director.
Division of Anesthetic, Critical Care and Addiction Drug Products

Elan Pharmaceuticals	Title
Ronald Kartzinel, M.D., Ph.D.	Senior Director, Clinical Affairs
David Ellis, M.D., Ph.D.	Director, Clinical Affairs
Charles Davis, Ph.D.	Senior Director, Biostatistics
[redacted]	
[redacted]	
Robert Spencer	Senior Clinical Research Associate (Medtronic)
Mark Brunswick, Ph.D.	Director, Regulatory Affairs
Steven Morrissey, MPA	Associate Director, Regulatory Affairs
Nancy Santilli	Sr. Director, Project Management
George Shopp, Ph.D.	Senior Scientist, Pharmacology
Sheri Barrack, Ph.D.	Sr Director, Pharmaceutical Development
[redacted]	Title
Bob Rappaport, M.D.	Acting Division Director
Sharon Hertz, M.D.	Team Leader, Analgesics
Shaun Comfort, M.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Mike Theodorakis, Ph.D.	Chemistry Reviewer
Tom Permutt, Ph.D.	Statistical Team Leader
Stella Grosser, Ph.D.	Statistical Reviewer
Tim McGovern, Ph.D.	Pharmacology Supervisor
Sara Stradley, M.S	Regulatory Project Manager
Patricia Love	Office of Combination Products
Donald Fink	Office of Combination Products

Meeting Objective: The primary objective of this meeting was to discuss the clinical plans of the pivotal trial 301. The meeting package, dated February 20, 2003, was reviewed for this meeting.

Clinical and Statistical

Question 9.1
During our December 3, 2001 meeting there was agreement to continue to collect adverse event data from Study 31 and for the NDA resubmission using COSTART rather than MEDRA. Is this still the Agency's desire?

The Agency agreed.

Question 9.2
Does the Agency agree that it is also acceptable to continue to collect adverse events associated with the SynchroMed infusion system using COSTART? Does the Agency agree with the new sponsor-defined preferred terms to describe device AE and some the CNS AE? These events will then be included in their PMA supplement to the Device division

The Agency stated that it is acceptable to continue to collect adverse events associated with the SynchroMed infusion system using COSTART. However, the Agency stated that the new sponsor-defined preferred terms to describe device adverse events (AEs) were not entirely clear (i.e., What is the difference between catheter site inflammation, hypersensitivity and reaction, or pump site inflammation, hypersensitivity and reaction?). The Sponsor described that these were just variations from the COSTART terms for injection site inflammation, hypersensitivity and reaction. They stated that they will provide reverse mapping for adverse events they will code to the new terms.

The Agency also stated that the new sponsor-defined preferred terms to describe some of the central nervous system (CNS) AE are not entirely clear (i.e.,What is the difference between amnesia and memory impairment and why would both be used? How does impaired verbal expression differ from aphasia or dysphasia? New onset stuttering may reflect cortical injury, not just a motor disorder comparable to dysarthria. How does difficulty concentrating differ from mental slowing?). The Sponsor stated they will provide descriptions for the defined terms.

The Agency stated that AEs of particular clinical interest (e.g. Table 8.8.35, P. 86) mentions confusion, difficulty concentrating, impaired verbal expression, memory impairment, mental slowing, somnolence but excludes many of the terms from the Expert Panel and FDA lists (Table 8.8.5, P. 56) including aphasia and thinking abnormal. The Sponsor stated that they are trying to get specifics from the investigators and added terms to make the descriptions more specific. The Agency expressed concern that there may be an under-estimation of the occurrence of the spectrum of symptoms that are characteristic of an encephalopathy. The Sponsor will provide the verbatim terms along with the mapped

new terms and are willing to work with us on the database. The Agency agreed that it was important and useful for the Sponsor to create their own interpretation of these encephalpathy-related events in the ISS. As long as the verbatim terms were also available, the Agency would be able to evaluate these encephalpathy-related events using a variety of definitions to fully explore this CNS adverse event syndrome.

The Sponsor agreed to submit a safety database incorporating adverse events in verbatim and preferred terms, dose at onset, duration of therapy at onset, duration of event, and outcome of event.

Question 9.3 and Question 9.4
Our partner, Medtronic, will be supplementing their PMA for use with PRIALT. When should they submit this information?

Are the approval of the PRIALT NDA and the Medtronic's PMA supplement linked? If they are linked, is it reasonable to expect simultaneous approvals?

The Agency recommended that Medtronic work with CDRH on the timing of the PMA resubmission. CDRH is also considering what User Fee category would be appropriate. The Sponsor will contact CDRH to discuss further details of the submission.

Question 9.5 and 9.6 (combined)
Elan plans to provide an ISE for all pivotal trials but does not plan to provide a separate ISS for all studies. We will be providing safety data from new study 301. Our rationale for not providing an ISS is that the previous trials (95-001, 96-002) used a much more aggressive titration scheme (5-6 days) associated with a large number of adverse events. The current study 301 uses a much slower titration (21 days) and is expected to demonstrate a much better safety profile. We will be providing finalized study reports from the long-term extension studies 95-002 and 98-022. Since 98-022 and 301 have similar slow titrations we will provide an ISS for these two studies. Does the Agency concur with this proposal? Does the Agency have any comments on the proposed table shells that will be submitting to our NDA??

The Agency asked for clarification on the ISS Table Shells as described on page 10 of the meeting package, where the Sponsor describes combining adverse events from studies 301, 95-001, 96-002 into a group, and then separating them by "slow titration" and "fast titration". The Sponsor explained that the final titration schedule from the original NDA studies 95-001 and 96-002 would be considered "fast titration" and the 21-day titration schedule from study 301 would be considered the "slow titration." The events during the original titration schedule from studies 95-001, and 96-002 would not be part of this comparison.

The Agency stated that there are approximately 3 different titration schedules among these 3 studies (i.e., two from 95-001 and 96-002: the early, more rapid and the later, less rapid titration schedules and one from 301, a much slower schedule). Given the differences

between study 301 and studies 95-001 and 96-002, the Agency stated that it is important to be able to evaluate the adverse events that occurred during the titration and double-blind period of 301 independent of the other studies. The Sponsor stated that there will be complete safety results included in the study report for study 301 and integrated safety from a group composed of 301 and 98-022.

The Agency also requested clarification about whether data from the [redacted] site would be included in the new Integrated Summary of Safety of Efficacy (ISE). The Sponsor replied that they were intending to include this data. The Agency recommended that no data from the [redacted] site be used in any efficacy analysis since the site has been disqualified The Agency stated the [redacted] data should, however, be included in the ISS.

Question 9.7
Does the Agency agree with the statistical analysis plan for 301 to be included in the NDA amendment?

The Agency stated that the statistical analysis plan was acceptable.

Question 9.8
Elan intends to provide CRFs for SAEs, withdrawals and deaths only for study 301. Is this acceptable?

The Agency reminded the Sponsor that in addition, CRFs for SAEs, withdrawals and deaths from studies 351, 352 and any new occurrences in 98-022 and 95-002 should be submitted as well. The Sponsor concurred.

Question 9.9
We intend to submit NDA items 11 (case report form tabulations) and 12 (case report forms) electronically. Is this acceptable?

The Agency agreed. The Sponsor stated that item 11 would be in electronic format. Item 8 and 10 are identical and item 10 would refer to item 8 to avoid duplication. The Sponsor will send in the appropriate review copies.

Questions 9.10
Is the trade name PRIALT tentatively approved on April 24, 2001, still acceptable?

The Agency stated that the name and labeling must be re-evaluated prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based on approval of other proprietary names/NDA's.

Chemistry

The Agency had several comments on the submission dated December 3, 2002, regarding impurity limits in the ziconotide injection.

The original comment from the approvable letter dated July 25, 2001 was as follows:

O. Include acceptance criteria for each individual impurity in the regulatory specification for the drug product. In addition, provide a general specification for unspecified impurities, e.g., any unspecified impurity: less than 0.1%. In your response, provide data supporting impurity specifications.

The Sponsor stated in their December 3, 2002, submission that the specification for impurities in the drug product that was previously listed in the NDA included the following acceptance criteria: Not less than [redacted], no individual impurity greater than 1%. The Sponsor stated that the wording of this specification was unclear, in that it did not specify the total impurities limit of [redacted] or the limit for unidentified impurities as 1%. Accordingly, the Sponsor revised the specification to read:

Total impurities:	Not more than [redacted]
Known impurities [redacted]	No single impurity more than 1%
Unknown impurities:	No single impurity more than 1%

The Agency requested further clarification on each impurities and qualification at the levels proposed in the July 25, 2001. The Sponsor stated that quantification at < 1 microgram was too difficult for their analytical system. In addition, they are seeing irregular peaks frequently. The Agency questioned the anomalies and if the sponsor has attempted to determine the nature of the peaks by changing the analytical method (e.g., use of isocratic conditions).

A proposal for qualification of impurities [redacted] has been submitted but no additional qualification information for other impurities was provided. The Agency has not yet reviewed the proposed qualification for impurities [redacted] are present when the drug is stressed in the pump at 60 degrees. Impurities [redacted] are in the drug substance. Furthermore, all of the impurities are not found in one sample at one time. The Sponsor stated the impurities are real but question the value as they are below the limit of quantitation. The Sponsor stated that the levels are 100-fold less than the ICH specification for an intrathecal dose. The Agency expressed concern over the impurities since this is an intrathecal drug.

The Agency requested clarification of the qualification of the drug product and the drug in the pump. The Sponsor stated that the information has been provided previously to the Agency and in the December 2, 2002, submission.

The Agency requested that the Sponsor send in a package containing a proposal to address the issues with the impurities and their inability to provide a general specification for unspecified impurities, e.g., any unspecified impurity: less than 0.1%. The possibility of performing toxicology qualification of highly degraded sample(s) of drug product was discussed; this may be acceptable in lieu of continuing control of degradation products at < 0.1%, and 1% threshold would than be acceptable. The Sponsor agreed to submit the information.

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/s/

Sara Stradley
4/14/03 11:06:36 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

3/18/03 mtg

Elan Pharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Mark Brunswick, Ph.D.
Director Regulatory Affairs

Dear Dr. Brunswick:

Please refer to the teleconference between representatives of your firm and the FDA on March 18, 2003. The purpose of the teleconference was to discuss the results of a rat teratology study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: March 18, 2003

APPLICATION NUMBER: NDA 21-060 (ziconotide)

BETWEEN:

Name: George Shopp, Ph.D., Senior Scientist, Pharmacology
Michael Skov, Ph.D., Associate Scientist, Pharmacology
Ron Kartzinel, M.D., Ph.D., Senior Director, Clinical Affairs
Mark Brunswick, Ph.D., Director, Regulatory Affairs
Ruben Sanchez, Associate II, Regulatory Affairs
Keith J. Robinson, B.Sc., DABT, Scientific Director, [redacted]
Jill Rogers, Project Manager

Representing: Elan Pharmaceuticals, Inc.

AND

Name: Tim McGovern, Ph.D., Pharmacologist Supervisor
Sharon Hertz, M.D., Team Leader, Analgesics
Shaun Comfort, M.D., Medical Reviewer
Sara Stradley, M.S. Regulatory Project Manager

Representing: Division of Anesthetics, Critical Care and Addiction Drug Products

SUBJECT: Discuss results of a rat teratology study (February 11, 2003 meeting package)

The Sponsor summarized their teratology study. Briefly, embryolethality due to early resorptions was noted in the low- and mid-dose groups in the ongoing rat teratology study, but did not occur at the high dose. However, preliminary data from the high-dose group showed that incomplete ossification of the pubic bone in fetuses was resolved in pups. Analyses of plasma from the high dose dams showed the expected exposure to ziconotide. The Sponsor stated that these findings show that the decreased ossification seen in the fetuses at gestation day 20 in both the initial and the second teratology studies was due to a delay in ossification and not a teratogenic outcome. The Sponsor concluded that the second study showed that delayed ossification was the end result and that cartilage was present. The Sponsor stated that there was no teratogenic outcome but there was embryo toxicity.

Dr. McGovern questioned the result of the PK study and the plasma levels in Table 3.1 and 3.2 in the meeting package. The plasma levels were 2-to-10-fold higher in the first study versus the second study on gestation days 6 and 10. The Sponsor agreed there was a slight trend and stated a different rat species was used in the second study. The Sponsor stated that a dose-ranging study was performed with this rat strain to confirm comparable kinetics. Dr. McGovern requested that the Sponsor analyze the individual

animal data to show that some animals received comparable exposure to animals in the first study. The Sponsor should provide that information at resubmission and compare with the data from the first study.

Question 1
Does the Agency agree that the second teratology study provided sufficient evidence to support that the decreased ossification seen in the fetuses was due to a delay in ossification and not a teratogenic outcome ?

Dr. McGovern stated that the preliminary report noted only delayed ossification and indicated no absence of bone. The Sponsor confirmed this. However, with the delayed ossification there is concern about the reduced mean blood plasma levels, which should be addressed in the final study report. Adequate maternal toxicity will be confirmed when the final study report is submitted.

Question 2
Does the Agency agree that repeating only the teratology phase of the study to address the issue of embryolethality will be sufficient for completion of the nonclinical program in support of the Prialt NDA?

Dr. McGovern stated that repeating the teratology phase would be adequate assuming that the previously mentioned concerns regarding exposure levels are adequately addressed. If the concerns cannot be addressed, the teratology and littering phase should be repeated. The final study report will need to be reviewed for a definitive response. Although the initial teratology study results showed a lack of embryolethality, the Sponsor should continue its efforts to seek out the cause of the findings in the second study.

The Sponsor stated their concern over the timing of the studies. Dr. McGovern stated that a single study would be appropriate, however if the sponsor does not think the data addresses the plasma level concerns than the teratology and littering phase should be repeated.

The Sponsor questioned if the labeling would be changed based on the results of the study. "Teratology" could be removed from the label if the final study report shows only delayed ossification and no absence of bone. However, data from the studies has shown embryolethality that appears to be drug-related and the label will remain with the pregnancy C label. The Sponsor agreed.

In regards to the discrepancies in kinetics between the two studies, the Sponsor was encouraged to incorporate kinetic data from their Segment III rat study into their assessment of the issue since there may have been problems with the kinetic assessment from the first teratology study.

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/s/

Sara Stradley
4/10/03 11:12:06 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

2/27/02 mtg

Elan Pharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Dana Redhair
Director, Regulatory Affairs

Dear Mr. Redhair:

Please refer to the meeting between representatives of your firm and FDA on February 27, 2002. The purpose of this meeting was to discuss the SynchroMed Infusion System.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

ADM-8

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Sara Shepherd
3/27/02 07:48:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

Elan Pharmaceuticals
7475 Lusk Boulevard
San Diego, CA 92121

12/3/01 mtg

Attention: Dana Redhair
Director, Regulatory Affairs

Dear Mr. Redhair:

Please refer to the meeting between representatives of your firm and FDA on December 3, 2001. The purpose of the End-of-Review meeting was to discuss issues from the approvable letter dated July 25, 2001.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 3, 2001

Location: Parklawn Building, Conference Room C (11:30-1:00)

NDA: 21-060 (Prialt/ziconotide)

Sponsor: Elan Pharmaceuticals

Type of Meeting: End of Review meeting

Meeting Chair: Cynthia McCormick, Division Director.
Division of Anesthetics, Critical Care and Addiction Drug Products

Meeting Recorder: Sara E. Shepherd, Regulatory Project Manager

Elan Pharmaceuticals	Title
Lars Ekman, M.D., Ph.D.	President, R&D
Ronald Kartzinel, M.D., Ph.D.	Vice President, Project Team Leader
David Ellis, M.D., Ph.D.	Director, Clinical Affairs
Sheri Barrack, Ph.D.	Director, Technical Affairs
Jim Beck, Ph.D.	Scientist, Pharmacology
[redacted]	
Nancy Santilli	Senior Director, Strategic Marketing
[redacted]	
Dana Redhair	Director, Regulatory Affairs
Jennifer Martorana	Associate Director, Reg. Affairs
[redacted]	
DACCADP	**Title**
Cynthia G. McCormick M.D.	Division Director
Bob Rappaport, M.D.	Deputy Director
John Jenkins, M.D.	Director, ODEII
Sharon Hertz, M.D.	Medical Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Mike Theodorakis, Ph.D.	Chemistry Reviewer
Tim McGovern, Ph.D.	Pharmacology Supervisor
Suzanne Thornton, Ph.D	Pharmacologist
Thomas Papoian, Ph.D.	Pharmacologist
Tom Permutt, Ph.D.	Statistician Team Leader
Stella Grosser Ph.D.	Statistician
Paul Stinavage, Ph.D.	Microbiology Reviewer
Sara Shepherd, M.S	Regulatory Project Manager

Meeting Objective: The primary objective of the End of Review meeting was to discuss the clinical issues from the July 25, 2001, approvable letter for Prialt (ziconotide) Injection.

General Discussion: Following introductions, the discussion focused on comments from the primary reviewers concerning the information package dated November 2, 2001.

