DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 208592

ANDA TENTATIVE APPROVAL

Mylan Pharmaceuticals Inc.
U.S. Agent for Mylan Laboratories Limited
781 Chestnut Ridge Road
Morgantown, WV 26505
Attention: Anil Sachdeva
Senior Director - Regulatory Affairs,

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 22, 2015, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylnaltrexone Bromide Subcutaneous Injection, 12 mg/0.6 mL single-dose vial.

Reference is also made to the complete response letter issued by this office on October 12, 2016, and to your amendment received on February 7, 2017.

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. The Office of Bioequivalence has determined your Methylnaltrexone Bromide Subcutaneous Injection, 12 mg/0.6 mL single-dose vial, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Relistor Subcutaneous Injection, 12 mg/0.6 mL of Salix Pharmaceuticals, Inc. (Salix).

However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the FD&C Act.

The RLD upon which you have based your ANDA, Salix's Relistor Subcutaneous Injection, 12 mg/0.6 mL, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,559,158 (the ‘158 patent)	November 3, 2017
8,247,425 (the ‘425 patent)	December 31, 2030
8,420,663 (the ‘663 patent)	September 30, 2029
8,552,025 (the ‘025 patent)	April 8, 2024
8,822,490 (the ‘490 patent)	September 30, 2029
9,180,125 (the ‘125 patent)	September 30, 2029

With respect to the ‘158 patent, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the FD&C Act stating that Mylan Laboratories Limited (Mylan) will not market Methylnaltrexone Bromide Subcutaneous Injection, 12 mg/0.6 mL, prior to the expiration of the patent. Therefore, final approval of your ANDA may not be granted pursuant to section 505(j)(5)(B)(ii) of the FD&C Act until the ‘158 patent has expired, currently November 3, 2017.

With respect to the ‘425, ‘663, ‘025, ‘490 and ‘125 patents[1], your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Methylnaltrexone Bromide Subcutaneous Injection, 12 mg/0.6 mL, under this ANDA. You have notified the Agency that Mylan complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and litigation was initiated within the statutory 45-day period against Mylan for infringement of the ‘425, ‘663, ‘025, ‘490, and ‘125 patents in the United States District Court for the District of New Jersey [Valeant Pharmaceuticals International, Inc., Salix Pharmaceuticals, Inc., Progenics Pharmaceuticals, Inc., and Wyeth LLC, formerly known as Wyeth v. Mylan Pharmaceuticals, Inc., Mylan Laboratories Ltd., and Mylan Inc, Civil Action No. 15-08180 (SRC) (CLW)].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) of the FD&C Act,

   b. the date the court decides[2] that the ‘425, ‘663, ‘025 and ‘490 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the FD&C Act), or

   c. the ‘158, ‘425, ‘663, ‘025, and ‘490 patents have expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

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[1] The Agency notes that the ‘125 patent was submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to this patent would not create a statutory stay of approval.

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 90 days for Agency review. Accordingly, such a request for final approval should be submitted no later than 90 days prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, e.g., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to November 3, 2017, you should amend your ANDA accordingly.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage

forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Scott Dallas, Regulatory Project Manager, at (240) 402-8618.

Sincerely yours,

{See appended electronic signature page}

Carol A. Holquist, RPh
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Carol Holquist

Digitally signed by Carol Holquist
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