DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021692/S-015

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENTS
NEW POSTMARKETING REQUIREMENT
POSTMARKETING REQUIREMENTS FULFILLED

Valeant Pharmaceuticals North America LLC
400 Somerset Corporate Center Blvd.
Bridgewater, NJ 08807

Attention: Mary Harrell, BsBM, RAC
Director, Regulatory Affairs

Dear Ms. Harrell:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 17, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ULTRAM ER (tramadol HCl) Extended-Release Tablets.

We also refer to our letter April 20, 2017, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for ULTRAM ER. This information pertains to the risk of life-threatening respiratory depression in children associated with use of tramadol-containing products and the risk of life-threatening respiratory depression in breastfed infants whose mothers were treated with tramadol-containing products.

This supplemental new drug application provides for revisions to the labeling for ULTRAM ER, consistent with our April 20, 2017, letter, as well as additional revisions to the Package Insert related to postmarketing requirements (PMRs) 1909-1 and 1909-2.

APPROVAL & LABELING

We have completed our review of this supplemental 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

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RELEASE FROM POSTMARKETING REQUIREMENT

FDA previously determined that you were required to conduct the following postmarketing studies in our letter dated March 25, 2013:

2022-1 Deferred pediatric study under PREA to assess efficacy of tramadol in pediatric patients 7 to less than 17 years of age.

Final Protocol Submission:	March 30, 2014
Study/Trial Completion:	July 30, 2019
Final Report Submission:	November 30, 2019

2022-2 Deferred pediatric study under PREA to assess the pharmacokinetics, safety and tolerability of tramadol in pediatric patients 7 to less than 17 years of age.

Final Protocol Submission:	April 30, 2014
Study/Trial Completion:	July 30, 2020
Final Report Submission:	October 31, 2020

We have determined that you are released from the above postmarketing requirements because, with the approval of this supplement, ULTRAM ER is contraindicated in children less than 12 years old, and the use of ULTRAM ER should be avoided in 12 to 18 year old patients who have risk factors that may increase their sensitivity to the respiratory depressant effects of ULTRAM ER.

The above postmarketing requirements will be replaced by the new postmarketing requirement as described below:

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81(b)(2)(vii) and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

2022-3 To study the pharmacokinetics, efficacy, and safety of ULTRAM ER for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in pediatric patients ages 12 to less than 17 years.

Final Protocol Submission:	02/2018
Study Completion:	01/2020
Final Report Submission:	07/2020

For the required PK, safety, and efficacy studies in pediatric patients 12 to less than 17 years of age, you must exclude patients in that age range who have risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol such as obesity, obstructive sleep apnea, and other respiratory conditions, as described in the prescribing information .

The protocols you previously submitted that are intended to fulfill your pediatric study requirements (i.e., Study TRAM-PAI-3001 and Study TRAM-PAI-3002) do not reflect the Division's current approach to pediatric studies involving opioid products that are to be used on an around-the-clock basis (i.e., for chronic pain). We recommend that you request advice from the Division on the design of your protocols and submit drafts prior to the final protocol submission milestone date to obtain agreement from the Division prior to study initiation.

Submit the protocol(s) to your IND 059023, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received the submissions made by the consortium of tramadol NDA holders, received August 29, 2014, and April 19, 2016, containing the final reports for the following postmarketing requirements listed in the September 26, 2012, "POSTMARKETING REQUIREMENTS AFTER APPROVAL" letter:

1909-1 A multiple ascending dose clinical trial in healthy adult volunteers to determine the maximum tolerated dose of tramadol and to inform the dosing for a thorough QT trial of tramadol.

Draft Protocol Submission:	02/2013
Final Protocol Submission:	05/2013
Trial Completion:	01/2014
Data Analysis Completion:	03/2014
Final Report Submission:	09/2014

1909-2 A clinical trial in healthy adult volunteers to assess the risk of QT prolongation with tramadol, i.e., a thorough QT (tQT) trial. This trial will provide information on cardiac depolarization and conduction effects of tramadol at therapeutic and supratherapeutic dose regimens. The tQT trial may be conducted as part of the multiple ascending dose trial.

Draft Protocol Submission:	04/2014
Final Protocol Submission:	07/2014
Trial Completion:	01/2015
Final Report Submission:	07/2015

We have reviewed your submissions and conclude that the above requirements were fulfilled.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
FDA/CDER
Office of Prescription Drug Promotion (OPDP)
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/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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).

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 Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

JUDITH A RACOOSIN
08/29/2017