Chemistry and Microbiology Issues

1 *Has the issue of microbial growth, based upon the data previously submitted, been resolved (question 1a)?*

The Division stated this issue has been resolved. Strict aseptic techniques should be used when filling the reservoir. The Sponsor stated that currently the drugs are prepared by a pharmacy and filtered through a [redacted] filter at the physician's office.
There were no meningitis cases in the NDA database but the Division requested that this should be monitored closely. The Sponsor stated that the literature on various preservatives have been explored, but nontoxic preservatives were not available.

2. *Is the current preservative-free formulation acceptable (question 1b)?*

The Division stated this was acceptable. However the Division reminded the Sponsor to follow any occurence of meningitis at post marketing. The Sponsor confirmed that more cases occur with the external pump versus the implanted pump.

3. *Does the Agency agree that the "differential stability of the drug product and the adsorption of the drug substance to the pump reservoir" have been adequately characterized to allow the proposed clinical trials to proceed (question 2)?*

The Sponsor sent additional information on November 30, 2001, at the request of the review chemist (this was not reviewed in detail by the Division due to it late arrival). The Division requested information on how the losses due to adsorption, dilution (dead space) and degradation affect the concentration of ziconotide injection, especially when this injection is released at the lower limit of the assay specification [redacted]

The Division questioned whether or not there would be a significant effect in the efficacy of the drug product in situations where the losses in naïve pump, especially when filled with a 25 µg/mL ziconotide solution, are combined with the possibility that the injection was released at the lower limit of the assay specification [redacted]

The Division requested an additional meeting (Q1, 2002) with Elan and the manufacturer of the pump (Medtronic) to discuss how the pump will be used, variability in the dose due to dilution, adsorption and degradation, and instructions for use, specifically for Prialt. The Sponsor stated that an updated instruction brochure will not be available until after the clinical trial. The Sponsor stated that nothing would be done with the device labeling until after approval of Prialt.

4. *Does the information provided regarding [redacted] current action limit for contamination in media fills address the Agency's concerns? If not, what specific changes should be implemented at [redacted] (question 6)?*

   The Division stated that this information was adequate.

5. *Does the Agency agree that this validation type study is an acceptable alternative to conducting periodic testing in pumps (question 7)?*

   The Division replied that periodic testing (for adsorption to the pump) must be performed. Further discussion needs to take place to determine the timeframe for the periodic testing. The Division stated this issue can be discussed in more detail at the next meeting (Q1, 2002) with Elan and Medtronic.

6. *Will FDA accept a partial NDA response to resolve all outstanding CMC issues (question 8)?*

   The Division stated this was acceptable, but that the review clock will not start until the complete NDA submission is received. The CMC will be reviewed as resources permit, prior to the start of the clock.

Pre-Clinical Issues

7. *Does the Agency agree with the proposed toxicology trial design (question 5a)?*

   The trial design appears acceptable. The Division requested that individual fetal body weights be recorded for correlation of fetal findings. The Division stated that the results of the reproductive toxicity studies are under review by the Pharmacology and Toxicology Coordinating Committee (PTCC) Reproductive Toxicology Committee. Comments will be forwarded to the Sponsor following the mid-December meeting.

8. *Does the Agency agree that Elan can use the CDR(SD) [redacted] instead of the CDR(SD) strain in the proposed rat teratology study (question 5b)?*

   The Division stated this was acceptable if there were pharmacokinetic (PK) and toxicity data available for the [redacted]. The approvable letter stated that "If the same supplier, strain, age, and weight of rat can not be employed, you should use doses of ziconotide that approach the maximum-tolerated dose, utilize double-staining techniques (Alizarin Red S/Alcian Blue) for bone and cartilage visualization, and assess exposure levels by performing toxicokinetic analysis." The Division requested that the Sponsor should investigate a full range of doses in the IGS rat since the rat strains are different. The Sponsor indicated that they would perform a dose-range-finding study. The Sponsor replied they would be starting the study in March 2002, which would allow any comments from the PTCC Reproductive Toxicology Committee to be incorporated into the protocol.

9. *Does the Agency agree with Elan's position that ziconotide should not be considered teratogenic at the low and mid doses that were tested in the rat teratology study (95625) (question 5c)?*

Before commenting, the Division will need to review the results of the proposed embryo-fetal developmental IGS rat study. The design of the study, including the use of dual staining, should determine if the pubic bones are absent or if the bones are unossified. This study should address the remaining non-clinical issues.

Clinical and Statistical Issues

10. *Will the results of the two proposed studies in the context of prior studies provide the "substantial evidence" required for approval? What if only one study provides positive results (short version of question 3)?*

The Division stated that if the results confirm efficacy and demonstrate a clinically reasonable risk/benefit analysis, the requirements for approval may be met. However, if the slower titration study fails, this would cast doubt about the durability of effect. The Division will look at the overall direction and trends in the data when making a final determination concerning efficacy.

11. *Is the proposed collection and analysis of adverse events (AEs) adequate (question 4a)?*

The Division stated it was unclear how this differs from prior studies. COSTART is preferred by the Division, given its use in prior database. Additional terms should be added to COSTART. The Division also stated that a narrative would be useful and the Sponsor concurred. The safety database will need to be able to provide data necessary for full analysis including:

- Verbatim and mapped term
- AE onset and stop dates
- Dose at AE onset, dates of decrease or d/c
- Concomitant meds at onset
- Intervention

The Division stated it will be important to capture not just the occurrence of AEs, but to capture the onset and stop dates, and ziconotide dose from onset through resolution. Particular care should be taken to accurately document the AEs involving the central nervous system (CNS). The Division requested any AEs involving: thinking, memory, speech, confusion, level of consciousness, unusual behavior, hallucinations, change in mood, dizziness, ataxia, gait abnormalities should be captured.

An effort should be made by investigators to elicit the true nature of the AEs and not just provide a verbatim term that may be ambiguous. For instance, speech disorders should be differentiated by the clinician investigator between disorders of the motor production of speech (dysarthria) versus impairment of the production of language (aphasia or dysphasia). Confusion and memory symptoms should be clarified as to whether the

patient is drowsy, aphasic, or having difficulty organizing thoughts. Difficulty with gait should be differentiated between ataxia and weakness.

The Division stated that from existing experience the use of ziconotide can be expected to result in clinically relevant adverse events involving the central nervous system. Whether this is called encephalopathy or neurocognitive dysfunction, it must be fully explored with respect to any relationship with rate of titration, duration of treatment, and reversibility of events.

There was discussion concerning the use of the term encephalopathy vs. neurocognitive dysfunction and the specific terms used to define this area of adverse events. The Division stated that there was need for agreement on which terms were to be included in this adverse event analysis. The original list of terms in the analysis by the Division in the first review cycle was very long because it included neuropsychiatric terms and several individual verbatim terms. The final five items chosen by the Sponsor was too limited. The nine item list of COSTART terms identified by the panel of investigators convened by the Sponsor could be the proper approach. In order for that to be the case, it would be necessary for the investigators to make an effort to characterize the adverse events sufficiently to result in an assignment of preferred terms that accurately reflect the event.

The Sponsor stated that they plan to capture more baseline data on preexisting symptoms and conditions. In addition, a neurocognitive screen was being evaluated for use at baseline screening. The Division agreed this was an acceptable approach.

The Sponsor inquired as to whether the Division anticipated the description of an AE syndrome associated with the use of ziconotide. The Agency responded that the spectrum of CNS related adverse events observed to date did not appear specific to ziconotide, but common to many products active centrally, so a specific syndrome definition was not anticipated.

12. *Do the protocol designs and data collection strategies address concerns of possible interactions between opiates and Prialt (question 4b)?*

The Division stated that the current designs appear to adequately address these concerns.

13. *Are the two proposed titration schedules acceptable (question 4c)?*

The Division stated that the proposed IT morphine titration for Study 2 may be too aggressive for some patients, particularly those naïve to IT morphine. Reviews of the available literature and texts on the topic of IT morphine was limited and no specific recommended titration schedule could be identified by either the Division or the Sponsor's expert. The Division noted that the literature did support the overall dosing range, however, the rapid rate of titration appeared to be significantly faster than the titration reported. The Sponsor's expert indicated that in his experience, some patients

could tolerate this rate. Concern centered around patients naïve to IT morphine and those not using the higher range of doses of systemic opioids.

The planned rapid ziconotide titration may be too aggressive as well, given the high rate of adverse events noted in the original database. The Sponsor responded that the adverse event rate from the original pivotal trials was also reflective of the higher doses used.

14. *Are the durations of double-blind treatment proposed appropriate (question 4d)*

The Division stated that the 3-week period was appropriate. The 7-day trial faces toxicity and safety risks similar to the original trials.

15. *Are the proposed patient population acceptable (question 4e)?*

The Division stated that patients with severe chronic pain treated with IT opioids or for whom that would be the next step would be an acceptable population. The Sponsor should capture the full range of clinically relevant patients and should be careful of exclusion as it will effect the package insert label. The Sponsor specifically inquired as to whether patients not previously on IT morphine would be acceptable. These patients were included in the original trials. The Sponsor explained that part of the rational for including an IT morphine arm in one of the trials now was to gain further information on relative toxicity. The Division responded that this population was acceptable. However, in the absence of information confirming that the titration schedules for morphine and ziconotide were comparable therapeutically, comparative statements concerning adverse events would not be considered legitimate. The Division agreed with the Sponsor that the proposed trial would represent a reasonable beginning to gaining information on the use of both products

16. *Are the proposed efficacy measurements and statistical analyses acceptable (question 4f)?*

The Division stated that the percent change in VASPI was an acceptable primary outcome measure. The Sponsor should consider reviewing prior study results for the most robust and clinically relevant findings. The Sponsor expressed concern that for some patients, the quality of life was better but the VASPI does not capture it. The Sponsor asked if they could include a coprimary end point. The Division stated that a single, clinical relevant endpoint should be specified. However, the amount of rescue medications should certainly be recorded and possibly incorporated into a measure of efficacy, that included pain, as the primary endpoint.

17. *Does the proposed statistical methodology for handling early terminations and LOCF adequately address the Agency's concerns on the synopsis of the proposed protocol AN92045-401 (question 4g)?*

The Division stated that the Sponsor needs a fuller sensitivity analysis or inclusion of early withdrawals as failures. An imputation of worst-case values might be acceptable.

The Division will review any written statistical proposal submitted by the Sponsor and provide feedback.

18. *It is proposed to unblind patients at the completion of their trial participation .... Is this acceptable from a statistical standpoint (question 4h)?*

The Division stated this was acceptable.

19. *Do these protocol modifications address the previously identified issues (ECG, CK) appropriately (question 4i)?*

The Division stated that there is no ECG scheduled beyond baseline. Both studies should have 12-lead ECGs with a qualified central reader performed at baseline and at study termination.

20. *Did our submissions of July 11 and July 17, 2001 adequately respond to your concerns regarding ECG data, as cited in item 2e in the July 25, 2001 approvable letter (question 4j)?*

The Division stated that this issue was still under review.

At the end of the meeting, the Sponsor requested input on initiating Phase 1 studies which combine Prialt with other intrathecal medications. The Division stated this would provide useful information.

Action Items

a. An additional meeting will be planned with the Sponsor and Medtronic to discuss the pump.

b. The Division will provide the Sponsor with any comments from the PTCC Reproductive Toxicology Committee.

c. The Division will review the ECG data (issue #20) and provide comments.

d. The Sponsor will submit a statistical proposal for dropouts.

Meeting minutes concurred by meeting chair, Cynthia McCormick, M.D. (12/17/01)

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/s/

Sara Shepherd
12/18/01 01:06:53 PM

ADRA Review #2 of Action Package for NDA 21-060, Prialt (ziconotide)

Reviewer: Lee Ripper, HFD-102
Date: July 18, 2001

Dates volumes received in HFD-102: Chem and P/T – July 18, 2001
Admin and Clinical – July 20, 2001

Indication: Adjunctive therapy for the management of severe, chronic pain in patients who are not adequately controlled and/or intolerant to systemic opioids and for whom intrathecal therapy is warranted.

Action type: AE
Drug Classification: 1P
User fee goal date: July 29, 2001
505(b)(1) application

RPM: Laura Governale, 7-7423
Date original NDA received: Dec 28,1999
ACTION GOAL DATE: July 25, 2001
Patent Info: Yes, acceptable

EER: EER signed AC on 4/2/01. However, [redacted] testing site needs to be added to EER and inspected. Site information not submitted in time to be inspected during this review cycle.
Clinical Inspection Summary: Two sites inspected. Data from [redacted] site were excluded from analysis. Addressed in statistics and medical reviews.
OPDRA review of tradename: Yes, Prialt acceptable
DDMAC review of PI: No review by DDMAC in action package, but labeling comments are not being provided to firm at this time due to nature of deficiencies.
Debarment statement: Acceptable
EA: Categorical exclusion
Financial disclosure information/review: See pp. 25-26 of MOR finalized 7/17/01
Safety update: Pp. 7-25 of MOR finalized 7/17/01

Comments:

1. On the eSignature page and pages 1-3, 9, 11, 12, et al. of Chem Rev #2, words are all run together with no spaces in between them. When this happens, need to pull doc up again from DFS and/or run off on another printer to get spacing correct. I reprinted the pages and put them in the jackets.

2. Routing history of draft letter should be included in package.

3. See minor editorial comments on letter.

C:\Data\Wpfiles\N21060AE.doc

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/s/

Leah Ripper
7/23/01 03:53:33 PM
CSO

Hi, Gus:

We have another information request from the medical officer regarding ɔnotide. For the sake of timeliness, I am attaching these questions ɔn this e-mail. I will follow with a formal information request letter later during the week. Thank you in advance for your assistance. Your timely response is greatly appreciated. If you have any questions please do not hesitate to contact me.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

301-827-7423 (direct line)
301-443-7068 (fax)

We note while examining subject line listings of ECG data for study 98-022 that approximately 58 subjects are reported to have QT/QTc prolongation as an ECG descriptor following exposure to ziconotide. Approximately 26 of these subjects were reported to have "normal" ECGs at screening/baseline. Approximately 24 other subjects are reported to have "abnormal" ECGs at screening/baseline, with no mention of QT/QTc prolongation at screening/baseline, but subsequently are reported to have QT/QTc prolongation after ziconotide exposure. We also note that QT/QTc prolongation is not listed as a treatment emergent event in your tables of all adverse events for Group A studies (Table 8.8.2.7-1), serious adverse events for Group A studies (Table 8.8.2.8-6), or Group C study (Table 8.8.2.8-9). These observations raise two serious concerns regarding the adverse event database for ziconotide. The first concern is the completeness with which all treatment emergent events were captured across the development program because the treatment emergent event, QT/QTc prolongation, is not listed in any of the adverse event tables mentioned above. Yet we note at least 58 reports. The second concern relates directly to the collection and interpretation of ECG data.

To address these concerns you will need to address the following issues regarding ECG data collection and interpretation for Study 98-022:

1. Describe how ECG data were collected, specifically addressing the methods and equipment used and explaining what ECG was considered baseline prior to entry into this open-label extension study.

2. Describe how and by whom ECGs were read including the number and succession of R-R intervals examined, blinding to patient and administration phase, and lead selection for any given multi-lead ECG tracing.

3. Explain what definition was used to declare QT/QTc prolongation and describe what method of QTc computation was used to correct for heart rate.

4. Reexamine your database and account for type and number of the ECG abnormalities that are treatment emergent and were not quantified in adverse event tables.

5. Catalog in tabular format, for each of the 58 subjects in study 98-022 with a treatment emergent ECG with QT or QTc prolongation, the baseline QT/QTc interval length, the abnormal QT/QTc interval length, and any follow-up ECG QT/QTc interval values. Include the date of the ECG.

6. Specifically examine and catalog in tabular format each report of the following treatment emergent events: ardiac arrest, sudden death, torsades de pointes, and ventricular arrhythmia/ tachycardia/ fibrillation. syncope, hypotension, postural hypotension, orthostasis, orthostatic hypotension, lightheadedness, and fainting, in association with QT/QTc abnormality. Please include patient identification, QT/QTc interval length, and magnitude of change from screening/baseline.

Based on the review of the data from Study 98-022, additional reanalyses of the ECG database may be necessary, from the intrathecal studies and possibly from the epidural and intravenous studies.

