DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208042

NDA APPROVAL

Teva Pharmaceuticals USA
425 Privet Road
Horsham, PA 19044

Attention: Cherri Petrie
Senior Director, Regulatory Affairs, US Generics

Dear Ms. Petrie:

Please refer to your New Drug Application (NDA) dated and received October 9, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CASSIPA (buprenorphine and naloxone) sublingual film, 16 mg/4 mg.

We acknowledge receipt of your amendment dated March 8, 2018, which constituted a complete response to our September 30, 2016, action letter.

This new drug application provides for the use of CASSIPA for the maintenance treatment of opioid dependence.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the instruction of use and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, submitted on September 6, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208042**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of QT prolongation associated with CASSIPA.

Currently, the mechanism underlying buprenorphine-induced QT prolongation has not been fully elucidated. For logistical and ethical reasons, a conventional thorough QT study for CASSIPA as defined in ICH E14 is not feasible.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of QT prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3486-1 Conduct a QT trial using alternative designs as described in ICH E14 Q&A 6.1 in patients who are initiating treatment with buprenorphine and naloxone in the clinical setting, across the therapeutic dose range. Placebo and positive controls are not necessary. Base the timing of the ECG collection on the known pharmacokinetic properties of buprenorphine and naloxone and include ECGs collected at baseline, after the first dose, and at steady state. Conduct this trial in the inpatient setting and collect time-match pharmacokinetic samples so that the data can be analyzed using concentration-QTc analysis. The assessment must include an evaluation of any potential delayed effects.

The timetable you submitted on August 30, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	March 2019
Final Protocol Submission:	September 2019
Study Completion:	September 2020
Final Report Submission:	December 2020

Submit the draft clinical protocol(s) to your PIND 118625 with a cross-reference letter to this NDA. Ensure that the draft protocol is clearly identified as being for comment purposes only, and not for implementation until finalized.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for CASSIPA (buprenorphine and naloxone) sublingual film to ensure the benefits of the drug outweigh the risks of accidental overdose, misuse, and abuse.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that CASSIPA poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of CASSIPA. FDA has determined that CASSIPA is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use CASSIPA, and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks of accidental overdose, misuse, and abuse.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed CASSIPA.

Pursuant to 505-1(f)(1), we have also determined that CASSIPA can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of accidental overdose, misuse, and abuse. Your REMS includes the following elements to mitigate these risks:

- The drug is dispensed to patients with evidence or other documentation of safe-use conditions; and
- Each patient using the drug is subject to certain monitoring.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on March 27, 2018, amended and appended to this letter, is approved. 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.

Your REMS must be fully operational before you introduce CASSIPA into interstate commerce.

This REMS will use a waiver-granted shared system for the elements to assure safe use. This waiver-granted shared system is known as the buprenorphine-containing transmucosal products for opioid dependence (BTOD) REMS. The waiver-granted shared BTOD REMS was originally approved on February 22, 2013, and currently includes the products listed on the FDA REMS website available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
Other products may be added to the BTOD REMS in the future if additional BTOD NDAs or ANDAs are approved.

Because CASSIPA will be a member of the BTOD REMS, the assessment plan will be the same assessment plan required for the other products covered by this waiver-granted shared system. The assessment reports for CASSIPA will align with the seventh assessment (due August 2019), and subsequent assessments of the BTOD REMS assessment plan. Therefore, your REMS assessment plan should include, but is not limited to, the following:

a. An evaluation of patients' understanding of the serious risks associated with buprenorphine-containing products;

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24;

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance;

d. An evaluation of prescribers' awareness and understanding of the serious risks associated with buprenorphine-containing products;

e. An evaluation of pharmacists' awareness and understanding of the serious risks associated with buprenorphine-containing products;

f. An analysis to evaluate utilization patterns of CASSIPA including frequency of office visits, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important to safe use;

g. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from

signals of abuse, misuse, overdose and addiction. Surveillance will include, among other sources, reports of pediatric exposures;

h. Monitoring and evaluation of the implementation of the ETASU; and

i. An assessment of the extent to which the REMS is meeting its goals. Specific measures that will be proposed to increase awareness if surveys of patients, prescribers, and pharmacists indicate that awareness is not adequate.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 208042 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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

NDA 208042 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 208042/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 208042/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 208042/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 208042/S-000

REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 208042

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. 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 prescribing information, 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 20705-1266

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/GuidanceCompliance RegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a

Form FDA 2253. 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.

EXPIRATION DATING

CASSIPA is granted an expiry dating of 24-months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
09/07/2018