

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272

CORRESPONDENCE

ORIGINAL



58 T.W. Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709
tel 919.485.8350
fax 919.485.8352



NEW CORRESPONDENCE

N-600-C

**New Drug Application -
General Correspondence**

April 2, 2002

Douglas Throckmorton, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 21-272
Remodulin™ Injection

Dear Dr. Throckmorton:

Reference is made to a telephone conversation today with Ed Fromm of your Division concerning our April 1, 2002, complete response letter.

United Therapeutics herewith commits to the timelines in the February 8, 2002, approvable letter for Protocol P01:13 ("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").

Should you have any questions concerning this amendment, please do not hesitate to contact me by phone at 919-485-8350, ext. 192, by facsimile at 919-485-8352, or by email at dbunce@unither.com.

Sincerely,

A handwritten signature in black ink, appearing to read "Dean Bunce".

Dean Bunce
Senior Director, Regulatory Affairs

cc: Robert Temple, M.D., ODEI

Electronic Mail Message

Date: 4/13/01 7:44:03 AM
From: Edward Fromm (FROMME)
To: Dariush Farahifar * (FARAHIFARD)
Cc: Natalia Morgenstern (MORGENSTERN)
Subject: NDA 21-272, Remodulin Injection

Dariush,

Per instructions from Dr. Temple, please classify United Therapeutic's submission dated April 12, 2001 as a Major Multi-discipline Amendment (AZ).

This should extend the review clock by 3 months; the new goal date should be July 16, 2001.

Thank you,

Ed



NDA 21-272

United Therapeutics Corporation
Attention: Mr. Dean Bunce
P.O. Box 14186
68 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We acknowledge receipt of your July 3, 2001 correspondence notifying us that you are withdrawing your October 16, 2000 new drug application (NDA) for Remodulin (treprostinil sodium) Injection.

Therefore, in accordance with 21 CFR 314.65, this application is withdrawn as of the date of our receipt of your notification, July 5, 2001. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn application be considered in conjunction with any future submission.

If you have any questions, please call:

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

Sincerely,

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug 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/

Natalia Morgenstern
7/5/01 03:23:03 PM



NDA 21-272

United Therapeutics Corp.
Attention: Mr. Dean Bunce
68 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We acknowledge receipt of your resubmitted new drug application (NDA) for the following:

Name of Drug Product: Remodulin (treprostinil sodium) Injection

Review Priority Classification: Priority (P)

Date of Resubmitted NDA: August 9, 2001

Date of Receipt: August 9, 2001

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 8, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 9, 2002.

All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

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

Sincerely,



{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug 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/

Natalia Morgenstern
8/15/01 05:14:26 PM

**New Drug Application -
Amendment to a Pending Application**

April 12, 2001

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
1451 Rockville Pike
Rockville, Maryland 20852



Re: NDA 21-272
Remodulin™ (treprostinol sodium) Injection

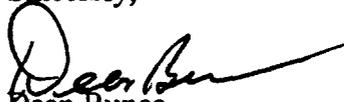
Dear Dr. Lipicky:

Reference is made to our meeting on April 11, 2001, with Dr. Temple, yourself and representatives of your Division. As discussed at the meeting, we are submitting herewith additional statistical analyses correlating the primary endpoint of exercise tolerance and Borg Dyspnea score in our pivotal studies, P01:04 and P01:05.

Please note that we intend to submit additional analyses in the next few weeks, including analyses to further support the correlation of exercise tolerance and Borg Dyspnea scores, to support the robustness of the principal reinforcing and secondary endpoints in respect to the FDA's concern on the potential for unblinding bias, and clarification on the use of opioids.

Should you have any questions concerning this package, please do not hesitate to contact me by phone at 919-485-8350, ext. 192, by facsimile at 919-485-8352, or by email at dbunce@unither.com.

Sincerely,


Dean Bunce
Director Regulatory Affairs

cc: Dr. Robert Temple, HFD-101

Hand Delivered

New Drug Application – General Correspondence

December 14, 2000

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
1451 Rockville Pike
Rockville, Maryland 20852

Re: NDA 21-272
UT-15 Injection

Dear Dr. Lipicky:

Reference is made to the December 8, 2000, meeting between yourself and representatives of your Division and representatives of United Therapeutics to discuss NDA 21-272. Reference is also made to a teleconference with Dr. Throckmorton and Mr. Fromm of your Division on December 12, 2000.