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/s/

Laura Governale
7/17/01 10:49:03 AM
CSO

Electronic Mail Message

Date: 6/19/01 1:22:21 PM
From: Laura Governale (GOVERNALEL)
To: Gus Aromin (GAromin@elanpharma.com)
Cc: Laura Governale (GOVERNALEL)
Subject: NDA 21-060/ziconotide

Hi, Gus:

Please provide the pain syndrome responsible for entering Study 98-022 for subjects #63-1485 and #172-1427. Thanks in advance for your assistance. If you have any questions, please do not hesitate to contact me.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

301-827-7423 (direct line)
1-443-7068 (fax)

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/s/

Laura Governale
7/17/01 10:47:24 AM
CSO

Electronic Mail Message

Date: 6/13/01 4:30:34 PM
From: Laura Governale (GOVERNALEL)
To: Gus Aromin (GAromin@elanpharma.com)
Cc: Laura Governale (GOVERNALEL)
Subject: NDA 21-060/Question

Hi, Gus:

I'm writing to see if you can help us get some clarity on a table in the ziconotide submission. The table in question is "Table 8.8.2.9-2: Change from Screening to Study Termination in Serum Chemistry Tests - All IT Clinical Studies (Group A)" in I. 8 V. 005 P. 114. The numbers listed in the column titled "Ever Received Ziconotide" appears different from the numbers in the original ISS table. Could you help clarify why that is or provide an explanation for the discrepancy? Thanks in advance for your assistance. If you have any questions, please do not hesitate to contact me.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

301-827-7423 (direct line)
301-443-7068 (fax)

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/s/

Laura Governale
6/11/01 06:04:36 PM

Electronic Mail Message

Date: 6/11/01 5:08:20 PM
From: Laura Governale (GOVERNALEL)
To: GAromin@elanpharma.com
Cc: Laura Governale (GOVERNALEL)
Subject: NDA 21-060/ziconotide clinical questions

Hi, Gus:

The medical officer has the following questions regarding ziconotide and the pump.

Questions:
1. What is the lowest rate at which the Synchromed pump can be set?
2. Can it pump as little as [redacted]
3. Using 100 ug/ml solution, what are the actual steps a physician would follow to initiate an infusion of 0.1 ug/hr?
4. How much ziconotide 100ug/ml solution would be placed in the pump reservoir?
5. Would the solution by diluted at any point with sterile normal saline or other diluent?

Please send a response to these questions to me via e-mail at your earliest convenience. Your help is greatly appreciated.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

301-827-7423 (direct line)
301-443-7068 (fax)

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/s/

Laura Governale
5/29/01 04:34:07 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Dana Redhair
Director, Regulatory Affairs

Dear Mr. Redhair:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mcg/mL in 1, 2, and 5 mL fill vials.

Reference is also made to your submission dated January 26, 2001.

As discussed by telephone on April 10, 2001, between representatives of your firm and Dr. Thornton, Dr. Papoian, and Dr. Governale of this Division, please provide a written response to the following comments and information requests regarding the teratology studies.

1. For Study [redacted] 95625, provide tables for the following in the same format as the table presented on page 22, serial number N 000, Volume 1:

   a. [redacted] - irregular ossification
   reduced ossification.

   b. [redacted] – irregular ossification
   reduced ossification.

   c. Thoracic vertebrae centrum – semi-bipartite.

2. Provide a complete written argument to justify why the food consumption in the rat study correlates with the observed retarded skeletal ossification.

3. Provide analysis of the toxicokinetic data for the following studies:

a. Study no. [redacted] 95625 – A continuous infusion teratology study of SNX-111 in the rat.

b. Study no. [redacted] 95627 – A continuous intravenous infusion teratology study of SNX-111 in the rabbit.

For your reference, a copy of our minutes of the meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at 301-827-7410.

Sincerely,

{See appended electronic signature page}

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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/s/

Laura Governale
4/25/01 09:15:43 AM
CSO

MINUTES OF TELECON

DATE: April 10, 2001

APPLICATION NUMBER: NDA 21-060

BETWEEN:

Name: Dana Redhair, Director, Regulatory Affairs, Elan Pharmaceuticals
Gus Aromin, Associate, Regulatory Affairs, Elan Pharmaceuticals
George Shopp, Senior Scientist, Elan Pharmaceuticals
Jim Beck, Scientist, Elan Pharmaceuticals
[redacted]

Representing: Elan Pharmaceuticals

AND

Name: Tom Papoian, Ph.D., Supervisory Pharmacologist
Suzanne Thornton, Ph.D., Pharm/Tox Reviewer
Laura Governale, Pharm.D., Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: Rat teratology studies

A teleconference was held between the pharmacologists of this Division, and the sponsor in order to discuss the interpretation of the rat teratology (Segment II) study. Dr. Suzanne Thornton requested clarification on the definitions used by the [redacted] for "minor anomaly, variation, and absent" which were used as descriptors for the fetal skeletal findings in the rat teratology study. The sponsor replied that a major anomaly would entail a finding which result in fetal death or significantly impair survival of the pup. A minor anomaly would entail structural alterations that are relatively rare and are not detrimental to the survival of the animal. A variation would involve structural alterations which occur commonly in the species.

A general discussion between Dr. Thornton and the sponsor regarding the definition of "absent" in a skeletal finding occurred. Dr. Thornton inquired if "absent" meant that the bones, such as the pelvic bones, were truly absent or unossified. [redacted] indicated that since double staining of the fetal skeletons was not performed there is no way at this time to determine if the bones are truly absent or unossified. He also indicated that by Day 21 in the pre- and post-natal study (Segment III), all the pups appeared normal and therefore the CRO assumed that the pelvic bones had ossified albeit a transitory delay in ossification. Dr. Thornton stated that if the pelvic bones are absent, the drug will be labeled as a teratogen.

The sponsor stated that in this incidence the pelvic bone anomalies were considered minor due to what appeared to be a transitory retardation in bone development.

Dr. Thornton also requested an explanation from the sponsor regarding their position on the correlation between the reduced food consumption and observed retarded skeletal ossification. The sponsor replied that their position is supported in the literature published by Collins, *et al* and other references listed in their submission. Dr. Thornton requested a more complete written explanation for their position from the sponsor.

Dr. Thornton inquired whether the sponsor planed to analyze the plasma levels collected from the embryo-fetal studies in order to measure drug exposure levels. This request was previously made during a telephone conversation with Dana Redhair of Elan on February 28, 2001. The sponsor replied that they are in the process of analyzing the data and that they will forward the analysis to the Agency once completed.

Dr. Thornton requested clarification on the information presented for dam #1515, fetus #5; the pelvic bones for fetus #5 were noted as absent due to damage during examination. She inquired how only the pubic bones were damaged during the examination, since there were no notes by the examiner that other bones in the area were affected. She also inquired how the sponsor determined absent versus damaged in the report. The sponsor replied that during the examination of the lower abdominal organs, the pelvic bone may have been damaged incidentally. Incidental damages are reported in the appendices.

Dr. Papoian inquired whether the sponsor had considered conducting another focused reproductive toxicology study to examine bone development. The sponsor replied that they needed to discuss the matter further with the team before committing to another study. The sponsor inquired whether the results of the focused repro/tox study would lead to a Pregnancy Category B labeling. Dr. Papoian stated that conducing another study would not necessarily lead to a Pregnancy Category B labeling. This would depend on the interpretation of all existing data.

The Agency will forward a letter to the sponsor documenting the minutes of this telecon and relay action items via an advice letter.

The telecon adjourned.

Laura Governale, Pharm.D.
Regulatory Project Manager

Electronic Mail Message

Date: 4/4/01 2:31:29 PM
From: Laura Governale (GOVERNALEL)
To: GAromin@elanpharma.com
Subject: Questions for NDA 21-060

Hi, Gus:

The medical officer has several information requests regarding NDA 21-060/ziconotide. I decided that e-mail would probably be the most efficient method of communicating these requests. Please provide the following when you get a chance. If you have any questions, please do not hesitate to contact me.

Sincerely,
Laura Governale
301-827-7423

*****A****
In SAS transport file format, provide separate tables for the entire population, the low-dose population and the open-label population with the following information:

1. patient identification number
   site number
3. adverse event in verbatim term
4. adverse event in preferred COSTART term
5. adverse event by body system
6. date of onset of adverse event
7. date of resolution of adverse event
8. duration of ziconotide treatment at time of adverse event
9. dose of ziconotide during onset of adverse event
10. patient pain etiology - due to malignancy or not

**********B**********
Page 229 of I8, V.004, second paragraph, states that no specific AEs were reported for a statistically significantly greater porportion of ziconotide than placebo patients in the low-dose population. However, Table 8.8.2.7-9, p.231 reveals several statistically significant differences. Please provide an explanation for this discrepancy.

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/s/

Cathie Schumaker
4/24/01 11:12:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060

DISCIPLINE REVIEW LETTER

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Dana Redhair
Director, Regulatory Affairs

Dear Mr. Redhair:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mcg/mL in 1, 2, and 5 mL fill vials.

Reference is also made to your submission dated January 26, 2001.

Our review of your proposed proprietary name is complete. We have determined that the name "Prialt" is acceptable at this time. However, if the approval of this NDA application is delayed beyond 90 days from the date of this letter, the trade name "Prialt" must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Cathie Schumaker, R.Ph.
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Cynthia McCormick
3/21/01 07:07:28 PM

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 02-08-01	**DUE DATE:** 04-13-01	**OPDRA CONSULT #:** 01-0042

TO: Cynthia McCormick, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Laura Governale
Project Manager
HFD-170

PRODUCT NAME: **Prialt** (Ziconotide Injection) 100 mcg/mL 1, 2, and 5 mL **NDA #: 21-060**	**MANUFACTURER**: Elan Pharmaceuticals, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products, OPDRA conducted a review of the proposed name, Prialt, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA has no objections to the use of the proprietary name, "Prialt".

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the Name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Carol Holquist, R.Ph. for
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Julie Beitz, M.D. for
Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **April 10, 2001**

NDA NUMBER: **21-060**

NAME OF DRUG: **Prialt**
(Ziconotide Injection) 100 mcg/mL
1, 2, and 5 mL vials

NDA HOLDER: **Elan Pharmaceuticals, Inc.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products for assessment of the proposed proprietary drug name, Prialt, regarding potential name confusion with other proprietary/generic drug names. In addition, the container label, carton, and package insert labeling were also submitted for review of possible interventions in minimizing medication errors.

The sponsor, Elan, originally submitted the proposed proprietary name, ~~~ OPDRA completed a Proprietary Name Review for this product and did not recommend the use of the proprietary name, ~~~ The sponsor has submitted a new proprietary name, Prialt.

PRODUCT INFORMATION
Prialt contains ziconotide, and it is the synthetic equivalent of a naturally occurring peptide found in venom of the piscivorous marine snail, *Conus magus*. Prialt is the first of a new class of calcium channel blockers that selectively blocks neuronal N-type, voltage-sensitive, calcium channels. *In vitro* data suggests that Prialt may produce analgesia through blockage of neurotransmitter release at the primary afferent nerve terminals in the spinal cord. Prialt is indicated as adjunctive therapy for the management of severe, chronic, pain in patients who are not adequately controlled and/or intolerant to systemic opioids and for whom intrathecal therapy is warranted. The recommended dose is as follows:

Time (Days)	Hourly Dose (mcg/hr)	Total Daily Dose (mcg/24 hrs)
Day 1	0.1	2.4
Day 2	0.2	4.8
Day 3	0.3	7.2
Day 4	0.6	14.4
Day 5	1.2	28.8
Day 6	2.4	57.6

Prialt dose should be adjusted according to the severity of pain and incidence of adverse events. There is little evidence of additional clinical benefit above the recommended dose of 2.4 mcg/hr. Prialt should be used with a totally implantable programmable micro infusion system, or alternatively, an external delivery system. Prialt should only be administered intrathecally by or under the direction of a physician experienced in the technique of administering Prialt. Prialt is supplied as a 100 mcg/mL solution in single-use glass vials containing 1 mL, 2 mL, and 5 mL. It can be used undiluted or diluted with 0.9% Sodium Chloride Injection using aseptic procedure.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Prialt to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, Prialt. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Four products were identified in the Expert Panel Discussion that was thought to have potential for confusion with Prialt. These products are listed in Table 1 (page 4), along with the dosage forms available and usual FDA-approved dosage. Of these products, Maxalt and Pletal, were considered to be most significant, because they sound like and/or look like the proposed name, Prialt.

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

TABLE 1

[illegible]	[illegible]	[illegible]	[illegible]
Maxalt and Maxalt-MLT	Rizatripan benzoate tablets: 5 mg and 10 mg Orally disintegrating tablets: (MLT) 5 mg and 10 mg	A single dose of 5 mg or 10 mg at the onset of headache; may repeat in 2 hours. Maximum dose: 30 mg in 24 hours	S/A *per OPDRA
Pletal	Cilostazol tablets: 50 mg and 100 mg	50 mg to 100 mg po BID.	S/A, L/A per OPDRA
Priadel		**Not marketed in the United States.**	S/A, L/A per OPDRA
Priatan		**Not marketed in the United States.**	S/A, L/A per OPDRA

*Frequently used, not all–inclusive.
**L/A: look-alike, S/A-sound-alike.

DDMAC did not have any concerns about the names with regard to promotional claims.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

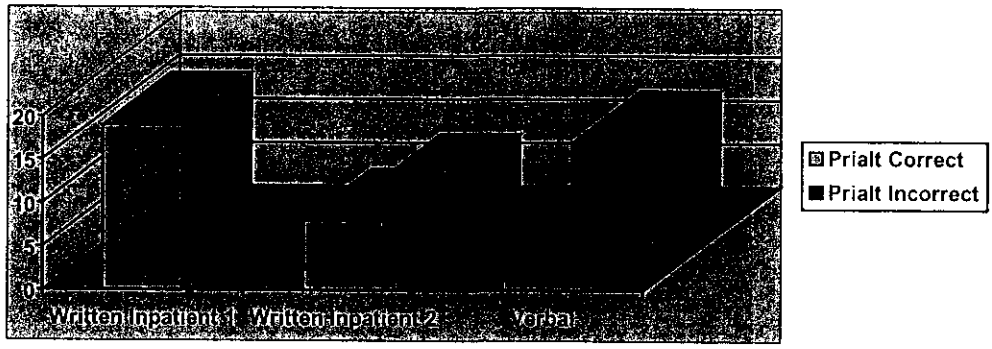
Three separate studies were conducted within FDA, to determine the degree of confusion of with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote two inpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Prialt. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient order that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Prialt	
Inpatient 1: Increase Prialt to 2.4 mcg/hr.	*Inpatient 1:* Increase Prialt to 2.4 microgram per hour.
Inpatient 2: Increase Prialt to 2.4 mcg/hr	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Prialt" response	Other response
Written: Inpatient 1	30	15 (50 %)	8 (53 %)	7 (47 %)
Inpatient 2	28	13 (46 %)	5 (38 %)	8 (62 %)
Verbal: Inpatient 1	28	13 (47 %)	1 (8 %)	12 (92 %)
Total:	86	41 (48 %)	14 (34 %)	27 (66 %)



Among participants in the two written inpatient prescription studies for Prialt, 13 of 28 respondents (46%) interpreted the name incorrectly. *Eight participants interpreted the name incorrectly as "Priatt." Three participants interpreted the name incorrectly as "Prialb." Other incorrect responses were "Priaet", "Ariact", and "Prialb."*

Among participants in the verbal prescription study for Prialt, 12 of 13 (92 %) participants interpreted the name incorrectly. *Three participants interpreted the name incorrectly as "Priol." Other incorrect responses were "Pryol", "Priopta", "Pial", "Priopt", "Prial", "Prile", "Prialt", and "Pri."*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, "Prialt," the expert panel identified *Pletal and Maxalt* as *most problematic with the potential for name confusion.* In addition, there was concern that Prialt closely resembles *Priadel* and *Priatan.* However, Priadel and Priatan are not marketed in the United States. We conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. Our study did not confirm confusion between *Prialt* and *Maxalt* or *Pletal.* The misinterpretations did not overlap with any currently approved drug names. The majority of incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Prialt. However, a negative finding does not discount the potential for name confusion given the small sample size.

Maxalt is a selective 5-hydroxytryptamine $_{1B/1D}$ (5-HT $_{1B/1D}$) receptor agonist that contains rizatriptan benzoate. Maxalt is indicated for acute treatment of migraine attacks with or without aura in adults. The risk of potential confusion between Prialt and Maxalt is unlikely, because Prialt is available as 100 mcg/mL intrathecal injection and Maxalt is available as 5 mg and 10 mg tablets. In addition, Prialt injection must be administered under the supervision of a physician experienced in the use of intrathecal agents and it must be administered in a facility that is prepared to manage complications that are associated with Prialt. The strict use of Prialt will further decrease the risk of name confusion with Maxalt. Lastly, Maxalt may sound similar to Prialt, however, the prefixes, "Max" and "Pri" differ enough to distinguish one name from another.

Prialt and *Pletal* sound and look alike, however they differ in dose, dosage form, and indication. Pletal (cilostazol) is indicated for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance. Pletal is available in 50 mg and 100 mg tablets for oral administration. The recommended dosage of Pletal is 100 mg twice daily taken at least half an hour before or two hours after breakfast and dinner. It is unlikely that Prialt, an intrathecal injection solution, would be confused for Pletal, an oral tablet. In addition, Prialt injection must be administered under the supervision of a physician experienced in the use of intrathecal agents and it must be administered in a facility that is prepared to manage complications that are associated with Prialt. Although Prialt sounds and looks similar to Pletal, the strict use of Prialt will further decrease the risk of name confusion with Pletal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

[redacted]

[vi] USP 24/NF 19: U.S. Pharmacopeia and National Formulary, 1999, The United States Pharmacopeial Convention, Inc., Rockville, MD, p.2112, "Injections".

