CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210583Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210583

COMPLETE RESPONSE

Recro Pharma Inc.
490 Lapp Road
Malvern, PA 19355

Attention: Diane P. Myers,
SVP, Regulatory and Quality

Dear Ms. Myers:

Please refer to your New Drug Application (NDA) dated and received July 26, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Meloxicam Injection, 30 mg/mL.

We acknowledge receipt of your amendment dated September 24, 2018, which constituted a complete response to our May 23, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Meloxicam Injection has an onset of action in the range of 2 to 3 hours (possibly longer if patients receiving early rescue had been excluded from this analysis). The delayed onset fails to adequately meet prescriber expectations for intravenous (IV) drugs. Meloxicam Injection is unfit for use as an IV drug for acute pain as monotherapy. Furthermore, the analgesic effect wanes approximately 18 hours after dosing. This makes Meloxicam Injection of questionable utility as a component of multimodal analgesic therapy when dosed every 24 hours, as one would expect the dosing instructions to reflect adequate efficacy throughout the dosing interval. The proposal to label the product (b) (4) based on pharmacokinetic modeling, fails to adequately address the efficacy deficiencies noted and does not provide a benefit that could outweigh the additional safety risks associated with the higher meloxicam levels that would result from a shorter dosing interval.

    a. Regarding efficacy, the available efficacy and pharmacokinetic data do not support a finding of an exposure/response relationship suitable to rely on pharmacokinetic modeling to support a change in dosing interval. Measures of pain intensity are not

well correlated with drug concentration data at the same time point. Specifically, high plasma meloxicam concentrations are achieved shortly after the first dose but the median onset of pain relief is not reported until Hour 2 or 3. The pharmacokinetic data also do not explain the end-of-dose failure as there is little change in plasma meloxicam levels between Hours 18 and 24, (a decline from approximately 1700 ng/mL to approximately 1500 ng/mL). Therefore, the proposed changes to dosing instructions do not adequately address the observed efficacy deficiencies.

b. The available safety data for Meloxicam Injection are inadequate to support the safety (b) (4) Many of the adverse events associated with nonsteroidal anti-inflammatory drugs such as meloxicam are dose- and exposure-related. The meloxicam levels predicted by the pharmacokinetic modeling are higher than the measured levels with 24-hour dosing. (b) (4)

PRESCRIBING INFORMATION

2. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

   If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

3. We refer to your revised draft carton and container labeling submitted on February 25, 2019. When you resubmit your application, revise the draft carton and container labeling as follows:

   1. Container Label
      a. Add the lot number in accordance with 21 CFR 201.10(i)(1).

      b. Add the expiration date in accordance with 21 CFR 201.17 and 21 CFR 211.137. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends

that the expiration date appear in YYYY-MMDD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. Carton Labeling-Single Vial
    a. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.1 The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugsgen/documents/document/ucm621044.pdf

    b. See Container Label comments a and b.

3. Carton Labeling (b) (4)
    a. See Carton Labeling-Single Vial comment a.

PROPRIETARY NAME

4. Please refer to correspondence dated December 19, 2018, which addresses the proposed proprietary name, ANJESO. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/

SHARON H HERTZ
03/22/2019 10:30:55 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210583

COMPLETE RESPONSE

Recro Pharma Inc.
490 Lapp Road
Malvern, PA 19355

Attention: Diane P. Myers,
SVP, Regulatory and Quality

Dear Ms. Myers:

Please refer to your New Drug Application (NDA) dated and received July 26, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ANJESO (meloxicam) injection, 30 mg/mL.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Although you have demonstrated a statistically significant difference between ANJESO and placebo on the primary endpoint in Studies REC-15-015 and REC-15-016, the results of the secondary analyses, including pain intensity difference over time curves, SPID18-24, and SPID42-48, indicate that the analgesic effect does not persist through the dosing interval. This results in a significant period of inadequate analgesic effect of approximately six hours with your product. Additionally, the results for time to meaningful pain relief and time to first rescue use indicate a delayed onset of action that is not consistent with expectations for an intravenous analgesic for acute pain, and the frequent use of rescue medication suggests that ANJESO does not provide analgesia suitable to manage postoperative pain.

