CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-272

United Therapeutics Corporation
Attention: Mr. Dean Bunce
68 T.W. Alexander Drive
Research Triangle Park, N.C. 27709

Dear Mr. Bunce:

Please refer to your new drug application (NDA) dated October 16, 2000, withdrawn July 5, 2001 and resubmitted on August 9, 2001. This application was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) Injection, 1.0, 2.5, 5.0, and 10.0 mg/ml.

We acknowledge receipt of your submissions dated February 12, 13, 20 (two), 25, and 28, March 14 and 20 (two), April 1 and 2, and May 8, 2002. Your submission of April 1, 2002 constituted a complete response to our February 8, 2002 approvable letter.

This new drug application provides for the use of Remodulin (treprostinil sodium) Injection 1.0, 2.5, 5.0, and 10.0 mg/ml for the treatment of pulmonary arterial hypertension (PAH).

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Remodulin (treprostinil sodium) Injection 1.0, 2.5, 5.0, and 10.0 mg/ml for use as recommended in the final printed labeling (package insert and immediate container and carton labels included in your submission of March 21, 2002). Accordingly, the application is approved under Subpart H of the Code of Federal Regulations (21 CFR 314.510). Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H post marketing commitments) specified in your submission dated April 1, 2002. These commitments, along with any completion dates agreed upon, are listed below.

We note your submission of April 1, 2002, in which you committed to the performance of a clinical study, P01:13 as outlined in your amendment dated April 1, 2002. This study is titled "*A multicenter, randomized, parallel placebo-controlled study of the safety and efficacy of subcutaneous Remodulin™ therapy after transition from Flolan® in patients with pulmonary arterial hypertension.*" In this study a total of approximately 100 patients who are clinically stable on regimens for their pulmonary hypertension are to be withdrawn from Flolan and randomized to receive either placebo or Remodulin. The primary endpoint of the study is the time to clinical deterioration defined as the time from

initiation of study drug to earliest incidence of clinical worsening of PAH symptoms requiring reinstitution of Flolan therapy, to rehospitalization, or to death. As patients will be closely monitored, deaths are not expected. The study is powered based on the expected occurrence of at least 50 events.

The time-lines for completion of P01:13 (and affirmed in your April 2, 2002 submission) are as follows:

50% of Planned Enrollment:	by June 2, 2003
Full (100%) Enrollment:	by December 2, 2003
Submission of Complete Study Report:	by June 2, 2004

Please note that failure to adhere to these time lines may be considered a failure to show due diligence (21 CFR 314.510) and may trigger Agency action to withdraw marketing approval under 21 CFR 314.530.

The final study report should be submitted to this NDA as part of a supplemental application. For administrative purposes, all submissions relating to this post marketing commitment must be clearly designated "Subpart H Post Marketing Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please be note that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred as described in the Federal Register notice of December 2, 1998 (63 *FR* 66632). We acknowledge your request of October 16, 2000 asking for a waiver of the pediatric study requirement for this action on this application. In accordance with 21 CFR 314.55(d), we agree to waive that requirement for this application for all pediatric study groups covered by the Pediatric Rule.

In a telephone conversation with Mr. Edward Fromm, Division of Cardio-Renal Drug Products, on May 14, 2002, you agreed to make the following changes to the package insert at the time of your next printing:

1) Under **PRECAUTIONS, Hepatic and Renal Impairment**, the phrase "**SPECIAL POPULATIONS**" should not be capitalized and should be changed to "**Special Populations**".

2) Under **HOW SUPPLIED**, the sentence that reads "Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F)" should be deleted.

Please report these changes in your first annual report.

In addition, under **Clinical Trials in Pulmonary Arterial Hypertension** and **Adverse Reactions,** please add a discussion of whether differences were seen in demographic subgroups. This information should be submitted as a prior approval supplemental application.

