DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 077337

Teva Pharmaceuticals USA, Inc.
Attention: Scott D. Tomsky,
Vice President, Regulatory Affairs, N.A., Generics
425 Privet Road
Horsham, PA 19044

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated October 22, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Rosiglitazone Maleate and Metformin Hydrochloride Tablets, 2 mg (base)/500 mg, 4 mg (base)/500 mg, 2 mg (base)/1 gram, and 4 mg (base)/1 gram.[1]

Reference is also made to the tentative approval letter issued by this office on April 19, 2007; and to your amendments dated December 21, 2009; February 23, February 24, and April 10, 2012; and March 25, April 16, April 22, April 29 and May 2, 2014. In addition, we acknowledge receipt of your correspondence dated July 25, 2008; August 13, 2010; and February 10, 2012, addressing the patent issues associated with this ANDA.

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 [redacted] (b) (4), effective on the date of this letter. The Division of Bioequivalence has determined your Rosiglitazone Maleate and Metformin Hydrochloride Tablets, 2 mg (base)/500 mg, 4 mg (base)/500 mg, 2 mg (base)/1 gram, and 4 mg (base)/1 gram, to be bioequivalent and, therefore, therapeutically equivalent

[redacted] (b) (4)

to the reference listed drug (RLD), Avandamet Tablets of SB Pharmco Puerto Rico, Inc. (SB Pharmco). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, SB Pharmco's Avandamet Tablets, is subject to periods of patent protection.
The following unexpired 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
5,741,803 (the '803 patent)	October 21, 2015*
5,965,584 (the '584 patent)^	June 19, 2016
6,166,042 (the '042 patent)^	June 19, 2016
6,288,095 (the '095 patent)^	August 11, 2017*
7,358,366 (the '366 patent)	October 19, 2020*
8,236,345 (the '345 patent)	October 7, 2022

*with pediatric exclusivity added
^Listed only for the 1 mg (base)/500 mg, 2 mg (base)/500 mg, and 4 mg (base)/500 mg strengths

With respect to each of these patents, 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 Rosiglitazone Maleate and Metformin Hydrochloride Tablets, 1 mg (base)/500 mg, 2 mg (base)/500 mg, 4 mg (base)/500 mg, 2 mg (base)/1 gram, and 4 mg (base)/1 gram, under this ANDA. You have notified the agency that Teva Pharmaceuticals USA (Teva) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was initiated against Teva for infringement of the '803 patent within the statutory 45-day period in the United States District Court for the District of New Jersey [SmithKline Beecham PLC, et al. v. Teva Pharmaceuticals USA, Inc., Civil Action No. 05-CV-536]. You have also notified the agency that litigation was dismissed.

With respect to 180-day generic drug exclusivity, we note that Teva was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Teva is eligible for 180 days of generic drug exclusivity for Rosiglitazone Maleate and Metformin Hydrochloride Tablets, 2 mg (base)/500 mg, 4 mg (base)/500 mg, 2 mg (base)/1 gram, and 4 mg (base)/1 gram. 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

FDA determined that a REMS is necessary for Rosiglitazone Maleate and Metformin Hydrochloride Tablets to ensure the benefits of the drug outweigh the risks. The Avandamet (rosiglitazone maleate and metformin hydrochloride) REMS was originally approved on May 18, 2011. The single, shared system REMS program for rosiglitazone-containing medicines, the Rosiglitazone REMS Program, was approved on January 25, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(i) of the Act, an abbreviated new drug application (ANDA) is required to have a REMS if the applicable listed drug has an approved REMS. The details of the REMS requirements were outlined in our REMS notification letter dated February 14, 2012. 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 applicants of Rosiglitazone products.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of the rosiglitazone-containing medicines outweigh the risks. We remind you that the Medication Guide will continue to be part of the approved labeling for Rosiglitazone Maleate and Metformin Hydrochloride Tablets in accordance with 21 CFR 208.

We have also determined that elements to assure safe use that require that healthcare providers who prescribe rosiglitazone-containing medicines for outpatient or long-term care use are specially certified, that rosiglitazone-

containing medicines be dispensed only by specially certified pharmacies, and that rosiglitazone-containing medicines be dispensed only to patients with evidence or other documentation of safe use conditions are no longer necessary to ensure the benefits of the drug outweigh the risks.

Your proposed REMS, submitted on February 24 2012, and amended on July 27 and December 20, 2012 ; and April 16, April 22 and May 2, 2014, and appended to this letter, is approved.

The REMS consists of elements to assure safe use to provide training on the current state of knowledge concerning the cardiovascular risk of rosiglitazone-containing medicines to health care providers who are likely to prescribe rosiglitazone-containing medicines and a timetable for submission of assessments of the REMS.

The REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. This single shared system, known as the Rosliglitazone REMS Program, currently includes the following products:

NDA 021071 Avandia (rosiglitazone maleate)
NDA 021410 Avandamet (rosiglitazone maleate and Metformin hydrochloride)
NDA 021700 Avandaryl (rosigltiazone maleate and glimepiride)
ANDA 076747 Rosiglitazone Maleate
ANDA 077337 Rosiglitazone Maleate and Metformin Hydrochloride

Other products may be added in the future if additional NDAs or ANDAs are approved.

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.

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).

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

ANDA 077337
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 077337
PROPOSED REMS MODIFICATION

PROMOTIONAL MATERIALS

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.

REPORTING REQUIREMENTS

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.

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.

CONTENT OF LABELING

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*}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attached: Labeling
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

05/07/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.