CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208193

COMPLETE RESPONSE

Metacel Pharmaceuticals, LLC
Attention: Jeff Bryant, Chief Operating Officer
137 N. Broad Street, Suite E
Winder, GA 30680

Dear Mr. Bryant:

Please refer to your New Drug Application (NDA) dated January 9, 2016, received March 11, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ozobax (baclofen) oral solution 1mg/mL.

We acknowledge receipt of your amendment dated January 1, 2018, which constituted a complete response to our January 11, 2017, 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.

PRODUCT QUALITY

(b) (4)

It was clearly stated in the January 11, 2017, Complete Response Letter, item #7, that if the identity, assay, or related substance method has to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated, since the current data would not reliable. Therefore, you should place an additional 2 batches of the drug product on stability, according to ICH Q1A (R2), and submit sufficient long-term stability data to support the proposed shelf life.

NONCLINICAL

(b) (4)

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
Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the 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.

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 include annotations that support any proposed changes.

PROPRIETARY NAME

Please refer to correspondence dated, March 30, 2018, which addresses the proposed proprietary name, Ozobax. 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.

ADDITIONAL COMMENTS

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

1. **Product Quality**
   - Perform a risk assessment screening [redacted] (b) (4)
   - Provide batch analysis data on the drug product, batch C0412.
   - Provide reference standard source information [redacted] (b) (4)

2. **Container Labels**
   - As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either DDMMMYYYY (e.g., 31JAN2013), MMMYYYY (e.g., JAN2013), YYYY-MMM-DD (e.g., 2013-JAN-31), or YYYY-MM-DD (e.g., 2013-01-31).
   - The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. We recommend you ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges to increase clarity. For example, revise [redacted] (b) (4) to read [redacted] (b) (4)
   - The following cautionary statement is present on the container label [redacted] (b) (4) which may mislead users [redacted] (b) (4) [redacted] (b) (4) In response to an Information Request sent to the Sponsor on June 3, 2016, the Sponsor submitted an amendment to its NDA on June 10, 2016. [redacted] (b) (4) We recommend you remove the statement from the container label.

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, contact Taura Holmes, PharmD, MS, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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/

ERIC P BASTINGS
06/25/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208193

COMPLETE RESPONSE

Metacel Pharmaceuticals, LLC
Attention: Jeff Bryant
Chief Operating Officer
137 N. Broad Street, Suite E
Winder, GA 30680

Dear Mr. Bryant:

Please refer to your New Drug Application (NDA) dated January 9, 2016, received March 11, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ozobax (baclofen) oral solution 1 mg/mL.

We also acknowledge receipt of your amendment dated October 14, 2016, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this 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.

PRODUCT QUALITY

The proposed manufacturing and control strategy for Ozobax (baclofen oral solution) is inadequate to assure the identity, purity, strength, and quality of the commercial drug product. The strategy lacks sufficient controls over all of the identified critical quality attributes, at release and over the product shelf life. You will need to address the gaps in the control strategy outlined below. Note that any changes made to the product, manufacturing process used for registration batches, analytical procedures, or container closure system in order to address these deficiencies will require new stability studies.

Manufacturing Process

(b) (4)

(b) (4)

Control of Drug Product (Validation)

(b) (4)

(b) (4)

Control of Drug Product (Release and Stability Specifications)

(b) (4)

Drug Product Stability

(b) (4)

Labeling

12. The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains (b) (4) information, which is not appropriate for the dosage form and strength section. Remove this information.

13. The drug substance structure in the description section is blurry. Update the label with a clear structure.

14. The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g., color). It also does not have information for in-use storage. Update the how supplied section with this information.

PREA REQUIREMENTS

We note that, in your January 9, 2016, submission, (b) (4) We also note that, in our March 4, 2016, Unacceptable for Filing letter, you were notified that this baclofen oral solution application is not exempt from PREA requirements. As such, as part of your response to this letter, please submit a revised iPSP. (b) (4)

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf . In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm .

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

PROPRIETARY NAME

Please refer to correspondence dated, April 8, 2016, which addresses the proposed proprietary name, Ozobax. 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.

ADDITIONAL COMMENTS

We have the following comment that is not an approvability issue:

1. Certificates of analysis (CoAs) for three drug substance batches used for manufacture of the drug product were provided. The CoAs indicate that the related compound specification for any individual unspecified impurity is NMT (b) (4)%. This is in contrast to specification of NMT (b) (4)% proposed in 3.2.S.4.1. Furthermore, quantitative results for related substances were not reported, as the CoAs only indicate that the drug substance meets requirements. Please request updated CoAs from you supplier that reflect the specification proposed in 3.2.S.4.1, and include quantitative results for individual unspecified impurities.

OTHER

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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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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, contact Taura Holmes, PharmD, MS, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
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/

ERIC P BASTINGS
01/11/2017