CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208276Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208276

COMPLETE RESPONSE

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 T. W. Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your New Drug Application (NDA) originally submitted December 26, 2015, received December 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Implantable System for Remodulin (treprostinil) solution for injection.

We acknowledge receipt of your amendment dated December 15, 2016, which constituted a complete response to our October 8, 2016, 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. As noted in our October 8, 2016, Complete Response letter, the device component of this combination product received a Not Approvable letter on the PMA on March 11, 2016. As stated in our October 8, 2016, letter, until such time as the device is determined to be approvable for use in combination with your proposed drug under this NDA, your NDA for the drug-device combination product cannot be approved.

2. Sufficient human factors (HF) data has not been provided to demonstrate that the Implantable System for Remodulin (ISR) user interface supports safe and effective use for the intended users, uses and use environments. Therefore, the original HF deficiencies included in the Not Approvable letter issued by FDA's Center for Devices and Radiological Health (CDRH) on March 11, 2016 and the HF deficiencies identified by CDRH on February 9, 2017, with respect to the PMA resubmission to CDRH, remain outstanding. In addition, pursuant to 21 CFR 820.30, the ISR user interface, including the training plan, should be optimized and validated prior to approval to ensure the ISR can be used safely and effectively by the intended users, for the intended use, and in the intended use environment. We recommend that the device component of this combination

product undergo a re-evaluation of the HF validation study results, implementation of additional mitigations, finalize the intended training program, and supply additional HF validation data to demonstrate that representative users can use the product safely and effectively before the product is approved. Submit the HF validation study protocol for Agency review and feedback before commencing the study to ensure that the methodology is acceptable.

PRESCRIBING INFORMATION

3. We reserve final comment on the proposed labeling until the application is otherwise adequate. We have, however, decided to incorporate the use of the Implantable System for Remodulin into the existing Remodulin label.

   When you resubmit your application, please propose a unified Prescribing Information incorporating use of the Implantable System for Remodulin in the existing label for Remodulin.

   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

   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

4. Please refer to correspondence dated, April 7, 2017 which addresses the proposed proprietary name, Implantable System for Remodulin. 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/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.
   - Present tabulations of the new safety data combined with the original/supplemental application data.
   - Include tables that compare frequencies of adverse events in the original /supplemental 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/supplemental 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/product. Include an updated estimate of use for drug/product 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," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.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, call Wayne Amchin, RAC, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal 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/

WAYNE S AMCHIN
06/02/2017

NORMAN L STOCKBRIDGE
06/02/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208276

COMPLETE RESPONSE

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 T. W. Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your New Drug Application (NDA) dated December 16, 2015, received December 16, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the Remodulin (treprostinil) Implantable System.

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. The proposed device in this drug-device combination product was submitted to FDA under a Premarket Approval Application (PMA). On March 11, 2016, FDA issued a Not Approvable letter on the PMA. Until such time as the device is determined to be approvable for use in combination with your proposed drug under this NDA, your NDA for the drug-device combination product cannot be approved.

PRODUCT QUALITY

2. There are insufficient data to evaluate the risk of potential patient exposure to microbial contaminants when the Remodulin drug product is used in the proposed implantable pump system. Reference is made to the 24 May 2016 Medtronic response to the 08 May 2016 FDA information request regarding the low concentration of m-Cresol in the drug product following delivery by Medtronic PAH1 System. We note the response states in part, “The loss of m-Cresol from the sterile drug product solution during the infusion process would not impact the microbial quality since the high levels of preservative in the pump reservoir would be expected to control any potential microbial contamination and the implanted pump and catheter is a closed system”. However, the application does not contain data demonstrating that the catheter is a “closed system” from the standpoint of microbial ingress. Consequently, it is not clear as to whether insertion of the device into a patient may result in microbiological contamination of the tip of the catheter which may not be killed by the low concentration of the antimicrobial preservative once the drug

traverses from the pump reservoir to the end of the catheter. Provide data demonstrating that the device is a closed system with regard to microbial ingress at the tip of the catheter.

PRESCRIBING INFORMATION

3. 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

4. The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. 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 Remodulin Implantable System 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.
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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 the Remodulin Implantable System. Include an updated estimate of use for Remodulin 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.

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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, call Wayne Amchin, RAC, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal 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/

WAYNE S AMCHIN
10/07/2016

NORMAN L STOCKBRIDGE
10/08/2016