CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 079040

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 079040

Actavis Elizabeth LLC
Attention: Janak Jadeja, R.Ph.
Director, Regulatory Affairs
200 Elmora Ave
Elizabeth, NJ 07207

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 2, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg.

Reference is also made to your amendments dated September 5, October 23, and October 25, 2007; January 2, March 25, June 5, and October 3, 2008; October 2, October 9, and November 12, 2009; January 12, January 13, May 4, May 7, and December 3, 2010; January 6, March 23, April 11, June 6, July 28, and August 15, 2011; February 29, March 23, April 10, April 20, June 1, June 14, June 19, July 20, September 11, September 28, October 18, December 3, and December 13, 2012; and January 10, 2013.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Avinza® Extended-release Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg and 120 mg, respectively, of King Pharmaceuticals, Inc. (King).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The “interim” dissolution specifications are as follows:

> Dissolution Testing should be conducted in 900 mL of phosphate buffer, pH 6.8 using USP Apparatus II (paddle) with sinkers at 50 rpm.
>
> The test products should meet the following “interim” specifications:

Time (Hours)	Percent Dissolved
1	(b) (4)
3	
6	
12	
24	

These “interim” dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a “Supplement – Changes Being Effected” if there are no revisions to be made to the “interim” specifications, or if the final specifications are tighter than the “interim” specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, King’s Avinza Extended-release Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”), U.S. Patent No. 6,066,339 (the '339 patent), is scheduled to expire on November 25, 2017.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the ‘339 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg, under this ANDA. You have notified the agency that Actavis Elizabeth LLC (Actavis) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Actavis for infringement of the '339 patent within the statutory 45-day period in the United States District

Court for the New Jersey [King Pharmaceuticals, Inc., King Pharmaceuticals Research and Development, Inc., Elan Corporation, plc and Elan Pharma International Ltd., v. Actavis, Inc., and Actavis Elizabeth LLC, Civil Action No. 07-5041]. You have informed the agency that this litigation was dismissed.

With respect to 180-day generic drug exclusivity, we note that Actavis was the first ANDA applicant for Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Actavis may be eligible for 180 days of generic drug exclusivity for Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Actavis failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) (forfeiture of exclusivity for failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of the eligibility of Actavis for 180-day generic drug exclusivity. It will do so only if another paragraph IV applicant becomes eligible for full approval (a) within 180 days after Actavis begins commercial marketing of Morphine Sulfate Extended-release Capsules USP, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg, or (b) at any time prior to the expiration of the ‘339 patent if Actavis has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated April 19, 2011. In that letter, you were also notified that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class of extended-release or long-acting (ER/LA) opioids.

We remind you that section 505-1(f)(8) of the Act prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, appended to this letter, is approved. The REMS consists of a Medication Guide and elements to assure safe use. This REMS will use a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system is known as the ER/LA Opioid Analgesic REMS. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) and (D), FDA can require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy, or if FDA determines that there may be a cause for action by FDA under section 505(e). Additionally, the details for what should be included in any joint assessments completed under the ER/LA Opioid REMS are listed in Appendix 1.

Prominently identify the submission containing the REMS or any REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

ANDA 079040
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 079040
PROPOSED REMS MODIFICATION

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment:
Appendix 1
Medication Guide
REMS

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

/s/

ROBERT L WEST

01/16/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.