DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022207/S-007, S-008

SUPPLEMENT APPROVAL

West-Ward Pharmaceuticals International Limited
C/O Hikma Pharmaceuticals USA, Inc.
1809 Wilson Road
Columbus, OH 43228

Attention: Jerald Andry, PharmD, MS
Senior Director, Drug Regulatory Affairs and Medical Affairs

Dear Dr. Andry:

Please refer to the following Supplemental New Drug Applications (sNDAs) dated and received April 2, 2018, and June 28, 2018, and your amendments, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for Morphine Sulfate Tablets.

We also refer to our letter dated September 28, 2017, notifying you that under section 505-1 of the FDCA, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for certain immediate-release (IR) opioid analgesic products, including Morphine Sulfate Tablets, to ensure the benefits of the drugs outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Finally, we refer to our letter dated June 1, 2018, notifying you, under section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Morphine Sulfate Tablets. This information pertains to the addition of the REMS program details to product labeling for the class of opioid analgesics intended for use in the outpatient setting.

Supplement S-007 provides for the REMS required under section 505-1 of the FDCA, consistent with our September 28, 2017, letter.

Supplement S-008 provides for revisions to the labeling for Morphine Sulfate Tablets consistent with our June 1, 2018, Safety Labeling Change Notification letter.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

Note that your approved Medication Guide is now part of the REMS approved in supplement S-007.

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, 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).

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

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) post-approval if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of an approved drug outweigh the risks.

The details of the REMS requirements for certain immediate-release (IR) opioid analgesics intended for use in the outpatient setting were outlined in our REMS Notification letter dated September 28, 2017, informing you that a REMS is necessary to mitigate the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse of these drugs.

Your proposed REMS, submitted to Drug Master File (DMF) (b) (4) on March 26, 2018, amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. This shared system, now known as the Opioid Analgesics REMS Program, 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 in the future if additional NDAs or ANDAs are approved.

The REMS assessment plan must include, but is not limited to, the following:

1. REMS Outreach and Communication

    a. For each healthcare provider (e.g., prescriber, pharmacist) to be sent information regarding REMS-compliant accredited continuing education (CE), provide the date when the letters were sent; the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable

    b. For each professional society, association, and licensing board to be sent information regarding REMS-compliant accredited CE, provide the number of

letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable

2. REMS Implementation and Operations

    a. Status of grants

        i. The status of the request for proposals for grants for REMS-compliant accredited CE including:

            1. Request for Application (RFA) issued: date and number of applications submitted in response to each RFA
            2. RFAs awarded: date, number, and name of grantee
            3. Date/timeframe next RFA to be issued

        ii. The status of the requests for proposals for any grants to CE Providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct evaluations of health care providers who have taken REMS-compliant accredited CE funded under this REMS.

    b. Grant review committee

        i. Individuals from the REMS Program Companies (RPC) reviewing grants will include the following clinical licensures: pharmacists, nurses, physicians. Additionally there will be involvement by individuals with regulatory and pharmacovigilance experience. The job title, licensure and professional degree of individuals will be provided for each grant review cycle.

        ii. Include any external members (non RPC) involved in the grant review, including those from the broad-based CE community. Provide the job title, licensure and professional degree of the individual for each grant review cycle.

    c. For CE programs awarded during the assessment period:

        i. Description of each grantee and projected number of completers

        ii. For the first assessment, the date the first program based upon the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (“FDA Blueprint”), became available

iii. Description of CE program:

1. Level of outcome the activity[1] is designed to impact
2. CE format (live, webinar, etc.)
3. Duration of activity for live or webinar activities
4. Average duration to complete for internet/enduring activities
5. Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)[2,3]

iv. All reports submitted to the RPC by CE grantees during the assessment period.

d. Number of participants and completers during the assessment period; provide description of learners by standard learner category data[4].

e. Independent Audit: The results of independent audits of the CE. Audits must be conducted on a random sample of at least 10% of the REMS-compliant accredited CE funded under the Opioid Analgesic REMS and must include/evaluate:

i. a description of the organization(s) conducting the audit(s)

ii. whether the content of the REMS-compliant accredited CE covers all elements of the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint") approved as part of the REMS;

iii. whether the integrated or post-course knowledge assessment measures knowledge of all sections of the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"); and

iv. whether the REMS-compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies

[1] Stevenson R, Moore DE. Ascent to the Summit of the CME Pyramid. *JAMA* 2018;319(6):543-544
[2] Cervero R, Gaines J. The Impact of CME on Physician Performance and Patient Health Outcomes: An Updated Synthesis of Systematic Reviews *J Contin Educ Health Prof* 2015;35(2):131–138
[3] Agency for Research Health and Quality. (2007). *Effectiveness of Continuing Medical Education*. Retrieved May 9, 2018, from https://archive.ahrq.gov/downloads/pub/evidence/pdf/cme/cme.pdf
[4] Standard Continuing Education (CE) learner data to be captured by all CE Providers for Opioid Analgesic REMS includes geographic location (state of primary practice), DEA prescriber status (individual registration or institutional authorization), profession, practice area, and length of time in practice.

f. Concurrent Educational interventions

i. For the year prior to the assessment period through the assessment period, provide an evaluation of the overall pain/opioid CE landscape including but not limited to:

