CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211988Orig1s000

OTHER ACTION LETTERS

NDA 211988

COMPLETE RESPONSE

Heron Therapeutics, Inc.
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Attention: Kimberly J. Manhard
Executive Vice President, Drug Development

Dear Ms. Manhard:

Please refer to your new drug application (NDA) dated and received October 30, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zynrelef (bupivacaine and meloxicam) Solution 60mg / 1.8mg, 200mg / 6mg, 300mg / 9mg, 400mg / 12mg.

We acknowledge receipt of your amendment dated September 26, 2019, which constituted a complete response to our April 30, 2019, action letter.

We acknowledge receipt of your major amendments dated December 23 and 31, 2019, which extended the goal date by three months.

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.

NONCLINICAL

1. You have not provided adequate data to support your request for a waiver of reproductive and developmental studies for triacetin. Although you have concluded that the primary metabolites of triacetin do not represent a risk for reproductive and developmental effects, you have provided no data to support the conclusion that triacetin instilled into a wound at the maximum daily dose will not result in systemic exposure to the triacetin molecule.

   Information needed to resolve deficiency:
   Provide data to support the conclusion that triacetin levels are not present in the systemic circulation via your drug product or conduct reproductive and developmental toxicology studies with triacetin via a route that mimics the clinical exposure to this excipient. If you elect to continue to rely upon the cited oral rat reproductive and developmental study, provide justification that the animals in that study were exposed to triacetin at levels comparable to those that will occur

following clinical use of your drug product at the maximum recommended human dose.

2. You have not provided an adequate scientific bridge to the referenced oral reproductive and developmental studies submitted to qualify the safety of DMSO exposure via your drug product. Instillation of the drug product may result in higher C_{max} and AUC compared to oral studies and therefore it is not clear if the referenced studies adequately address the safety of your product.

   Information needed to resolve deficiency:
   Provide data to support your conclusion that these referenced oral studies resulted in exposures to DMSO that exceed the exposure to DMSO via your drug product or conduct studies using an appropriate route of administration.

3. You have not provided adequate data to support the proposed drug product specification (b) (4) at NMT (b) (4) %. The nonclinical and clinical lots tested to date in your development program did not contain this high of a percentage of (b) (4) and therefore does not qualify this specification. Further, you did not provide data to support your conclusion that (b) (4) would not contribute to the local tissue effects of the drug product.

   Information needed to resolve deficiency:
   Either conduct a local tissue toxicity study that tests drug product that contains at least the maximum specified level (b) (4) reduce the specification (b) (4) to that which was tested in the nonclinical toxicology studies, or provide data to support your hypothesis that the (b) (4) in the product does not contribute to local tissue effects of the drug product.

4. Your embryofetal development study in rabbits tested maleic acid via an oral route of administration rather than the proposed route of administration of your drug product and you did not provide an adequate scientific bridge to support your conclusion that the study provides adequate characterization of the developmental effects of maleic acid exposures via installation into a wound.

   Information needed to resolve deficiency:
   Submit justification that the oral toxicology study resulted in exposures (C_{max} and AUC) that provide adequate coverage for the exposure via your drug product when the product is instilled into a wound. In addition, submit the final study report for the oral maleic acid embryofetal development study in the rabbit to the NDA.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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 FDA.gov.[3]

PROPRIETARY NAME

Please refer to correspondence dated, December 6, 2019, which addresses the proposed proprietary name, Zynrelef. 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 product 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.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Although not listed as a deficiency in the first cycle, your proposed specification for DMSO of (b) (4)% has an upper limit that has never been tested in your clinical or nonclinical development program. As DMSO may contribute to local tissue toxicity, either revise the specification to reflect the testing completed by your development program, conduct a new study to characterize the local effects of your to-be-marketed drug product containing DMSO at the upper limit of your proposed specification, or justify why DMSO at (b) (4)% will not contribute to the local tissue effects of the drug product.

