DEPARTMENT OF HEALTH AND HUMAN SERVICES

**Food and Drug Administration**
**Silver Spring, MD 20993**

ANDA 202118

**ANDA APPROVAL/TENTATIVE APPROVAL**

Teva Pharmaceuticals USA, Inc.
425 Privet Road
Horsham, PA 19044
Attention: John Derstine
Director, Regulatory Affairs, US Generics

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 23, 2010, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Darunavir Tablets, 75 mg, 150 mg, 400 mg, and 600 mg.[1]

Reference is also made to the tentative approval letter issued by this office on December 23, 2013, and to any amendments thereafter.

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 Darunavir Tablets, 75 mg, 150 mg, 400 mg and 600 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Prezista Tablets, 75 mg, 150 mg, 400 mg and 600 mg, of Janssen Products, LP (Janssen).

However, we are unable to grant final approval to your Darunavir Tablets, 75 mg, 150 mg, and 400 mg, at this time because of the exclusivity issue noted below. Therefore, your ANDA is **approved** insofar as it pertains to Darunavir Tablets, 600 mg. Your Darunavir Tablets, 75 mg, 150 mg, and 400 mg, are **tentatively approved**.

The RLD upon which you have based your ANDA, Janssen's Prezista Tablets, 75 mg, 150 mg, 400 mg and 600 mg, is subject to periods of patent protection. The following 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"):

[1] We note that the reference listed drug (RLD) upon which you have based this ANDA, Janssen's Prezista Tablets, 400 mg, is no longer being marketed in the United States and is currently listed in the discontinued section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). The Agency has determined that Janssen's Prezista Tablets, 400 mg, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in the *Federal Register* (79 FR 18558; April 2, 2014). This determination allows the Agency to approve ANDAs for the discontinued drug product.

| U.S. Patent Number | Expiration Date |
|---|---|
| 7,470,506 (the '506 patent) | December 23, 2019 |
| 7,700,645 (the '645 patent) | June 26, 2027 |
| 8,518,987 (the '987 patent) | August 16, 2024 |
| 8,597,876 (the '876 patent) | December 23, 2019 |

Your ANDA contains paragraph IV certifications to each of the patents[2] 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 Darunavir Tablets, 75 mg, 150 mg, 400 mg and 600 mg, under this ANDA. You have notified the Agency that Teva Pharmaceuticals USA, Inc. (Teva) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that litigation was initiated within the statutory 45-day period against Teva for infringement of the '506 and '645 patents in the United States District Court for the District of New Jersey [Janssen Products, L.P., et al. v. Lupin Limited et al., Civil Action No. 10-cv-05954 (consolidated)] and the '987 patent in the United States District Court for the District of New Jersey [Janssen Products, L.P. et al. v. Teva Pharmaceuticals USA, Inc. et al., Civil Action No. 13-cv-07576]. You have also notified the Agency that these cases were dismissed.

However, we are unable to grant final approval to with respect to the 75 mg, 150 mg, and 400 mg strength products at this time. Prior to the submission of your ANDA, another applicant or applicants submitted a substantially complete ANDA providing for Darunavir Tablets, 75 mg, 150 mg, and 400 mg, and containing a paragraph IV certification. Your ANDA for these strengths will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

Upon the foregoing, your ANDA is **approved** insofar as it pertains to the 600 mg product. Your 75 mg, 150 mg, and 400 mg products are **tentatively approved**.

## I. Approval of Darunavir Tablets, 600 mg

With respect to 180-day generic drug exclusivity, we note that Teva was one of the first ANDA applicants to submit a substantially complete ANDA with a paragraph IV certification for Darunavir Tablets, 600 mg. Therefore, with this approval, Teva may be eligible for 180 days of shared generic drug exclusivity for Darunavir Tablets, 600 mg. The Agency notes that Teva failed to obtain tentative approval of this ANDA within 40[3] months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for

[2] The Agency notes that the '987 and '876 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[3] For applications submitted between January 9, 2010, and July 9, 2012 containing a paragraph IV certification (or amended to first contain a paragraph IV certification during that period of time), and approved or tentatively approved during the period of time beginning on July 9, 2012, and ending on September 30, 2015, section 1133 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) extended the 30-month period to 40 months.

failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of Teva's eligibility for 180-day generic drug exclusivity.

At least one first applicant remains eligible for 180-day generic drug exclusivity for Darunavir Tablets, 600 mg.[4] This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing by any first applicant, as identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of FD&C 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 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.

## REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Office of Generic Drugs should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Office of Generic Drugs in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

[4] See also draft guidance for industry on *180-Day Exclusivity: Questions and Answers*, Q. 42, at 26 (Jan. 2017).

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf)

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[5] 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.

## 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

[5] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

## II. Tentative Approval of Darunavir Tablets, 75 mg, 150 mg, and 400 mg

Our decision to tentatively approve your Darunavir Tablets, 75 mg, 150 mg, and 400 mg, is based upon information currently available to the agency (i.e., date in your ANDA and the status of current good manufacturing practice (cGMP) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

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.

## 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, 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/MAJOR AMENDMENT TO ORIGINAL #2 – 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.

## ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[6] 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.

[6] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Tiffany Houser, Regulatory Project Manager, at (240) 402-4742.

Sincerely yours,

*{See appended electronic signature page}*

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Sarah Kurtz

Digitally signed by Sarah Kurtz
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