CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-217

OTHER ACTION LETTER(s)

milstein / [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 27 2000

NDA 21-217

Knoll Pharmaceutical Co.
300 Continental Drive, North
Mt. Olive, NJ 07828

Attention: Richard A. Vogel, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Vogel:

Please refer to your new drug application (NDA) dated December 28, 2000, received December 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dilaudid (hydromorphone hydrochloride) extended-release Tablets.

We acknowledge receipt of your submissions dated January 13, February 16, April 28, and May 4, 2000.

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

1. The data submitted in support of this NDA have failed to demonstrate the efficacy of Dilaudid extended-release for the intended indication of analgesia for moderate to severe pain. The following item must be addressed.

   Conduct an adequate and well-controlled study, with multiple dosing of the to-be-marketed formulation, in the setting of moderate to severe pain, to establish the efficacy of the product.

2. This application lacks sufficient information on the manufacture of the drug substance. Acceptance testing of raw materials, in-process controls, and drug substance specifications are insufficient to ensure the quality and purity for use of the drug substance in manufacture of the drug product. To address these deficiencies, provide adequate responses to the following comments.

   a. Provide a detailed description for the preparation of morphine sulfate or a Letter of Authorization to a Drug Master File (DMF) where this information is provided.

   b. The acceptance testing of morphine sulfate is not described adequately.

      (1) Establish an additional specific identity test, such as IR, HPLC, or MS.

      (2) Provide a detailed description of the test methods used for acceptance.

(3) Provide the Certificates of Analysis from Mallinckrodt and Knoll on the same batches.

c. [redacted] (b) (4)

d. [redacted] (b) (4)

e. [redacted] (b) (4)

f. Provide a description of the differences in the optimized process and original process for the manufacture of hydromorphone hydrochloride.

g. Provide the detailed description of the preparation, characterization and specifications for the in-house reference standard of hydromorphone hydrochloride.

h. Provide the NMR, MS, and HPLC chromatogram of [redacted] (b) (4), [redacted]

i. Provide data on the characterization of reference standards for (b) (4) [redacted] (b) (4)

j. Provide a limit of less than 0.1 % for individual unspecified related substances. Qualify any impurity at 0.1% or higher for safety. Tighten the specifications for total impurities to better reflect the observed data.

k. The drug substance specifications listed on page 3/1.26 do not contain tests for hydromorphone hydrochloride assay, [redacted] (b) (4), and particle size. Revise the table to include these attributes.

l. Tighten the stability specification for individual unspecified related substances in the drug substance to less than 0.1 % each, and revise the limits on all impurities to better reflect the observed data.

m. Provide the sampling plan for the testing of the drug substance.

n. Provide a specification for melting range of the drug substance.

o. Provide a revised drug substance stability protocol incorporating the following.

(1) Specifications for the related substances.

(2) Specifications for the particle size.

(3) A statement that regardless of the year of production, all stability batch samples will be tested quarterly in the first year, semi-annually in the second and annually in the subsequent years of the stability program.

3. There are insufficient data on the acceptance criteria for the components of the drug product and in-process controls for the manufacturing process are insufficient. To address these deficiencies, provide adequate responses to the following comments.

    a. Provide limits for the hold-times for the intermediates in the manufacture of the drug product.

    b. Submit COAs for cellulose acetate, hydroxypropylmethylcellulose, and polyethylene oxide used in the manufacture of the three registration batches of the drug product.

    c. [redacted] (b) (4)

    d. Provide a sampling plan for the in-process tests for weight and hardness of tablet cores, with samples from beginning to end of the process.

    e. Provide a detailed description of the in-process method for measuring the weight of the drug layer and push layer for tablet cores.

    f. Revise the in-process specifications for weight and hardness of tablet cores to include acceptance criteria for individual tablets.

    g. Tighten the in-process specifications for tablet core hardness and tablet orifice diameter.

    h. Provide a detailed description of the laser drilling. Provide in-process tests and methods for ensuring drilling on the correct side of the tablet, orifice diameter, and orifice depth. [redacted] (b) (4)

4. The drug product specifications are inadequate to ensure the safety and consistent performance of the drug product. The stability data provided are of insufficient duration to support the proposed expiration dating period. Insufficient information has been provided to ensure the performance of the packaging. To address these issues, provide adequate responses to the following comments.

    a. Tighten the level for individual unspecified impurities in the drug product to less than 0.1 %. Individual impurities at 0.2% or higher should be qualified for safety.

    b. Establish a specification for [redacted] (b) (4) in the drug product, either as an in-process control or as a release control.

    c. Revise the dissolution specifications to include the following limits for all dosage strengths at release and stability:

        (1) Establish a minimum limit of dissolution at 0-4 h.