ADM-9

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

IV. RECOMMENDATIONS

1. OPDRA has no objection to the use of the proprietary name, Prialt.

2. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

Hye-Joo Kim
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Carol Holquist, R.Ph. for
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Hye-Joo Kim
4/12/01 11:01:19 AM
PHARMACIST

Carol Holquist
4/12/01 11:23:21 AM
PHARMACIST

Julie Beitz
4/12/01 11:46:01 AM
DIRECTOR
Signing for Martin Himmel, MD

MEMORANDUM OF TELECON

DATE: February 6, 2001

APPLICATION NUMBER: NDA 21-060

BETWEEN:

Name: Ron Kartzinel
Michael Scaife
Dana Redhair
Phone: 650-794-4281
Representing: Elan Pharmaceuticals

AND

Name: Cynthia G. McCormick, M.D., Director
Sharon Hertz, M.D., Medical Reviewer
Laura Governale, Pharm.D., Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: Class 2 resubmission dated January 26, 2001

Dr. McCormick informed the sponsor that the submission does not qualify as a Class 1 resubmission as stated in the sponsor's cover letter of the January 26, 2001, submission. This submission will be reviewed as a Class 2 resubmission under the 6-month clock. Furthermore, the request for Accelerated Approval is not appropriate at this time; this is a matter for review. Ultimately, a post hoc analysis of the secondary endpoint is not acceptable as a surrogate endpoint. It appears that the sponsor has responded to all the issues in the Approvable letter dated June 27, 2000, except for conducting a new clinical trial. It is in the sponsor's best interest to conduct a new clinical trial as soon as possible. The sponsor may also opt to submit a Treatment IND to defray the cost of running another study. In addition, the NDA is not eligible for orphan drug designation due to the fact that the NDA was filed before the orphan designation request.

Dr. Kartzinel stated that an orphan drug designation would aid in conducting an additional clinical study. The sponsor did not realize at the start of the development of this program that the drug would be used in a smaller population. Dr. McCormick replied that the Office of Orphan Products will have to make the final evaluation on whether ziconotide will qualify for orphan status.

In regard to the synopsis of the planned new clinical trial, Dr. Hertz stated that the sponsor should incorporate a slower titration schedule. At the August 17, 2000, meeting, it was suggested that the final dosing regimen was still too aggressive and that a slower titration was better tolerated by the patients. The new study should be designed to show a useful and

safe dose titration schedule which could easily be written into the label for dosing instructions. The sponsor replied that patients seem to respond best to the 2-3 week titration period; however, it will be difficult to keep the study blinded because the placebo patients may drop out of the study. Dr. Hertz added that a 2-3 week titration period is not unreasonable with adequate rescue in the protocol. The sponsor replied that they will consider this point while designing the protocol and added that this may be a challenge to have a comparison group unless last-observation-carried-forward (LOCF) is used. For morphine resistant patients, Dr. Hertz recommended that the sponsor may choose enteral, systemic or transdermal opiods. Other intraspinal agents should not be mixed with intraspinal opioids.

Dr. McCormick encouraged the sponsor to submit the new protocol to IND 45,718 as soon as possible. In addition, the sponsor was requested to provide a re-indexed table of contents for the January 2001, submission and transfer data from the tapes onto CD ROMs.

The telecon adjourned.

_____

Laura Governale, Pharm.D.
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,718

Elan Pharmaceuticals
800 Gateway Bldv.
South San Francisco, CA 94080

Attention: Ronald Kartzinel, MD., Ph.D.
Vice President, Project Team Leader

Dear Dr. Kartzinel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ziconotide.

We also refer to your amendment dated February 23, 2001, (serial # 200), containing the protocol synopsis for the confirmatory clinical study of ziconotide.

We have completed the clinical review of your submission and have the following comments and recommendations.

1. The overall design described in this protocol synopsis appears appropriate to meet the stated objectives. However, the full protocol will need to be reviewed prior to our issuing a final opinion.

2. There should be a period of stabilization of at least 48 hours prior to the final assessment at the end of the three-week titration period.

3. You should consider methods for the handling of missing data other than LOCF which may bias in favor of the study drug in this type of study.

If you have any questions, call Laura Governale, Regulatory Project Manager, at 301-827-7410.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ADM-10

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NDA 21-060

COPY

Elan Pharmaceuticals
800 Gateway Boulevard
South San Francisco, CA 94080

Attention: Ronald Kartzinel, M.D., Ph.D.
Senior Vice President
Regulatory Affairs.

Dear Dr. Kartzinel:

Please refer to the Type A meeting between representatives of your firm and FDA on August 17, 2000. The purpose of the meeting was to discuss the items on the Approval letter dated, June 27, 2000, and the specific questions submitted in the meeting package dated, July 24, 2000.

A copy of our minutes of the meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: August 17, 2000 **IMTS#** ~
Time: 10:30 am – 12:30 pm
Location: Potomac Conference Room
Drug: Ziconotide solution 100 mcg/mL
Sponsor: Elan Pharmaceuticals
Indication: management of severe, chronic pain
Type of Meeting: Type A Meeting
Meeting Chair: Cynthia G. McCormick, M.D., Director
Minutes Recorder: Laura Governale, Pharm.D., Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
John Jenkins, M.D.	Office Director	HFD-102
Cynthia McCormick, M.D.	Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Steve Koepke, Ph.D.	Chemistry Supervisor	HFD-820
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Sharon Hertz, M.D.	Medical Reviewer	HFD-170
Michael Theodorakis, Ph.D.	Chemistry Reviewer	HFD-170
Chien-Hua Niu, Ph.D.	Protein Chemistry Reviewer	HFD-510
Paul Stinavage, Ph.D.	Microbiology Reviewer	HFD-805
Patricia Cricenti, M.D.	CDRH	HFZ-480
Peter Cooney, Ph.D.	Supervisory Microbiologist	HFD-805
Sammie Beam, R.Ph.	OPDRA	HFD-400
Carole Pamer, R.Ph.	Safety Evaluator, OPDRA	HFD-400
Gerald Dal Pan, M.D.	Medical Officer	HFD-170
Patricia Hartwell, M.D.	Medical Officer	HFD-170
Nancy Chang, M.D.	Medical Officer	HFD-170
Laura Governale, Pharm. D.	Regulatory Project Manager	HFD-170

Participants:	Titles:
Ronald Kartzinel, M.D., Ph.D.	Sr. Vice President, Regulatory Affairs
Michael Scaife, Ph.D.	Vice President, Regulatory Affairs
Kent Shellenberger, Ph.D.	Vice President, Clinical Affairs
Dave Ellis, M.D., Ph.D.	Medical Director, Clinical Affairs
Martha Mayo, Pharm.D.	Senior Director, Clinical Affairs
Jim Callaway, Ph.D.	Vice President, Pharmaceutical Development
Sherri Barrack, Ph.D.	Director, Technical Affairs
David Burke, Ph.D.	Director, Technology Development

[redacted]

John Groom — President, Chief Operating Officer, Elan Corporation, plc

Meeting Objective: The primary objective of this meeting was to discuss the issues raised in the Approvable letter dated June 27, 2000, and answer specific questions raised in the meeting package dated July 24, 2000. The sponsor's questions appear in italics.

General Discussion: Following introductions, Dr. McCormick outlined the agenda for the meeting. The questions submitted in the meeting package dated July 24, 2000, have been reframed in order to direct focus on what needs to be done to approve the drug. The format of the meeting will take place in three parts.

- Part 1 will deal with issues on microbial growth, drug adsorption, and efficacy. These are the three main outstanding issues that stand in the way of drug approval.
- Part 2 will deal the issue of safety data reanalysis and how some of the data from the NDA can be resurrected. Case report forms (CRFs) will also be discussed.
- Part 3 will address regulatory options for future submissions.

The Division will answer the questions that can be resolved quickly first, and then proceed with the agenda.

1. *Question 13: Does the FDA agree that the proposed NMR method and specification are adequate? If not, what are the concerns with the use of this test?*

   Dr. Niu replied that the proposal is adequate. He would like the sponsor to assign a specific value for the NMR specifications. The sponsor agreed with Dr. Niu's statement.

2. *Question 5: Does the FDA agree with this approach to confirm biological activity addressed in Item 4 (D)?*

   Dr. Theodorakis replied that the Agency is generally in agreement with the sponsor's proposal as stated on page 5 of the July 24th meeting package with the exception that the sponsor must provide binding assay testing data for the samples on stability testing before approval can be granted.

Dr. McCormick returned to the items addressed in the agenda.

Part 1 deals with three critical issues which were not adequately presented in the NDA.

1. The question of whether the peptide solution can or cannot support the growth of microorganisms should accidental inoculation occur must be addressed. The Agency cannot have an informed discussion about reformulation without this information.

2. The adsorption of drug onto the inner surface of the reservoir needs to be addressed in terms of the capacity to facilitate infection and the actual delivery of the drug during clinical trials. The Agency would like to see data to put these concerns to rest.

3. The efficacy of the drug is still in question. The NDA presented insufficient evidence of efficacy. This can only be remedied with another clinical trial.

Part 2 deals with the reanalysis of the safety data to provide informed labeling and Part 3 deals with regulatory options for future submissions.

For the first issue in Part 1, the sponsor has posed three questions related to this critical issue; whether the peptide solution can or cannot support the growth of microorganisms if accidental inoculation occurs.

3. *Question 1: Is FDA aware of incidences of meningitis with implanted infusion systems beyond the two reported in the NDA?*

Dr. McCormick replied that the Agency is aware of only 2 cases of meningitis as reported in the NDA. However, the small number of cases of fatal meningitis does not provide an adequate response to the underlying question. Other reasons why the clinical reports of meningitis are not sufficient to assuage concerns regarding safety are due to the nature of clinical trials. In these trials, the drug was administered under controlled situations, using careful technique, and the patients were concomitantly treated with antibiotics. To use an example set by [redacted] brand of propofol, post-marketing surveillance revealed a high number of incidences of sepsis and infection due to accidental contamination of the product during drug administration. These adverse events were not detected during clinical trials; however, this report resulted in a strict warning on the label and reformulation of the product.

The studies that were provided, specifically, the microbial growth promotion study, do not provided adequate assurance that the peptide broth in vivo does not have the capacity to act as a culture medium.

4. *Question 2: Do the final results of the microbial growth studies provide adequate assurance that ziconotide has sustained sterility comparable to other approved intrathecally administered drugs?*

Question number 2 as stated in the meeting package has been revised to one that is more relevant. The microbial growth promotion study provided references to growth in other products; however, it does not remove the burden from Elan to establish that ziconotide, a peptide product, does not support the growth of microorganisms should an accidental

inoculation occur. There are two reasons for concern. One reason is that any serious infection that can be prevented should be. The second is that the bacterial growth may digest the drug peptide and compromise the stability and the potency of the product over time. The reframed question that the Agency will answer is: ***Do the final results of the microbial growth studies provide adequate assurance that ziconotide has sustained sterility?***

In response to the reframed question, Dr. Stinavage replied that he is not satisfied with the results of the microbial growth studies. More specifically, the growth pattern of [redacted] is in conflict with the growth pattern of [redacted] in the study results. Since these two organisms are in the same genus, the growth characteristics are expected to be similar. Secondly, given the lack of growth in the saline controls, one is led to question the results of the entire study. The Agency is therefore unable to answer the underlying question whether this product can support the growth of microorganisms. The following information is needed in order for the Agency to assess sustained sterility for the drug product.

1. Repeat the microbial growth promotion study. The need to complete the other two studies is dependent on the results obtained in this study.

   The sponsor should submit a new protocol for review for the microbial growth promotion study. Essentially, the original protocol may be used with the exception of removing mycobacterium and increasing the inoculation level (greater number of organisms). The new protocol may include morphine as a comparator, but it is not necessary. Also, the duration of culture should be increased to 60 days if the labeling recommends a refill of every 60 days. The organisms should continue to be cultured in low nutrient media.

2. Validate the bacterial retention of the [redacted] filter with organisms cultured in the product solution.

   The [redacted] filter does not eliminate all problems should an accidental contamination occur. The filter itself may serve as a matrix for bacterial growth, and continually seed the intrathecal space with microorganisms, setting up an environment for meningitis. In published studies, [redacted] has been shown to pass through [redacted] filters; therefore, the Agency would like to review data that would verify the bacterial retentive capabilities of this filter.

3. Conduct a biofilm study of the pump reservoir and lines to show that there is no loss of activity of the drug product, and no formation of toxic metabolites from the microorganisms. Even though the relative carbon mass is much lower for ziconotide compared to morphine, the microbial organisms can still potentially survive in the ziconotide solution and contribute to loss of activity. The study should assay the active drug and the viable organisms.

These studies should allow the sponsor to predict the growth supporting characteristics of the drug product solution. The burden is on the sponsor to show that meningitis will not occur with this product.

5. *Question 3: Given the above data, will FDA confirm that a reformulation is not warranted?*

At this time, the Agency cannot answer this question in the absence of repeat microbial growth studies. Dr. Theodorakis stated that any reformulated product will require stability and compatibility studies with the pump, catheters, infusions and drug administered intrathecally, as well as, re-validation of some of the regulatory testing procedures for acceptance of the drug product. The Agency will accept the submission of the microbial reports as a condition of reformulation of the product.

The second issue in part 1 of this discussion deals with the adsorption of drug onto the inner surface of the reservoir. The question posed by the sponsor is as follows:

6. *Question 4: Does elimination of the [redacted] dilution and simplified instructions resolve concerns in Item 3? If not, what is the specific concern regarding adsorption?*

The concerns regarding adsorption are threefold:

- The infection control issue. The possibility that if ziconotide is a good culture medium, the adsorption of the drug can provide a continuous inoculum into the intrathecal space and if this occurs, stability may also be affected.

- The Agency must have convincing evidence that the adsorption does not lead to unreliable or variable delivery of the drug.

- The new repertoire suggested in the package for drug delivery must be identical with that given in the last protocol regimen in the clinical trial in which the drug was shown to be effective.

The sponsor presented information to demonstrate the adsorption characteristics for naive pumps versus pre-treated ziconotide pumps. The sponsor stated that the amount of drug adsorbed during the adsorption phase is approximately [redacted] of peptide, which is very low. By using a higher concentration of the drug, the amount of drug absorption is small enough overall to not have a significant clinical effect. In order to overcome the miniscule loss of the drug when using a naïve pump, the sponsor proposes to advise a refill time of 14 days, [redacted]

Dr. Jenkins inquired whether the drug remains attached to the lining of the pump. The sponsor replied that the [redacted]
Dr. McCormick raised the issue of sensitization and allergic reactions which was also brought up in the March 24, 1997, advisory committee meeting. Since the drug remains in the pump

lining and the reservoir, this may pose a danger for those patients who develop sensitivity to ziconotide. The sponsor stated that are no data to support evidence of sensitization. The sponsor also stated that the peptide forms a layer on the surface quickly and thickly. The overall amount absorbed is low and the drug can be delivered reliably within [redacted] of the target range which is well within the appropriate range. Also, ziconotide is a poor food source for microbes due to the low carbon mass. Dr. Rappaport commented that the Agency's main concern is with microbial growth. The other issues are a matter of adequacy of clinical data. Dr. Hertz stated that if the conclusion was made that ziconotide does not support the growth of microorganisms, the adsorption study would not be necessary and the Agency will evaluate the clinical data. Dr. Stinavage reiterated that if the repeated microbial growth studies yielded similar results of no growth, a reservoir study would not be required.

Furthermore, no instructions for refilling the pump were provided by the sponsor. Dr. McCormick instructed the sponsor to determine which diluant was used during the clinical trials in order to provide an instruction for refilling the pump.

Dr. Theodorakis inquired whether radio-tracer studies were conducted in order to elucidate the nature of binding of the drug product to the lining of the pump. The sponsor replied that [redacted] was not used because it will affect the ziconotide molecule. Dr. Theodorakis indicated that [redacted] labels could have been used. Dr. Theodorakis further stated that the pump manufacturer, Medtronic, should address the issue of treating the surface of the pump chamber in order to minimize adsorption.

Dr. Jenkins inquired what kind of effect a pump pre-treated with a different drug would have on the adsorption of ziconotide. The sponsor replied that this was not studied and that they would assume a conservative stance by advising a refill time of 14 days for all pumps that have not been pre-treated with ziconotide. Dr. Jenkins inquired whether the ziconotide would release what was previously in the pump. The sponsor replied that it is standard procedure to wash the pumps before filling with a new drug.

Dr. Koepke commented that pre-treating the pump will address the dosing and the clinical issue; however, the above hypothetical questions posed should be answered. Refilling the pump will only skirt the real problem of adsorption but not resolve the issue.

The third issue in part 1 of the discussion involves the efficacy of the drug. The following question posed by Elan relate to the issue of drug efficacy.