1. States requiring prescribers, pharmacists, or nurses to complete opioid or pain management continuing education for licensing/renewal of licensing:

a. enumeration of these states and their requirements. for continuing education on either pain or safe opioid use,
b. estimates of annual licensed prescribers in those states
c. which, if any, opioid analgesic or ER/LA Opioid Analgesic REMS CE were permissible in which states, for prescribers to meet requirements

2. Health systems, including government (DOD, VA, IHS, etc.), that require opioid or pain management continuing education; include number of completers if available

3. Any additional available data on continuing education programs available during this time with a focus on pharmacological pain management or safe opioid use

3. Health Outcomes and/or Surrogates of Health Outcomes

a. Surveillance and monitoring of data relating to opioid analgesic use, misuse, abuse, addiction, overdose, and death. Surveillance data should include the following:

i. Nationally representative data or data from large stable populations on opioid analgesic misuse, abuse, addiction, overdose, and death, to allow reliable assessment of national trends and demographic patterns (e.g., age group specific rates and trends)

ii. Both overall and drug-specific outcome rates, as available, in each data source

iii. Data on trends and patterns of illicit opioid (e.g., heroin) use and related morbidity and mortality

b. Evaluation of drug utilization patterns: Nationally-projected data on drug utilization trends and patterns, including an evaluation of trends in:

i. Dispensing of opioid analgesics subject to the Opioid Analgesic REMS, by drug, age group, prescriber specialty

ii. An evaluation of opioid tolerance for products that require patients to be opioid tolerant prior to use

iii. An evaluation of concomitant prescribing of gabapentinoids, benzodiazepines, and other CNS depressants with opioid analgesics

c. Evaluation of patient experiences around pain management

d. An evaluation of patients' experiences with acute and chronic pain management in various settings: this may include a survey, focus group, or other assessment of patient experience, including but not limited to access to coordinated pain management care, non-pharmacological options, and judicious and informed prescribing of opioids. The evaluation may also include an assessment of negative patient experiences, such as perceived overprescribing of opioids, providers' refusal to provide care, or forced rapid tapering or discontinuation

e. Evaluation of prescriber behavior and patient outcomes: The results of an evaluation of the effect of REMS-compliant CE on prescriber behavior and patient outcomes. This evaluation should include the following:

i. Development and use of metrics that assess prescriber behaviors and patient outcomes relating to key messages in the *FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* ("FDA Blueprint"). The assessment should also include an evaluation of potential unintended adverse patient outcomes resulting from changes in prescribing practices (e.g., withdrawal symptoms or increased pain due to inappropriate rapid opioid tapering, patient abandonment, seeking of illicit opioids, suicide attempts/completion)

ii. Use of an appropriate control group (i.e., providers who have not completed REMS-compliant accredited CE), and rigorous control for confounding, to allow an assessment of whether any observed changes in prescriber behaviors or patient outcomes can be attributed to the CE

4. Knowledge

a. Evaluation of CE participants: The results of evaluations to determine the impact of REMS-compliant accredited CE on participants' knowledge, attitudes, and self-reported behavior around pain management and appropriate opioid prescribing. All evaluations should be representative and generalizable to the targeted health care professionals taking the REMS-compliant accredited CE and assess understanding of key elements from all sections of the FDA Opioid

Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"). Multiple methodologies should be used, including but not limited to the following:

i. Pre- and post-activity assessments using validated instruments. These assessments could be integrated into live, online, or multimedia formats using interactive approaches to enhance the educational value of the activity. Different versions or subsets of questions from a standardized assessment tool could be employed to cover all key messages and sections of the *FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* ("FDA Blueprint"), in aggregate, while reducing the time burden for individual participants and allowing the assessment to be tailored for different types of healthcare professionals.

ii. A long-term follow-up evaluation of participants to assess retention of knowledge and skills, application of learning to clinical practice, self-reported change in behavior, and barriers to change. Consider incentivizing participation in follow-up assessment, for example through additional CE credits.

b. Evaluation of Patient Understanding: The results of an evaluation of patients' and caregivers' understanding of the serious risks of opioid analgesics and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients from a representative sample of patients taking opioid analgesics with respect to education level, insurance status, and geographic location.

5. During transition from the ER/LA Opioid Analgesics REMS to Opioid Analgesic REMS, data to be included until the last enduring activity has been reported:

a. For each CE activity released under the ER/LA Opioid Analgesics REMS that remains active, provide the name of the CE Provider, the title of the activity, and the date the activity will expire

b. Aggregate data on participants and completers should be collected using original MEMS 2.0 definitions

6. Methodologies: A timeline for submission of the assessment protocols, including data sources and the methodologies used to conduct all the above described analyses. Each assessment report should update the dates of submission for each component of the assessment.

The first REMS assessment for the Opioid Analgesic REMS, due 6-months from the date of this letter, will include only information outlined in items 1, 2a, 2b, and 2c, and any additional

information the REMS Program Companies (RPC) deems necessary to describe REMS implementation.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

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) of the FDCA. 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 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 that 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 REMS modifications*, 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 022207 REMS 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.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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 022207 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022207/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022207/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022207/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022207/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 REVISIONS FOR NDA 022207

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, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

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 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 prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
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 prescribing information, 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 LCDR Mark A. Liberatore, PharmD, RAC, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Medication Guide
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/

JUDITH A RACOOSIN
09/18/2018