

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

APPROVAL LETTER



NDA 21-260

Elan Drug Delivery, Inc.
1300 Gould Drive
Gainesville, GA 30504

Attention: Sharon Hamm, Pharm. D.
Sr. Vice President R& D Technical Services

Dear Dr. Hamm :

Please refer to your new drug application (NDA) dated May 25, 2000, received May 30, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avinza (morphine sulfate extended-release) 30, 60, 90, and 120-mg capsules.

We acknowledge receipt of your submissions dated August 29, October 12, 27, and 30, November 29, and December 20, 2000, January 19, 25, and 30, February 6, 9, and 21, March 8 and 16, July 26, and September 17 and 20, 2001, January 8 and 29, and March 7, 12, 13, 14, 15, 18, 19, and 20, 2002. Your submission of September 20, 2001, constituted a complete response to our March 30, 2001, action letter.

This new drug application provides for the use of Avinza (morphine sulfate extended-release) capsules for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (immediate container and carton labels submitted March 20, 2002) with the following revisions.

1. The prominence of the established name of the drug product (currently black) will be increased relative to that of the tradename (currently red). This may be accomplished by making the tradename and established name the identical color.
2. The strength designations on the labels of the bottles and the blister cartons will consist of black numerals in a white box. The white box will be within a box of the respective designated color codes for the 30, 60, 90, and 120 strength drug products. The colors used in the labeling will match that of the capsules of respective strength.

3. The numerical designations of strength (currently black) on the blister lidding will be examined for legibility when used with the actual shade of color of the commercial drug product.
4. The legibility of the established name on the bottles, blister cartons and blister lidding will be improved (e.g., by use of a different font).

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-260." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated March 20, 2002. These commitments are listed below.

1. Conduct a GLP toxicology study to further characterize the pre-clinical safety profile of fumaric acid.

Protocol Submission: Within 6 months of completion of the dose finding studies.

Study Start: Within 3 months of the FDA protocol approval.

Final Report Submission: Within 18 months following study initiation.

2. Conduct a Long term safety study to further support the administration of Avinza and the safety profile of fumaric acid in high dose patients. The study will be conducted in approximately 100 patients receiving Avinza doses in excess of 500 mg per day including an adequate representation in doses as high as 3-5 gm per day for the treatment of pain. Patients will be followed for 6 months.

Protocol Submission: Within 5 months of the date of this letter.

Study Start: Within 3 months of receiving comments/approval from FDA
on
the study protocol.

Final Report Submission: Within 33 months of study initiation.

3. Conduct a morphine carcinogenicity study in two rodent species using the lifetime (two year) bioassay.

Protocol Submission: Within 22 months of the date of this letter.

Study Start: Within 3 months of receiving FDA comments on the protocol.

Final Report Submission: Within 32 months of study initiation.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, we have the following comments.

1. The following shelf life is granted for the drug product:
 - ~~_____~~ Bottle configurations-24 months
 - Blisters-12 months
2. Based on the analysis of the stability data, in light of the discussion during the teleconference on March 18, 2002, and with reference to the description in the "Data handling" section of the stability protocol submitted March 18, 2002, we remind you that you have agreed to submit a Prior-Approval supplement for any future shelf life extensions for the bottle and blister configurations of Avinza.
3. We remind you of your agreement to provide 3-months stability data at 25°C and 40°C both under low relative humidity for the drug product in open dish and in the blister package.

Submit three copies of an updated methods validation package including all test methods and revised specifications. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 31, 2004. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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 review your pediatric drug development plan and notify you of its adequacy. 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.

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 submit 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, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

**APPEARS THIS WAY
ON ORIGINAL**

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

Enclosure

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

/s/

Cynthia McCormick
3/20/02 08:00:02 PM

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ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

APPROVABLE LETTER



NDA 21-260

Elan Pharmaceutical Research Corporation
1300 Gould Drive
Gainesville, GA 30504

Attention: Sharon Hamm, Pharm.D.
Sr. Vice President, R&D Technical Operations

Dear Dr. Hamm:

Please refer to your new drug application (NDA) dated May 25, 2000, received May 30, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate extended-release capsules.

We acknowledge receipt of your submissions dated April 14, August 29, September 22, October 12, 27, and 30, November 29, December 20, 2000, January 19, 25, and 30, 2001, February 6, and 21, 2001, March 5, 8, and 16, 2001.

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 *in vitro* stability of pellets mixed with applesauce and left standing for a period of 30 minutes has not been demonstrated. Provide results of appropriate *in vitro* testing to support this manner of dosing.

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.

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 Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

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

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Cynthia McCormick
3/30/01 08:46:44 PM

**APPEARS THIS WAY
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