7. *Question 6: In Elan's view, resolution of the inconsistencies discussed above show studies 95-001 and 96-002 to be adequate to establish efficacy. Does the FDA concur?*

Dr. Permutt replied that all relevant analysis of the studies were post-hoc in nature, as the original protocol made no allowances for protocol changes which were numerous. The results fell short of demonstrating efficacy, and reanalysis will not likely resolve the problem. Also, the analysis of the sub-populations yielded bewildering results. While the significance of these differences among subgroups is not clear, the effectiveness of the drug has not been adequately demonstrated and characterized.

Dr. McCormick added that the dose finding was not done until the end of the trials and the PK/PD work was uncovered in the midst of the trials. Only a portion of each of the trials tested the regimen proposed in the label and in the case of study 001, there were questionable procedures which put the integrity of the data in question. The end result was a study which does not meet FDA standards for approval. This is not a matter of a single trial that showed borderline efficacy. This is a matter of a trial which was problematic from the outset, underwent reconstruction several times, was flawed with methodological problems, was probably unblinded in at least one center, and ultimately had too few patients left to be viable. This is not just a p-value problem. Even patched together, looking at the cohort that received close to the same regimen, a robust effect was not achieved. In addition, no mention of any opiate interaction on efficacy was analyzed as discussed in the March 24, 1997, advisory committee meeting. The only way to resolve the lack of demonstrable efficacy is to conduct another placebo-controlled clinical trial using the planned dosing regimen. It is feasible to conduct a short clinical trial using rescue medications in order to assuage ethical issues.

The sponsor inquired whether the Agency conducted further subgroup analysis on protocol revision number 3. Dr. Hertz replied that consideration was made in order to obtain the greatest number of patients for analysis. The patients were initially separated by initial dose and final dosing protocol. Dr. Mayo stated that it was not necessary to exclude the patients from the [redacted] site and that the conduct of the entire study was appropriate. Dr. Permutt replied that the Agency's view is that the study cannot be characterized as "adequate and well-controlled" unless the site is excluded. Dr. McCormick added that the recommendation to exclude the data from this site was made by the Division of Scientific Investigations and this Division has made the decision not to rely on that data.

The sponsor inquired whether orphan drug status could be granted [redacted] Dr. McCormick replied that the sponsor should be in contact with the Office of Orphan Drug Products for advice on this matter. Dr. Jenkins added that the standard of approval remains the same for all drugs whether or not orphan status is granted which includes two successful, adequate and well-controlled trials. The best way to resolve issues with efficacy is to conduct another study with the to-be-marketed regimen. He added that when problems exist at a clinical site the Agency will exclude the site from analysis and not search for a reason to retain it.

8. *Question 7: Can Study 98-022 be used as the basis for additional data requests from the Agency regarding the dosing regimen and target population proposed for labeling?*

In response to question number 7 posed by the sponsor, Dr. McCormick replied that an open label study such as 98-022 will provide additional safety data but will not support efficacy.

In regard to the dosing regimen, the sponsor stated that the investigators titrated the drug much more slowly in study 98-022 than what was allowed in the pivotal trials. The titration period lasted an average of 2 – 3 weeks. The dosing regimen was not exactly consistent with labeling but titrated to effect using a 1 – 2 μg/mL dosing increment per week. Since this was an open-label study, a forced titration was not used. Dr. Rappaport inquired how long it took

to get an appropriate level of effect. The sponsor replied that the drug reached an effect level at an average of 1- 3 weeks. The sponsor indicated that since the investigators are using a slower titration scheme which appear to be better tolerated, it is not ethical to use the faster titration scheme as was used in studies 95-001 and 96-002. Dr. McCormick added that since the dosing regimen for Study 98-022 differs from the regimen used in the pivotal trials, the safety and efficacy profiles will also differ. The sponsor will have to confirm which safety data correspond to which regimen. Dr. Kartzinel inquired as to what safety issues must be covered if another clinical trial is conducted. Dr. McCormick replied that another clinical trial using the regimen used in the previous pivotal trials should be conducted and that the safety profile should be described.

The sponsor stated that an advisory committee meeting may be requested in the future in order to gather opinions on the issue of conducting another clinical trials. Dr. Jenkins replied that the sponsor has the right to request an advisory committee meeting; however, the decision to grant the meeting remains in the Division's jurisdiction. The sponsor added that the patients' safety remains the primary concern in these trials. These patients have failed on all other pain medications and enrollment for a trial typically takes over 2 years. Dr. Hertz replied that Study 95-001 completed enrollment in 18 months and that many patients had not yet tried intrathecal morphine.

The sponsor requested clarification on the interaction by sex and age. Dr. Permutt replied that the Agency is not looking for statistical effect between the sexes and ages. The concern is that there is little information in the database that the drug works in general and the purported differences seen in the sexes and age groups are not reliable.

The second part of the agenda deals with safety data reanalysis and issues with the case report forms (CRFs). The questions posed by the sponsor are as follows.

9. *Question 8: Are the 98-022 data sufficient to satisfy the remaining safety and tolerability concerns in Item 1 and A(1)?*

10. *Question 9: Will the proposed analyses satisfy safety and tolerability concerns in Item I and A(l)? If not, what-other analyses would FDA suggest?*

11. *Question 10: Will FDA: accept the definition of "the subset of patients in Study 95-001 and Study 96-002 who were treated with the final revision of the dosing regimen" as all patients who received an initial dose of 0.1 μg/hour?*

In terms of numbers, the data from Study 98-022 will have to be folded into the overall cumulative safety update. The sponsor should redo the integrated summary of safety (ISS) and discuss what cohort to use with the Division. The sponsor should also study opiate interactions with ziconotide and possible withdrawal effects that may occur with concomitant use. The sponsor needs to develop a case definition and description of adverse drug reactions. Dr. Hertz stated that by remapping some of the case definitions such as confusion, thinking abnormal, and other comparable processes involving the CNS, the actual number of events for encephalopathy is higher than what was reported in the NDA. The sponsor should

consider a manner of mapping of the terms that would bring similar underlying problems together. Another problem with the CRFs was inadequate descriptions of adverse events that failed to include outcome or follow up. Some of the reported cases of encephalopathy did not reverse in a number of patients and were ongoing at the conclusion of the trial. There were 16 cases of ongoing encephalopathy at the end of reporting and 5 cases ongoing at the time of death. Additional information on the primary toxicity of the drug should be gathered.

12. *Question 11: What is the nature of inadequate documentation of important clinical information mentioned in Item 1(f)? Please provide some example CRFs.*

13. *Question 12: Is there a preferred format for CRF data that we should use for the Amendment?*

The above two questions were answered in the above discussion.

The third part of the agenda deals with the logistics of amendment submission and other regulatory options.

14. *Question 14: Will the Agency accept a rolling submission of the Complete Response to the Approvable letter of June 27, 2000?*

Dr. McCormick replied that the Agency will accept a rolling submission; however, the submission will not be considered a complete response until the last piece of information is submitted to the Agency. Furthermore, the Agency will do its best to respond to the issues as they roll in, however, the Agency cannot commit to a specific turnaround time.

Other regulatory options that may be available to the sponsor are treatment INDs and orphan designation. These options, if available, may help curb the cost of conducting the additional clinical trial as requested by the Agency.

Several key factors must be addressed before an additional clinical trial is initiated. The issue of microbial growth and adsorption must be addressed before any thought can be given to reformulation of the product, if that need arises. Once these issues have been satisfactorily addressed, the sponsor may move forward with the clinical trial.

The sponsor replied that they are committed to resolving the microbial growth and the adsorption issues before moving forward with a clinical trial.

Dr. McCormick adjourned the meeting.

Action Items:

- The Agency will provide the sponsor with a copy of the official meeting minutes.
- The sponsor will submit a protocol for the microbial growth study to the Agency before initiating the study.

Minutes prepared by: Laura Governale, Pharm.D.

_____

Minutes concurred by Chair: Cynthia G. McCormick, M.D., Director

_____

CC:

HFD-170/Division Files
HFD-170/L. Governale
HFD-170/S.Hertz, D.Brase, T.Permutt, S.Kim, S.Grosser, D.Koble, M.Theodorakis, R.Uppoor
HFD-820/S.Koepke
HFZ-480/P.Cricenti
HFD-510/C.Niu
HFD-805/P.Stinavage, P.Cooney
HFD-400/S.Beam, C.Pamer
HFD-170/C.Schumaker, B.Rappaport, C.McCormick

Drafted by: L. Governale/8-21-00

Initialed by	Date
C.Schumaker	8-30-00
P.Stinavage	8-30-00
M.Theodorakis	8-30-00
Tom Permutt	8-31-00
Sharon Hertz	8-31-00
Bob Rappaport	9-6-00
John Jenkins	9-8-00

Final: C.McCormick/9-15-00

FILE NAME: 21060(Elan)MM081700.doc

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Sheldon Mullins

Date: 6-27-00

Fax #: 650-616-5053

Pages: 4
(INCLUDING THIS COVER SHEET)

From: Laura Governale

Subject: Discipline Review letter - cmc

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

DISCIPLINE REVIEW LETTER

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Sheldon Mullins
Regulatory Affairs

JUN 2 7 2000

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application for ziconotide 100 mg/mL in 1, 2, 5, mL vials.

We also refer to your amendments dated January 12, March 10, 22, April 7, 14, May 1, 11, 19, 22, and May 26, 2000.

Our review of the chemistry, manufacturing, and controls section of your submissions is complete and we have identified the following deficiencies. Please provide an amendment to address the following concerns.

1. Provide information about the maximum batch size that you are planning to manufacture at both the facilities.

2. Clarify the time that is required for the glass vials

3. The following comments pertain to the stability studies.

   a. Provide your proposed post-approval stability protocol. Include binding assay and total impurities monitoring at all time points.

   b. The binding assay values reported on page 317 of Volume 1.1 should have included data on lots placed on stability at the proposed expiration dating period. The stability tables that you submitted on pages 46 –112 of Volume 6.1, did not include results of the binding assay. Provide data to show that the drug product will meet the specification for binding assay at the end of the expiration dating period.

   c. Please explain why total impurities were not included in your stability report.

d. In order to grant an expiration dating period of 24 months for the 5 mL [redacted] drug product, demonstrate that the drug product will meet the specification for binding assay at the end of that period.

e. The requested expiration dating period of [redacted] for the 1 mL and 2 mL drug product, cannot be granted on the basis of [redacted] stability data. It is proposed that a [redacted] expiration dating period be assigned to these drug products, provided that you demonstrate that at the end of the [redacted] period the drug product met the specification for binding assay.

4. The following comments pertain to compatibility and stability of the drug product with the implantable Medtronic SynchroMed infusion pump.

a. Explain the late variability observed in the pumps, both ziconotide naive and ziconotide pre-treated, loaded with [redacted] concentration (see pages 141 and 195, volume 1.11).

b. [redacted]

c. On page 133 of Volume 1.11, you referred to Medtronic SynchroMed Programmable Pump Model Number [redacted] This model does not appear in the report. Please clarify.

d. On the Data Summary Tables (pages 182-184, volume 1.11), on the top of each table you are referring to Day 15. Should this be Day 16?

e. [redacted]

f. You have stated that there were no substances extracted from the catheter (see page 64, Appendix 49, Volume 1.12). However, the HPLC chromatograms on pages 71-76 of Volume 1.12 included peaks labeled as extractables. In addition the [redacted] report stated clearly that an extraneous peak was present and that it appeared only in samples pumped through the catheter (see page 79, Volume 1.12). Provide information to explain the apparent contradiction.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Sheldon Mullins

Date: 6-26-00

Fax #: 650-616-5053

Pages: 2
(INCLUDING THIS COVER SHEET)

From: Laura Governale

Subject: Advice letter - Biopharm

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

JUN 2 6 2000

Attention: Sheldon Mullins
Regulatory Affairs

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application for ziconotide 100 mcg/mL in 1, 2, 5, [redacted] mL vials.

We also refer to your amendment dated April 28, 2000.

We have completed the clinical pharmacology and biopharmaceutics review of your submissions and have the following comments and recommendations.

> A more specific assay method for ziconotide needs to be developed and used for future studies.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

DISCIPLINE REVIEW LETTER

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Sheldon Mullins
Regulatory Affairs

MAY 2 5 2000

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We also refer to your amendments dated April 12 and 27, 2000.

Our review of the pharmacology and toxicology section of your submissions is complete, and we have identified the following deficiencies concerning the pregnancy category labeling for the drug product. Please provide an amendment to address the following concerns.

1. Review of the rat teratogenicity study has led to the conclusion that when administered by continuous IV infusion, ziconotide is teratogenic in rats. Consequently, ziconotide should be classified under Pregnancy Category C.

2. When exposure levels in terms of plasma concentration or AUC are not known for the dose(s) studied, the standard mode for expressing animal dosage as a multiple of the maximum recommended daily human dose is to compare animal and human doses on a mg/m^2 body surface area basis, using 1.62 m^2 as the reference body surface area for a 60 kg human.

The following draft revision of the labeling is recommended, which incorporates the above two issues.

Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted]

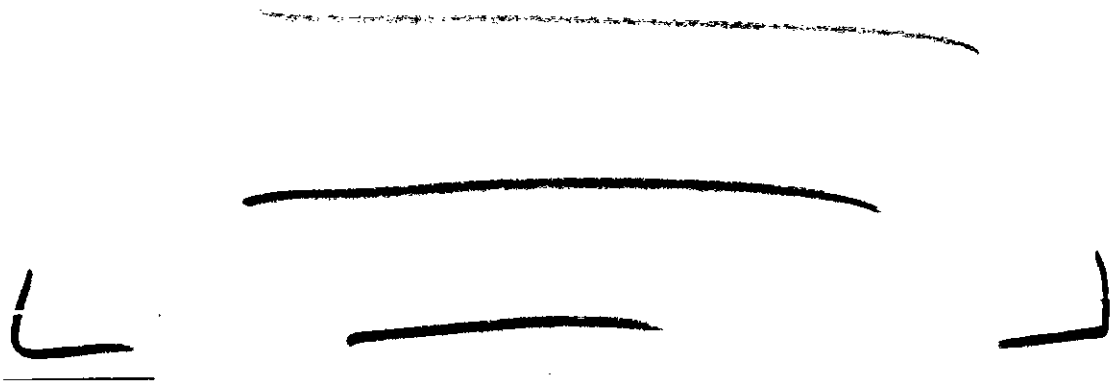
ADM-11

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Phase 4 Commitments:

Not applicable at this time.

Appears This Way
On Original

FDA revised Labels & Labeling and Reviews:

Not applicable at this time.

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Sheldan Mullins

Date: 5-15-00

Fax #: 650-616-5053

Pages: 2
(INCLUDING THIS COVER SHEET)

From: Laura Gavernale

Subject: clinical information clarification.

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

FAXED

MAY 15 2000

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Sheldon Mullins

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the clinical section of your submission and have the following request for clarification. We need your prompt response to continue our evaluation of your NDA.

Table 8.8.3.5.3 (I8, V004, P052) reports 11 patients who terminated from studies early due to intolerable adverse events, and 70 deaths. From the narratives, I8 V184 P 260 and I8 V184 P135, there are a total of 23 patients who discontinued due to adverse events, and 75 deaths. Please clarify why these totals are different.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC:
Archival NDA 21-060
HFD-170/division file
HFD-170/C.McCormick, B.Rappaport, C.Schumaker
HFD-170/S.Hertz, L.Governale

Drafted by: lg/5-15-00
Initialed by: Hertz/5-15-00
Final: L.Governale/5-15-00
filename: 21060(Elan)IR051500.doc

INFORMATION REQUEST LETTER (IR)

ADM - 12

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Sheldon Mullins

Date: 5-10-00

Fax #: 650-616-5053

Pages: 3
(INCLUDING THIS COVER SHEET)

From: Laura Governale

Subject: Information request - CRF's

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

FAXED

INFORMATION REQUEST LETTER

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Sheldon Mullins

MAY 1 0 2000

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the clinical section of your submission and have the following information request. We need your prompt response to continue our evaluation of your NDA.

Please provide us with the following CRF's. Electronic format would be preferable to paper.

501-81	35-1309
5006-25	35-1382
5007-77	35-1436
5012-51	63-1202
5015-50	66-1081
5029-1	78-1246
5029-93	80-1002
6055-106	82-1439
6060-112	87-1212
6068-102	91-1034
6069-101	91-1041
6069-102	91-1058
6069-113	116-1279
6073-101	118-1023
6073-103	118-1411
6076-103	119-1186
6085-103	119-1322
6090-113	119-1030
6091-102	151-1220
204-68	152-1373
12-1126	157-1451
122-1144	171-1433
124-1487	174-1422

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY - 9 2000

Steven Charapata, M.D.
Research Medical Center
The Pain Institute
2316 East Meyer Blvd.
Kansas City, MO 64132

Dear Dr. Charapata:

Between March 8 and 15, 2000, Ms. Linda Kuchenthal, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (Protocols # 95-001 and 96-002) of the investigational drug Ziconotide (SNX-111) administered intrathecally. You conducted this study for Elan Pharmaceuticals.

