

021060\_Original\_Approval\_Pkg

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**21-060**

*Trade Name:* Prialt 25 mcg/mL in 20 mL fill vials and  
100 mcg/mL in 1, 2, and 5 mL fill vials

*Generic Name:* ziconotide intrathecal infusion

*Sponsor:* Elan Pharmaceuticals

*Approval Date:* December 28, 2004

*Indications:* Provides for the use of Prialt 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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-060**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-060**

**APPROVAL LETTER**



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

Attention: Mark Brunswick, PhD  
Director, Regulatory Affairs

Dear Dr. Brunswick:

Please refer to your new drug application (NDA) dated December 28, 1999, received December 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prialt (ziconotide intrathecal infusion), 25 mcg/mL in 20 mL fill vials, and 100 mcg/mL in 1, 2, and 5 mL fill vials.

We acknowledge receipt of your presubmission dated October 29, 1999, and your submissions dated January 12, March 10, 22 (2), and 31, April 6, 7, 12, 14, 17, 20, 24, 27, and 28, May 1, 11, 19, 22 (2), and 26, June 23, July 13, 19, and 24, August 7, September 15, 20 (2), and 29, October 13 (2), November 29, and December 28, 2000, and January 26, February 9, 20, and 28, March 13, 20, 23, and 29, April 9, 20, 26, and 27 (2), May 24, and June 1, 13, 19, 21, 25, and 26, July 11 (3) and 17, August 3 and 16, September 17, October 31, November 2, 20, and 29, and December 21, 2001, January 25, March 8, October 7 and 8, and December 3, 2002, January 27 and 31, February 11 and 20, April 3 and 28, May 2, July 25, August 12, and September 8 and 23, 2003, and January 6 and 16, June 25, August 16, October 20 (2) and 26(2), November 1 and 22, and December 2, 6, 8, 9, 14 (2), 20 (2), and 27, 2004.

Your submission of June 25, 2004, constituted a complete response to our July 25, 2001, action letter.

This new drug application provides for the use of Prialt (ziconotide intrathecal) 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.

We have completed our review of this application, as amended and it is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the text for the package insert, immediate container and carton labels submitted December 27, 2004. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidances for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format-Content of Labeling*. Alternatively, except for the content of labeling, which must be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission “**FPL for approved NDA 21-060.**” Approval of this submission by FDA is not required before the labeling is used.

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 are deferring submission of your pediatric studies for ages 0-16 years until December 28, 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA 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 in pediatric patients ages 0-16 years.

Final Report Submission: December 28, 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated “**Required Pediatric Study Commitments**”.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 21-060

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The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

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

Sincerely,

*{See appended electronic signature page}*

Robert J. Meyer, MD  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration

Enclosure

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

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Robert Meyer  
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-060**

**APPROVABLE LETTER 2**



NDA 21-060

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

Attention: Ronald Kartzinel, M.D., Ph.D.  
Vice President

Dear Dr. Kartzinel:

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

We acknowledge receipt of your submissions dated June 23, July 13, 19, and 24, August 7, September 20, October 13, November 29, and December 28, 2000, and January 26, February 20 and 28, March 13, April 20, 26, and 27, May 24, and June 19, 2001. Your submission of January 26, 2001, constituted a complete response to our June 27, 2000, action letter.

We also refer to your amendments dated July 11 (2) and 17, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. The data submitted do not adequately establish the effectiveness of this product for the proposed indication. The two pivotal trials, Studies 95-001 and 96-002, were not adequately designed to assess the effectiveness of ziconotide when used according to the titration regimen in the dosage and administration section of the proposed label. The specific reasons for the determination that these studies were inadequate were detailed in our letter dated June 27, 2000. The additional analyses requested for the pivotal trials were intended to complement a new, adequate and well controlled trial, not to replace such a trial.
2. The data submitted do not adequately establish the safety of this product for chronic administration. A risk-benefit analysis to establish the viability of ziconotide in the

treatment of chronic malignant and non-malignant pain cannot be accomplished until the safety profile of the product has been adequately characterized. Specifically, deficiencies remain in the analysis and risk assessment as identified in the following items:

