



ANDA 078936

TENTATIVE APPROVAL

Mylan Pharmaceuticals, Inc.
U.S. Agent For: Mylan Laboratories Limited
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Attention: Shane Shupe
Senior Manager, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 3, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg.

Reference is also made to the complete response letter issued by this office on April 17, 2014, and to your amendments dated June 25 and October 20, 2014; and January 15, 2015.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore 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 Act.

The reference listed drug (RLD) upon which you have based your ANDA, Nexium Delayed-release Capsules, 20 mg and 40 mg, of AstraZeneca Pharmaceuticals LP (AstraZeneca), is subject to periods of patent protection. The following unexpired patents and expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

<u>U.S. Patent Number</u>	<u>Expiration Date</u>
5,900,424 (the '424 patent)	November 4, 2016
6,147,103 (the '103 patent)	April 9, 2019
6,166,213 (the '213 patent)	April 9, 2019
6,191,148 (the '148 patent)	April 9, 2019

6,369,085 (the '085 patent)	November 25, 2018
6,428,810 (the '810 patent)	May 3, 2020
7,411,070 (the '070 patent)	November 25, 2018
8,466,175 (the '175 patent)	November 25, 2018

Also listed in the Orange Book are U.S. Patent Numbers 5,690,960 (the '960 patent) and 5,714,504 (the '504 patent). The '960 patent expired on November 25, 2014, and the '504 patent expired on February 3, 2015. Pediatric exclusivity periods associated with the '960 and '504 patents expire on May 25, 2015, and August 3, 2015, respectively.

With respect to the '175 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act that this is a method of use patent that does not claim any proposed indication for which you are seeking approval under your ANDA.

With respect to each of the seven other unexpired patents listed above, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Esomeprazole Magnesium Delayed-release Capsules USP, 20 mg and 40 mg, under this ANDA. You have notified the agency that Mylan Laboratories Limited (Mylan) complied with the requirements of section 505(j)(2)(B) of the Act, and that no litigation for infringement of any of these unexpired patents was brought against Mylan within the statutory 45-day period.¹

The RLD upon which you have based your ANDA, AstraZeneca's Nexium (esomeprazole magnesium) Delayed-release Capsules, 20 mg and 40 mg, is subject to periods of exclusivity. As noted above, the pediatric exclusivity periods associated with the '960 and '504 patents are scheduled to expire on May 25, 2015, and August 3, 2015, respectively. Therefore, final approval cannot be granted until expiration of the pediatric exclusivity period associated with the '504 patent.

Please note that if FDA requires a Risk Evaluation & 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 Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will

¹ It is noted that litigation for infringement of the '504 patent was brought against Mylan within the statutory 45-day period in the United States District Court for the District of New Jersey [AstraZeneca AB, Aktiebolaget Hässle, AstraZeneca LP, KBI Inc., and KBI-E Inc. v. Mylan Laboratories Limited and Mylan Laboratories, Inc., Mylan, Inc., Matrix Laboratories Limited, and Matrix Laboratories, Inc., Civil Action No. 12 CV 1378], as well as in the United States District Court for the District of Delaware [AstraZeneca AB, Aktiebolaget Hässle, AstraZeneca LP, KBI Inc., and KBI-E Inc., v. Mylan Laboratories Limited, Mylan Laboratories, Inc., Mylan, Inc., Matrix Laboratories Limited, and Matrix Laboratories, Inc., Civil Action No. 12 CV 00300 UNA]. Although this litigation remains ongoing, the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your ANDA, has expired.

Moreover, it is noted that your paragraph IV certification to the '504 patent, as well as your paragraph IV certification to '960 patent (on which Mylan was not sued), are deemed to be paragraph II certifications upon expiration of each of these patents.

be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., 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 MINOR AMENDMENT – 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 the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMP are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either “major” or “minor” changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also 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 of the 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 Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the Orange Book.

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 1 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.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Edward Taylor, Regulatory Project Manager, at (240) 402-6094.

Sincerely yours,

**William P.
Rickman -S**

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

 Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300043242,
cn=William P. Rickman -S
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