DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-370

NDA TENTATIVE APPROVAL

Cipher Pharmaceuticals
(c/o) Willcox & Savage, P.C.
One Commercial Place, Suite 1800
Norfolk, VA 23510

Attention: Conrad M. Shumadine, Esq.
U.S. Agent

Dear Mr. Shumadine:

Please refer to your new drug application (NDA) dated April 14, 2008, received April 15, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride extended-release capsules 100 mg, 200 mg, and 300 mg.

We acknowledge receipt of your submissions dated May 22, June 27, September 8, October 20, and November 14 and 17, 2008, January 6, and February 10, 2009.

(b) (4)

This NDA provides for the use of tramadol hydrochloride extended-release capsules for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

We have completed our review of this application, as amended, and it is tentatively approved under 21 CFR 314.107 for use as recommended in the enclosed agreed-upon labeling text and immediate container and carton labels. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product upon which you based your application is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3)(B)of the Act (21 U.S.C. 355(c)(3)(B)) may not be made effective until the period has expired, i.e., May 10, 2014.

Any significant changes in the conditions outlined in this NDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to our review before final approval may be granted. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to the established timelines for class 1 and class 2 resubmissions. See the guidance for industry *Classifying Resubmissions in Response to Action Letters*, http://www.fda.gov/cber/gdlns/actionltr.pdf.

Two or six months prior to May 10, 2014, as appropriate, or when requested, amend and resubmit this application, identifying any changes in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing, and controls data, and a safety update.

Failure to resubmit this application will prompt a review of the application that may result in rescission of the tentative approval letter.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letters before May 10, 2014, you should amend and resubmit your application accordingly.

PROPRIETARY NAME

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation. For additional information, refer to the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*, http://www.fda.gov/cder/guidance/7935dft.pdf.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 waiving the pediatric study requirement for ages 0 to 2 years.

Your request for deferred pediatric studies required under section 2 of the Pediatric Research Equity Act is denied. Pediatric studies may not be deferred until final approval. You must study the pharmacokinetics, efficacy, and safety of your product for the management of moderate to moderately severe chronic pain in pediatric patients ages $\geq$ 2 to 17 years at this time.

OTHER

We have the following comments and recommendations. These requests are not approvability issues; however, a response to them is requested.

1. Revise the drug release acceptance criteria after production and evaluation of twenty commercial (production scale) batches of your product.

2. Upon completion, submit process validation study reports to the NDA. These studies should include an assessment of blend uniformity/in-process content uniformity of drug product intermediates, e.g., immediate-release beads, and revised acceptance criteria for the dissolution testing of the treated beads.

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

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205**.**

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures
Package insert dated February 13, 2009
Carton and immediate container labels dated February 13, 2009

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

/s/

Sharon Hertz

2/13/2009 04:05:17 PM