Once approved, the following PREA PMRs will be required:

1. Conduct a juvenile animal study in the rodent model to characterize the impact of DMSO on the developing brain to support clinical studies in pediatric patients under three years of age.

2. Conduct a juvenile animal study in an appropriate model to characterize the impact of meloxicam on the developing kidney, liver, lung, and testes to support clinical studies in pediatric patients under three years of age.

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 guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

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 Allison Meyer, Regulatory Project Manager, at 301-796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
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/

RIGOBERTO A ROCA
06/26/2020 03:11:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211988

COMPLETE RESPONSE

Heron Therapeutics, Inc.
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Attention: Lynley Thinnes
Executive Director, Regulatory Affairs

Dear Ms. Thinnes:

Please refer to your New Drug Application (NDA) dated and received October 30, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Bupivacaine and Meloxicam Extended Release Solution 60 mg/1.8 mg, 200 mg/6 mg, 400 mg/12 mg.

We have completed our review of this application 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.

PRODUCT QUALITY

1. The limited data provided on leachables in the drug product, [redacted] (b) (4) is not adequate to assure that the leachables remain within permitted daily exposure limits through the end of shelf-life. [redacted] (b) (4) is not sufficient to establish the safety of leachables present in HTX-011.

   Information needed to address this deficiency:

   Provide test data for all potential leachables, identified through the various extraction studies, monitored at release and at multiple timepoints during the stability testing of HTX-011 batches using validated analytical methods. Further refer to the Additional Nonclinical Comment 5 regarding study design considerations.

2. During a recent inspection of the [redacted] (b) (4) (FEI: [redacted] (b) (4)) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility.

Information needed to address this deficiency:

Satisfactory resolution of these deficiencies is required before this application may be approved.

NONCLINICAL

3. You have not provided adequate data to support the safety of the DMSO or triacetin, in your drug product. The levels in the product exceed the maximum potency listed in the CDER Inactive Ingredient Database (IID) and are, therefore, considered novel. Specifically, your NDA did not include any discussion of the impact of these two excipients on the standard reproductive and developmental battery of studies.

   Information needed to address this deficiency:

   Submit adequate data to fully characterize the impact of the proposed doses of DMSO and triacetin on all endpoints normally characterized via the standard battery of reproductive and developmental toxicology studies. Should you elect to address this via literature, justify the adequacy of the literature based on current standard study protocols and provide copies of all referenced literature. In the absence of adequate published data, GLP nonclinical toxicology studies should be completed.

4. Your toxicological risk assessment for the excipient maleic acid, which exceeds the maximum potency listing in the CDER Inactive Ingredients Database (IID), does not address the potential impact of maleic acid on embryo-fetal development in a second species (typically rabbit).

   Information needed to address this deficiency:
   Submit adequate justification for the safety of the proposed maximum daily dose of maleic acid, specifically with respect to the effects of this compound on rabbit embryo-fetal development.

5. You have not provided adequate data to qualify the proposed drug product degradant (b) (4) which exceeds the ICH Q3B(R2) qualification threshold.

   Information needed to address this deficiency:

   Either tighten the drug product specification (b) (4) to NMT (b) (4)% or provide adequate qualification in accordance with ICH Q3B(R2) as follows:

   a. Complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

c. Alternatively, provide adequate data to support your position [redacted]. However, we note that if you elect to pursue this option, the data may not address the local safety concerns via this drug product's proposed dosing regimen.

6. You have not provided adequate data to support the safety of the drug product specification [redacted]. The proposed specification of NMT [redacted]% exceeds the appropriate qualification threshold of NMT [redacted]% or [redacted] whichever is lower, for a drug product with a maximum recommended human dose of greater than 2 grams as outlined in the ICH guidance for industry: *Q3B(R2) Impurities in New Drug Products*. [redacted] We also acknowledge that [redacted] was detected in the clinical HTX-011 lot that was tested in the pivotal 28-day toxicology studies in dogs and rats; however, the level detected in these stability batches do not support the proposed specification.

