

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203496Orig1s000

OTHER ACTION LETTERS



NDA 203496

COMPLETE RESPONSE

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, and resubmitted January 31, 2013 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for treprostinil diolamine 0.125 mg, 0.25 mg, 1 mg, and 2.5 mg Tablets.

We acknowledge receipt of your amendments dated February 14 and 15, 2013. Your submission of January 31, 2013 constituted a complete response to our October 23, 2012 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.

Our first complete response letter for this application (23 October 2012) listed issues. We provide them again, summarize your response, and provide our current thinking.

You were able to demonstrate an effect on 6-minute walk only in study 302. The effect in that study was quite small and of dubious clinical importance. The estimated mean effect probably exaggerates the true effect, as much of the effect seems to be attributable to how values are imputed to subjects missing week 12 data. (This appears to have been less of an issue with inhaled treprostinil. In addition, we note our disagreement about how some subjects in study 302 were categorized for the purposes of imputation.)

You do not dispute the overall treatment effect size, but point out that it is similar to the effect of other formulations of treprostinil. This effect of oral treprostinil is achieved at peak (where plasma levels are 7 to 10 times levels at trough) with twice daily dosing. At trough, a statistically significant effect on oral treprostinil was not demonstrated, but the nominal effect was 13 m, about half the effect at peak. Therefore we do not agree that the effect of oral treprostinil is similar to that of treprostinil administered continuously or more frequently by other routes.

In defense of the clinical significance of this effect, you say that, with a similar effect on 6-minute walk, subcutaneous treprostinil was able to avert clinical worsening in patients discontinuing Flolan. However, we are skeptical that oral treprostinil would recapitulate this benefit, as subcutaneous administration does not result in peak-trough excursions of 7- to 10-fold.

You point out that survival in open label use of oral treprostinil is similar to that of subcutaneous treprostinil and that of bosentan and better than that seen in historical data. While this is somewhat reassuring from a safety perspective, neither subcutaneous treprostinil nor bosentan have mortality claims based on these open-label, historically controlled data, and there is no basis for attributing such good outcomes to oral treprostinil either.

You note that in the long-term open-label study, only 19% of subjects add another vasodilator in the first year. We do not know how to interpret that observation, but we are skeptical that it reflects normalization of subjects' symptoms on oral treprostinil.

In the primary analysis of study 302, 21% of subjects on oral treprostinil and 14% of subjects on placebo had imputed values, with the imputation differences being among subjects assigned average placebo rank (4% on treprostinil vs. 0% on placebo) and those assigned last rank carried forward (8% on treprostinil vs. 1% on placebo).

Clinical deterioration and death were similar on study drug and placebo. The differences that resulted in net better rank on oral treprostinil probably reflect its poorer tolerability. The effect on the ranked analysis is not large, but it does not accurately reflect an advantage to treatment.

Pre-specified sensitivity analyses that (a) carry forward last rank for all missing data, (b) analyze completers only, or (c) use data obtained post-withdrawal, all show similar effect sizes and nominal p-values. Analyses based on the FDA reviewer's opinion of cause for withdrawal or on Dr. Wittes's "worst reasonable case" all retain a similar effect size and at least nominal statistical significance. Thus you show that the results are not highly sensitive to the imputation process, and we agree.

You were unable to demonstrate an effect on time to clinical worsening in three phase 3 studies.

While this comment in the first Complete Response letter was intended to note merely that no benefit existed of greater clinical importance than the effect on 6-minute walk, you again remind us that subcutaneous treprostinil has the claim noted previously. Again, we are skeptical that this finding can be expected with the highly fluctuating plasma levels that accompany twice-daily dosing of oral treprostinil.

You were unable to show an effect on 6-minute walk in two well-powered studies (301 and 308) in which subjects were on background therapy with other, possibly more effective but certainly better tolerated vasodilators. Given the meager effect of treprostinil and its poor tolerability, it is difficult to name a clinical scenario in which use of oral treprostinil is appropriate.

You do not refute the findings of studies 301 and 308, but you note that 40 and 45% of subjects in these studies were on both a PDE5 inhibitor and an endothelin receptor antagonist. We agree that this could have contributed to the difficulty in demonstrating an effect.

In response to characterization of oral treprostinil as poorly tolerated, you note that 824 subjects have participated in open-label studies, of whom 641 remained on treatment at 1 year. Whether that constitutes good tolerability is a matter of perspective, but we concede that some people tolerate long-term use. We also agree that no novel toxicity was associated with the oral formulation, and that the oral formulation avoids formulation-specific problems with inhaled, intravenous, and subcutaneous administration.

