21-038

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 21-038

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 21-038

Trade Name Precedex

Generic Name dexmedetomidine

Sponsor Abbott Labs.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-038

Food and Drug Administration
Rockville MD 20857

Abbott Laboratories
Hospital Products Division
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Attention: Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs

DEC 17 1999

Dear Dr. Willer:

Please refer to your new drug application (NDA) dated December 18, 1998, received December 18, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRECEDEX (dexmedetomidine hydrochloride injection) 2 mL ampule/2 mL vial, 100 mcg/mL.

We acknowledge receipt of your submissions dated February 4, March 10, 15, 30 and 31, April 30, May 4, 10, 12, 21, and 24, June 17 and 18, July 2, August 12, 17, 20, and 27, September 2, 3, 10, 16, and 20, October 1, 5, 8, 19, and 27, November 1, 4, 17, and 19, December 2, 3, 5, 6, 7, 9, 14, 16, and 17, 1999.

This new drug application provides for the use of dexmedetomidine hydrochloride 2 mL ampule/2 mL vial, 100 mcg/mL, for sedation of initially intubated and mechanically ventilated patients in an intensive care unit (ICU) setting.

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) and to the carton and container labels submitted on December 17, 1999. Marketing the product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case 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 21-038." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated December 16, 1999. These commitments, including completion dates agreed upon, are listed below.

1. Conduct a 2-week study in dogs, followed by a 2-week recovery phase, to evaluate general toxicology and effects on the HPA axis.

   Protocol Submission: Completed
   Study Start: Completed
   Final Report Submission: Within 6 months following the date of this letter

2. Conduct a 2-week study in dogs to evaluate changes in drug metabolism following 2 weeks of drug infusion.

   Protocol Submission: Completed
   Study Start: Completed
   Final Report Submission: Within 6 months following the date of this letter

3. Conduct a study to evaluate the effects of the three major human metabolites that are absent in the rat and the dog in a human-relevant animal species or, alternatively, by direct administration of these metabolites in an appropriate animal species.

   Protocol Submission: Within 4 months following the date of this letter
   Study Start: Within 6 months following the date of this letter
   Final Report Submission: Within 12 months following the date of this letter

4. Conduct an in vitro human lymphocyte chromosomal aberration assay using the human liver S-9 fraction as the metabolic activation system.

   Protocol Submission: Within 4 months following the date of this letter
   Study Start: Within 6 months following the date of this letter
   Final Report Submission: Within 12 months following the date of this letter

5. Conduct a study to assess the effect of temperature on the in-vivo micronucleus assay in mice.

   Protocol Submission: Within 4 months following the date of this letter
   Study Start: Within 6 months following the date of this letter
   Final Report Submission: Within 12 months following the date of this letter

6. Conduct a long-term continuous infusion study in patients to evaluate the pharmacokinetics, safety, and extended effectiveness of Precedex in the ICU setting.

   Protocol Submission: Within 10 months following the date of this letter
   Study Start: Within 12 months following the date of this letter
   Final Report Submission: Within 36 months following the date of this letter

7. Conduct a second long-term, continuous infusion study in patients with renal failure. This study should include an adequate number of patients with mild, moderate, and severe renal failure to fully assess that patient population. Metabolite levels should be quantified to assess their accumulation with long-term use of Precedex in patients with renal failure.

   Protocol Submission: Within 4 months following the date of this letter
   Study Start: Within 6 months following the date of this letter
   Final Report Submission: Within 36 months following the date of this letter

Submit protocols, data, and final reports for clinical studies to your IND for this product and send a copy of the cover letter to this NDA. For other types of Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each clinical study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated **"Phase 4 Commitments."**

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. We are deferring submission of your pediatric studies until December 2, 2000. 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 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 of Anesthetic, Critical Care, and Addiction Drug Products 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.

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-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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 Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

/S/

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL