DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020281/S-039

SUPPLEMENT APPROVAL
POSTMARKETING REQUIREMENTS FULFILLED

Janssen Pharmaceuticals, Inc.
C/O Janssen Research & Development LLC (JRD)
1000 US Highway 202
PO Box 300
Raritan, NJ 08869-0602

Attention: Kelly Rudnick, MSPH
Manager, Global Regulatory Affairs

Dear Ms. Rudnick:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 19, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) ULTRAM (tramadol HCl) 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. 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, 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.

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).

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received the submissions made by the consortium of tramadol NDA holders, received May 28, 2014, and February 29, 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. This completes all of your postmarketing requirements acknowledged in our September 26, 2012, letter.

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