CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208042

REFUSAL TO FILE

Teva Pharmaceuticals USA
425 Privet Road
Horsham, PA 19044

Attention: Scott D. Tomsky
Vice President, Regulatory Affairs

Dear Mr. Tomsky:

Please refer to your New Drug Application (NDA) dated and received October 29, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for buprenorphine and naloxone sublingual film, 16 mg / 4 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. Your application does not contain the following required components: Introduction (Section 2.2), Clinical Overview (Section 2.5), Clinical Summary (Section 2.7), Integrated Summary of Safety and Efficacy (Sections 5.3.5.3), and an overall Table of Contents for the submission.

2. Your Application does not address several issues which are required to be included in the Integrated Summary of Safety (ISS). These include datasets of adverse events including all levels of MedDRA hierarchy (if MedDRA was used), and appropriate tabulations by System Organ Class and Preferred Term. If another coding system was used, information about the coding system must be submitted. Submit narratives for any deaths, serious adverse events, and subjects discontinuing due to adverse events. The Integrated Summary of Safety is to be based on all current worldwide knowledge regarding this product.

   Note that if the length of the ISS fits within the restrictions of Module 2.7, it may be submitted in Module 2, but all required information must be included.

3. Your submission lacks an integrated summary of the risks and benefits of the product, and a section addressing abuse liability. These may be brief, making reference to the established findings concerning the reference product, but must nevertheless be submitted.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. Regarding labeling:
   a. The labeling submitted includes reference to [redacted] (b) (4). The wording of the labeling must explain how the prescriber can use the specific product proposed (e.g., that it is to be used only in patients already titrated to a dose of 16 mg on another product). [redacted] (b) (4)

   b. Aspects of text that are specific to the reference product (e.g., descriptions of local tolerability, comparative pharmacokinetics between Suboxone tablets and films) should not be included.

   c. The "Recent Major Changes" section should not be included in the initial version of labeling for this product.

   d. Section 8.1 appears to have been entirely deleted and should be restored.

   e. The findings of the pH-effect study should be translated to a recommendation to avoid high-pH beverages prior to dosing.

   f. Information about [redacted] (b) (4) should be omitted [redacted] (b) (4)

2. Your evaluation of the bioequivalence for unconjugated naloxone between your product and the reference product in Study 3007599 employed the Reference Scaled Average Bioequivalent method. Note that the acceptability of this method will be determined during the course of the review.

3. We acknowledge the data submitted to determine the impact of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution. Provide data, e.g. dissolution profiles, in graphical and tabular form as a function of the critical attributes identified using the proposed QC method supporting your conclusions in terms of the impact (or lack of impact) of these attributes on the dissolution profile of your proposed product.

4. Submit individual and mean dissolution values from all pivotal batches used in setting the dissolution acceptance criterion.

5. Reduce the specification for the [redacted] (b) (4) impurity in buprenorphine, in accordance with ICH Q3A and as supported by the batch data, wherein the impurity is controlled at < [redacted] (b) (4) % in three batches.

6. Propose in-process controls for [redacted] (b) (4).

7. Provide a detailed method description, including sampling, for assessing the product description during stability. Provide details on how the film flexibility and color (including at the film edges) are assessed, as well as film removal from pouch.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
12/19/2014