This inspection is part of FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

From our evaluation of the inspection report, we conclude that you conducted your study in compliance with the applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Kuchenthal during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

David A. Lepay, M.D., Ph.D.
Director
Division of Medical Policy, HFD-45
Center for Drug Evaluation and Research
Room 125
7520 Standish Place
Rockville, MD 20855

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Sheldon Mullins/Elan Pharmaceuticals, Inc.
Phone Number: 650-616-2636
Fax Number: 650-616-5053

FROM: Cathie Schumaker

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: May 5, 2000

COMMENTS: Please call Laura Governale at 301-827-7410 if you have any questions. She will return to the office this afternoon. CS

NDA 21-060/Ziconotide 100 mg/mL

Please provide the following information as soon as possible.

1. On I9, v001 P259 , it states that 282 of 887 patients had SAEs in the IT 120 day safety update, 240 of 704 in the IT ISS and 28 of 183 from the new patients not previously included. 282

   -240

   -28

   14

   Are these additional 14 patients SAEs from patients enrolled previously but for whom the SAE occurred or was reported after the cut off date for the original NDA submission?

   Please identify these patients.

2. Page I9V001 P259 states that there were 16/887 patients with meningitis. My review of the narratives and tables of patients with SAEs results in the following 29 cases of meningitis. Please clarify which patients are included in the count of 16 and why the remaining 12 patients were not included.

1. Patient 100-107	15. Patient 091-1032
2. Patient 400-403	16. Patient 012-1189
3. Patient 400-405	17. Patient 101-1088
4. Patient 501-75	18. Patient 012-1190
5. Patient 5002-25	19. Patient 012-1378
6. Patient 5006-75	20. Patient 134-1253
7. Patient 5012-73	21. Patient 135-1087
8. Patient 5025-73	22. Patient 135-1100
9. Patient 5029-27	23. Patient 135-1127
10. Patient 5097-50	24. Patient 135-1192
11. Patient 6058-101	25. Patient 138-1350
12. Patient 6060-113	26. Patient 6059-108
13. Patient 6086-103	27. Patient 063-1485
14. Patient 6090-105	28. Patient 123-1555

3. Only 3 narratives for patients in Table 6.1, Additional Serious Adverse Events, I9 V 051 P 350 were provided. Please provide narratives for the remaining patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

FAXED

APR 2 8 2000

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

Attention: Sheldon Mullins

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the CMC section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

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.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

FAXED

APR 2 6 2000

Attention: Sheldon Mullins

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the PK section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. To facilitate evaluation of the 'Dose-Response' relationship following IT infusion of ziconotide, please provide the following information: This request pertains to the study Nos. 95-001 and 96-002. Provide infusion rate, cumulative dose and the mean percent improvement in VASPI score from baseline per Day (treatment) (Mean % change) for ziconotide-treated patients as well as for subjects in placebo group, using table format (example is shown below). Also provide the same information (and same format) for subjects who received the final protocol dose schedule (34 subjects for the study 95-001) in a separate table (i.e., 3 tables per study, total 6 tables). Please provide the tables on a diskette in EXCEL format.

Treatment Day	Infusion Rate (μg/hr)	Cumulative Dose (μg)	Mean % Change
Day 1 Subject 1 Subject 2 ..... Subject n			
Day 2 Subject 1 Subject 2 ..... Subject n			
Day 3 Subject 1 Subject 2 ..... Subject n			
Day 4 Subject 1 Subject 2 ..... Subject n			
Day 5 (or 6) Subject 1 Subject 2 ..... Subject n			

1. Please provide full assay performance report for the RIA method used for study Nos. 95-001, 96-002, 95-002, 94-004 and 96-003.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CC:
Archival NDA 21-060
HFD-170/division file
HFD-170/C.McCormick, B.Rappaport, C.Schumaker, R.Uppoor
HFD-170/S.Kim, S.Hertz, L.Governale

Drafted by: lg/4-26-00
Initialed by: C.Schumaker/4-26-00, S.Hertz/4-26-00, S.Kim/4-26-00
Final: L.Governale/4-26-00
filename: 21060(Elan)IR042600.doc

INFORMATION REQUEST LETTER (IR)

ADM-13

10 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

ADM-14

16 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

FAXED

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

APR 1 8 2000

Attention: Linda B. Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Table 8.8.2.7.1 presents the incidence of adverse events for all of the intrathecal studies combined. The clinical reviewer would like to look at some of the adverse events mapped to different COSTART terms. Table 4.1 in Appendix 1 already uses the remapped terms. There are AE.xpt files for studies 95-001, 95-002, 96-002 and 98-022 and not the remaining 5 studies which contribute to the safety data. Please provide the source data for table 8.8.2.7.1.9 and Appendix 1, IT Table 4.1. or AE.XPT files for the remaining 5 studies so that the reviewer can re-map the adverse event terms and recalculate the incidences of adverse events for the intrathecal safety group.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

2. Please provide full assay performance report for the RIA method used for study Nos. 95-001, 96-002, 95-002, 94-004 and 96-003.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

APR 17 2000

FAXED

Attention: Linda B. Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, [redacted] mL vials.

We are reviewing the clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Table 8.8.2.7.9 presents the incidence of adverse events for the initial titration phase of studies 95-001 and 96-002 together. This represents the placebo controlled, double blinded portion of these studies. The clinical reviewer would like to look at some of the adverse events mapped to different COSTART terms. Table 4.2 in Appendix one already uses the remapped terms. The tables entitled AE.XPT in the 95-001 and 96-002 CRT listings do not specify which adverse events took place during the initial titration phase. Please provide the source data for table 8.8.7.9 and Appendix 1, IT Table 4.2 or an amended AE.XPT for each pivotal study so that the reviewer can re-map the adverse event terms and recalculate the incidences of adverse events for the initial titration period. Please provide this information in a format from which subgroup analyses for gender and age can be performed.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Fax

élan
pharmaceuticals

REGULATORY AFFAIRS, 700 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 616-2636 - Fax (650) 877-7699

TO:	FOOD AND DRUG ADMINISTRATION	FAX NO.:	301-480-8682
ATTN:	LAURA GOVERNALE, PHARM.D.	DATE:	13 Apr 00
FROM:	SHELDON MULLINS	TOTAL PAGES:	9
SUBJECT:	ZICONOTIDE NDA 21-060	CC:	

PLEASE DELIVER IMMEDIATELY. THANK YOU.

Dear Dr. McCormick,

Per your request, attached is a copy of the responses from [redacted] regarding the inspection conducted March 13-16, 2000.

Regards,
Sheldon Mullins

ADM-15

8 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Electronic Mail Message

Date: 4/10/00 11:14:08 AM
From: Laura Governale (GOVERNALEL)
To: lfradkin@elanpharma.com
Subject: Pharm/Tox Information Request NDA 21-060

Dear Ms. Fradkin:

Per our telecon on April 10, 2000, the following is an information request from the Pharm/Tox perspective:

Please provide historical control data on malformation, anomalies, and variations/retardations for rats and rabbits used in the reproductive toxicology studies in the contract lab.

If you have any questions, please do not hesitate to contact me. Thank you in advance for your attention.

Sincerely,

Laura Governale, Pharm.D.
301-827-7410 (main)
1-827-7423 (direct)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

INFORMATION REQUEST LETTER

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

APR 0 4 2000

FAXED

Attention: Linda B. Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 28, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1, 2, 5, mL vials.

We are reviewing the clinical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Referring to Table 8.8.2.7.2 (I8 V003 P 209, vol. 2.93) First Occurrence of AE's In ≥ 20 Patients, the overall numbers are less than the sum of the individual numbers. Please clarify what the numbers in the overall row represent.

2. Why does Table 8.8.2.8.5, (I8, V003, P 328, vol. 2.93) report only 3 deaths in the "while receiving ziconotide" column? Table 8.8.2.8.3 (I8, V003, P319) reports 35 deaths on drug and Listing 2.1, Appendex 2 reports 20 deaths while on ziconotide. Please clarify and indicate how the data for this table were obtained.

If you have any questions, call me at (301) 827-7410.

Sincerely,

Laura Governale

Laura Governale, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Gannah

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080

MAR 2 2 2000

Attention: Linda Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 29, 1999, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziconotide 100 mg/mL in 1 mL, 2 mL, 5 mL, [redacted] fill vials.

We also refer to your submission dated, October 29, 1999.

We are reviewing the CMC section of your submission and have the following comments and information requests concerning sterility assurance. We need your prompt written response to continue our evaluation of your NDA. Please provide an amendment to address the following concerns.

Provide data indicating the bacterial growth supporting characteristics of the drug product. The data should not be limited to ATCC strains prepared in high nutrient media such as trypticase soy. Minimally, the Agency suggests the following organisms:

1. Isolates from the safety study meningitis cases (if available).
2. Skin isolates.
3. USP preservative effectiveness test organisms.
4. *Pseudomonas cepacia.*
5. *Staphylococcus epidermidis.*
6. Hospital environmental isolates.

If you have any questions, call Laura Governale, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

FILE COPY

MEMORANDUM OF TELECON

DATE: March 10, 2000

APPLICATION NUMBER: NDA 21-060

BETWEEN:

Name: Linda Fradkin
Phone: 650-614-1053
Representing: Elan Pharmaceuticals, Inc.

AND

Name: Stella Grosser, Ph.D., Sharon Hertz, M.D., Tom Permutt, Ph.D., and Laura Governale, Pharm.D.
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: Analysis of patients and protocol revisions

The Agency requested the following information from the sponsor:

1. How can we tell which patients were treated under which version of the protocol in each of studies 95-001 and 96-002? The changes in the protocols that concern us are the modifications in dosing regimens.

2. Was the primary efficacy analysis done separately by revision? In particular, we are most interested in an analysis of the patients treated under the final revision of the protocol in each of studies 95-001 and 96-002. If this was not done, could the sponsor do it?

The sponsor stated: 1. This information is in pencil-and-paper form at each of the study sites and is not on the case report forms or entered electronically; 2. The primary efficacy analysis was done in each of the two pivotal studies separately for patients with an initial dose of <= 0.1 ug/hr and > 0.1 ug/hr. This corresponds roughly but not exactly to patients treated under the final revision and before the final revision, respectively.

The sponsor agreed to provide information on which protocol was used for each patient in EXCEL spreadsheet or SAS transport file format and repeat the primary efficacy analysis for patients treated under the final protocol revision.

Stella Grosser 4/5/01
Stella Grosser, Ph.D.
Biostatistics Reviewer

Laura Governale 4-5-00
Laura Governale, Pharm.D.
Regulatory Project Manager

cc:
Archival NDA 21-060
HFD-170/Division Files
HFD-170/S.Grosser, S.Hertz, T.Permutt
HFD-170/B.Rappaport, C.McCormick, C.Schumaker

Drafted by: lg/3-20-00
Initialed by: C.Schumaker/3-30-00, Hertz/4-5-00, Grosser/4-5-00, Permutt/4-5-00
Final: L.Governale/4-5-00, Grosser/4-5-00
Filename: 21060(Elan)TCMM031000.doc

TELECON

800 Gateway Blvd., South San Francisco, CA 94080

Elan Pharmaceuticals

Fax

To:	Laura Governale	**From:**	Linda B. Fradkin
Fax:	(301) 480-8682	**Pages:**	2
Phone:	(301) 827-7410	**Date:**	02/28/00
Re:	NDA 21-060	**CC:**	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Ms Governale:

Attached is a draft of a press release to be issued on 29 February by our corporate office. I am providing this copy to you prior to its release. Should you have any questions, please do not hesitate to contact me at (650) 614-1053.

Sincerely,

Linda B. Fradkin

Linda B. Fradkin
Director, Regulatory Affairs
Elan Pharmaceuticals

FOR IMMEDIATE RELEASE

Contact: Mary Ansaldi
(U.S.) Director, Investor Relations
Elan Corporation, plc
Ph: 212-407-5740
800-252-3526
email: mansaldi@elancorp.com

Contact: Emer Reynolds
(Europe) Director, Investor Relations
Elan Corporation, plc
Ph: 353-1-709-4080
00800 28352600
email: ereynolds@elancorp.com

ZICONOTIDE NDA APPLICATION FILED BY FDA -- SIX-MONTH REVIEW COMMITMENT

DUBLIN, IRELAND, February XX, 2000 -- Elan Corporation, plc (NYSE: ELN) ("Elan") today announced its New Drug Application ("NDA") for ziconotide, which was submitted on December 28th, 1999, had been accepted as filed by the U.S. Food and Drug Administration ("FDA"). The FDA has agreed to a six-month review of this NDA.

Ziconotide, a novel N-type neuronal calcium channel blocker, is being developed for the treatment of severe chronic pain via the intrathecal route.

Elan is a leading worldwide specialty pharmaceutical company headquartered in Ireland, with its principal research, development, manufacturing and marketing facilities located in Ireland, the United States and Israel. Elan shares trade on the New York, London and Dublin Stock Exchanges.

The statements in this press release may include forward-looking statements that involve risks and uncertainties including the difficulty of predicting regulatory approvals, as well as other risks and uncertainties detailed from time to time in periodic reports, including Elan's annual report of Form 20-F for the fiscal year ended December 31, 1998, as amended by Elan's Form 20-F/A1, both filed with the Securities and Exchange Commission. Actual results may differ from the forward-looking statements.

FAX
TRANSMISSION

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
5600 Fishers Lane
HFD-170, Rm. 9B-45
Rockville, Maryland 20857
Office: 301-827-7410
Fax: 301-480-8682/301-443-7068

To: Linda Fradkin

Date: 2/14/00

Fax #: 650-877-7699

Pages: 3
(INCLUDING THIS COVER SHEET)

From: Laura Governale

Subject: NDA 21-060
Questions from Medical Reviewer

Comments:

PLEASE CALL (301) 827-7410 IF RE-TRANSMISSION IS NECESSARY

Questions for sponsor:

1. Was forced titration present in the protocol for study 96002?

2. Please list which patients underwent a forced titration in study 95-001.

3. Please clarify the number of patients entering crossover in the placebo group in study 95-001. The text states 25, (I8 V006 P109), while Table 8.1 states 26, (I8 V006 P113).

4. In study 96-002, (I8 V017 P106) section 8.3, it states that there were 20 patients originally randomized to ziconotide who were considered to be nonresponders but who went into maintenance after the initial titration phase. The table provided, 8.2, only identifies 15 patients titrated on ziconotide in the initial titration who as nonresponders were kept on ziconotide during maintenance. Please specify which patients are the remaining 5.

5. Violations of inclusion and exclusion criteria are presented in Listing 1.2, app 3, (I8 V018 P047). Only one patient is listed as not withdrawn from all intrathecal meds, but 4 are noted in table 8.2 and 5 are identified in listing 3.1, appendix 3.

Please explain this discrepancy and provide the correct number of patients and patient ID numbers for those not withdrawn from all intrathecal medications within 3 days of enrollment in the initial titration.

6. Three patients are listed as not having VAS > 50, 6062-102, 6093-105 and 6074-104 However, line listing 8.1 (app 3) reports the initial VASPI as follows:

6062-102	75
6093-105	99
6071-103	72

In listing 8.1 the following 6 patients are noted with preinfusion VASPI scores not >50:

6052-103	46
6052-104	33
6056-101	50
6079-105	49
6091-102	50
6606-101	50

Please explain this discrepancy and provide the correct number of patients and patient ID numbers for those patients who entered the study with VASPI scores that were not >50.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Garnal

NDA 21-060

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

FEB 1 1 2000

Attention: Sheldon Mullins

Dear Mr. Mullins:

Please refer to your December 28, 1999, new drug application for ziconotide 100 ug/mL in 1 mL, 2 mL, 5 mL, [redacted] fill vials.

As discussed by telephone on February 10, 2000, between you and Laura Governale of this Division, the following agreement was reached regarding CMC requirements for the bioassay data.

1. The Agency concurs with your proposal to use the calcium flux assay. Please provide the agency with a detailed protocol for this assay for review.

2. The Agency has decided that the bioassay should be conducted on the reference material only. For the lot-to-lot release, one of the following tests should be preformed in order to insure that the drug substance has the correct disulfide linkages:

    - Bioassay
    - 2-D NMR
    - Peptide matting with tryptic digestion. The fragment with three disulfide linkages should be further treated to elucidate the correct linkages.
    - Amino acid sequencing with the material isolated from chymotrypsin digestion.

    The calcium flux assay may also be performed for the lot-to-lot release.

3. The HPLC retention times for the reference material and the release material should be compared.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker

Cathie Schumaker
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-060
HFD-170/Div. Files
HFD-170/L.Governale
HFD-170/M.Theodorakis, A.D'Sa, B.Rappaport, C.McCormick, C.Schumaker
HFD-510/C.Niu
DISTRICT OFFICE

Drafted by: lg/February 10, 2000
Initialed by: C.Schumaker/2-10-00
final: C.Schumaker/2-11-00
filename: 21060(Elan)GC021000.doc

2-11-00

GENERAL CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

FEB 0 8 2000

Attention: Linda Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 28, 1999, new drug application for ziconotide 100 ug/mL in 1mL, 2mL, 5mL, [redacted] fill vials.