- a. The analysis of adverse events reported fails to adequately address the problem of inconsistent mapping of similar events to different COSTART terms. This is particularly true regarding adverse events related to central nervous system toxicity.
  - b. The extent and reversibility of central nervous system toxicity has not been adequately addressed.
  - c. The data submitted have not adequately characterized the interaction between ziconotide and opiates, in particular the effects of coadministered opioids on safety and efficacy.
  - d. The extent to which the loss of drug substance associated with the lowest ziconotide concentration utilized during the trials with a ziconotide-naïve intrathecal pump impacts the safety and efficacy data obtained during the pivotal trials has not been adequately addressed.
  - e. A detailed analysis of treatment-emergent ECG findings, specifically QT prolongation, has not been carried out.
3. The methodology used in the rat embryo-fetal study that demonstrated the absence of ischial and pubic bones in the highest dose group was not capable of distinguishing between absent bones and unossified cartilage. The possible contribution of maternal toxicity to these findings has not been fully explored.
  4. Regarding the aseptic media fill process, the specifications set for sterility upon fill are not sufficiently rigorous to ensure sterility of this product for human intrathecal use.
  5. The compatibility of the ziconotide solution with the Medtronic micro-infusion pump has not been adequately characterized and the controls ensuring the compatibility have not been adequately described.
  6. The test method provided for the 2D-NMR test for the drug substance is inadequate, the drug substance specification does not include this test, and the analytical testing site performing this test has not been inspected due to missing information.
  7. The acceptance criteria for impurities in the drug product is incomplete, lacking specifications for total impurities.

In order to correct these deficiencies it will be necessary for you to:

- A. Submit the results of a new randomized, double-blind, placebo-controlled study of the safety and effectiveness of ziconotide conducted in the target population and at the dosing

regimen (i.e., initial dose, dose titration schedule, and titration interval) proposed for marketing. The design of this study has been discussed in reference to IND submissions N200 dated February 27, 2001, and N206 dated April 22, 2001.

- B. Submit a detailed and complete reanalysis of the safety data from Study 95-001 and Study 96-002 that adequately addresses the deficiencies noted in #1 (a), (b), (c), (d), and (e).
- C. The results from the previous studies and the new placebo-controlled trial should be incorporated into the ISS segment in your future resubmission.
- D. Perform a focused embryo-fetal development study in rats which will be capable of demonstrating whether the previous finding of absence of pubic and ischial bones was due to delayed bone maturation (ossification) or due to absence of bone and cartilage. The rat embryo-fetal development study should:
  - i. Utilize the same experimental design as in the previously conducted rat embryo-fetal development study, including using the same supplier, strain, age, and weight of rat;
  - ii. Include the following two treatment groups: vehicle and 15 mg/kg/day ziconotide;
  - iii. Utilize double-staining techniques (Alizarin Red S/Alcian Blue) for bone and cartilage visualization;
  - iv. Assess exposure levels by performing toxicokinetic analysis;
  - v. 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; and
  - vi. Provide further analysis of the literature submitted to support the findings of maternal toxicity on GD9 and provide correlation with the findings of maternal toxicity (alterations in body weights and/or food consumption) in the dams whose fetuses demonstrated absent ischial and pubic bones in the NDA study.
- E. Base the media fill action limits for large numbers of units filled on a contamination rate less than  $\frac{1}{1000}$  using modern aseptic filling technology which is capable of producing large numbers of units without contamination.
- F. Provide tabulated data for the amount of ziconotide that is lost to degradation in the Medtronic SynchroMed pump with 18 mL reservoir over the 60-day maximum refill interval for the 25,  $\frac{1}{10}$ , and 100  $\mu\text{g}/\text{mL}$  solutions.
- G. Submit the individual data used in generating the graphs in Figures 1, 3, 4, 5 and 6, in I.4, V.001, P.009-014, of your January 26, 2001, submission.

- H. On I.4, V.001, P.005, of your January 26, 2001, submission, you indicated that Medtronic currently employs a technique to \_\_\_\_\_  
\_\_\_\_\_ Provide information about the technique and state whether this technique has been approved by the Agency. Alternatively, reference to the appropriate information in the Medtronic application would be acceptable.
- I. Provide a protocol for periodic compatibility testing of ziconotide injection with the Medtronic Pump. Include ziconotide assay, individual impurities, and total impurities in the tests and acceptance criteria. Testing should begin immediately after fill of naïve pumps and continue through the maximum refill period (60 days). The compatibility testing should capture the effects of dilution, adsorption, and degradation.
- J. Revise the SOP entitled Structure Verification for Ziconotide Drug Substance 2D-NMR (I.4, V.001, P.072, of your January 26, 2001, submission) to eliminate the phrase \_\_\_\_\_  
\_\_\_\_\_ A change in analytical testing laboratory requires a supplemental application.
- K. Revise the regulatory specifications for the drug substance, ziconotide, to include the test for Structure Verification for Drug Ziconotide Drug Substance by 2D-NMR.
- L. Provide the address and CFN number of the \_\_\_\_\_ facility. Also provide the name of a contact person and a telephone number for that facility.
- M. Provide updated stability data and statistical analysis of the data for the drug product.
- N. Include an acceptance criterion for total impurities in the regulatory specifications for the drug product.
- 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 the proposed impurity specifications.