You responded to the challenge of naming a clinical scenario for use of oral treprostinil by again noting open-label, long-term use and the low uptake of additional therapy. We reiterate our skepticism that this is a reflection of benefit of oral treprostinil rather than a benefit of remaining in a study.

You argue that oral treprostinil has been adequately shown to work in some definable setting, asserting that it should be approved for use in that setting (monotherapy). We disagree. When there were only a few such drugs, it made sense to approve them without concern about their interactions (or the small effect). Now there are multiple drugs in multiple classes. The symptomatic effect of any of them is so small as to be indiscernible by individual patients against the background of the day-to-day variability in symptoms; this is why it takes hundreds of subjects to detect a treatment effect. The magnitude of the effect matters here, and if a new product or new formulation cannot be shown to achieve a clinically important effect alone, it ought to be demonstrated to contribute to a meaningful effect; oral treprostinil has done neither.

In summary, we concur that study 302 distinguishes the effects of oral treprostinil and placebo on 6-minute walk, but we find the effect observed to be too small to be clinically meaningful without demonstration that it contributes to a clinically meaningful effect of other vasodilator therapy.

We recognize that oral treprostinil has a safety profile that should avoid some risks of treprostinil by other routes of administration, so we would hope that a pathway forward can be found. We strongly recommend a regimen with more than twice-daily dosing in any subsequent study. If you pursue a claim relating to 6-minute walk or dyspnea, a new study should be performed with a background of other vasodilator therapy, as in studies 301 and 308, but novel claims probably would not require this.

LABELING

We acknowledge your revisions to the package insert as well as to the carton and container labeling in your resubmission. However, we defer review of the labeling in your resubmission until the clinical issues identified above are resolved.

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 the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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's "Guidance for Industry - Formal Meetings Between the 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, please call Edward Fromm, RPh., RAC, Regulatory Project Manager, at (301)796-1072.

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/

NORMAN L STOCKBRIDGE
03/22/2013



NDA 203496

COMPLETE RESPONSE

United Therapeutics Corp.
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55 TW Alexander Drive
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We acknowledge receipt of your amendments dated January 13, 26, and 31, February 10, 27, and 28, March 20, April 12 and 26, June 6 (two) and 25, August 3 and 10, September 11, 20, 21, 28, and October 16 and 18, 2012.

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.

You were able to demonstrate an effect on 6-minute walk only in study 302. The effect in that study was quite small and of dubious clinical importance. The estimated mean effect probably exaggerates the true effect, as much of the effect seems to be attributable to how values are imputed to subjects missing week 12 data. (This appears to have been less of an issue with inhaled treprostinil. In addition, we note our disagreement about how some subjects in study 302 were categorized for the purposes of imputation.)

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We are unsure whether an additional clinical study can alter these impressions, but if you undertake an additional study, we advise you to consider

- a fixed-dose design (titration to different target doses), so that you have the ability to generate data to support exposure-response analysis,
- more frequent dosing, to reduce the large peak-to-trough ratio you get with twice daily dosing and maybe reduce the impact of exposure-related tolerability issues, and
- a setting in which you think you can defend the context of use as standalone therapy.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format and include CMC-specific DLDE tables for each strength 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.

Please submit draft carton and container labeling revised as follows:

Container Labels

1. [REDACTED] (b) (4)
This may be confusing (b) (4)
Therefore, we recommend removing this [REDACTED] (b) (4)
2. We acknowledge you have attempted to differentiate the (b) (4) strengths within your product line; [REDACTED] (b) (4)
Therefore, utilize an alternate color for differentiation of the (b) (4) strength to minimize the risk of selection error.
3. Decrease the prominence of the “Rx Only” statement by debolding its font and relocating it away from the center to either side of the principal display panel to avoid crowding of important information.
4. Decrease the prominence of the net quantity “100 Tablets” statement by debolding its font and relocating it away from the statement of strength.
5. Increase the prominence of the [REDACTED] (b) (4) statement by bolding its font and relocating it from the side panel to the bottom of the principal

display panel. Consider relocating the manufacturer information from the principal display panel to the side panel to accommodate this change.

6. Revise the storage statement to read: “Store at 25°C (77°F); excursions 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature]. Keep out of reach of children.” We recommend dashes not be used in order to provide clarity and prevent the potential for misinterpretation of the “-” symbol as a negative sign, especially for a temperature designation.

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If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

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

ENCLOSURE:
Labeling

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NORMAN L STOCKBRIDGE
10/23/2012