Information needed to address this deficiency:

Either tighten the specification [redacted] to be within the qualification threshold of NMT [redacted]% or provide adequate qualification in accordance with ICH Q3B(R2) as follows:

a. Complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

7. You have not provided adequate leachable data to permit substantive toxicological evaluation of the safety of the container closure system [redacted] for this drug product. Specifically:

a. You have not tested at least three drug product stability batches over the entire course of the stability protocol (e.g., 0, 3, 6, 12 months) in order to identify trends for leachables over the course of stability.

b. You have not tested your drug product for extractable compounds detected above the safety concern threshold (SCT) of [redacted]mcg/day [redacted] in Extractable Study 3 (RPT-694).

c. You have not fully identified all of the compounds above the SCT in your extraction studies.

d. In your risk assessment [redacted] you have not provided adequate justification for the use of the [redacted] as a surrogate for the [redacted]

e. The variability of [redacted] present in the existing leachable data do not identify any clear trends and suggest the potential for these compounds to be derived from [redacted] As such, the maximum levels potentially in the product cannot be ascertained for risk with an adequate degree of certainty.

Information needed to address this deficiency:

Conduct new leachables studies based on all of the extractables identified in Extractable Study 3 identified above the safety concern threshold (SCT) of [redacted]mcg/day [redacted] according to USP <1663> and <1664>. In addition, since Extractable Study 3 did not address non-volatile compounds, conduct new leachable studies based on the non-volatile compounds identified in Extractable Studies 1 (RPT-701) and 2 (RPT-693). As you design these studies, note the following comments intended to guide your efforts:

a. Include at least three to-be-marketed drug product batches, each tested over the entire course of the stability protocol (0, 3, 6, 12 months) to identify trends for leachables over the course of stability. The three drug batches should be stored in the planned commercial container closure.

b. Of note, you used a conservative SCT of [redacted] mcg presumably based on genotoxic concerns. However, for acute products (duration of < 1 month) an SCT of 120 mcg/day can be used for genetic toxicity assessment. However, for general toxicity concerns, employ a SCT of 5 mcg/day in the leachable study. The leachable study should use an AET that accurately reflects the potential total daily intake of potential leachables from the drug product and how the product will be dosed. For example, if multiple vials are to be used to deliver a dose, this could affect the AET calculation. In addition, as you have proposed multiple drug product packaging presentations, the AET and toxicological risk assessment must be based on the worst-case clinical use of the product, which may result in the use of more than one packaging configuration per procedure, unless adequately justified otherwise.

c. Multiple compounds were not fully identified from your extraction/leachable studies. This included the leachable identified in the final drug product samples from Leachable Study 3 as [redacted]. Provide descriptions of the methods and procedures used to attempt to identify these compounds and justify why these compounds could not be identified or provide further data supporting identification of these chemicals.

d. Provide adequate justification to support that use of [redacted] is appropriate to represent the potential toxicity of [redacted] either by providing literature references or performing adequate QSAR analysis.

e. Provide a root-cause analysis to identify the source of the [redacted] or confirm that the [redacted] present are derived from either [redacted] If they are derived from [redacted] justify how you intend to adequately control [redacted] to ensure product consistency and quality. In addition, submit a detailed discussion of the extractables leachables correlation and specifically discuss any discrepancy between the compounds identified in the leachable studies compared to those that were predicted to be potentially present based on the extractable data.