As discussed by telephone on February 7, 2000, between representatives of Elan Pharmaceuticals and Dr. McCormick, Dr. Chien Hua Niu, Dr. Theodorakis, Dr. D'Sa, Dr. Koepke, Cathie Schumaker and Laura Governale of this Division, the following agreement was reached regarding CMC requirements for NMR and bioassay data.

1. Elan will repeat the literature study on the reference drug for proton NMR spectroscopy.

2. You will provide information on calcium flux assay in order for the Agency to make a determination on what kind of bioassays are acceptable.

3. By the end of this week, the Agency will notify you whether the bioassay needs to be conducted on only the reference material or both the reference material and the release material.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Fax

élan
pharmaceuticals

REGULATORY AFFAIRS, 700 Gateway Blvd., South San Francisco, CA 94080
Telephone (650) 616-2636 - Fax (650) 877-7699

Attached is our understanding of the issues discussed. Included are the publications referenced in the text.

Should you have any questions do not hesitate to contact me at (650) 616-2636.

Sincerely,

Sheldon Mullins
Senior Associate, Regulatory Affairs

ADM-16

19 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Gouvnale

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-060

Food and Drug Administration
Rockville MD 20857

DISCIPLINE REVIEW LETTER

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, CA 94080

FEB 0 4 2000

Attention: Linda B. Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to your December 28, 1999, new drug application for ziconotide 100 mg/mL in 2, 5, [redacted] mL vials.

We also refer to your pre-submissions dated October 29, 1999.

Our review of the microbiology section of your submissions is complete, and we have identified the following deficiencies concerning sterility assurance. Please provide an amendment to address the following concerns.

The following comments pertain to the manufacturing and filling of the [redacted] mL configuration of the product at [redacted]

1. [redacted]

2. [redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we

may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Laura Governale, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Cathie Schumaker
Acting Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-060
HFD-170/Div. Files
HFD-170/L.Governale
HFD-170/Reviewers and Team Leaders
HFD-820/DNDC Division Director - only for CMC related issues
DISTRICT OFFICE

2/4/00

Drafted by: lg/January 27, 2000
Initialed by: C.Schumaker/1-28-00, P.Stinavage, A.D'Sa, M.Theodorakis/2-4-00
final:

filename: 21060(Elan)DR012700.doc

DISCIPLINE REVIEW LETTER (DR)

24 January 2000

Attn: **Nancy Chamberlin**

Re: **NDA 21-060**
Ziconotide Solution (Preservative Free)
Item 4 - CMC

Dear Ms. Chamberlin,

Regarding the CMC issues posed in our conversation (24 Jan 00);

1) Item 4, Volume 1.1, Section 4.1.1.4 Elucidation of Structure, page 64, provides references to the nmr structure of ω-conotoxin MVIIA (Ziconotide is the synthetic equivalent of ω-conotoxin MVIIA) of using 2D NMR spectroscopy. These references are contained in the submission (Appendix 7).

2) Item 4, Volume 1.1, Section 4.1.4.5 Analytical Methods, page 145 (beginning at the bottom of the page), provides a description and rationale for the ziconotide binding assay (bioassay).

3) The reviewer has requested a spectrograph of the final drug substance. Please indicate what type of spectrograph is required.

If the information included in the above reference pages is insufficient please contact me immediately. If possible, we can have a brief teleconference with the CMC reviewer to determine what will be required to expedite the review of the document.

Regards,

Sheldon Mullins

Sheldon Mullins

(650) 616-2636

Chambers

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-060

Elan Pharmaceuticals
800 Gateway Blvd.
South San Francisco, California 94080

JAN 10 2000

Attention: Linda B. Fradkin
Director, Regulatory Affairs

Dear Ms. Fradkin:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ziconotide solution, preservative free

Therapeutic Classification: Priority (P)

Date of Application: December 28, 1999

Date of Receipt: December 28, 1999

Our Reference Number: NDA 21-060

We have not received the appropriate user fee for this application. The application fee required for NDA applications for Fiscal Year 2000 is $285,740. Please remit the balance using the same user fee ID number (3873) as soon as possible.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 25, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 28, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should

submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

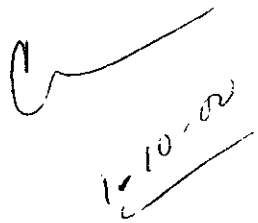
If you have any questions, call Nancy Chamberlin, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

/S/

Cathie Schumaker
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-060
HFD-170/Div. Files
HFD-170/N.Chamberlin
HFD-170/McCormick/Rappaport/Hertz
HFD-170/ Brase/Jean
HFD-170/ Theodorakis/D'Sa
HFD-170/ Grosser/ Permutt
HFD-870/ Kim/ Uppoor



DISTRICT OFFICE

Drafted by: nc/January 6, 2000
Initialed by: C.S. 1-7-00
final: nc 1-7-00
filename: N21060AC.LTR

ACKNOWLEDGEMENT (AC)

Chamberlin

DEPARTMENT OF HEALTH & HUMAN SERVICES

IND 45,718

Food and Drug Administration
Rockville MD 20857

JUL 22 1999

Elan Pharmaceuticals
190 Independence Drive
Menlo Park, California 94025

Attention: Linda Fradkin, M.S.
Director, Regulatory Affairs

Dear Ms. Fradkin:

Please refer to the telecon between representatives of your firm and FDA on June 22, 1999. The purpose of the meeting was to clarify the FDA's recommendations on the carcinogenicity testing and whether they could be phase iv commitments.

As requested, a copy of our minutes of that telephone conference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/Chamberlin\ C Moody
HFD-170 C McCormick
B Rappaport
D Brase\ L Jean

Drafted by: N.Chamberlin 7-22-99
Revised: 7-22-99 nc
Initialed by: C. P. Moody 7-22-99
Final:
filename: 45718ltr622.doc

Meeting Minutes

MINUTES OF TELECON WITH SPONSOR

Meeting Date: June 22, 1999
Location: Parklawn Building 9B-45
IND: 45, 718

Time: 5:00- 5:30 P.M.
Sponsor: Elan
Drug: Ziconotide

Type of Meeting: Clarification of Carcinogenicity Tests
Meeting Chair: Cynthia McCormick, M.D., Division Director
External Participant Lead: Robert Luther, M.D., Executive V.P., Development
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Attendees:	**Titles:**	**Offices:**
Cynthia McCormick, M.D.	Division Director	HFD 170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

External Attendees:	**Titles:**
Janice Castillo	Vice President, Regulatory Affairs
Kent Shellenberger	Sr. Director, Clinical Affairs, Clinical Pharmacology
Linda Fradkin, MS.	Director, Regulatory Affairs

Meeting Objective: The sponsor asked for a teleconference to clarify for the FDA's request for conducting carcinogenicity studies for Ziconotide and to explore the possibilities that they could be performed as phase IV commitments.

Discussion:

- Dr. McCormick asked the firm how long it would take to prepare and conduct a TG.AC test. Dr. Shellenberger stated that for the TG.AC parameters they would need 4 weeks to perform a dose ranging study, 6 months "in life", followed by 3 or more months to prepare and QC the study report. Therefore, he concluded that it would probably take a minimum of 10 months to conduct the study.

- Dr. McCormick suggested a compromise that the sponsor notify the Agency or submit a preliminary report if the SHE cell test is positive, and if so, to immediately start the TG.AC test.

- The sponsor proposed to send in the SHE cell test protocol for the Agency to comment on.

- Dr. Shellenberger mentioned that [redacted] was having trouble ordering the specific strain of mouse that was required for the test. It appears the mouse strain tends to regress to the genetic wild type. The sponsor could not confirm that this study would done by the time that the NDA review was completed, but would try to work on it right away. They would expect the preliminary TG.AC results in May and would talk with the Agency.

- Dr. McCormick mentioned that these factors may affect the labeling.

- It was agreed that the sponsor would take one step at a time, file as planned, and proceed as discussed today. The SHE cell test results would be submitted by filing. The sponsor would

proceed with TG.AC if the SHE cell test is positive. The Agency would get at least preliminary results on the TG.AC during the review cycle.

- Dr. Jean mentioned that the Agency will have to take the TG.AC protocol to the Carcinogenicity Assessment Committee and she asked the sponsor to provide the protocol right away. The sponsor agreed.

CONCLUSIONS:

Dr. McCormick concluded the meeting. The sponsor agreed to conduct the appropriate carcinogenicity testing in a stepwise fashion, and to inform the Agency if the SHE cell test was positive.

ACTION ITEMS:

- **FDA will provide the sponsor with a copy of the meeting minutes from this teleconference**
- **Sponsor will submit the protocols for the Agency's input right away.**
- **Sponsor will provide the SHE cell test results in the NDA and if it is positive inform the Division right away, and begin to conduct the TG.AC test almost immediately.**

Minutes Prepared By: N. Chamberlin, Pharm.D. Nancy Chamberlin

Minutes Concurred By Chair: C. McCormick, M.D. Cynthia McCormick MD

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick\ Rappaport
L Jean
D Brase
C Moody

Drafted by: N.Chamberlin 7-21-99
Revised: 7-22-99 per Lucy, Corinne and Dr.McCormick
Initialed:
Final:
Filed under: #45718Minutes622.DOC
MEETING MINUTES

DEPARTMENT OF HEALTH & HUMAN SERVICES

IND 45,718

Food and Drug Administration
Rockville MD 20857

Elan Pharmaceuticals
190 Independence Drive
Menlo Park, California 94025

MAY 17 1999

Attention: Helen P. Shu, Ph.D.
Director, Regulatory Affairs

Dear Dr. Shu:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on April 8, 1999. The purpose of the meeting was to clarify the FDA's recommendations on what would be required in an NDA for Ziconotide.

As requested, a copy of our minutes of that telephone conference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/Chamberlin\ C Moody
HFD-170 C McCormick
B Rappaport
D Brase\ L Jean
M Theodorakis\ A D'Sa
S Wang\ T Permutt
S Doddapaneni\ R Uppoor
M Klein

Drafted by: N.Chamberlin 5-4-99
Revised: 5-4-99 per Abi,
Initialed by: C. P. Moody 5-6-99 nc
Final:
filename: 45718ltr48.doc

Meeting Minutes

MINUTES OF TELECON WITH SPONSOR

Meeting Date: April 22, 1999 **Time:** 3:30- 4:30 P.M.
Location: Parklawn Building 9B-45 **Sponsor**: Elan
IND: 45, 718 **Drug: Ziconotide**

Type of Meeting: Clarification of Carcinogenicity Briefing Package
Meeting Chair: Bob Rappaport, M.D., Deputy Director
External Participant Lead: Robert Luther, M.D., Executive V.P., Development
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Attendees:	**Titles:**	**Offices:**
Bob Rappaport, M.D.	Deputy Director	HFD 170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

External Attendees:	**Titles:**
Janice Castillo	Vice President, Regulatory Affairs
Kent Shellenberger	Sr. Director, Clinical Affairs, Clinical Pharmacology
	Manager, Preclinical Drug Safety
Paul Woods, Ph.D	Senior Vice President, Preclinical Drug Development
Mary Pendergast, J.D.	Executive Vice President, Government Affairs
Linda Fradkin, MS.	Director, Regulatory Affairs
Scott Bowersox, Ph.D.	Director, Pharmacology
Dave Ellis	Director, Clinical Research
George Shopp	Sr. Scientist

Meeting Objective: In past conversations with the sponsor, Dr. Jean stated that they may need a carcinogenicity study for Ziconotide in the NDA. The sponsor agreed to provide a briefing package for the carcinogenicity committee by April 15th. The sponsor was having difficulty putting together the briefing package and asked for a telecon to clarify for the firm the FDA's request.

The following issues were clarified for the firm:

- Dr. Rappaport stated that the division has theoretical concerns at this point and that we would ask for carcinogenicity studies on any NME.
- It was suggested that the sponsor address in their briefing package why they do not think a carcinogenicty study would be necessary.
- Dr. Brase asked the sponsor to consider both systemic and spinal toxicities
- Dr. Jean was planning to present this issue to the Pharm/Tox Coordination Committee (PTCC) on the third Thursday in May.

- The division would ask the PTCC to give guidance on whether a carcinogenicity study should be requested and assist the division in answering the sponsor's questions.

- It was requested that the sponsor provide information on the available ADME/PK data of Ziconotide in the briefing package.

CONCLUSIONS:

Dr. Rappaport concluded the meeting with the sponsor agreeing to submit the carcinogenicity briefing package.

ACTION ITEMS:

- **FDA will provide the sponsor with a copy of the meeting minutes from this meeting**
- **Sponsor will provide the carcinogenicity briefing package as soon as possible.**

Minutes Prepared By: N. Chamberlin, Pharm.D.

Minutes Concurred By Chair: B.Rappaport, M.D.

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick
B Rappaport
L Jean
D Brase
C Moody

Drafted by: N.Chamberlin 5-12-99
Revised: 5-20-99 per David B., 5-21-99 per Lucy, 5-21-99 per Bob
Initialed: C.P. Moody 5-21-99
Final:
Filed under: # 45718Minutes422.DOC
MEETING MINUTES

TELCON WITH SPONSOR MINUTES

Meeting Date: April 8, 1999 Time: 10:00 -11:30 P.M.
Location: Parklawn, 3rd Floor Potomac Room **Sponsor**: Elan
IND: 45, 718 **Drug: Ziconotide**

Type of Meeting: PRE- NDA
Meeting Chair: Cynthia G. McCormick, M.D., Director
External Participant Lead: Robert Luther, M.D., Executive V.P., Development
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Monte Scheinbaum, M.D.	Medical Reviewer	HFD-170
Tom Permutt, Ph.D.	Biostatistics Team Leader	HFD-170
Michael Klein, Ph.D.	Team Leader, Controlled Substance Evaluation Team	HFD-170
Michael Theodorakis, Ph.D.	Senior Chemistry Reviewer	HFD-170
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokinetics Reviewer	HFD-870
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170
Steve Koepke, Ph.D.	Deputy Director DNDC-II	HFD-820

External Attendees:	Titles
Robert Luther, MD.	Senior Vice President, Development
Dawn McGuire	Vice President of Medical and Clinical Research
David Ellis, M.D.	Director, Clinical Affairs
Annelies De Kater, Ph.D.	Manager, Preclinical Safety
Linda Fradkin, M.S.	Director, Regulatory Affairs
Mary Pendergast, Esq.	Executive Vice President, Government Affairs, Elan Corporation
Paul Goddard, Ph.D.	President and CEO
Scott Bowersox, Ph.D.	Director, Pharmacology and Toxicology
Jan Wallace, M.D.	Senior Vice President, Clinical and Regulatory
Janice Castillo	Vice President, Regulatory Affairs
Jere Fellmann, Ph.D.	Director, Clinical Affairs
Martha Mayo, Pharm.D.	Director, Clinical Affairs
Helen Shu, Ph.D.	Director, Regulatory Affairs

Meeting Objective: The primary objective of this PRE-NDA meeting was to assist the sponsor with organizing their NDA submission and address any outstanding issues.

Background: The Division had a telephone conference with the sponsor on February 16, 1999 about pharm/tox and clinical requirements for the NDA submission. As stated during the previous telephone conference of January 28, 1999, the Division still expects an NDA for an NME to have **1000 patients in the safety data base at a minimum at the time of filing**, with sufficient

numbers of these involving the route of administration for which the sponsor seeks labeling, i.e., intrathecal.

[redacted]

DISCUSSION POINTS:

Dr. Wallace provided an overview of what they planned to submit to the NDA. He mentioned that there were dose-limiting side effects during titration. Dr. McCormick asked if the sponsor would present these side effects in the NDA by dose. The sponsor responded that they were not sure.

Dr. Wallace mentioned that the carcinogenicity would be done as a phase IV commitment if it is required. He also noted that they would provide a briefing package for the carcinogenicity committee.

Dr. Wallace stated that they are working to increase the numbers of IT patients to have over 1000 total patients at the time of submission and they will continue to follow these patients after approval and launch. It is expected at the time of NDA filing that the firm will have 700 IT patients, 58 patients exposed at 6 months, and over 100 patients with exposure beyond the 6 months time period.

Dr. McCormick commented that half of the exposures were of less than 1 month duration . The sponsor responded that there were rate-limiting side effects and patients go on and off these types of treatments, and that a typical dropout rate for these treatments was 50% of the cancer patients.

Discussion was held on whether the firm's proposed numbers were acceptable. Dr. McCormick stated that they would need 1000 patients at the time of NDA submission, 100 with 1-year exposure and 300 to 500 patients with 6 months exposure. The sponsor commented that the prospective non-malignant study mean exposure was 60 days while the malignant study mean exposure was 46 days. The sponsor mentioned that it is a challenge to obtain data beyond a 2-3 month exposure.

Dr. McCormick reiterated that the Agency uses the ICH guidelines. The sponsor suggested that they were considering a post-marketing registry to obtain chronic numbers. [redacted] She asked the sponsor if they could wait to accrue the data before they submit the NDA. Dr. Wallace stated that the firm would continue enrollment in the long-term study attempting to accrue 300 patients with 3-month exposure at the time of the 4-months safety update.