Based on these discussions, we agree with the FDA that NDA 21-272 will not be presented to the Cardiovascular and Renal Drugs Advisory Committee. We welcome the continued opportunity to work in cooperation with representatives of your Division in the review of NDA 21-272.

Should you have any questions concerning this submission, please do not hesitate to contact me at by phone at 919-485-8350, ext. 192, by facsimile at 919-485-8352, or by email at dbunce@unither.com.

Sincerely,



Dean Bunce
Director, Regulatory Affairs



E. FROMM

Food and Drug Administration
Rockville MD 20857

NDA 21-272

ORIGINAL
Submission
- WITHDRAWN
7/5/01

OCT 19 2000

United Therapeutics Corp
Attention: Mr. Dean Bunce
68 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Uniprost (treprostinol sodium) Injection 1.0, 2.5, 5.0, 10.0 mg/mL

Review Priority Classification: Priority (P)

Date of Application: October 16, 2000

Date of Receipt: October 16, 2000

Our Reference Number: NDA 21-272

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 15, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 16, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

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

Sincerely yours,

/s/

Natalia A. Morgenstern
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Archival NDA 21-272

HFD-110/division file

~~HFD-110/ef~~

HFD-110/Team Leaders and reviewers

DISTRICT OFFICE

Drafted by: ef/10/18/00

Initialed by:

Final: asb/10/18/00

Filename: 21-272(ac).doc

ACKNOWLEDGMENT(AC)

New Drug Application

October 16, 2000

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 21-272
UT-15 Injection

Dear Sir/Madam:

Reference is made to our August 11, 2000 presubmission of Item 4 - Chemistry Section (Volumes 1.1 – 1.9) and Item 5 - Nonclinical Pharmacology and Toxicology Section (Volumes 1.10 – 1.35) of NDA 21-272.

We are submitting herewith the remainder of NDA 21-272 for review by the Division of Cardio-Renal Drug Products.

UT-15 Injection is submitted for the indication of Pulmonary Arterial Hypertension (PAH). United Therapeutics was granted Orphan designation for the indication Pulmonary Arterial Hypertension November 2, 1999. A copy of the letter is attached.

We are requesting priority review classification for UT-15 Injection. UT-15 Injection is indicated for the treatment of PAH, a life-threatening disease for which the life expectancy is less than 2.5 years from diagnosis. UT-15 Injection is also more stable and thus is able to be delivered via subcutaneous infusion as compared to the central intravenous infusion of the current approved therapy. This mode of therapy provides for increased convenience and compliance, primarily due to the lack of serious complications with the delivery of the current therapy.

By this letter, we are requesting, in accordance with 21 CFR 314.55(d), an exemption for pediatric use information for UT-15 Injection.

By this letter, in accordance with 21 CFR 314.108(b)(2), we also hereby request a five-year period of exclusivity for UT-15. We hereby certify that UT-15 has never been approved either as a single entity or as part of a combination product.

We are also attaching the April 11, 2000, letter granting UT-15 Injection an exemption from conducting carcinogenicity studies.



UT-15 Injection
NDA 21-272

Page 2 of 2

United Therapeutics certifies, by this letter, that we did not and will not use in any capacity the services of any person debarred as defined in the Food, Drug and Cosmetic Act Section 306.

Should you have any questions concerning the enclosed application, please do not hesitate to contact me at 919/485-8350, ext. 192.

Sincerely,

A handwritten signature in cursive script that reads "Dean Bunce".

Dean Bunce
Associate Director, Regulatory Affairs

MESSAGE CONFIRMATION

02/08/02 19:31
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
829	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics Corporation

Phone: (919) 485-8350

Subject: Approvable Letter for Remodulin (treprostinil sodium) Injection, NDA 21-272

Date: February 8, 2002

Pages including this sheet: 21

From: Edward Fromm

Phone: 301-594-5313

MESSAGE CONFIRMATION

03/26/01 10:36
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
03/26 10:35	01'15"	919194858352	004/004	OK		0000

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Rockville, MD 20852

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Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: Minutes of Telecon, March 12, 2001

Date: 03/26/01

Pages including this sheet: 4

From: Edward Fromm
Phone: 301 594 5317

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: **Confirmation of meeting with FDA, March 28, 2002**
Remodulin (treprostinil sodium) Injection
NDA 21-272

Date: March 14, 2002

Pages including this sheet: 2

From: Edward Fromm
Phone: 301-594-5313
Fax: 301-594-5494