CENTER FOR DEVICES AND RADIOLOGIC HEALTH

8. You provided shelf-life and package integrity summary results for the syringe tip cap. However, you did not provide enough information to ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life. This information should be provided to ensure that your device is safe for use. Provide the following:

   a. A description of the sterilization method [redacted] as well as the sterilization site.

   b. In case of [redacted] sterilization [redacted]

   c. For [redacted] the maximum levels [redacted] and an explanation why these levels are acceptable.

   d. A description of the sterilization validation method with a citation of the relevant standard(s), but not the validation data itself.

   e. The sterility assurance level.

   f. Pyrogenicity testing, including a description of the test method, the chosen endotoxin test limit, and your testing frequency. Alternatively, you may provide a scientific justification for why endotoxin testing is not required.

   g. A description of the packaging used to maintain the sterility of the device and a description of the test methods, but not the package integrity test data itself. Please note that the Agency recommends seal strength and a package integrity test after accelerated (and/or real time) aging and visual inspection and a package integrity test after simulated shipping and distribution.

PRESCRIBING INFORMATION

9. 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.

PROPRIETARY NAME

10. Please refer to correspondence dated, January 25, 2019, which addresses the proposed proprietary name, ZYNRELEF. 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.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. Although the current nonclinical data appear to support the safety of bupivacaine when the product is dosed up to 300 mg, the data do not provide adequate coverage for the maximum $AUC_{0\text{-}24h}$ via this drug product at your proposed maximum dose of 400 mg bupivacaine. Because your drug product exposures above 300 mg of bupivacaine via this drug product will exceed that of the referenced drug product, additional data will be required to support any proposed dose above 300 mg bupivacaine.

2. The numbers given under "Maximum intended dose volume (mL)" in Table 2, in section 3.2.P.1 Description and Composition, are not in agreement with the theoretical volume required for delivering labeled amount of each drug.

   Provide revised Table 2 with the corrected theoretical dose volume (mL) required for each dose strength, up to second decimal point (e.g., [redacted] (b) (4) g) in your resubmission.

3. Based on the fact [redacted] (b) (4) and your statement on sensitivity of viscosity of HTX-011 solution to temperature changes, we recommend that you test for 'dynamic viscosity' of HTX-011 and 'syringeability' of HTX-011 solutions stored at 15°C and 25°C temperatures and report the test results in the resubmission. Syringeability studies on HTX-011 solution may be performed by simulating the steps described in IFU for preparation and use of HTX-011 and recording

the time required in seconds for a) withdrawal of HTX-011 from vials fitted with VVS and b) for application (Ejection from the syringe(s) fitted with LLAs) by using vials stored at 15°C and 25°C. Repeat the testing on at least two additional samples of HTX-011 at each storage temperature.

4. (b) (4)

   We recommend you tighten the acceptance criteria set for assay of bupivacaine and meloxicam (b) (4)

5. As it was stated in the foot note 'e' under the batch analyses results table-4, in section 3.2.P.5.4, (b) (4)

   Provide the laboratory investigation reports (LIRs) related to the failure of the two batches supporting your statement on the underlying cause for failure.

6. In your submission in section 3.2.P.6 it was stated that USP reference standards were used for identification and quantification of two APIs. USP reference standards for known bupivacaine and meloxicam impurities and (b) (4) (b) (4) were also used for preparation of standard solutions for identification of the respective know related impurities for the two APIs. However, certificates of analysis reference standards were not provided.

   Provide copies of certificates of analyses, for each of the reference standards (USP and in-house) used in the identification and quantification of the APIs and impurities in HTX-011.

7. (b) (4)

We disagree with these two statements and recommend that you acknowledge (b) (4) (b) (4) per ICH Q1(R2) and delete the two misleading statements from future submissions.

8. In Section 3.2.P.5.4, Batch Analyses, you have stated (b) (4)

   If you prefer that the data from these supporting stability batches must be considered by the Agency in assignment of shelf-life for HTX-011, provide adequate justification along with the above quoted LIRs at the time of resubmission.

9. We also note that the two supporting stability batches that failed to meet the acceptance criteria (b) (4)

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 Ogochukwu Ogoegbunam, PharmD, BCGP, Regulatory Project Manager, at (240) 402-8807.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON H HERTZ on behalf of RIGOBERTO A ROCA
04/30/2019 05:37:37 PM