CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

CHEMISTRY REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-272 **DATE REVIEWED:** 05/17/02

REVIEW #: 03 **REVIEWER:** JV Advani

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
PRE-CMC submission	11-Aug-00	14-Aug-00	15-Aug-00
AMENDMENT (BC)	18-Sep-00	19-Sep-00	20-Sep-00
ORIGINAL SUBMISSION	16-Oct-00	18-Oct-00	19-Oct-00
AMENDMENT (BC)	04-Dec-00	05-Dec-00	12-Dec-00
AMENDMENT (BC)	22-Dec-00	29-Dec-00	08-Jan-01
AMENDMENT (N-BL)	16-Aug-01 & 2 & 21-Feb-02		

Letter dated November 1, 2001 – Non-proprietary name information

NAME & ADDRESS OF APPLICANT: United Therapeutics Corporation
P.O. Box 14186
Research Triangle Park, NC 27709

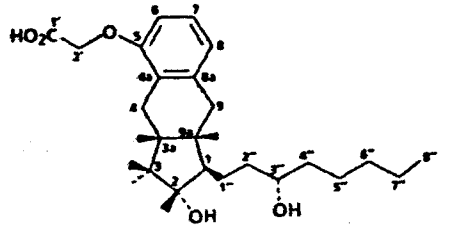
DRUG PRODUCT NAME

Proprietary:	Remodulin
Established:	Treprostinil sodium
Code Name/#:	UT-15, LRX-15, 15AU81, BW A15AU, U-62,840
Chem.Type/Ther.Class:	1 P
CAS Registry Number	81846-19-7

PHARMACOL. CATEGORY/INDICATION: Pulmonary Arterial Hypertension
DOSAGE FORM: Injection
STRENGTHS: 1.0, 2.5, 5.0, and 10.0 mg/mL
ROUTE OF ADMINISTRATION: Subcutaneous injection
Rx/OTC: _x_ Rx ___ OTC
PATENT STATUS: U.S. Patent pending
SPECIAL PRODUCTS: ___ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:
[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt



Na^+

Molecular Formula $C_{23}H_{33}NaO_5$ **Molecular weight** 412.49

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date

Material technical data sheets for Type I USP 20 mL Glass is provided. Refer Vol.1.3, pp. 854-877.

RELATED DOCUMENTS (if applicable):

(Submission of 5/95 for UT-15 Injection)

CONSULTS: Microbiology: Micro deficiencies have been resolved. Micro data is acceptable. Microbiologist recommends approval.

REMARKS:

UT-15 Injection is a tricyclic benzindene analog of prostacycline (PGI2) with potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. Unlike Flolan (epoprostenol sodium), which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternate therapeutic route of administration.

All strengths (containing 1.0 mg, 2.5 mg, 5.0 mL and 10.0 mg treprostinol per mL), of UT-15 Injection, is packaged in Type I USP 20 mL . The 20 mL vial is sealed with

The differ in color for product identification.

An EER for establishments was requested on 08/18/00. Overall recommendation for all sites is ACCEPTABLE

Mr. Edward Fromm (PM) sent the labeling and package information provided by firm (in vol.2.9) to current Labeling committee OPDRA for their review. OPDRA review and recommendations are received. Uniprost is not acceptable but Remodulin proprietary name is acceptable.

Expiration date months is proposed when stored at 25°C for the 1.0 mg/mL, 2.5 mg/mL, and 5.0 mg/mL, and expiration date of months for 10-mg/mL strength. Proposed expiration periods will be reviewed when the updated stability data is received from the applicant.

Statistical analysis: Firm has performed the linear regression analysis at 25°C on potency data for lots stored in proposed commercial packaging.

Methods validation will be requested to be performed by 2 district laboratories.

The information submitted in this submission has been previously reviewed under and its amendments.

Firm in letter of November 1, 2001, has indicated that USAN has adopted on July 25, 2001, treprostinil sodium as the non-proprietary name for Remodulin Injection.

CONCLUSIONS & RECOMMENDATIONS: There have been no other changes in chemistry since last review dated 03/06/01. This NDA is satisfactory as far a chemistry is concerned.

Copy of statement on USAN adopted non proprietary name TREPROSTINIL SODIUM is attached with this review.

JV Advani, Review Chemist

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

/s/

J. V. Advani
5/17/02 04:35:47 PM
CHEMIST

Kasturi Srinivasachar
5/17/02 05:10:55 PM
CHEMIST

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-272 **DATE REVIEWED:** 03/06/01

REVIEW #: 02 **REVIEWER:** JV Advani

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL SUBMISSION	16-Oct-00	18-Oct-00	19-Oct-00
AMENDMENT (BC)	23-Feb-01	26-Feb-01	27-Feb-01
AMENDMENT (BL)	26-Feb-01	27-Feb-01	28-Feb-01
AMENDMENT (N-BC)	28-Feb-01	01-Mar-01	01-Mar-01
AMENDMENT (N-BC)	01-Mar-01	02-Mar-01	02-Mar-01

NAME & ADDRESS OF APPLICANT: United Therapeutics Corporation
P.O. Box 14186
Research Triangle Park, NC 27709

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ROUTE OF ADMINISTRATION:	Subcutaneous injection
Rx/OTC:	_x_ Rx __ OTC
PATENT STATUS:	U.S. Patent pending
SPECIAL PRODUCTS:	__ Yes _x_ No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:

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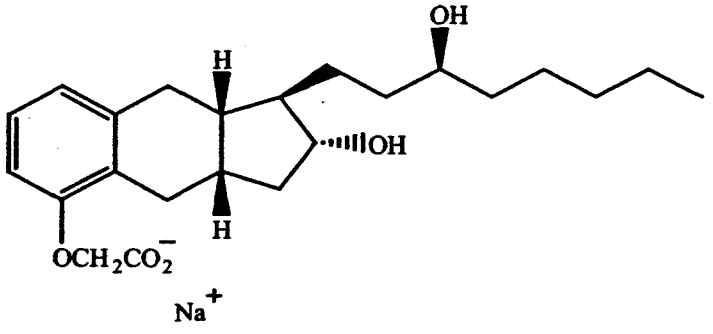

Molecular Formula $C_{23}H_{34}O_5$ **(free acid)** **Molecular weight** 390.52

SUPPORTING DOCUMENTS: ———

RELATED DOCUMENTS (if applicable): ———
(Submitted on 5/95 for UT-15 Injection)

CONSULTS: Microbiology. There are no pending issues regarding sterility assurance.

REMARKS:
UT-15 Injection is a tricyclic benzindene analog of prostacycline (PGI2) with potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. Unlike Flolan (epoprostenol sodium), which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternate therapeutic route of administration.
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The differ in color for product identification.
The amendment of 23 Feb. 01 provides some of the responses to deficiencies noted in my Review #1 and discussed with the applicant in the December 7, 2000 meeting. Applicant has provided specifications, test methods validation for one of the starting materials for use in the UT-15 synthesis process. Also firm has now provided, —month stability data for some of the primary stability batches of all strengths.
The amendment of 26 Feb, 01 provides the revised labeling incorporating new trade name, Remodulin and other changes. USAN requested that the proposed generic name be changed to treprostinol sodium instead of triprostinol sodium (refer original -BL- amendment of 10/16/2000).
In an amendment of 28 Feb, 01 there is a reference to teleconference meeting on 02/28/01 for tightening the levels of impurities in drug substances and in the drug product and includes the commitment to provide the information on the levels of ——— impurities if present, in the drug substance. The amendment provides the method validation data for second starting material of the drug substance synthesis process.
The amendment of 01Mar, 01 provides the revised test methods for drug substance and drug product, with revised specifications as per commitment made on 2/28/01 in teleconference meeting and also provides requested specifications or certificates of analysis for drug substance raw materials.

CONCLUSIONS & RECOMMENDATIONS:
The NDA may be approved from the CMC viewpoint. All pending issues identified in review #1 have been resolved in recent amendments. The storage statement in the package insert should be changed to conform to the storage statement on the carton labels. The ingredient "Water for Injection" should be included in the list of ingredients in "Description Section" of package insert and containers. These revisions are reflected in the marked up draft labeling which will be sent to the Applicant.

JV Advani, Review Chemist

/s/

J. V. Advani
3/13/01 07:01:37 AM
CHEMIST

Kasturi Srinivasachar
3/13/01 08:53:36 AM
CHEMIST

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-272 **DATE REVIEWED:** 02/15/01

REVIEW #: 01 **REVIEWER:** JV Advani

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
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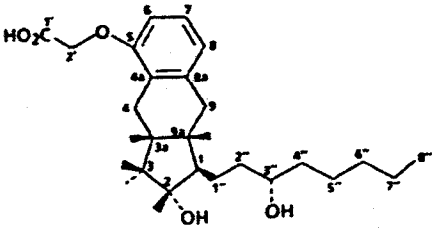

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The information submitted in this submission has been previously reviewed under and its amendments. The firm has addressed some of our recommendations that were made during the meetings on 7/15/99 and at pre NDA meeting on 11/08/99. I have highlighted the firm's actions in these regards in this review

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approvable pending a satisfactory response to the deficiencies noted in the draft letter on page 19, which will be conveyed to the applicant.

JV Advani, Review Chemist

A. DRUG SUBSTANCE:

22 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

/s/

J. V. Advani
3/1/01 05:51:46 PM
CHEMIST

Kasturi Srinivasachar
3/5/01 09:01:25 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21272/000** Priority: **1S** Org Code: **110**

Stamp: **16-OCT-2000** Regulatory Due: **16-AUG-2001** Action Goal: District Goal: **17-AUG-2001**

Applicant: **UNITED THERAP**
68 TW ALEXANDER DR
RESEARCH TRIANGLE PARK, NC 27

Brand Name: **UNIPROST(TREPROSTINOL SODIUM)1.0/2.5/10.**

Established Name:

Generic Name: **TREPROSTINOL SODIUM**

Dosage Form: **INJ (INJECTION)**

Strength: **1.0; 2.5; 5.0;10; MG/ML**

FDA Contacts:

E. FROMM	**(HFD-110)**	**301-594-5300**	**, Project Manager**
J. ADVANI	**(HFD-110)**	**301-594-5300**	**, Review Chemist**
K. SRINIVASACHAR	**(HFD-110)**	**301-594-5376**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 26-SEP-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:

AADA No:

Profile: **SVS** OAI Status: **NONE**

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **26-SEP-2000**

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE**

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **17-AUG-2000**

Decision: **ACCEPTABLE**

Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: **CSN** OAI Status: **NONE**

Last Milestone: **OC RECOMMENDATION**

Milestone Date: **21-SEP-2000**

Responsibilities [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Environmental Assessment (EA)

Dr. Advani in his February 15, 2001 review states that the firm should be granted exclusion.