DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208653

NDA APPROVAL

KemPharm, Inc.
1170 Celebration Blvd., Suite 103
Celebration, FL 34747

Attention: Marcus Juliano
Sr. Director of Regulatory Affairs

Dear Mr. Juliano:

Please refer to your New Drug Application (NDA) dated and received December 9, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for APADAZ (benzhydrocodone and acetaminophen) Tablet, 6.12 mg/325 mg.

We acknowledge receipt of your amendment dated August 23, 2017, which constituted a complete response to our June 10, 2016, action letter.

This new drug application provides for the use of APADAZ for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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 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 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 208653**." 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, 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.

We are deferring submission of your pediatric studies for ages 0 to less than 2, 2 to less than 7 years and 7 to less than 17 years for this application, because this product is ready for approval for use in adults, and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3037-1 An open-label PK and safety study in ages 7 to less than 17 years of age.

Draft Protocol Submission:	10/2019
Final Protocol Submission:	04/2020
Study Completion:	05/2021
Final Report Submission:	08/2021

3037-2 An open-label PK and safety study in ages 2 to less than 7 years of age.

Draft Protocol Submission:	08/2021
Final Protocol Submission:	04/2022
Study Completion:	05/2023
Final Report Submission:	08/2023

3037-3 A PK, safety, and efficacy study in ages 0 to less than 2 years of age.

Draft Protocol Submission:	08/2023
Final Protocol Submission:	02/2024
Study Completion:	03/2025
Final Report Submission:	06/2025

3037-4 Conduct a juvenile animal toxicology study in the rat with benzhydrocodone to support dosing of APADAZ in children ≤ 2 years of age.

Draft Protocol Submission:	12/2020
Final Protocol Submission:	06/2021
Study Completion:	08/2021
Final Report Submission:	03/2022

Submit the protocols to your IND 108038, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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.

The details of the REMS requirements for APADAZ were outlined in our General Advice letter dated December 22, 2017, to ensure the benefits of the drug outweighs the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

Your proposed REMS must include the following:

Medication Guide: 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 APADAZ 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 APADAZ. FDA has determined that APADAZ 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 APADAZ. Under 21 CFR Part 208 and in accordance with 505-1 of FDCA, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed APADAZ.

Communication Plan: We have also determined that a communication plan targeted to healthcare providers who are likely to prescribe APADAZ will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about APADAZ, including the Medication Guide and other prescriber education materials.

The communication plan must include, at a minimum, the following:

1. Communication materials to inform health care providers about the REMS Program and the risks and safe use of APADAZ.

2. A description of the audience for the communication plan, stating specifically the types of health care providers to which the communication plan will be directed as well as the professional societies and licensing boards.

3. A schedule for when and how the plan's materials are to be distributed to healthcare providers, professional societies, and licensing boards.

Your proposed REMS, submitted on February 14, 2018, appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The development of the shared system opioid analgesic REMS is currently underway. Once that shared system REMS is approved, we will notify you in writing, and you will be required to submit a modified REMS consistent with the shared system REMS approved for the class.

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

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

1. Date of product launch of APADAZ.
2. Date when APADAZ REMS website becomes operational.
3. Number and date of REMS letters sent via mail and email stratified by audience (e.g., prescriber, pharmacists); a tabular format is preferred.
4. An evaluation of patients' understanding of the serious risks of APADAZ and how to use APADAZ safely.
5. An evaluation of healthcare providers' awareness and understanding of the serious risks and safe use of APADAZ.

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

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

8. 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 (Section 505-1(g)(3).

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 208653 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 208653 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 208653/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 208653/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 208653/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 208653/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 208653

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 REMS_Website@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/GuidanceComplianceRegulatoryInformation/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.

EXPIRY DATING PERIOD

A 36-month expiry period is granted for APADAZ (benzhydrocodone and acetaminophen) Tablet, 6.12 mg/325 mg, in 100 count HPDE bottles when stored at 20°C to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F). A 12-month expiry is granted for tablets packaged in blister strips when stored at 20°C to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 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 Diana L. Walker, PhD, Senior Regulatory Health Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
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 and this page is the manifestation of the electronic signature.

/s/

SHARON H HERTZ
02/23/2018