We also note that there were minor editorial changes made throughout the package insert.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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APPLICATION NUMBER:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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United Therapeutics Corporation
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68 T.W. Alexander Drive
Research Triangle Park, N.C. 27709

Dear Mr. Bunce:

Please refer to your new drug application (NDA) dated October 16, 2000, withdrawn July 5, 2001 and resubmitted on August 9, 2001. This application was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) Injection, 1.0, 2.5, 5.0, and 10.0 mg/ml.

We acknowledge receipt of your pre-submissions dated August 11, September 18, and 22, 2000 and your submissions dated October 16, November 3, 10 (two), 13, and 16, December 1, 4, 14, and 22 (two), 2000, and January 5 (two), 10, 11, 23, and 25, February 15 (three), 19, 23, 26, and 28 (two), March 1, April 4, 9, and 12, May 14, and June 5, 14 (two), 25, and 27, August 16, October 2, and November 1, 2001.

This new drug application provides for the use of Remodulin (treprostinil sodium) Injection for the treatment of pulmonary arterial hypertension.

We have completed the review of this application, as amended, and have considered the discussions at the Cardiovascular and Renal Drugs Advisory Committee meeting of August 9, 2001. The application is approvable under 21 CFR 314 subpart H (314.500-560), based on the statistically strong results of the combined exercise/Borg score analysis, an end point that is reasonably likely to predict clinical benefit (21 CFR 314.510), but is not as well-established as a clear effect on exercise alone. The effect of Remodulin on exercise was statistically marginal. Remodulin is used to treat a life-threatening illness, and for at least some patients, it has potential safety advantages compared to alternative available therapy. Approval is contingent upon your demonstrated commitment to conduct a post-approval, controlled clinical trial to test the effects of Remodulin on end points that are clearly clinically relevant. In addition, before this application may be approved, it will be necessary for you to submit final printed labeling (FPL) for Remodulin. The labeling should be identical in content to the enclosed marked-up draft labeling. Please also submit carton and container labeling that reflect the new established name for the product.

There are several acceptable designs for the post-marketing clinical trial. Two possibilities are outlined below. Your study must obtain placebo-controlled data unambiguously demonstrating clinical benefit or approval of Remodulin may be withdrawn as specified under 21 CFR 314.530.

Double-blind, placebo-controlled withdrawal study

Patients with pulmonary hypertension who have been receiving treprostinil for at least 2 months and are clinically stable could be randomized to continued treatment or withdrawal to placebo or to tapering doses of treprostinil. The primary end point would be time to the first occurrence of death, hospitalization for complications of pulmonary hypertension, or well-defined clinical deterioration requiring reinstitution of treatment. We note that with careful monitoring, few or no fatal outcomes would be expected. Changes in exercise tolerance (6 minute walk) and Borg score should be secondary end points.

Double-blind, placebo-controlled study on a background of therapy with bosentan or epoprostenol

A more attractive study, because it would improve on available treatment, would be to randomize patients with pulmonary hypertension, who are receiving stable doses of bosentan or epoprostenol but remain significantly symptomatic, to additional treatment with placebo or treprostinil. The principal end point in this study would be time to the first occurrence of death, hospitalization for complications of pulmonary hypertension, need for epoprostenol, or other clear evidence of deterioration. It may be possible to develop a persuasive symptomatic end point as an alternative or secondary end point.

Final approval is contingent upon an agreement between United Therapeutics Corporation and the Division of Cardio-Renal Drug Products regarding the final protocol for the post-marketing study, including the choice of primary end point and the identification of investigators.

From the date of marketing approval, 50% of planned enrollment for the study should be accomplished within 12 months, with full enrollment by 18 months, and a complete study report should be submitted within 24 months. Failure to adhere to these time lines may be considered a failure to show due diligence (21 CFR 314.510) and may trigger Agency action to withdraw marketing approval under 21 CFR 314.530.

Promotional Materials: As required by 21 CFR 314.550, you must submit for consideration during the preapproval review period, three copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

After 120 days following marketing approval you must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

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

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
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/

Robert Temple
2/8/02 05:45:09 PM

68 page(s) of revised draft labeling has been redacted from this portion of the review.