NONCLINICAL

2. The NDA did not include an adequate extractables/leachables evaluation to justify the safety of potential leachables in the drug product. The structures of six potential leachable compounds (e.g., (b) (4)) were not fully elucidated, but were detected at above the Analytical Evaluation Threshold (AET) and at levels exceeding the requested qualification threshold of 5 mcg/day. In addition, the compound (b) (4) was detected above 5 mcg/day from extractions

with (b) (4) manufacturing contact material and an unknown compound (b) (4) was detected above 5 mcg/day from the aged drug product. Your rationale to dismiss these compounds as not being potential leachables because they were not detected in both the extraction studies and one lot of aged drug product at one time point is unacceptable as leachables may be produced at earlier or later time points on stability and sampling from several batches over the course of the stability studies, which is best practice for definitive leachables testing, is needed to provide reasonable assurance of capturing peak levels of individual leachable compounds. In addition, the definitive leachables stability testing was inadequate because it only targeted two compounds and did not monitor for all compounds detected in the extraction studies over the 5 mcg/day threshold, including those unknown compounds. Unknown compounds must be identified if they are present as a leachable over the recommended qualification threshold of 5 mcg/day. Note that the results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any (b) (4) manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation.

To resolve this deficiency, monitor for all compounds, both identified and unidentified, that were detected in extraction studies and in the aged product assessment at above 5 mcg/day in your leachables stability testing. Evaluate at least three batches of the to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. Include any secondary container closure systems in the materials tested, if present, and subject these to the same sterilization methods as the final product, as appropriate. These data are essential to determine the appropriate shelf-life of your product.

For all drug products, establish an AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more 120 mcg/day for your proposed acute indication). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect any leachable that is present in the product at 5 mcg/day and higher, unless justified otherwise, to permit an adequate toxicological risk assessment. Note that any unknown leachable compound detected at levels that exceed 5 mcg/day must be identified and adequately justified for safety.

For additional guidance on extractables and leachables testing, refer to the following documents:

- USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

- USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

- FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf

In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

- Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your drug product formulation.

- Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel leachable.

PRODUCT QUALITY

3. The sample size used to evaluate the presence of leachables greater than 5 mcg/day on stability was not sufficient.

   To resolve this deficiency, increase sampling and continue to test the identified extractables as leachables for at least 3 batches of drug product through expiry.

4. According to USP <1663> and <1664>, there must be a good correlation between the extractables and leachables identified such that leachables are not identified that are also not found to be extractables. A lack of correlation may imply that the extractable study was not conducted vigorously enough to extract all possible impurities.

   To resolve this deficiency, provide a root-cause analysis for the leachables detected that were not also observed during the extraction study. If the lack of correlation between the extraction and leachable study cannot be justified, then commit to monitoring the four unknown impurities identified in the leachable study (and not observed at the corresponding RRT in the extractable study) on at least three batches of drug product during stability studies. Measure the impurities at each timepoint for the duration of the stability study.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling with the revisions previously submitted January 26, 2018.

PROPRIETARY NAME

Please refer to correspondence dated October 10, 2017, which addresses the proposed proprietary name, ANJESO. This name was found acceptable pending approval of the application in the

current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments that are not approvability issues:

1. Analyze and report the frequency of bleeding events and anemia (adverse events of special interest analysis) by surgical procedure and by dose based on the pooled Phase 2 and 3 postoperative safety data. Also analyze and report the frequency of these events for each of the Phase 2 and Phase 3 studies separately and tabulate the data by dose. With each table, summarize if any of the events were classified as serious, if any treatments were required, and any outcomes for the patients included in each of the tables and/or provide links to this information in the application.

2. The timeline for completion of juvenile toxicity studies was not included in the agreed PSP. Therefore, amend the agreed PSP to include the juvenile toxicity study in the timeline. Include the amended PSP in the Complete Response resubmission.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

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The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Diana L. Walker, PhD, Regulatory Project Manager, at (301) 796-4029.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ELLEN W FIELDS
05/23/2018