FIRM'S QUESTIONS:

NDA Format

1. *As discussed in July 1998, this NDA will be a paper submission. The text of the clinical trials reports will also be provided on disk, in Word version 7.0.*

   Division response:
   - Dr. Scheinbaum suggested that the case report forms be in PDF and the data listings be in SAS transport.

   - Dr. McCormick mentioned that it would be difficult to meet the proposed timeline unless the Division split the reviews. She suggested that the ISS and ISE should be in Word version 7.0.

2. *For the ISS, Elan proposes to provide all IT studies as one integrated safety database. Epidural studies exist as a separate database. IV studies exist as several separate databases. Integration will be performed within each route of administration for the IT and epidural databases. Current plans do not provide for an integrated safety database across all routes of exposure.*

   Division response:
   - Dr. Scheinbaum stated that he does prefer them to be separate. Dr. McCormick expressed concern that rare adverse side effects could be missed by this approach.

   - The Division and the sponsor agreed that the AEs could be separated by route of administration, but that the sponsor would address AEs occurring across all routes of administration.

3. *Data sets for the two pivotal trials (95-001 and 96-002) will be provided in SAS Transport form, the version number to be designated by FDA. Current plans do not include SAS Transport data sets for other clinical trial reports.*

   Division response:
   - Dr. Scheinbaum suggested that the case report forms be in PDF and the data listings be in SAS transport.

   - Dr. Scheinbaum asked the sponsor whether they planned to provide lab data such as EKG changes in SAS with the patients identified. The sponsor responded that the patients in the IV study did have halter monitors and that changes in the IT patients were sporadic. Dr. McCormick commented that we expect their submission to contain a discussion of the cardiac effects in the ISS.

- Dr. Rappaport noted that it would be useful if the sponsor could provide all the data electronically.

- It was agreed that the Division would like the ISS and ISE in Word 7, and it was noted that they could use Word 6.

Clinical and Statistical Sections of NDA

4. *In order to avoid duplication, Elan proposes to provide data listings from clinical studies in Item 11, in paper form, only and not as part of the clinical trial reports.*

   Division response:
   Data listings may be submitted in Item 11 only. However, Dr. McCormick noted that if the division splits the clinical reviews, it would be useful to duplicate the information in the clinical study reports and it would be even nicer to have them provided electronically.

5. *In order to avoid duplication, Elan proposes to provide individual patient narratives for deaths, SAEs, and dropouts due to adverse events as part of the individual clinical trial reports in Item 8 only, and not in the ISS. The ISS will discuss the safety data in an integrated format.*

   Division response:

   - Dr. McCormick stressed the importance of a good index, especially if the division has 2 clinical reviewers on this application. It would be best if the firm would provide copies of the narratives in both Item 8 and the ISS.

   - Dr. McCormick stated that the sponsor needs to tabulate the data as old, new and cumulative in the safety update.

6. *Item 12, Case Report Forms, will be submitted as paper copies.*

   Division response:
   Dr. Scheinbaum asked the sponsor to provide the case report forms in Acrobat/PDF.

7. *The financial disclosure certification and investigator forms will be provided for clinical studies that were on-going or that started after February 2, 1999 (i.e., only studies 95-002, 98-021, 98-022, 98-023, and 98-029).*

   Division response: yes

8. *The NDA will include narratives for all patient deaths and discontinuations and for SAEs that may be associated with study drug. SAEs that are attributable solely to the delivery devices will be provided to CDRH by the device manufacturers.*

Division response:

- Dr. McCormick stated that the sponsor needs to provide to the NDA: all deaths, meningitis, overdose, drug-related AEs and device complications.

Dr. McCormick preferred to see all the SAEs and including those attributed to the device.

Sponsor response:

- The sponsor mentioned that there would be approximately 20 reports for devices and agreed to provide them to the NDA.

9. [redacted]

Sponsor response:

[redacted]

Division response:

- This was acceptable to the division at this time, until the safety of this drug is established.

CMC Section of NDA

10. *Elan proposes a separate follow-up meeting to discuss CMC topics in more detail than is possible at the current meeting. At this time, Elan seeks guidance from the Agency on selected topics.*

Division response: Dr. D'Sa agreed that Chemistry and Devices would meet with the sponsor after receiving a formal written request.

11. *Elan proposes to pre-submit the CMC section and to update the stability data at the time of the NDA submission.*

Division response:

- Dr. D'Sa stated that the firm could pre-submit the CMC section and update the CMC at the time of the NDA submission. However, when the clock starts, the full package should be submitted.

- Dr. D'Sa stated that the sponsor needs to file DMFs for the drug substance and the two drug products.

Sponsor response:

- The sponsor mentioned that they have done the stability testing on the commercial smaller fill sizes. The pre-submission will have limited data at [redacted] on the 1- and 2-ml sizes and they planned to have [redacted] in the update. Dr. McCormick mentioned that it would be a priority review and that it will have a short review clock. The sponsor provided a listing of available stability data (see below).

12. [redacted]

ADM-17

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

14. *In order to avoid duplication, Elan proposes to provide the microbiology information in the CMC section only and not to reproduce this information in the Microbiology Section, 7. Copies of the relevant CMC portions can be provided to the microbiology reviewer on request.*

Division response:

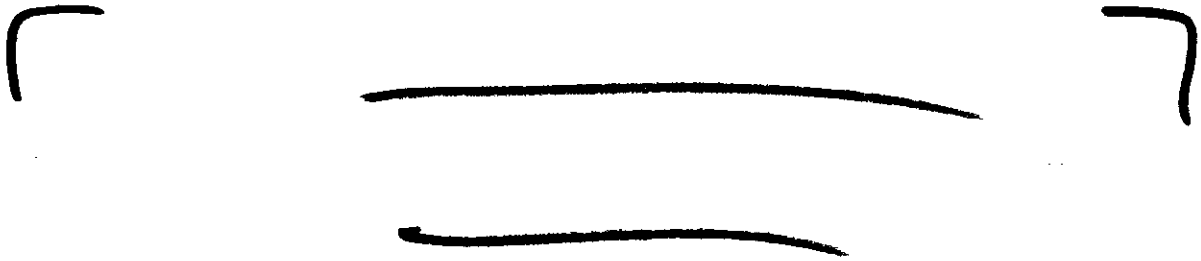
- The division would like a separate section for all microbiology issues to facilitate the microbiology consult.
- Dr. Theodorakis asked the sponsor to provide information on aseptic filtration, validation of process, bio burden test, pre- fill data, and sterility.

15. *The NDA will include data on drug product comparability with the external and the implanted drug delivery devices and catheters. The NDA will include information on extractability data provided by SimsDeltec, the manufacturer of the external drug delivery device. The NDA will not contain device compatibility or extractability data for the implanted delivery system. The manufacturer, Medtronic, will provide appropriate cross reference letters for the implanted delivery system to the Agency.*

Division response:Dr. D'Sa stated that the firm needs to develop the condition of use.

- The firm needs to show compatibility with the recommended devices.
- Need for clarification from the firm on the extractables.
- The sponosor needs to provide compatibility information on the drug and the diluent.
- The Division plans to invite Devices to the CMC meeting with the firm.

NDA Timing for Sections



ADM-18

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

FDA's Pharmacokinetics request:

- Dr. Doddapaneni requested that information on special populations, hepatic and renal impairment, and potential for drug interactions be addressed by the sponsor in the NDA.

- To assess the age and gender effects, he recommended a subset analysis from the available data.

Abuse Liability/ CSET Issues:

- **Sponsor needs to provide in the NDA section justification for their product not having any abuse liability, per 21 CFR 314.50 (5) (vii).**

Conclusion:

It was noted that the sponsor intends for the indication to be for management of severe chronic pain by continuous intrathecal administration.

ACTION ITEMS:

- FDA will provide the sponsor with a copy of the meeting minutes from this meeting
- FDA requested that the firm provide electronic pieces

Minutes Prepared By: N. Chamberlin, Pharm.D. Nancy Chamberlin

Minutes Concurred By Chair: C. McCormick, M.D. Cynthia McCormick MD

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick
B Rappaport
M Scheinbaum
L Jean
D Brase
C Moody
A D'Sa
M Theodorakis
S Wang
T Permutt
M Klein

Drafted by: N.Chamberlin 4-8-99
Revised: 4-29-99 nc, 5-4-99 nc, 5-4-99 per Suresh, Mike and Abi, 5-5-99 per Monte and Mike K., 5-5-99 by David & Lucy, 5-7-99 nc per Corinne and Bob
Initialed by: C. P. Moody 5-6-99
Final:
Filed under: #45718Minutes48.DOC
MEETING MINUTES

DEPARTMENT OF HEALTH & HUMAN SERVICES

IND 45,718

Food and Drug Administration
Rockville MD 20857

Elan Pharmaceuticals
190 Independence Drive
Menlo Park, California 94025

MAR 18 1999

Attention: Helen P. Shu, Ph.D.
Director, Regulatory Affairs

Dear Dr. Shu:

Please refer to the telephone conference between representatives of your firm and FDA on February 16, 1999. The purpose of the telephone conference was to clarify what would be required in an NDA for Ziconotide.

As requested, a copy of our minutes of that telephone conference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/Chamberlin\ C Moody
HFD-170 C McCormick
B Rappaport
M Scheinbaum
J Ross
D Brase
L Jean
A Dsa

HFD-870 /S Doddapaneni
R Uppoor

Drafted by: N.Chamberlin 3-3-99
Revised: 3-16-99 nc
Initialed by: C.P. Moody 3-16-99
Final:
filename: 45718ltr216.doc

Meeting Minutes

TELCON WITH SPONSOR MINUTES

Meeting Date: February 16, 1999 Time: 1:00 -2:30 P.M.
Location: Parklawn Building 9B-45 **Sponsor:** Elan
IND: 45, 718 **Drug: Ziconotide**

Type of Meeting: Clarification of Pharmtox and Clinical Development items prior to submitting their NDA
Meeting Chair: Cynthia G. McCormick, M.D., Director
External Participant Lead: Robert Luther, M.D., Executive V.P., Development
Minutes Recorder: Nancy Chamberlin/ Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD 170
Monte Scheinbaum, M.D.	Medical Reviewer	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
David Brase, Ph.D.	Pharmacology Reviewer	HFD-170
Anwar Goheer, Ph.D.	Covering for Team Leader/Pharmacology	HFD-170
Nancy Chamberlin, Pharm.D.	Project Manager	HFD-170

External Attendees:	Titles
Robert Luther, MD.	Senior Vice President, Development
Dawn McGuire, M.D.	Vice President of Medical and Clinical Research
Dr. Paul Woods, Ph.D	Senior Vice President, Preclinical
Annelies De Kater	Manager, Preclinical Safety
Linda Fradkin	Director, Regulatory
Mary Pendergast	Executive Vice President, Government Affairs
Paul Goddard	President and CEO
Scott Bowersox, Ph.D	Director, Pharmacology and Toxicology
Jan Wallace, M.D.	Senior Vice President, Clinical and Regulatory
Janice Castillo	Vice President, Regulatory Affairs
Dr. Jere Fellmann	Director, Project Management
Helen Shu, Ph.D.	Director, Regulatory Affairs

Meeting Objective: The primary objective of this meeting was to respond to the sponsor's meeting request regarding requirements for an NDA using a more restricted patient population of terminally ill, cancer pain patients, where the non-cancer patient data base would be used to support the claim for analgesia in cancer pain patients. Also the sponsor wanted to know if segments I and III and carcinogenicity testing would be required? Would the existing database of exposed patients be acceptable for the NDA filing?

Background:
The Division had a telephone conference with the sponsor on January 28, 1999 about pharm/tox and clinical requirements for the NDA submission.

The Agency during the telecon, stressed the need for the sponsor to meet ICH guidelines for a new molecular entity (NME) with a complete safety data base of 1000 to 1500 patients and fulfillment of the required pharm/tox studies, including segment I and III reproductive studies and carcinogenicity studies (the latter of which could be conducted as a phase 4 commitment).

During the telecon the Agency pointed out that the sponsor needed to ensure that they had an adequate safety data base prior to submitting an NDA and that it was the position of the Division that this drug did not qualify for a Priority review status.

The Division also recommended that Elan needs to consider scheduling a pre-NDA meeting in the future.

DISCUSSION POINTS:

CLINICAL

Dr. Luther stated that Elan is developing a safe and effective drug product. The total number of patients in the safety database from the all routes of administration is 704 patients.

As stated during the previous telephone conference of January 28, 1999, the Division still expects an NDA for an NME to have **1000 patients at a minimum at the time of filing**, with sufficient numbers of these involving the route of administration for which the sponsor seeks labeling, i.e., intrathecal.

Dr. Luther noted that it appears that the Agency and Division have adopted the ICH guidelines and Elan will commit to increasing their database to 1000 minimum. They propose to initiate a new chronic open intrathecal route study.

Dr. McCormick asked the sponsor to define their time frame for recruitment into the safety database in relation to actual filing of an NDA. The sponsor responded that they expected to have 300 more patients by August/September, 1999. In order to do this they will use an open label study where all patients receive drug and are not analyzed for efficacy.

The sponsor stated that the longest exposure was for 2 ½ years, 26 patients having received the drug over 1 year, 28 patients approaching 1 year, and that the average length of treatment was approximately 70 days.

Dr. McCormick stressed that if the sponsor is considering chronic exposure, they must provide enough long term exposure for us to get a sense of the drug's safety. The more exposure we have at the time of NDA submission the better for the public, the sponsor, and the Agency.

M. Pendergast asked what type of numbers would the Division expect to see in a database for chronic use and would they have to follow what was in the ICH guidelines. Dr. McCormick responded that we would expect the bulk of exposures to be at 3-6 months in 300 to 500 patients, and 100 patients at 1 year.

After the sponsor committed to obtaining 300 more patients for the intrathecal route of administration prior to submitting the NDA,

Dr. McCormick asked the sponsor to submit a meeting request for a face to face Pre-NDA meeting. Discussion at that meeting would include NDA format, electronic submission, section 11, and other issues.

Pharmacology

Dr. Luther commented that the Segment I dosing has started. The Segment III study was to start later this month. He committed the sponsor to conducting the segment I and III studies prior to NDA submission. The sponsor will submit final reports for the segment I and III studies at the time of NDA filing.

The sponsor was informed that they need to conduct carcinogenicity studies. However, the Division would consider a phase 4 commitment. The sponsor questioned the rationale for the carcinogenicity study. The sponsor was advised to put in a meeting request to discuss this matter Also, Dr. McCormick stated that the topic would be presented to the Carcinogenicity Committee and asked the sponsor to put together a briefing package. The sponsor agreed to do so.

Dr. Brase commented on the protocol in which the sponsor had proposed to save 3 animals per group for toxicokinetic measurements. He stated that he preferred 5 animals and that a test of 5 animals is standard for this type of study. Dr. Goheer stressed that there is a problem with only 3 animals if there is a lot of variation, and it makes interpretation of the data very difficult.

said that 25 males were used in phase I. Dr. Goheer suggested that they increase the number of animals in the segment III study (28 females/group, of which 5 would be for PK analysis).

Treatment IND:

Dr. Luther asked if the Treatment IND option is still acceptable with the Division. Dr. McCormick responded that it is. The sponsor will look into this option and then request a meeting to discuss it. The sponsor would like to use information from the treatment IND in their safety database.

M. Pendergast asked if they could let the public know that the Agency was planning a priority review. Dr. McCormick responded that she did not believe that the sponsor can publicly state that the Agency plans to expedite the review. However, she noted that she would look into this matter and get back to them.

CONCLUSIONS:

Dr. McCormick concluded that the sponsor needs to submit a stronger safety database, and that the NDA has to be complete for safety and pre-clinical data at the time of filing (with the possible exception of the carcinogenicity study being a Phase IV commitment).

ACTION ITEMS:

- **The sponsor will take the information discussed during this meeting under advisement and get back to the FDA with any responses.**
- **FDA will get back to the sponsor on the outstanding pharm/tox issues after further internal discussion.**
- **The sponsor will send in the 2 pre-clinical reproduction protocols for the FDA to comment on.**
- **FDA will provide the sponsor with a copy of the meeting minutes from this meeting**
- **Sponsor should submit a formal meeting request for a pre-NDA meeting prior to submitting the NDA.**
- **Sponsor should submit a formal meeting request for a meeting to discuss carcinogenicity studies prior to submitting the NDA.**
- **Sponsor should submit a formal meeting request to discuss a treatment IND prior to submitting the NDA if they choose to pursue that option.**

Minutes Prepared By: N. Chamberlin, Pharm.D.
Minutes Concurred By Chair: C. McCormick, M.D.

cc: Original IND 45,718
HFD-170/Div. Files
HFD-170/CSO Chamberlin
HFD-170 C McCormick
B Rappaport
M Scheinbaum
L Jean
D Brase
C Moody

Drafted by: N.Chamberlin 3-3-99
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_____ § 552(b)(5) Draft Labeling

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