        (2) Specify (b) (4) % drug release at 0-10 h.

        (3) Specify (b) (4) % drug release at 0-24 h.

d. Total related substances (drug substance impurities) increased significantly with time in batches 9801844, 9801229, 9801569, 9801633, MV9800108, MV9800117, 9801843, 9801844, 9801229, 9801569, and 9801633. Explain and justify why the specifications for these impurities are not established in the drug product.

e. Agreement on the expiration dating period and specifications awaits submission and review of updated stability data.

f. We remind you that the expiration dating period of the drug product begins no later than the time of quality control release of that batch, and the date of release should generally not exceed thirty days from the production date, regardless of the packaging date. The production date is the (b) (4)

g. The proposed expiration dating period and post-approval expiration dating period extension should be based on the statistical analysis of real time stability data of the registration batches.

h. DMFs (b) (4)) and (b) (4) are inadequate to support components of the container closure system of the drug product. The DMFs should be adequately amended in response to the FDA Letters dated July 28, 2000 (DMF (b) (4)), and May 25, 2000 (DMF (b) (4)).

i. Provide a detailed description of the drug product packaging operation, including in-process tests, test methods, specifications, and sampling plan to ensure proper sealing of the bottles and blisters.

j. Provide certification that the packaging used in the stability studies and the to-be-marketed product is in compliance with the Poison Prevention Packaging Act of 1970 as per 16 CFR 1700.14 (a)(4).

5. No carcinogenicity studies of hydromorphone hydrochloride were submitted. Before the approval of the application you will have to conduct studies to evaluate the carcinogenicity of hydromorphone hydrochloride in two rodent species.

The proposed label indicates that (b) (4) (b) (4) (b) (4)" This claim must be supported with data comparing the extended-release product with the immediate-release products.

Inclusion of the CR suffix in the trade name is not acceptable. In addition, revise the established name to hydromorphone hydrochloride extended-release tablets.

Further labeling comments will be deferred until you have provided adequate data to address the above concerns.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

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. 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. These tables should be cumulative and compare adverse events at the time of NDA, 120 day safety update, and final safety update submissions to facilitate review. The tables should include exposure by dose ranges, including all dose ranges up to the maximum.

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.

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 acknowledge receipt of the Proposed Pediatric Study Request (PPSR) dated August 14, 2000, submitted to IND (b) (4), which is currently under review. The terms of the Written Request, when issued, may or may not fulfill the requirements of 21 CFR 314.55 (or 601.27). In the interim, please submit your pediatric plan development plans within 120 days form the date of this letter unless you believe a waiver is appropiate.

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 this division 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 Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

Cynthia G. McCormick MD

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

cc:
Archival NDA 21-217
HFD-170/Div. Files
HFD-170/Judit Milstein/C. Schumaker
HFD-170/S. Hertz/ B. Rappaport
HFD-170/K. Haberny/T. Papoian
HFD-170/A. Chen/S. Doddapaneni
HFD-170/T. Permuttt
HFD-170/R. Harapanhalli/D. Koble

HFD-002/ORM
HFD-102/ADRA
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: jrm/October 10, 2000
Reviewed by: D. Koble 10-26-00, R. Harapanhalli 10-26-00, C. Schumaker 10-27-00, D. Koble 10-27-00
Initialed by: K. Haberny, T. Permutt, A. Chen, R. Harapanhalli, D. Koble, S. Hertz, T.Papoian, B.Rappaport, C. Schumaker 10-27-00
Final: 10-27-00
filename: E:\n21217 dilaudid\ae 10-27-00.doc

APPROVABLE (AE)