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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-671

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-671

Skye Pharma Inc.
10450 Science Center Drive
San Diego, CA 92121

Attention: Paula C. Adams, Ph.D.
Assoc. Director, Regulatory Affairs

Dear Dr. Adams:

Please refer to your new drug application (NDA) dated July 18, 2003, received July 18, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DepoDur (morphine sulfate extended-release liposome injection), 10 mg/mL.

We acknowledge receipt of your submissions dated August 25, September 3, 10, and 17, November 17, and December 15, 2003, and February 2, 12, and 20, March 15, 18, and 26, April 9, 21(2), and 22, May 7, 12, 13, 14, and 17, 2004.

This new drug application provides for the use of DepoDur for single-dose administration by the epidural route, at the lumbar level, for the treatment of pain following major surgery.

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 enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted May 12, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product(s) misbranded and (an) unapproved new drug(s). We remind you of your submission dated May 17, 2004 where you agree to revise the container and carton label so that the proprietary and established name are shown as follows:

DepoDur™ (morphine sulfate extended-release liposome injection)

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-671." 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 to 18 years until February 2008.

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 treatment of pain following major surgery in pediatric patients ages 0 to 18 years.

Final Report Submission: June 2008

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your postmarketing study commitment in your submission dated May 17, 2004. This commitment is listed below.

1. Description of Commitment: Conduct a 28-day epidural repeat-dose toxicity study in a second species. The study should either use the final clinical formulation of DepoDur or the isolated tricapyrylin component.

Protocol Submission: by July 2004
Study Start: by October 2004
Final Report Submission: by May 2005

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**."

We also remind you of your agreements to the following as stated in your May 14 and May 17, 2004 submissions.

1. You have agreed to develop and validate a method for the determination of (b)(4)----- content in the drug product, and include the test in the post-approval stabilit-----mit a prior-approval supplement, with supporting data, within four months from the date of this letter to set the specifications for b(4)-----in the drug product.

2. Submit a prior-approval supplement to include revised drug sub(b)(4)-----ations to include a limit on (b)(4)----- impurity based on the revisions made by -----
3. Reevaluate the *in-vitro* release specifications based on data from the first (b)commercial batches. Submit a prior-approval supplement with supporting data for an(4)hanges in the specifications.
4. (b)(4)-----

appropriate timeframes for conducting the studies and reporting the results to the Agency, within 30 days from the date of this letter.

5. Develop an educational program to be initiated at roll-out that will educate providers and practioners regarding the risks of medication errors associated with DepoDur and other intrathecally administered drug products, and that will assist in preventing these types of errors.

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).

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

Enclosure

**This is a representation of an electronic record that was signed electronically and
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/s/

Bob Rappaport
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