Labeling comments are deferred until the above comments have been addressed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
  4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
  5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
  6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
  7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial

reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

John K. Jenkins, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

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/s/

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John Jenkins

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-060**

**APPROVABLE LETTER 1**



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 27 2000

Attention: Sheldon Mullins  
Senior Associate  
Regulatory Affairs

Dear Mr. Mullins:

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

We also refer to your amendments dated January 12, March 10, 22 (2), and 31, April 6, 7, 12, 14, 17, 20, 24, 27, and 28, May 1, 11, 19, 22 (2), and 26, 2000.

We also acknowledge receipt of your submission dated June 23, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

1. The data submitted in the NDA are inadequate to support a definitive conclusion that ziconotide will be safe and effective in the target patient population using the dosing regimen recommended in the proposed draft labeling. While the two Phase 3 placebo-controlled studies (Study 95-001 and Study 96-002) were on their face adequately designed to evaluate the safety and effectiveness of ziconotide by intrathecal administration, insufficient attention was given to dose-ranging for safety and effectiveness and to delineation of the temporal pharmacodynamic profile of the drug prior to initiation of these studies. These failures resulted in the use of an initial dosing regimen (i.e., initial dose, dose titration schedule, and titration interval) in both studies that was associated with an unacceptably high rate of serious adverse events and patient withdrawals. The dosing regimen was significantly modified (e.g., changes in initial dose and dose escalation schedule, changes in dosing interval, change from dose escalation to toxicity to dose escalation to analgesia, etc.) on several occasions while these two studies were ongoing in an attempt to find a more tolerable dosing strategy.

As a result, only a relatively small number of patients were treated with the final dosing regimen, which most closely approximates the dosing regimen proposed in the draft labeling.

Analysis of the subset of patients enrolled in Study 95-001 and Study 96-002 who were treated with the final dosing strategy (after exclusion of patients enrolled at the clinical sites where unblinding may have occurred) suggested that ziconotide may be effective for management of severe chronic pain (i.e., the primary endpoint of percent change in visual analog scale of pain intensity (VASPI) for ziconotide-treated patients was statistically significantly different from placebo in Study 96-002 and there was a trend favoring ziconotide versus placebo in Study 95-001).

Interpretation of the data from this subset of patients, however, is limited due to the following factors:

- (a) This analysis represents a post-hoc subset of patients that was not pre-specified in the protocol and, as such, this analysis is best considered exploratory and not confirmatory of effectiveness of the final dosing regimen.
- (b) The small number of patients who were treated with the final dosing regimen in these two studies limits the conclusions that can be reached regarding the safety and tolerability of the final dosing regimen.
- (c) Analysis of the subset of patients who received the final dosing regimen has not been extended to include the secondary endpoints that were specified in the protocol nor to include standard analyses of safety and effectiveness generally reported in a complete clinical trial report (e.g., patient demographics, duration of exposure, adverse events, etc.).
- (d) The analyses submitted for the entire patient population studied and for the subset of patients who received the final dosing regimen have not adequately addressed the contribution of coadministered opiate analgesics to the safety and effectiveness of ziconotide. The analyses have also not adequately addressed the potential for opiate overdose and/or withdrawal during initiation and maintenance of treatment with ziconotide.
- (e) The data submitted and the analyses performed do not readily allow a determination of the dose and concentration over time administered to individual patients nor of the protocol amendment under which they were treated. The data submitted and the analyses performed also do not allow identification of the actual dose of ziconotide delivered to individual patients. This issue arises from the variable *in vitro* stability of the drug product depending on the concentration of drug product and the type of

infusion pump studied, the variable *in vitro* stability data depending on the diluent used, and the dosing instructions provided to investigators that allowed for use of a single fill of the pump reservoir for up to 30 days, which are at odds with the refill instructions proposed in the draft labeling and the stability data. This uncertainty regarding the dose of ziconotide that was actually delivered to patients during the clinical trials makes it impossible to write a dosing and administration section of the labeling that will assure the safe and effective use of the product under the conditions of use (e.g., initial fill time, refill timing, use of saline diluent, etc.) proposed in the draft labeling.

- (f) Numerous instances of inadequate documentation of important clinical information on the case report forms for patients enrolled in the two Phase 3 studies makes it difficult, and sometimes impossible, to adequately evaluate the specific details of adverse events and to make a reasonable assessment of causality.
2. Appropriate documentation has not been provided for financial disclosure as required under 21 CFR 54.4 and 314.50(k) for Studies 95-001 and 96-002.
  3. The differential stability of the drug product at various concentrations in the infusion pumps recommended in the proposed draft labeling has not been adequately investigated and the apparent adsorption of the drug substance to the pump reservoir has not been adequately resolved. The proposal to address the variable stability of the drug product and the adsorption of the drug substance to the pump reservoir by means of differential labeling instructions for initial fill and refill time based on the drug product concentration and the pump being used is confusing, likely to result in frequent and potentially serious and/or life-threatening dosing errors, and unacceptable.
  4. There has not been adequate evaluation of the drug product's continued biological activity in the pump for the duration of the 30-day capacity of the reservoir.
  5. There has not been adequate evaluation of the drug product's potential to sustain microbial growth if contamination were to occur in the pump. Thus, it is not possible to assess the risk of meningitis associated with the administration of ziconotide via an implanted intrathecal pump.
  6. The owners of the site proposed for the LAL (limulus amoebocyte lysate) testing of the drug substance report that this testing is not done at that facility; therefore, an inspection of the testing facility could not be completed.
  7. An appropriate analytical method has not been selected to assure the activity of the drug substance on lot-to-lot release.

8. The proposed proprietary name, \_\_\_\_\_ is unacceptable. The proposed name is too similar to that of other marketed drug products and, therefore, poses an unacceptable risk of medication dispensing error in practice.

In order to correct these deficiencies it will be necessary for you to:

- A. (1) Submit the results of a new randomized, double-blind, placebo-controlled study of the safety and effectiveness of ziconotide at the dosing regimen (i.e., initial dose, dose titration schedule, and titration interval) proposed for marketing conducted in the target population proposed for labeling. This study should be initiated only after the concerns raised by the differential stability of the drug product and the adsorption of the drug substance to the pump reservoir have been satisfactorily addressed (see Item D., below). The dosing regimen used in this study should take into account the actual drug delivered during the previous two placebo-controlled studies so as to provide corroborating evidence of effectiveness for the previously studied regimen. You are strongly encouraged to consult the Division of Anesthetic, Critical Care, and Addiction Drug Products regarding the design of the new clinical trial prior to initiation of the trial.
- (2) Submit a detailed and complete reanalysis of the subset of patients in Study 95-001 and Study 96-002 who were treated with the final revision of the dosing regimen that adequately address the deficiencies noted in item #1 (c), (d), (e), and (f) above or a subset that reasonably conforms to the proposed labeling, after the issues of actual drug delivery to patients have been addressed. You are strongly encouraged to consult the Division of Anesthetic, Critical Care, and Addiction Drug Products regarding the reanalyses of Study 95-001 and Study 96-002 prior to conducting the requested reanalyses.
- B. Provide the appropriate documentation for financial disclosure required for Studies 95-001 and 96-002 under 21 CFR 54.4.
- C. Conduct a thorough analysis of the causes of the apparent adsorption of the drug substance to the pump reservoir and develop a method to eliminate, or significantly reduce, the adsorption of the drug substance. This may involve altering the buffer for the drug product or altering the pump reservoir. Submit new stability data for the various concentrations of drug product in the infusion pumps recommended for use following implementation of the changes to address the adsorption of the drug substance to the pump reservoir.
- D. Conduct a study to adequately test the to-be-marketed drug product in the reservoir, for 30 days at normal body temperature, and assure that biological activity is preserved proportionately with chemical stability. The current ziconotide samples on stability must be tested to confirm that they meet the

binding assay specification. Future stability testing plans must be revised to include monitoring of the binding assay.

- E. Provide adequate assurance that the intrathecally delivered drug product has sustained sterility, either by providing evidence from microbial cultures or by reformulation with a non-toxic preservative. If reformulated, nonclinical safety studies (bridging studies), and/or additional clinical safety and efficacy data may be required.
- F. Submit the name and address of the inspection-ready facility that will be responsible for the LAL testing of the drug substance.
- G. Choose an appropriate analytical method for assuring the activity of the drug substance on lot-to-lot release and submit the data to support this choice.
- H. Submit a new proposed trade name(s) for review.

Labeling comments are deferred until the above comments have been addressed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that any response to this letter include all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

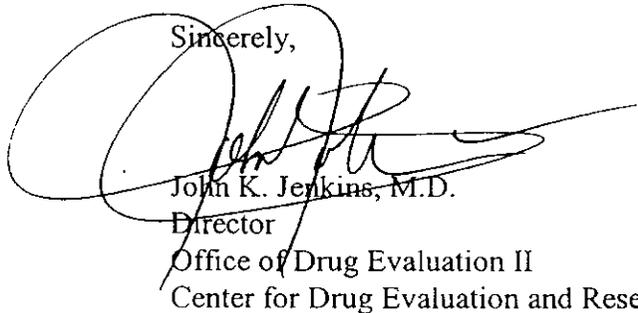
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Anesthetic, Critical Care, and Addiction Drug Products to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

A handwritten signature in black ink, appearing to read 'John K. Jenkins', is written over the typed name and title. The signature is fluid and cursive, with a large loop at the beginning and a long horizontal stroke extending to the right.

John K. Jenkins, M.D.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research