DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 204936

APPROVED

Apotex Corporation
US Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
Vice President, US Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 19, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Timolol Maleate Ophthalmic Solution USP, 0.5% (Once Daily).

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 Timolol Maleate Ophthalmic Solution USP, 0.5% (Once Daily), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Istalol Ophthalmic Solution of Bausch & Lomb Inc. (B&L).

The RLD upon which you have based your ANDA, B&L's Istalol Ophthalmic Solution, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,335,335 (the '335 patent) and 6,645,963 (the '963 patent) are scheduled to expire on November 2, 2018 and November 16, 2018, respectively.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Timolol Maleate Ophthalmic Solution USP, 0.5% (Once Daily), under this ANDA. You have notified the agency that Apotex Inc. (Apotex) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Apotex for infringement of the '335 patent within the statutory 45-day period in the United States District Court for the Southern District of New York [Senju Pharmaceutical Co., Ltd., Bausch & Lomb, Inc. and Bausch & Lomb Pharma Holdings Corp. v. Apotex Inc. and Apotex Corp., Civil Action No. 1:13-cv-04132 (PAC)]. You have also notified the agency that the case was dismissed. We note that the '963 patent was not listed in the Orange Book when your ANDA was received, and your paragraph IV certification was submitted in an amendment to your ANDA. Therefore litigation, if any, with respect to this patent would not be a bar to approval of your ANDA.

With respect to 180-day generic drug exclusivity, Apotex was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Apotex is eligible for 180-days of generic drug exclusivity for Timolol Maleate Ophthalmic Solution USP, 0.5% (Once Daily). This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

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.

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.

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(s) 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.

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.

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,

Carol A. Holquist -S

Digitally signed by Carol A. Holquist -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052464, cn=Carol A. Holquist -S
Date: 2015.04.17 14:01:27 -04'00'

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